KENNETH D.S. FERNALD

The Waves of Biotechnological Innovation in Medicine

Interfirm Cooperation Effects and a Venture Capital Perspective

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De golven van biotechnologische innovatie in geneesmiddelen: effecten van samenwerking tussen bedrijven en een investeerders perspectief

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Kenneth Dimitri Satia-Graha Fernald

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Doctoral Committee

Promotors:	Prof.dr. E. Claassen Prof.dr. H.P.G. Pennings Prof.dr. H.R. Commandeur
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Chapter 1

INTRODUCTION

This dissertation evaluates interfirm cooperation and venture capital investments in the context of biotechnological innovation and science-based business. After the rise of biotechnological innovation, several promising waves of technological development have emerged but as yet, the potential and initial expectations of biotechnology have not been realized. The studies in this dissertation aim to better understand how more biotechnological innovation can reach the market and which biotechnologies will revolutionize R&D productivity and global healthcare. Related processes are evaluated from different business perspectives (i.e. entrepreneurial biotech companies, established pharmaceutical firms and venture capitalists). The focus lies on the following themes: Technological development of initial biotechnological innovation (*chapter 2*); the dynamics of interfirm cooperation and how biotech companies can increase the likelihood of eventual product introduction (*chapter 3*); how pharmaceutical firms can adapt interfirm cooperation dynamics to increase R&D productivity and innovation performance (*chapter 4*); and which new fields of biotechnological innovation may shape the future of the science-business model from a venture capital perspective (*chapters 5* and *6*). The current chapter introduces the context as well as the central concepts of this dissertation. Section 1.2 provides an outline of the dissertation, including a schematic overview and brief summaries of the individual chapters. It also presents an overview of the various chapters (*table 1.1*), including their publication status. The central concepts are introduced in section 1.3, namely: biotechnology, the value chain, interfirm cooperation, and venture capital. Each subsequent chapter of this dissertation can be read independently.

1.1 Science-based business

Improving medicine and health is the ultimate purpose of medical biotechnological innovation, where basic science is used to develop new innovative diagnostics and therapeutics to improve the lives of patients worldwide. Concurrently, for three out of four stakeholder groups, the primary goal is to generate profitable business. These stakeholders are 'entrepreneurial' biotech companies, venture capitalists (VCs) and established pharmaceutical firms. A fourth group of stakeholders are the academic research institutions or universities, which provide much of the fundamental science and intellectual property (IP) that fuels biotechnological innovation.

Traditionally, business and science were two separate constructs. On the one hand, established chemical and pharmaceutical firms were in the business of developing new drugs based on chemistry and pharmacology [1]. On the other hand, universities and other research institutions were primarily focused on advancing basic science [2]. Scientific breakthroughs in understanding the fundamentals of DNA and genetic engineering opened the realm of possibilities of modern biotechnological innovation (see *glossary 1.3.1*).

New possibilities for developing innovative diagnostics and therapeutics led to a strong convergence of science and business, which in turn led to the evolution of a new organizational form, with science-based businesses at the centre of it [2, 3]. Advances in biosciences combined with three fundamental driving forces in the general innovation system co-shaped this evolution. Pisano [2] describes these driving forces as changes taking place in the convergence of science and business with the emergence of biotechnology in the latter decades of the 20th century.

The first significant change concerned the demise of central corporate research laboratories as fundamental research was increasingly viewed as a cost rather than an investment. Although this was a general trend, large pharmaceutical corporations have always been highly dependent on their internal research and development (R&D) efforts and operate corporate research laboratories to this day. However, these large incumbents started to realize that internal efforts alone were not sufficient to fuel pipelines with innovations [4, 5]. Therefore they started to look outside the boundaries of the firm for innovation, adopting the open innovation model [6, 7]. This is a trend that coincides with the rise of biotechnology and science-based business, and is further explored in *chapter 4*.

The second change was the universities' increasing focus on appropriating monetary returns on their intellectual property. Where academic knowledge institutions used to primarily focus on basic scientific research as opposed to applied science, the extent of their patenting, licensing and spin-off activities expanded dramatically in the latter decades of the 20th century [2, 8, 9].

Finally, there was the emergence of new science-based entrepreneurial businesses, mainly in life sciences, due to significant scientific advances in biosciences and biotechnology. Science-based businesses are defined as "entities that both participate in the creation and advancement of science and attempt to capture financial returns from this participation",

emphasizing that "they are not simply 'users' of science, but contributors to it as well" [2]. Noteworthy, the science underlying these new companies is not as well developed as the science underlying start-ups in other high-technology industries. Moreover, science-based entrepreneurial businesses in biotechnology face significantly higher risk profiles and longer R&D trajectories than start-ups in other industries such as electronics or software [2]. Biopharmaceutical products in development follow a very specific and highly regulated value chain, which is elaborated on in *glossary 1.3.2*. The path of the recent history of biotechnology and waves of innovation spurring from the scientific advancement of genetic engineering are specified in *glossary 1.3.1*.

These driving forces shaped the current 'science-business model', and Genentech, incorporated in 1976, laid its foundation. As the first biotech company, Genentech formed the first cooperative R&D agreement with Eli Lilly to further develop and market the first biologic (Humulin®, launched in 1982). In 1980 Genentech was the first biotech company to go public, while having no marketed products or revenue. This, however, successful initial public offering (IPO), and subsequent others [10], made the biotech sector increasingly attractive for VCs [2].

The success of this 'science-business model' inspired high expectations of biotechnological innovation, especially in light of the productivity gap and innovation deficits of large incumbent pharmaceutical firms [5, 11, 12]. Imminent patent expirations on blockbuster drugs and deficits of new potential ones led to enormous increases of R&D expenditures as well as an increasing trend of mergers & acquisitions (M&A) and alliances with biotech companies [13-15]. Biotechnology as a new source of external innovation was expected to be the answer to the challenges of the pharmaceutical industry [3, 16].

However, despite several success stories of biotech companies, optimistic expectations of biotechnology remain unsupported by empirical evidence and the "biotech revolution" has been disappointing in terms of new productivity and financial performance [2, 5, 16, 17]. Some insinuate that biotechnology would never deliver on its promising expectations of revolutionizing drug R&D [16, 17]. Others, however, believe that it can, provided that industry organization and anatomy are adapted [2, 18] or through new technological innovation such as personalized medicine [19, 20].

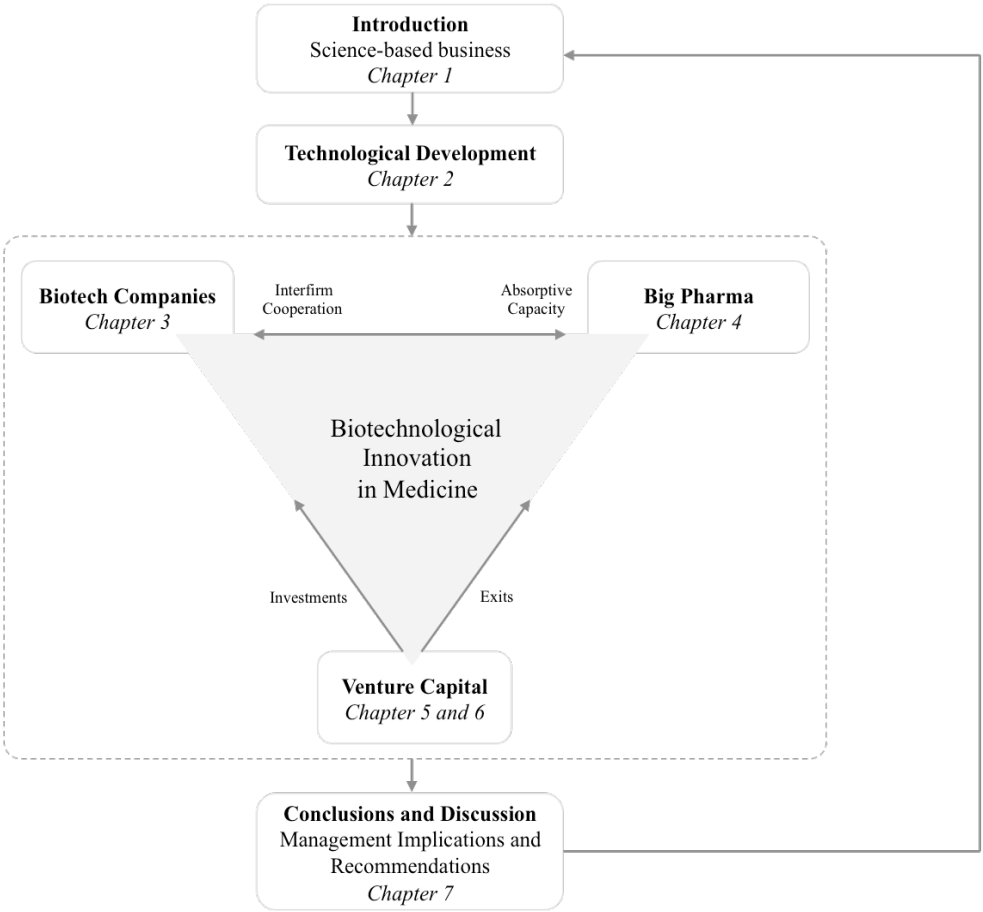
Different levels of uncertainty[21, 22] pertaining to science and waves of innovation require different management tools and strategic approaches to extract the technological potential. Regarding the organization of science and business, there is much to learn before we may reap the true benefits of biotechnology in medicine. The studies in this dissertation focus on the future of biotechnological innovation by, on the one hand, exploring the increasing trend of interfirm cooperation and its effects on innovation performance and productivity in the current industry setting; and, on the other hand, by exploring which type of innovation(s) will co-shape the future organization of science-based business. The aim is to better understand processes that take place from different business perspectives (i.e. entrepreneurial biotech companies, established pharmaceutical firms and VCs) with regards to how more biotechnological innovation can reach the market and which biotechnologies will revolutionize R&D productivity and eventually global healthcare. The focus lies on the following main themes: Technological development of initial

biotechnological innovation (*chapter 2*); the dynamics of interfirm cooperation and how biotech companies can increase the likelihood of eventual product introduction (*chapter 3*); how pharmaceutical firms can adapt interfirm cooperation dynamics to increase R&D productivity and innovation performance (*chapter 4*); and which new fields of biotechnological innovation may shape the future of the science-business model from a venture capital (VC) perspective (*chapters 5* and *6*).

1.2 Outline

This dissertation presents several studies from the perspective of three key stakeholders involved in the 'science-business model' regarding biotechnological innovation in medicine. It is important to note that the scope of the dissertation is limited to business interests of commercial stakeholders. For this reason, none of the studies presented in this dissertation pertain to the perspective of academic knowledge institutions or universities. Thus, the dissertation follows a triangular structure of distinct vantage points and business interests, with biotechnological innovation at the centre (*figure 1.1*).

Figure 1.1 Outline of the dissertation in a schematic view



Chapter 2 introduces technological forecasting of biotechnologies using technology S-curve theory [23, 24]. We assess the development stage of the first wave of biotechnological innovation, by analysing patents related to the recombinant DNA (rDNA) and monoclonal antibody (mAb) technologies. This chapter shows that, in terms of innovation entering the R&D pipeline, this first wave has reached a stage of saturation. Due to the average time-span of R&D between patent application and product approval, this saturation has not yet been reflected in biotechnological products on the market, but will affect future productivity.

Chapters 3 and *4* explore effects of interfirm cooperation on company-level productivity and innovation performance from two different perspectives. *Chapter 3* investigates innovation clusters, strategic alliances and acquisitions as three different dimensions of inter-firm cooperation, and their relationship with biotech companies' future product introductions and financial returns. The study focuses on the perspective of the technology supplier, in this case biotech companies, and their strategic options with regards to interfirm cooperation. A trade-off between risk and return is revealed for biotech companies looking to further develop and commercialize their innovative products.

Chapter 4 examines the effects of strategic alliances and M&A on the innovation performance of the technology recipient, in this case established pharmaceutical firms. In this context, the chapter further explores the role of technology relatedness and firms' absorptive capacity. M&A and consequential consolidation of the pharmaceutical industry have been an increasing trend that coincided with the evolution of science-based business and the rise of biotechnology. The study shows that pharmaceutical firms have increasingly preferred (unrelated) biotechnology companies as their alliance and acquisition targets as opposed to other (related) traditional pharmaceutical companies. However, it also shows that effects of such interfirm cooperation on established firms' innovation performance are moderated by their absorptive capacity.

Chapters 5 and *6* focus on the next waves of biotechnological innovation from a VC perspective. *Chapter 5* includes an analysis of the distribution of VC funding over various biotechnology fields and therapeutic areas, which are defined through interviews and literature research. In addition, it includes the transaction values and multiples realized in trade sale deals of VC-backed companies. The chapter is divided into two parts. First, it demonstrates the role of VCs as technology gatekeepers, based on an analysis of investments in- and trade sales of portfolio companies backed between 1999 and 2013, only including trade sale data from these respective companies. The second part shows which therapeutic areas and broad technology fields have benefitted VCs most by presenting an analysis of trade sales of VC-backed companies that occurred between 2010 and 2014.

Chapter 6 combines qualitative and quantitative research to conduct a systematic prioritization analysis of VCs' investment priorities in terms of biotechnologies and therapeutic areas, as well as associated investment barriers. The study reveals several niches of technology – therapeutic area combinations with high VC attractiveness. Furthermore, it exposes high-prioritized barriers specific to these niches, that when overcome at an early stage could significantly increase VC attractiveness of new ventures.

Finally, *chapter 7* summarizes the key findings and recapitulates how each chapter contributes to existing literature and the overall aim of the dissertation. Furthermore, the main conclusions are further discussed in the organizational context of science-based business and the dominant pharmaceutical business model. In conclusion, several management implications of organizational innovation are discussed, recommendations for transforming science-based business are made, and avenues for further research are suggested. *Table 1.1* presents a tabular overview of the individual dissertation chapters.

Table 1.1 In-depth overview of the individual dissertation chapters

Chapter	Title	Central Research Question	Sub-questions	Theoretical perspective	Methodology
1	**Introduction**				
2	**Limits of biotechnological innovation**	What is the current stage of the two first biotechnologies that are associated with marketed products?	- What is the relation with the innovation paradox? - How have radicalness and value of inventions progressed over time?	- Technology forecasting (S-curve).	- Technology trend analysis and forecasting. - Patent citation analysis
3	**Biotechnology commercializatio n strategies; risk and return in interfirm cooperation**	How do alliances with a technology recipient affect risks and returns in biotechnological product development?	- Effects of alliances (source vs. non-source) on product development and on product revenue? - Effects of being acquired on product development and on product revenue?	- Exploration and Exploitation - Inter-organisational cooperation and learning - Business clusters	- Database-research. - OLS regression analyses. - Tobit regression analyses
4	**The moderating role of absorptive capacity and the differential effects of acquisitions and alliances on big pharma firms' innovation performance**	How do acquisitions of- and alliances with biotech companies affect pharma firms' innovation performance?	- Main effects of alliances and acquisitions on innovation performance? - Interaction effects of alliances and acquisitions with R&D intensity (absorptive capacity) on innovation performance?	- Open innovation - Exploration and Exploitation - Absorptive capacity - Resource-Based View	- Database-research. - Poisson regression analyses - Negative binomial regression analyses.
5-I	**Venture capitalists as gatekeepers for biotechnological innovation**	In which therapeutic areas and technology fields have VCs invested and in which are they realizing highest returns?	- Which therapeutic areas? - Which technology fields? - Role of diagnostics and personalised medicine? - How do investments relate to trade sales? in terms of technology fields and therapeutic areas - Can we observe a general strategy of VCs from their investment behaviour?	- Portfolio theory - Asset pricing - Strategic venture investing	- Qualitative interviews - Database research - Analysis of investments
5-II	**Biotech trade sale returns on venture capital – 2010-2014**	Which type of companies and which therapeutic areas have benefitted VCs most between 2010-2014.	Overview of trade sales and their initial VC investments (gross returns/multiples) per therapeutic area and broad technology field?	- Portfolio theory - Asset pricing - Strategic venture investing	- Database research - Analysis of trade sales
6	**A quantitative prioritization and barrier analysis of biotechnology fields and therapeutic areas; A venture capital Perspective**	How do life sciences venture capitalists prioritise biotechnology fields and therapeutic areas and associated innovation barriers?	- Ranking of therapeutic areas and technologies (from VC perspective) - What are the investment barriers per top 3 therapeutic areas and top 3 technology fields?	- Portfolio theory - Investment behaviour - Investment selection	- Qualitative interviews - Quantitative Questionnaires - Prioritization analysis
7	**Conclusions and discussion; summary of main conclusions and contributions, management implications, recommendations, and suggestion for further research**				

Data	Main conclusions	Status	Outlet
Patent and product data related to rDNA and mAb technologies over the period 1980-2011 (Source: AcclaimIP; Espacenet)	Early biotechnologies have reached their technological limit and there is a lack of newer radically innovative technologies that are currently generating product innovations. These outcomes may be determinants for an innovation cliff in biotechnology.	**Published (2013)[14]**	**Technology & Investment**
Company data of biotech firms that own(ed) rDNA and mAb patents over the period 1980-2011. (Source: AcclaimIP; Espacenet; ThomsonReuter' SDC Platinum Database; Datastream; Compustat)	Strategic alliances involve a risk-return trade-off. Increased biotech company involvement in alliances, as technology suppliers, decreases risk by increasing the likelihood of future product introductions. However, biotech companies earn lower returns when their products are developed through such alliances. A similar trade-off exists for biotech clusters, as they positively affect product introductions, but have a negative effect on returns. Acquisitions, however, negatively affect the likelihood of introducing biotechnological products, but have no effect on revenues gained from these products.	**Published (2015)[25]**	**Journal of Product Innovation Management**
Pharma company data; NCEs; acquisitions and alliances; R&D intensity; over the period 1990-2013. (Source: ThomsonReuter' SDC Platinum Database; FDA (CDER and CBER); Datastream; Compustat)	Increases in the number of acquisitions of biotech companies have negatively affected big pharma firms' innovation performance. However, acquisitions of both pharma and biotech companies are complementary innovation activities at higher levels of absorptive capacity, whereas the general effects of these acquisitions appear to be negative. Noteworthy, pharma acquisitions outperform biotech acquisitions in this regard, illustrating the known influence of technology- and market-relatedness. The same complementarity exists between biotech alliances and absorptive capacity, while pharma alliances' main effect is positive but these alliances turn out to be substitutive strategic options at higher levels of absorptive capacity.	**Submitted/ Under Review[15]**	**R&D Management**
- Qualitative data from interviews with VCs - Data on 1,217 biotech/pharma VC-backed companies between 1999-2013. (Source: ThomsonReuter' SDC Platinum VentureXpert Database) - Relating technology fields, therapeutic areas of lead product(s).	In terms of therapeutic areas, VCs can balance their average investments valuations more in correspondence with what big pharma is willing to pay. But, VCs have formidable insight in the types of technologies that do well. VCs seem to employ a strategy focused on both short-term and long-term success: On the one hand they play it safe, minimizing risk by investing most in small molecules and proteins. On the other hand, they are investing heavily in DNA/RNA technologies, which up until now have not yet proven to be very profitable. The blockbuster business model directly affects new venture financing by VCs. However, VCs are also rebelliously investing in the biotechnologies that underlie personalized medicine.	**Published (2015)[26]**	**Journal of Commercial Biotechnology**
- Data on 115 VC-backed biotech/pharma ventures acquired between 2010-2014. (Source: ThomsonReuter' SDC Platinum VentureXpert Database). - Relating technology fields, therapeutic areas of lead product(s).	VCs have benefited most in the area of oncology; other beneficial therapeutic areas are infectious -, auto-immune - and central nervous system diseases. Furthermore, big pharma's predominant blockbuster paradigm guides their acquisition preference and therewith their innovation demand. VCs predict the corresponding innovation supply and act as visionary technological gatekeepers[27], building for big pharma.	**Accepted[28]**	**Nature Biotechnology**
- Qualitative data from interviews with VCs - Quantitative questionnaire data: prioritization of therapeutic areas, technology fields, and barriers to innovation.	VCs seem to be considering cell- and gene therapy technologies as future disrupters in terms of innovation and economic development. VCs might be jumping the S-curve of technological development from proteins to gene and cell therapy Solving high-prioritized barriers for specific niches with high VC attractiveness could significantly increase competitive advantages for entrepreneurs.	**Submitted/ Under Review[29]**	**Int. Journal of Biotechnology**

1.3 Glossary of central concepts

1.3.1 Biotechnology

Biotechnology is in fact an all-encompassing term for various fields of biosciences. This dissertation solely focuses on biotechnology for medicine, excluding applications of biotechnology in other sectors. The invention of genetic engineering greatly influenced medical biotechnological innovation. The possibility of this became apparent after the discovery of the structure of DNA by Watson and Crick [30] in 1953 and was realized in 1973 with the discovery of a recombinant DNA technique by Cohen et al. [31], using E.coli bacteria. Recombinant DNA (rDNA) technology was further developed and used to produce recombinant proteins as biotechnological products (i.e. biologics), with Genentech's Humulin® being the first [32]. These biologics were a totally new kind of therapeutics compared to the smaller chemical compounds traditionally developed and marketed by pharmaceutical companies. The technology has been used for the development of various kinds of recombinant proteins including cytokines, hormones, interferons, coagulation factors, fusion proteins, antibodies, and subunit vaccines. Many of these biologics became blockbuster products (i.e. selling over $1 billion/year). *Table 1.2* shows the top-selling biologics of 2013[33].

Table 1.2 Top-selling biologics of 2013 (adapted from Lawrence and Lahteenmaki [33])

Name	Type	Indication	Lead company	Approval date	2013 worldwide sales ($B)
Humira® (adalimumab)	mAb	Inflammation, auto-immune	AbbVie	Dec 31, 2002	10.66
Enbrel® (etanercept)	Protein	Inflammation, auto-immune	Amgen	Nov 2, 1998	8.74
Lantus® (insulin glargine)	Peptide	Diabetes	Sanofi	Apr 20, 2000	7.59
Rituxan® (rituximab)	mAb	Lymphoma, Leukemia	Roche (Genentech)	Nov 26, 1997	7.50
Remicade® (infliximab)	mAb	Inflammation, auto-immune	Johnson & Johnson (Centocor)	Aug 24, 1998	6.96
Avastin® (bevacizumab)	mAb	Angiogenesis	Roche (Genentech)	Feb 26, 2004	6.75
Herceptin® (trastuzumab)	mAb	Breast cancer	Roche (Genentech)	Sep 25, 1998	6.56
Neulasta® (pegfilgrastim)	Protein	Chemotherapy induced infection	Amgen	Jan 31, 2002	4.39
Copaxone® (glatiramer acetate)	Peptide	Multiple Sclerosis	Teva Pharmaceutical	Dec 20, 1996	4.36

Noticeably, most of the top-selling recombinant products are monoclonal antibodies (mAbs), which turned out to be the most profitable subsegment of recombinant proteins. Antibody technology, gradually improved from using murine mAbs, to chimeric, humanized and, finally, fully human mAbs [34]. In 1986, Orthoclone OKT3® became the first approved murine mAb [35]. Humira®, approved in 2002, was the first human mAb[33], and by 2013 there were 31 approved therapeutic mAbs on the U.S. market (*chapter 2*) [14]. The rise of these biologics as the first products of biotechnology can be considered the first wave of biotechnological innovation, which is further explored in *chapter 2*.

Recombinant DNA techniques provided the tools needed for the further development of human gene therapy [36]. It now became possible to modify viruses to incorporate and express foreign genes, including potentially therapeutic sequences. Recombinant SV40 became the first vector to transfer foreign DNA into mammalian cells, and the viral vector model for gene therapy was adopted as a promising approach in 1976 [37]. In 1980, an attempt of primal gene therapy was conducted in a study with human patients, but failed [36]. After much ethical contemplation, the first approved clinical trials were initiated around 1990, using retroviral vectors [36]. Two decades later, the first gene therapy product is approved for the European market, using an adeno-associated viral (AAV) vector (UniQure's Glybera®) [38, 39].

Similarly, with rDNA technologies, modification of whole cells (i.e. cellular engineering) became another possibility. Historically, cells were transferred since blood transfusions and the first bone marrow transplantation [40]. However, modern cell therapies are more complex, involving the manipulation and engineering of cells based on genes that program their development and functions, and can be divided into two types. First, there are stem cell therapies, where modified stem cells are used for regenerative medicine and tissue engineering [41]. Although 'embryonic stem cells' were discovered in 1981[42], the first clinical trial involving such stem cells was approved as late as 2009 [43], due to several ethical concerns and regulatory issues. The second type of cell therapies concerns those using modified mature cells to perform specific functions in fighting diseases. Many cell therapies that are currently in clinical development concern treatments of autologous immune cells (e.g. dendritic cells, T-cell) for oncology (i.e. immunotherapy or therapeutic cancer vaccines) [44].

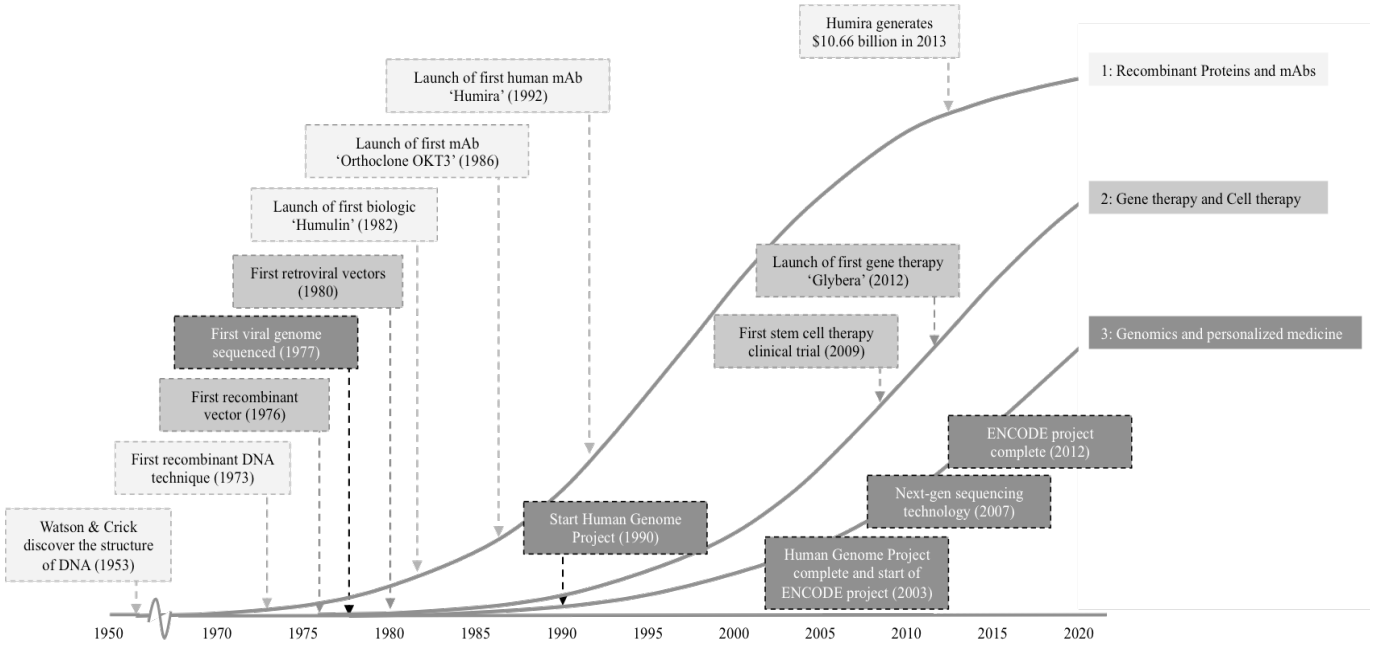
Although oncology is a common target, cell therapy is widely applicable, for example for cardiovascular diseases [45, 46] or neurodegenerative diseases [47]. However, apart from Dendreon's Provenge® and several tissue repair, transplantation, and cord blood products, there are no cell therapies that have reached market approval [48, 49]. Although gene therapy and cell therapy are separate developments in biotechnology, advances in terms of clinical research and product development have been relatively closely consecutive. Therefore, together, gene- and cell therapies can be considered the second wave of biotechnological innovation *(figure 1.2)*.

Considering a third wave, it would primarily concern technologies that have vastly increased our understanding of human biology, and have mainly led to advances in molecular diagnostics. DNA sequencing followed by genome sequencing and genomics, initiated this wave, aiming at studying the genome to find disease related genes. The first full genome was sequenced in 1977, namely that of bacteriophage ΦX174 [50]. In 1990, 'the human genome project' commenced, aiming to sequence the entire human genome [51]. It was completed in 2003, costing a total of $3 billion [52], and 'the ENCODE project' was initiated, aiming to identify and characterize all 20,000 – 25,000 genes found in 'the human genome project' [53]. In 2007, next-generation sequencing technologies, such as Applied Biosystems' SOLiD System, transformed biology research by causing a dramatic drop in sequencing costs [54]. Subsequently, in 2010, 'the 1,000 genomes project' consortium publishes a map of human genome variation, including the whole-genome analysis of

1,000 people. Genome analysis and our consequential understanding of various diseases on a molecular level, will provide increasing ways of applying personalized medicine [55]. Developing accompanying molecular diagnostics for existing or new therapeutics and therapies may revolutionize medicine and healthcare in the near future.

At its completion in 2012, the ENCODE study confirms that the human genome contains 20,687 protein-coding genes [56]. With data from 'the human genome project' and 'the ENCODE project', the possibility to systematically study the human proteome, the vast scala of human proteins, became apparent. The aim of proteomics is to provide detailed descriptions of structure, function and control of biological systems in health and disease[57], which will also play an increasingly important role in personalized medicine [19, 20]. Moreover, cross-disciplinary developments with bioinformatics or systems biology will increase the possibilities[19, 20]. Developments of other biotechnologies such as drug delivery technologies and nanobiotechnologies coincided with these waves of innovation. An overview of biotechnology fields is included in *chapter 5*.

Figure 1.2 General waves of biotechnological innovation



1.3.2 Biopharmaceutical value chain

The value chain essentially describes the full R&D trajectory from basic research to eventual registration and marketing of a new therapeutic biopharmaceutical product. This trajectory has proven to be extremely risky with an average duration of 11.9 years [58], and costs of $0.8–$1.3 billion [59]. Moreover there is an overall success rate of approximately 10% for product candidates that enter clinical development [25, 60, 61]. The current value chain has evolved along with high quality and ethical standards for clinical research, enforced by regulatory authorities [58].

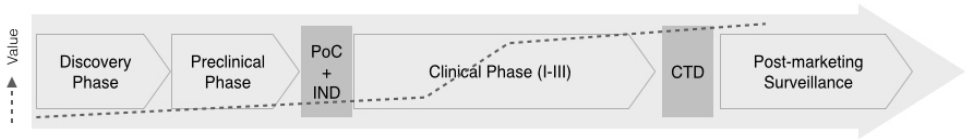
The links of the chains represent the phases in the R&D process, each concluded with milestones. With successful completion of each phase, value is created because risk of failure to reach the market is reduced. Evidently, some phases are riskier than others and, correspondingly, upon successful completion of those phases, more value is created (see *glossary 1.3.4*). As such, different kinds of products are associated with different risk profiles in their development, yet clinical phase II is usually most risky [62].

The first moment of value creation occurs when the intellectual property underlying a product candidate is properly protected, which in this industry mainly concerns protection by one or multiple patents. This is in fact the first milestone, which is preceded by the discovery phase [63]. In this phase various techniques and technologies can be used either to identify new lead compounds or engineer them. A potential product candidate is usually focused on a specific disease, often to validate a biotechnology platform that could also be used for other target diseases. The discovery phase mainly encompasses laboratory research resulting in a patent application. Although granting of patents can take up to several years, the invention is protected from the moment of application, provided that it is eventually granted. Therefore, early application forms a basis for further R&D.

Onward, the product candidate is subjected to further study in the pre-clinical phase, using animal models. In addition to its focus on chemistry, manufacturing and control (CMC), this phase is primarily focused on assessing the potential of human treatment, by collecting data on efficacy and toxicity [63]. After approval of a dossier of data from this phase by the respective regulatory authority, the product candidate may be further studied in clinical trials as an Investigational New Drug (IND) in the U.S. or under a Clinical Trial Agreement (CTA) in Europe. Reaching this milestone is the second moment of value creation, and is often referred to as pre-clinical ‘proof of concept’ (PoC).

In the clinical phases of R&D, human participants are used as research subjects to prove a product candidate’s safety and efficacy. Any participant enters the research with informed consent and clinical research pertains to any medication, diagnostic product, medical device or treatment regimen. Clinical R&D consists of four sub-phases of controlled trials, with milestones of their own.

Figure 1.3 Schematic view of the (bio)pharmaceutical value chain
(PoC, proof of concept; IND, investigational new drug; CTD, common technical document.
Adapted from Pronker et al.[63])



The first sub-phase (i.e. Phase I trials) is an exploratory study to assess first in-human safety for multiple dosages of the product candidate in approximately 20-80 healthy participants[64]. It studies the administration, delivery, metabolism and excretion pathways, and toxicology (ADMET) of the product candidate as well as pharmacokinetic/ pharmacodynamics properties (PK/PD), taking around 0.5-1 year [64, 65].

The second sub-phase (i.e. Phase II trials) often consist of a phase IIa and phase IIb trial. Phase IIa trials are still exploratory studies, but now aiming to assess safety and dose tolerability in 100-300 patients. Phase IIb trials aim to confirm effectiveness of the right dosage, studying delivery and biological activity, again with 100-300 patients. Phase II trials usually take between 1.5 and 2 years [63, 64]. Successful completion of phase I and phase II trials mitigates a substantial portion of the risk and paves the way to confirmatory phase III trials.

The third sub-phase (i.e. Phase III trials) concerns highly expensive, often multi-centre studies that aim to confirm safety, dosage and effectiveness in 1,000 to 5,000 patients, and taking between 3 and 4 years [64, 65]. This phase is relatively less risky and due to the high amount of required resources, these trials are usually conducted by large established (bio)pharmaceutical firms that are often more risk-averse (see *chapters 3* and *4)*. Upon successful completion, a Common Technical Document (CTD) containing all data from these studies according to specific safety and efficacy parameters, is submitted to the respective regulatory authority and reviewed for approval, which may take another 1 to 2 years [64].

Finally, after market entry, the product is subjected to additional post-marketing surveillance clinical trials (i.e. Phase IV trials). This fourth sub-phase of clinical research is aimed at monitoring short- and long-term (side) effects of the product in question, or at evaluating efficacy and safety in specific patient groups that are not included in the CTD (e.g. children). Such studies may continue for as long as the product is used in patients [63].

From the perspective of science-based entrepreneurial businesses, value created with each consecutive milestone in the chain can be captured through upfront- and milestone payments based on collaborative R&D agreements with established firms. In exchange, these firms capture the majority of value after the product is introduced on the market. Finally, VCs capture a portion of the created value as described in *glossary 1.3.4*.

1.3.3 Interfirm cooperation

Several important developments in the evolution of science-based business are related to interfirm cooperation and its various dimensions. Undoubtedly, there are numerous ways in which firms can cooperate to create and capture value that are mutually beneficial (e.g. joint-ventures, cooperative R&D, equity-investments). The difference between such forms most often lies in associated governance structures. For the purposes of the studies included in this dissertation, we have primarily focused on three dimensions of interfirm cooperation and their role in biotechnological innovation. These are: informal cooperation within biotech clusters; strategic alliances for R&D; and M&A (see *chapters 3* and *4*).

As shown in *chapter 3*, clusters stimulate and positively affect success in product innovation [25]. In biotechnology clusters, knowledge is mostly transmitted through informal relations and cognitive networks, making it fit most with the "new social network" type of cluster [66]. Such networks are fostered when science-based businesses are collocated and consequent interaction and transaction occurs among entrepreneurs, scientists, VCs, managers and other stakeholders, creating knowledge spillovers that facilitate and accelerate innovation [66-68]. By clustering, the infrastructure for knowledge transfer and valorisation is created, resulting in regional innovation systems [67, 69, 70]. The largest biotech clusters are situated in the U.S. (e.g. Greater Boston/Cambridge, MA; San Francisco Bay Area, CA; San Diego/ La Jolla, CA), although there are also a few large clusters in Europe (e.g. Cambridge, UK; BioValley, Switzerland/Germany/France; Medicon Valley, Denmark/Sweden) [25].

Although strategic alliances often occur within clusters, these are far more formal agreements that often last several years. Alliances can involve a range of different deal types (e.g. licensing, collaborative R&D, out-sourcing, joint ventures, technology transfer). In the context of the value chain, alliances are an important way for biotech companies to generate income while their products are in development. The 'science-business model' is largely based on this premise, first illustrated by the alliance between Genentech and Eli Lilly for Genentech's recombinant insulin, in which Lilly funded further development and would pay royalties on sales of the product that was later marketed as Humulin® (1982) [2]. Such deals often include upfront R&D funding, royalty payments and (minority) equity investments [15, 25]. As shown in *chapters 3* and *4*, strategic alliances for R&D can be beneficial and positively affect innovation performance for both technology suppliers and technology recipients.
Strategic alliances between biotech companies and established pharmaceutical firms often precede acquisitions [71]. In addition, larger scale M&A amongst established firms have marked significant consolidation of the pharmaceutical industry over the past decades (see *figure 4.1*) [15]. Increases in both large mergers and small-scale acquisitions [13], have been mostly motivated by innovation deficits in pharmaceutical R&D pipelines [72, 73]. Although increased M&A activity has been a response to significant challenges confronted by established firms, many doubt whether it has been an adequate solution [72, 74, 75]. Existing empirical evidence largely suggests that acquisitions of technology companies destroy value and negatively affect innovation performance [25, 76-79]. In the following chapters the relationship between acquisitions and innovation is further examined, both for biotech companies (*chapter 3*) and for established firms (*chapter 4*).

1.3.4 Venture capital

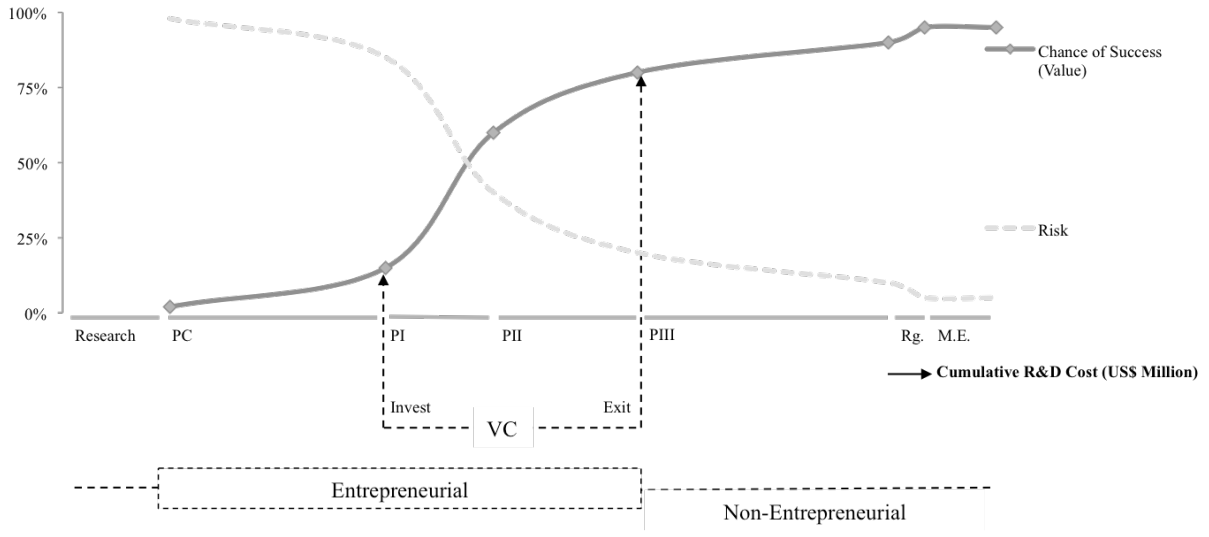
In the context of regional infrastructures and innovation clusters, VC plays a key role in the development of new firms in new markets [80, 81]. For a large part VCs are drivers of technological innovation and stimulate the formation of high technology innovation clusters [27]. Stimulating innovation, economic growth and regional competitiveness, is for some sectors even highly dependent on active VC industries [82].

VC is a kind of private equity risk capital that is an important intermediary in financial markets, mainly because it provides funding to typically young ventures that would normally have difficulty attracting capital due to high levels of uncertainty [83]. VCs usually take a very active role in monitoring and managing their portfolio companies with the primary goal of maximizing financial returns by exiting through a trade sale or initial public offering (IPO) [84]. Many VC firms prefer pre-seed, seed and early stage investments, and most are involved with high-technology investments [85, 86]. Moreover, most high-tech investments concern research-driven university spin-off companies[87], illustrating the fact that science-based business is highly dependent on this form of capital.

In addition to biotech companies' need for VC, the possibilities for biotech IPOs and the increasing M&A interest of pharmaceutical companies made clinical stage biotech companies increasingly attractive for VC firms. Due to the lengthy and costly R&D trajectories of biotechnological and pharmaceutical products and the fact that VCs are aiming to realize financial returns within three to five years after their initial investment, they invest during very specific stages of the value chain. In this context, VCs focus on 'the value step' that is realized when the most uncertain clinical phases are successfully completed (*figure 1.4*). Thus, from a VC perspective, a delicate balance must be found between money, time and risk.

The initial stages are often funded by R&D subsidies as well as informal investors and business angels and the later stages of clinical R&D are mostly funded by established (bio)pharmaceutical firms through alliances and acquisitions [15, 88, 89]. These incumbents will typically get involved after successful phase II clinical trials, as they are far more risk-averse [15]. Thus, VCs are essentially facilitating and profiting from the supply of biotechnological innovation originated from science while meeting the demand of the market, which mostly concerns established pharmaceutical acquirers.

Figure 1.4 Value and risk in biotech R&D and the value step for VCs



Chapter 2

LIMITS OF BIOTECHNOLOGICAL INNOVATION

Abstract

During the past two decades the biopharmaceutical industry has been facing an innovation deficit, characterized by in- creasing research & development costs and stagnant productivity. From its inception, biotechnology has been expected to counter this deficit by its revolutionary science-based approach to drug discovery. For this study we gathered patent and product data related to the technological development of the first two biotechnologies: recombinant DNA technology and monoclonal antibody technology. We studied the technological lifecycles of these technologies in terms of scientific discoveries and inventions as well as product innovations. Results indicate that over the years inventions related to these technologies have simultaneously become less radical and less valuable. Furthermore, our analysis shows that these biotechnologies have reached a stage of technological limit or saturation, which may be followed by an innovation cliff. Now, more than ever, it is crucial to examine new strategies and opportunities for value creation, capturing, and delivery, within the biopharmaceutical industry.

Fernald, K.D.S., Weenen, T.C., Sibley, K.J. and Claassen. E.
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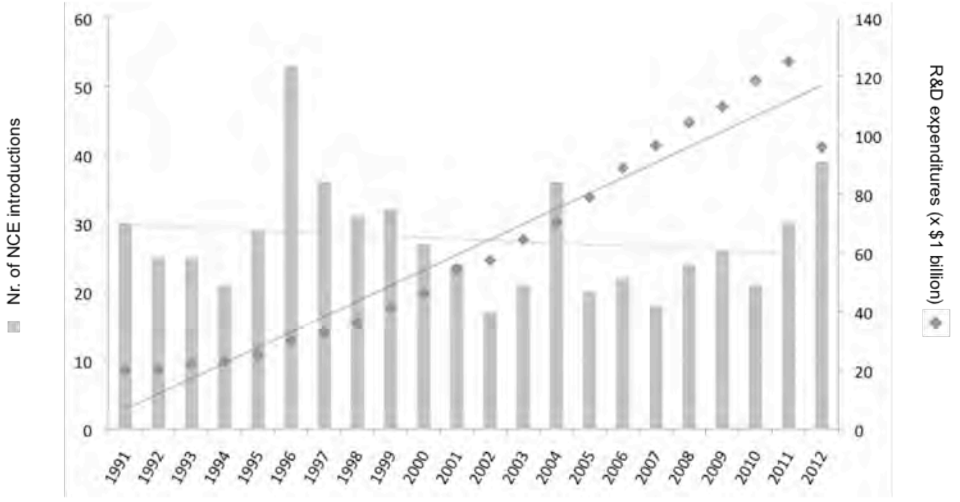
2.1 Introduction

The revolutionary characteristic of biotechnology is the fact that it is derived from advances in fundamental science, and can be used for discovery and development of new products to fulfil unmet medical needs. The rise of biotechnology transformed drug discovery and development from traditional pharmaceutical target screening to a science-deductive process [90, 91]. Consequently, it became possible to target new leads based on the understanding of complex biological systems.

From the first technological breakthroughs in the 1970s, high expectations arose that biotechnology would radically improve drug development and generate new classes of biological products. Moreover, specific biotechnological products were expected to counter declining pharmaceutical productivity [11, 92, 93]. Contrary to those initial expectations, several researchers have since suggested that those optimistic expectations of biotechnology are unsupported by empirical evidence[16] and that the 'biotech revolution' has been disappointing in terms of new products and financial performance [94, 95]. Based on their study of preclinical product development data covering 1992 and 1993, Drews & Ryser[5] already predicted that the output of biotechnology would be insufficient to counter the pharmaceutical innovation deficit.

Even with a dramatic five fold increase in research & development (R&D) spending there appears to be no effect on New Chemical Entity (NCE i.e. New Molecular Entity) production, resulting in a pharmaceutical 'productivity gap' (*figure 2.1*) [4, 12, 63]. In addition, patent expirations of blockbuster drugs might cause incumbent pharmaceutical firms to lose billions of US dollars in combined annual sales [96].

Figure 2.1 The pharmaceutical 'productivity gap'; The considerable rise of R&D expenditures versus a stagnant pattern of New Chemical Entity (NCE) introductions.
(Data obtained from fda.gov, Medtrack and literature[94, 97])



Evidently, pharmaceutical firms are in need of innovation to increase productivity. Therefore, it is important to study the innovation patterns and lifecycles of individual biotechnologies. Such specific patterns can be examined using technology forecasting, a useful tool for identifying phases of a given technology's lifecycle [98, 99].

In this chapter, we examine the patterns of innovation regarding the first two major medical applications of biotechnology: recombinant DNA (rDNA) technology and monoclonal Antibody (mAb) technology. These biotechnologies have generated a sufficient number of marketable biological products that are currently available as prescription drugs. We propose that identifying and analysing patterns in biotechnological innovation and product development is an important prerequisite for defining optimal innovation strategies needed to improve new product development and value creation in the biopharmaceutical industry.

2.2 Literature review

2.2.1 Biotechnology

The application of biotechnologies in medical product development has a relatively short history. The first publications on successful intracellular production of rDNA appeared in 1972 and 1973 [31, 100, 101]. In 1974, Stephan Cohen and Herbert Boyer from Stanford University applied for the first patent on rDNA [102]. Most practitioners of molecular biology and rDNA technology worked in universities and research institutions rather than within the industry [93].

In the late 1970s/early 1980s, private companies such as Genentech began to focus on rDNA technology [35]. This sparked a biotechnology revolution that led to multiple usages for rDNA technology (e.g. treating hemophilia, hepatitis, cystic fibrosis), as well as paving the way for new biotechnological platforms leading to monoclonal antibodies, 'the human genome project', genomics, and gene therapy [103]. Recombinant DNA technology was in fact the first revolutionizing biotechnology that was implemented in corporate R&D of biopharmaceutical companies and produced the first biotechnological product called "Humulin" (i.e. recombinant human insulin) introduced by Genentech and Eli Lilly in 1982 (*glossary 1.3.1)*[2, 103].

The potential for life-saving cancer treatments due to rDNA technology caused a subsequent wave of innovation in biotechnology involving mAb technology [104]. Advances in genetic engineering in the late 1980s provided the technology to humanize mAbs [105]. These advances spurred further R&D of many mAb applications for treatment of various medical needs (e.g. cancer, autoimmune diseases) [106, 107].
The two closely related technologies (rDNA and mAb) quickly became efficient methods of producing commercially important substances. Wright[93] described this process as a transformation of an area of basic scientific research that occurred in an intense pace of development. However, R&D durations of marketed biopharmaceutical products have increased from approximately 4 years in 1982 (e.g. Humulin) to approximately 12 years in the late 1990s (e.g. interferon- β1b), with an estimated average of 8 years [59].

2.2.2 Innovation

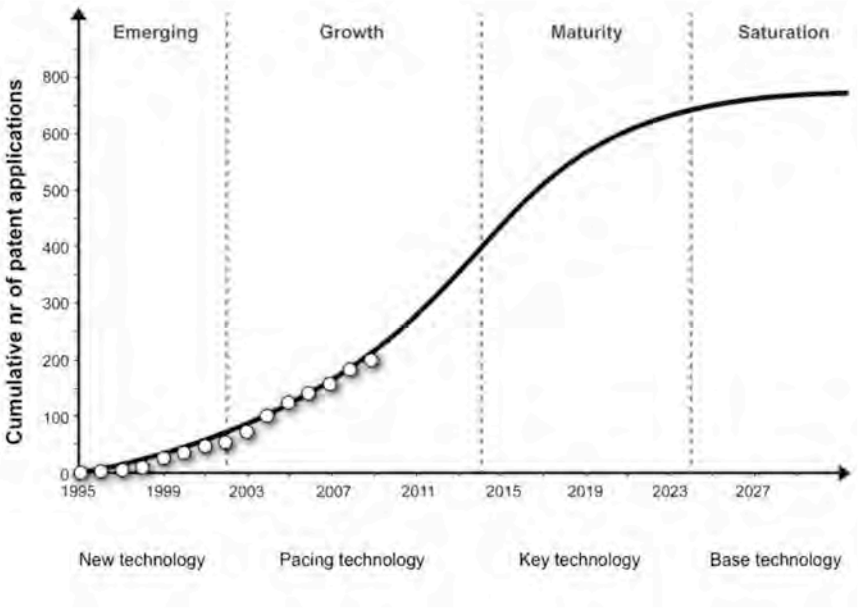
According to Garcia & Calantone (p.112)[108], the essence of innovation can best be described as: "an iterative process initiated by the perception of a new market opportunity for a technology-based invention which leads to development, manufacturing, and marketing tasks aspiring commercial success of the invention". As these authors indicate, this definition addresses two important aspects [108]. First, the innovation process comprises the combination of technological development of an invention and the market introduction of that invention to end-users. Application of this combination in the context of the industry as examined in this study is difficult because invention and market introduction are two activities separated by 10-14 years of R&D and hundreds of millions of R&D-spent US dollars [58, 109]. In addition, conducting these separate activities requires very different knowledge, expertise, resources and capabilities, typically illustrated by the need for nimble biotech companies and incumbent pharmaceutical firms to work in collaborations and alliances [110-112]. This is one of the reasons why biotechnological inventions that might lead to a product are often described as innovations and patents are often used as a measure for biotechnological innovation [113, 114].
The second important aspect of the above described definition is that innovation is an iterative process and therefore includes the introduction of new innovations on the one hand, and the reintroduction of improved innovations on the other. This brings us to the need to classify innovation according to various degrees of innovativeness, distinguishing, in particular, between radical and incremental innovation [108, 115 116].

2.2.3 Technological lifecycles

It is generally presumed that a technology follows a certain pattern throughout its lifecycle. The technology saturation-curve (S-curve) method of analysis has been described and employed to retrieve information on the lifecycle phase of a given technology (*figure 2.2*) [23, 24]. The technology S-curve can be illustrated by means of a certain technology's cumulative patent count against time or R&D expenditures.
According to Ernst[23], the lifecycle of a technology consists of four fundamental phases, namely *emerging, growth, maturity,* and *saturation*. *Emerging* is characterized by low technological growth performance compared to R&D input. *Growth* is identified by a positive growth progress compared to cumulative R&D input. *Maturity* is the opposite: negative growth progress occurs compared to R&D input. The final stage, *saturation*, is characterized by relatively few technological innovations despite a very large cumulative R&D input.

Technologies can further be classified according to two dimensions, namely the integration of the technology in products or processes and the competitive impact of the technology [23]. When a technology emerges, both the integration in products or processes, and the competitive advantage are low. As inventions related to the technology accumulate over time the competitive advantage increases and the technology becomes a pacing technology in the growth phase. When the pacing technology is increasingly integrated in products or processes it becomes a key technology. Subsequently, over time, the technology starts to lose its degree of competitive advantage and it becomes a base technology. At this point saturation or technological limit is reached.

Figure 2.2 The technology S-curve (adapted from Ernst[23]) with cumulative patent data related to medical nutrition (adapted from Weenen et al.[24])



The technology-forecasting tool is useful because it indicates the current life cycle phase of a technology, allowing companies to strategize for the future [98, 99]. For example, when Chen et al.[98] assessed technologies for generating and storing hydrogen; they showed that it had not yet reached the *maturity* phase. Therefore, they were able to recommend increased R&D funding for the technology to accelerate development [98]. Similarly, Weenen et al.[24] examined medical nutrition patent data and showed that the medical nutrition industry is currently in the growth stage (*figure 2.2*), indicating ample future innovation opportunities.

2.3 Methodology

2.3.1 Data collection

Patent applications are perceived as an important indicator, since patent analysis reveals information on historical developments of the technologies investigated in this study. The patent data for this study was gathered from several patent databases using AcclaimIP patent analysis software[i]. The acquired data was compared with data directly gathered from the World Intellectual Property Organization (WIPO)[ii], the United States Patent and Trademark Office (USPTO)[iii], and Thomson Reuters's Derwent Innovation Index[iv]. Over the period of 1980 until 2011, we gathered a total of 7,350 patents regarding mAb innovations and 9,111 patents regarding other rDNA innovations. Patent data is readily available and categorized according to a system of international patent classification (IPC). The IPC is a complex hierarchical classification system encompassing all areas of technology and is currently used by industrial property offices in more than 90 countries [117]. Each patent is given an IPC code that lists its section, class, subclass, group, and usually subgroup [117]. We used these codes to identify relevant patents in the databases.

Recombinant proteins can be divided into various sub-types, with monoclonal antibodies being the largest sub-type. Therefore, we decided to divide the sub-types of recombinant proteins so that two different biotech trends could be plotted separately. Falciola[118] states that patents involving antibodies commonly contained at least one of the following IPC codes: *C07K16/** (Immunoglobulins, as a class of proteins), *A61K39/395* (medicinal preparations containing antibodies), or *G01N33/53* (assays involving the use of antibodies). Therefore, we decided to only look at patents involving monoclonal antibodies containing at least one of these IPC codes *(C07K16/**, *A61K39/**, or *G01N33/53)*. For patents regarding rDNA technology we included all sub-types of recombinant protein products other than antibodies. These include recombinant blood factors, insulin, hormones, interferons, growth factors, interleukins, and thrombolytic proteins. For the gathering of this data we included the following IPC codes: *C07K14/*, C12N15/** or *A61K38/**. In the generative syntax we excluded IPC codes: *A01H5/*, C12N5/*, C12N15/29,* and *C12N15/82*, as these codes relate to inventions with no relevance to rDNA technology. Although data from both US and non-US companies are included in the study, only US patents were included in the analysis. This decision is justified by the fact that almost all companies, both US and non-US, choose to file their patents in the US, amongst other countries, in order to take advantage of the vast US market [119].

In addition, data on biopharmaceutical products was gathered by means of literature research and database development using the Food and Drug Administration (FDA) database[v], the FDA Orange Book and the Medtrack database[vi].

[i] www.acclaimip.com
[ii] www.wipo.int
[iii] www.uspto.gov
[iv] www.thomsonreuters.com
[v] www.fda.gov
[vi] www.medtrack.com

2.3.2 Patent citation analysis

When analysing patent data, citations form an important source of information. There are two types of citations: backward and forward citations. The former refers to patents that have been cited by the patent in consideration [120]. This is an indicator of preceding knowledge and the average number of backward citations has proven to be invertly related to the radicalness of the respective invention; lower numbers of backward citations are associated with more radical inventions [24]. Forward citations refer to the frequency with which a particular patent is cited by newer patent applications. Annual average forward citations of a patent serve as an indicator of technological importance and economic value of that invention [24, 116, 121]. In other words, patent citations describe the quality of a patent and the effects that a patent has had on later technological advances (i.e. other patents) [119]. Applicants of patents generally include citations in the patent application but the patent office examiners ultimately determine which citations are included [122]. Therefore, citation analysis is considered to be a valid and unbiased method of studying technological developments. We define the annual Average Backward Citations (ABC_k) and the annual Average Relative Forward Citations[vii] ($ARFC_k$), as follows:

$$ABC_k = \frac{\sum_{i=1}^{n_k} x_{ik}}{n_k}$$

(Results shown in *figure 2.3a*)

$$ARFC_k = \frac{\frac{\sum_{i=1}^{n_k} y_{ik}}{n_k}}{a_i}$$

(Results shown in *figure 2.3b*)

Where n_k is the number of patents in year k and x_{ik} are the number of backward citations for patent i in year k. y_{ik} are the number of forward citation for patent i in year k and a_i is the age of patent i.

[vii] The forward citations are corrected for age because more recent patents would normally have less forward citations.

2.3.3 Lifecycle analysis

The annual accumulation of patents in a specific area of technological innovation yields valuable information regarding technological lifecycle patterns and development phases of the respective technology [23, 98]. The technology S-curve was constructed by plotting the cumulative number of patents against time according to the file dates of those patents. Similarly to an S-curve based on patents, product introductions related to a specific technology can be plotted cumulatively against time, following a patent S-curve with a time lag of several years due to R&D. Furthermore, cumulative revenues generated by these products help gain insights into current returns on investments in these technologies as well as the future potential earnings from the respective technology related products. Analysis of these three independent parameters resulted in the curves as shown in *figure 2.4*.

2.4 Results

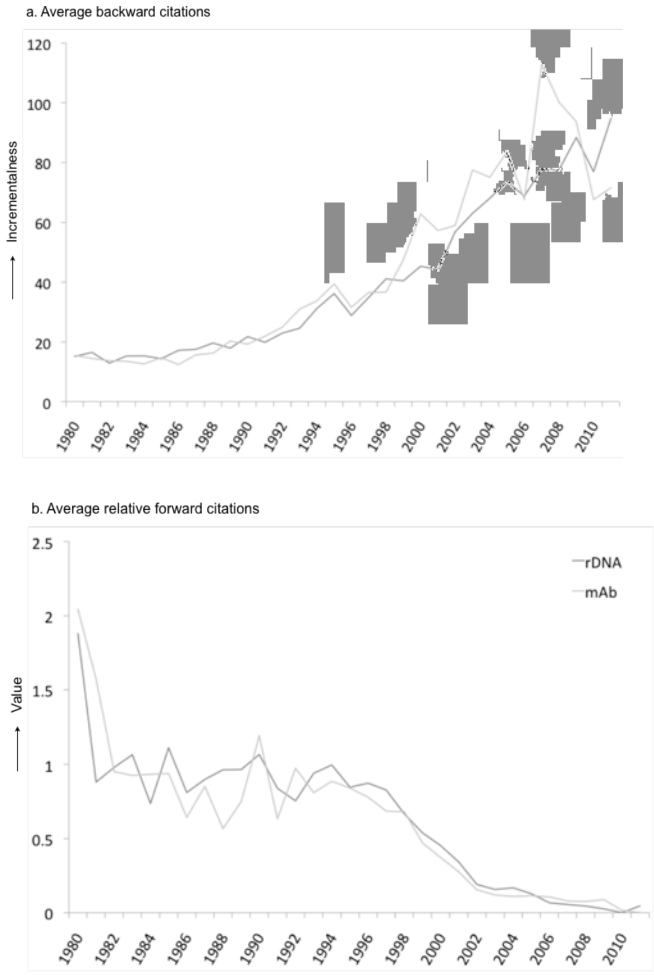
2.4.1 Citation analysis

Figure 2.3a shows the annual backward citations for recombinant protein and mAb patents. The graph clearly indicates that patents from the early 1980's had a relatively low number of backward citations compared to more recent patents. This rising trend of backward citations indicates that innovation in these technologies has become less radical and thus more incremental because newer patents appear to be more reliant on prior knowledge and IP.

Conversely, the average annual trend of forward citations is decreasing in *Figure 2.3b*. This indicates that the economic value of patented inventions related to both technologies has been decreasing over time. There appears to be a direct correlation between the radicalness and the value of an innovation[viii]. *Figure 2.3* clearly shows that radical inventions are more valuable than incremental inventions, and over time inventions have become more incremental, and therefore, less valuable.

[viii] $p < 0.01$

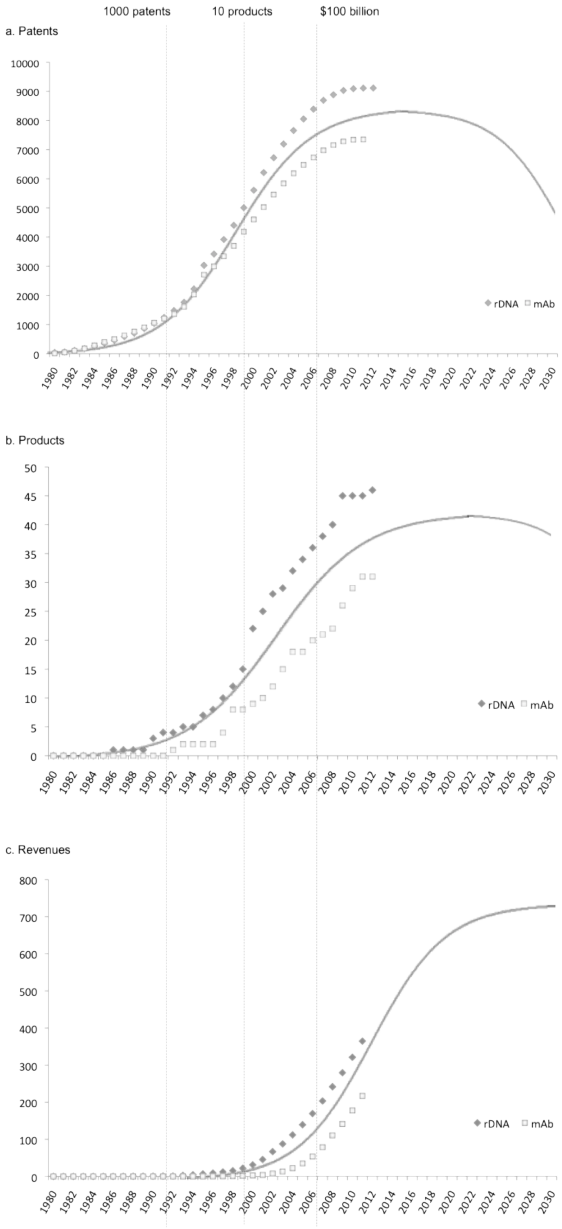
Figure 2.3 a) The average backward citations of rDNA and mAb patent applications indicating the degree of incrementalness of patents over time. b) The average relative forward citations of rDNA and mAb patent applications indicating the economic value of patents over time



2.4.2 Technology lifecycle

In *figure 2.4a* the lifecycles of both technologies clearly match an S-curve. Around 2007, it looks as though the lifecycles have reached the final phase of *saturation*, indicating that it is not likely that these technologies will instigate many subsequent innovative advances.

Figure 2.4 a) The cumulative number of rDNA and mAb patent applications illustrating the technology S-curves of these biotechnologies. b) The cumulative number of rDNA and mAb product introductions. c) Cumulative revenues generated by marketed rDNA and mAb products ($billions)



By comparing this technology S-curve to the patent citation trends (*figure 2.3*), we show that the patents that are being approved more recently could be considered less innovative since they rely so heavily on previous patents. The fact that the technologies have reached a point of saturation supports the idea that radical innovation is far more apparent at the emergence of a technology and innovation becomes more incremental during the course of technological development. These results fully correspond to the hypotheses of Haupt et al.[123], who predict patent citation indices during technology life cycle stage transitions.

2.4.3 Biopharmaceutical products

Overall, 81 recombinant protein products have reached the US market. 31 of these concerned monoclonal antibody products. *Figure 2.4b* shows that the majority of the products associated with the studied technologies were approved during the last decade. Considering average R&D timelines for pharmaceutical products of 8 years [59], it can be assumed that most products approved between 2000 and 2010 were products from the technological growth phase that took place between 1993 and 2000 as illustrated in *figure 2.4a*. Following this rationale, one can expect several more rDNA and mAb products of which the origin lies in patents filed during the subsequent maturity phase. However, these results do indicate that the peak in terms of inventions and products related to these technologies has past.

Similarly, revenues generated by the products included in our analysis have been plotted cumulatively against time (*figure 2.4c*). With these biopharmaceutical products the industry realized a combined sales volume of 582 billion USD, up until 2012. Monoclonal antibody products accounted for 217 billion USD of this total sales volume and other recombinant protein products generated the remaining 365 billion USD. In the context of the law of diffusion of innovation [124], it is safe to presume that product revenues peak several years after the introduction of the respective product. Similarly, our results indicate that revenues are still growing and companies can still expect growth in returns through sales of the products currently on the market. However, to put things in perspective, the global pharmaceutical industry has generated approximately 750 billion USD per year on average during the period 2003-2011[ix]. This means that products associated with the studied technologies have only accounted for approximately 5% of global pharma sales between 1995 and 2012. Evidently, these figures are insufficient to counter or at least compensate for part of the innovation deficit that pharma has been struggling with for years.

[ix] www.imshealth.com

2.5 Conclusions and discussion

At a relatively low level of 5% of global pharma sales over the past 17 years, we show that the first biotechnologies have reached a stage of technological limit. New patents related to these technologies are becoming less radical and less valuable and the technology S-curve analysis shows that the technological development currently finds itself in a saturation phase. In addition, the product curve appears to be reaching a plateau as well, making it difficult to expect future growth in product introductions generated by these technologies. On a positive note, our results indicate that revenues generated by biopharmaceutical products are still growing. However, given these results we conclude that these individual technologies will not live up to the expectation of biotechnology at its inception.

This conclusion gives a quantitative basis for earlier assumptions, which projected that the biotech output during the first years of the 21st century would not be sufficient to make up for NCE deficits [5, 94]. According to our results, even less recombinant proteins and monoclonal antibodies eventually reached the market than was projected in these studies [5, 94]. In the late 1990s and early 2000s other authors argue that it was too early to tell whether the structural industry change triggered by biotechnology, would measurably affect industry productivity [94, 125]. In hindsight, we can now conclude that so far, biotechnologies exerted little impact on overall pharmaceutical productivity. Moreover, the first biotechnologies that generated marketable products are already reaching their technological limits. Subsequent biotechnologies (i.e. combinatorial chemistry, cell-based assays, bioinformatics, genomics, pharmacogenetics and gene therapy) have not yet led to an increase in industry productivity either. In addition, the costs of developing a single innovative compound have risen from 750 million USD between 1995 and 2000 to 1.3 billion USD between 2005 and 2010 [59, 94]. The R&D costs for a single marketable product are expected to grow well beyond 2 billion USD, considering current R&D expenditures [97, 126].

It seems that the currently employed traditional pharmaceutical blockbuster business model may not be fully applicable to science-based technology and innovation, and the changes it caused in drug discovery [95, 127]. Our results imply several scenarios and developments within the industry that may involve different strategies and new opportunities.

2.5.1 Implications

The main conclusion of this study implies a rather pessimistic scenario for early biotechnologies as the saturation or the maturity phase might be followed by an 'innovation cliff' [112]. Early biotechnologies have reached their technological limit and there is a lack of newer radically innovative technologies that are currently generating product innovations. These outcomes may be determinants for an innovation cliff in biotechnology. This would be disastrous for the pharmaceutical industry at large as incumbent firms relied heavily on biotech to come forth with product innovations that would reverse the decline in productivity. In addition, patent expirations of current cash cow blockbuster drugs pose an even larger threat if a biotechnological innovation cliff would become imminent.

Subsequent losses in annual sales affect future R&D investments, which are needed for new product development and attracting new knowledge and innovation.

Another scenario might involve further development and innovation with respect to initial biotechnologies. During the growth/maturity phases of technological development it is useful to suggest a shift in focus regarding innovation towards the development of new technologies. In reference of the theory regarding technological development and innovation S-curves, rDNA and mAb technologies may have functioned as base technologies[23] for subsequent innovative technologies such as genomics and gene therapy that may spur a new S-curve of their own. In literature, this concept is described as 'jumping the S-curve' [112, 128]. Up to date, these subsequent technologies appear to have little to no impact on pharmaceutical productivity, as there are no examples of approved drugs that directly resulted from these technologies. Nonetheless, newer technologies might still have a significant impact on future biopharmaceutical productivity although counteracting the innovation deficit might require more than implementing these biotechnologies into new product development.

However, in discussion of the S-curve concept, which is broadly embraced in strategic literature, Sood & Gerard[129] dispute the notion of a single S-curve and state that 'technological evolution seems to follow a step function with sharp improvements in performance following long periods of no improvement'. A technological S-curve might simply represent such a sharp step of radical improvement. Within the context of this study, this would imply that following the S-curve of the rDNA and mAb technologies, we can expect a longer period of incremental innovation which might be followed by a future burst of radical innovation, of which the effects on productivity are unknown. If this process were real, it would imply that the possibility of 'jumping the S-curve' entirely depends on subsequent radical technological innovation. Regardless, it is fairly urgent and important to consider new strategies and opportunities for increased value creation, capturing, and delivery. Extensive exploration of such strategies is beyond the scope of this study. However, we will briefly discuss the implications of two suggested strategies that might yield significant opportunity for value creation.

According to some, an opportunity resides in reinventing the traditional pharmaceutical business model with respect to diagnostic-drug linked products (i.e. theranostics) and "personalized medicine" [127, 130, 131]. Newer technologies such as genomics and pharmacogenetics can enrich clinical research by defining patient groups with the most favourable risk-benefit ratio, making it easier to statistically determine efficacy, safety and appropriate dosage of a so-called theranostic in development [130-132]. Thereby, such technologies can function as a 'key resource' for a reinvented pharma business model. However, there are two simple but important determinants that form the basis for the current 'blockbuster model'; (1) very high and increasing new product development costs, as discussed earlier, and (2) very high attrition rates and thus high risks in new product development. Regardless of the technological possibilities of theranostics and personalized medicine, these determinants remain, and have to be met in any 'new' business model.

Perhaps a more realistic opportunity for short-term exploitation comprises industry convergence with the conventional and functional foods sector. Upcoming markets such as

the functional food market[133, 134] and medical nutrition market[24] may yield opportunities for biopharmaceutical companies. As Kickbusch & Payne[134] rightfully state, the line between foods, dietary supplements, and pharmaceutical products is becoming more difficult to draw. Weenen et al.[112] explain the differences and overlap between these product categories as well as convergence opportunities towards pharmanutrition. Another undeniable trend is the awareness and demand amongst end-users for increased functionality of foods in the context of healthy lifestyles including 'healthy-ageing'. In addition, wellness, health, and disease prevention, as opposed to curing, is increasingly stimulated by employers, as healthier employees reduce health insurance costs [133]. Innovation and technological development regarding pharmanutrition create an opportunity for incumbent pharmaceutical firms. According to Weenen et al.[24], the medical nutrition industry currently finds itself in the growth phase (*figure 2.2*) and pharmanutrition is an area filled with opportunities for enhancing discovery, technological, and development competencies [112, 135]. Further in-depth research is required to examine options and methods of capitalizing on these opportunities.

In conclusion, we show that biotechnological innovation with respect to the first two biotechnologies has saturated. By three independent parameters we have identified the growth, maturity and saturation stages, internally validating the S-curve for these biotechnologies (*figure 2.4*). A biotechnological limit might imply several, somewhat pessimistic, scenarios for future biopharmaceutical productivity. However, whether it involves the generation of a new business model to fully capture the value of following biotechnologies, or converging with other markets to serve health-oriented consumers, there seem to be several opportunities for biopharmaceutical companies to explore.

Chapter 3

BIOTECHNOLOGY COMMERCIALIZATION STRATEGIES: RISK AND RETURN IN INTERFIRM COOPERATION

Abstract

The management and exploitation of biotechnological product innovation have proven to be more difficult than initially expected because the number of currently marketed biotechnological products is far from sufficient to counter deficits in pharmaceutical innovation. This study provides insight into the role of governance structures in interfirm cooperation and their effects on biotechnological product innovation and company success. Most of the existing literature regarding alliances and mergers and acquisitions (M&A) examines their effects on technology recipients' innovation performance. Here, the effects of alliances and M&A on both the innovation success and financial performance of technology suppliers (i.e., sources) are examined. Drawing from a sample of 220 human therapeutic biotechnology and biopharmaceutical firms over a period of 32 years (1980–2011), an analysis of the effects of biotechnology clusters, strategic alliances, and acquisitions is provided. This study reveals the existence of a risk-return trade-off for strategic alliances between biotech companies and larger, more established firms. Increased biotech company involvement in product development alliances decreases risk by increasing the likelihood of future product introductions. The trade-off, however, is that biotech companies earn lower returns when their products are developed through such alliances. A similar risk-return trade-off effect is found for clusters. However, acquisitions generally affect both product introductions and product returns in a negative way. These findings have strategic implications not only for managing the development of biotechnological product innovations and technology platforms but also for commercialization strategies with respect to interfirm cooperation and risk reduction.

Fernald, K.D.S., Pennings, H.P.G. and Claassen, E.
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3.1 Introduction

Biotechnology represents a major change in the technology base of a mature pharmaceutical industry. From its inception, biotechnology has appeared to be the solution to a deficit in pharmaceutical innovation [5, 14]. Consequently, its rise has spurred a transition from traditional drug discovery to a scientifically deductive process of innovation, and as a consequence biotech and pharma have become knowledge-driven sectors [67, 90]. Although many researchers have shown that biotechnological innovation does not appear to be sufficient to counter the widely acknowledged deficits in pharmaceutical innovation [5, 14, 16, 94], it has revolutionized the current trajectories of drug discovery. Using biomedical science as the basis for discovering and developing new drugs, actors other than larger pharmaceutical firms now play a pivotal role in biopharmaceutical innovation. Universities; research and knowledge institutions; and usually spin-off, biotech small- and medium-sized enterprises (SMEs) have begun to facilitate and organize innovation processes in the biopharmaceutical industry. This reorganization of research and development (R&D) has resulted in the rise of biotechnology clusters [136].

For entrepreneurs, founders, and investors of biotech SMEs, product development is extremely risky in light of the fact that the average R&D duration is 11.9 years [58], R&D costs are $0.8–$1.3 billion for each new product [59, 94], and there is an overall success rate of approximately 10% for drugs that enter clinical development [60, 61]. In such a high-risk environment, to survive during the R&D of their innovations, new ventures require both large investments and multiple possibilities for cash flow generation. Sources of income for early stage SMEs include entering into licensing deals based on their intellectual property (IP), providing high-tech services, and receiving upfront or milestone payments through R&D partnerships with incumbent firms [137-139]. However, the eventual introduction of a product remains a crucial focus of any product-oriented biotech SME seeking long-term survival. In the current climate, early stage biotech SMEs must cooperate with external firms to gain the necessary knowledge, experience, and expertise to commercialize their innovations. Thus, interfirm cooperation has become a competitive advantage for high-technology firms [140, 141].

In this chapter, the effects of interfirm cooperation on the likelihood of product introductions and on revenues from product sales are examined, viewed from the perspective of biotech SMEs. Based on differences in governance structure, the construct of interfirm cooperation is disaggregated into three distinct dimensions: biotech clusters, strategic alliances, and acquisitions. First, the most informal mode of interfirm cooperation is cooperation within a biotech cluster. Such cooperation is not necessarily based on formal agreements, but instead exists by virtue of interactive knowledge exchanges through social networks and information infrastructure within a region [67, 70, 142]. Several studies have provided empirical evidence of the beneficial effects of biotech clusters [114, 143-145]. However, none of these studies have examined the effects of clusters on biotechnological product introductions and their corresponding sales, but they have instead used other performance measures (e.g., patents, initial public offerings, private equity placements, attracting alliance partners, dissolution of alliances, and products in development).

In contrast, the second dimension concerns more formal modes of cooperation, such as in- and out- licensing, collaborative R&D agreements, outsourcing, and other types of strategic alliances. Strategic alliances for new product development often involve a formal technology supply chain that comprised a technology supplier firm (i.e., "source") and a technology recipient firm [146, 147]. From a firm-level perspective, one can distinguish between alliances in which the firm acted as the technology source and alliances in which it did not. A few other articles have made similar distinctions and have studied the effects of various types of alliances on productivity and firm performance (e.g., horizontal and vertical alliances[148]; exploration and exploitation alliances[149]; upstream, horizontal, and downstream alliances[150]). The existing distinctions, however, do not focus on biotech firms as alliances' technology sources, and therefore do not reveal the effects of alliances that involve these types of knowledge flows.

The third dimension concerns acquisition, that is, when a smaller firm is "acquired" by a larger firm in exchange for a majority stake of the smaller firm's equity. This dimension often involves a partial or complete integration of innovative knowledge and activities into the larger firm. Although there are convincing theoretical arguments that suggest negative effects of acquisitions on product development [151-153], empirical findings on the effects of mergers and acquisitions (M&A) on performance appear to be mixed. Some researchers have reported negative effects [76-78, 154], whereas others have claimed to find no relationship between M&As and performance [74, 155]. Other researchers have reported that technology M&A have positive effects, given the relatedness between a target and its acquirer [77, 154, 156]. It is noteworthy that all of these studies have measured the effects of an M&A on the performance of the acquiring firm, whereas no existing articles have examined the effects of "being acquired" on product introductions originally developed by the target company.

Modes of interfirm cooperation and the management of externally acquired innovation can play an important factor in increasing firms' chances of success and performance. Therefore, the effective management of the innovation process through a proper mode of interfirm cooperation is of key concern to entrepreneurs, company leaders, and managers. Moreover, studying the effects of different dimensions of cooperation helps provide insight into better ways of managing biotechnological product innovations. This study provides an analysis of the different dimensions of cooperation in relation to the probability of a new product introduction (as an inverse measure of *risk*) and new product sales (as a measure of *return*), providing relevant insights with direct implications for strategic options to commercialize biotechnological innovations.

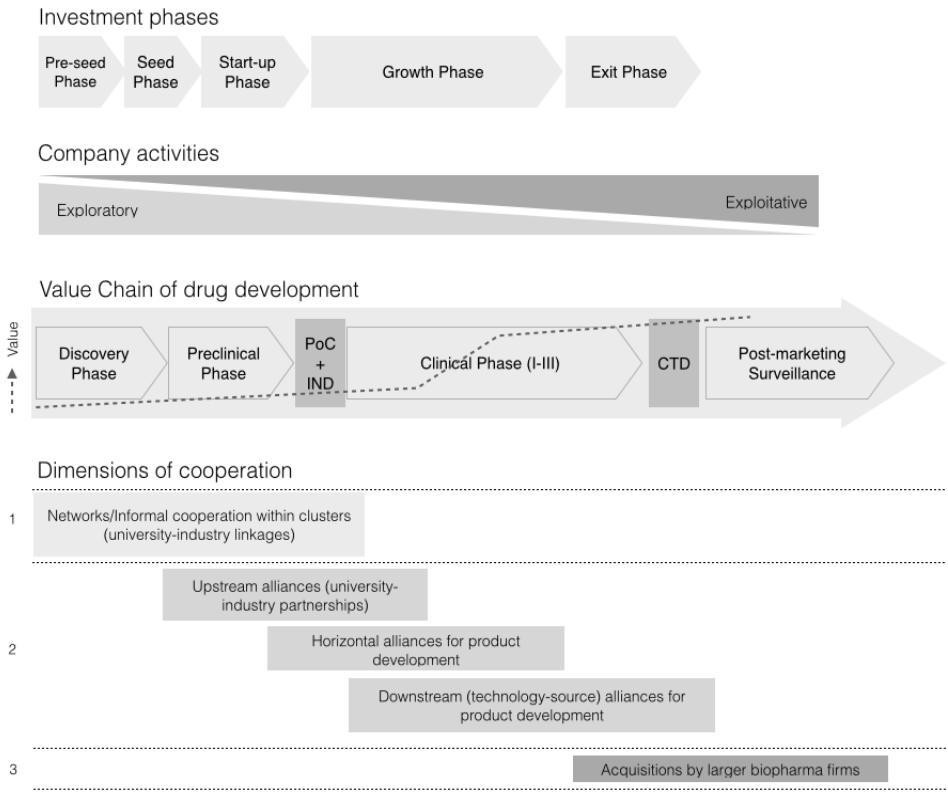
The present study addresses shortcomings in the existing literature, some of which have already been mentioned; more importantly, however, it links potential risk-return trade-offs with different modes of interfirm cooperation. It does so by empirically examining product introductions and sales for the three dimensions of interfirm cooperation using longitudinal data from 220 biotechnology and biopharmaceutical firms over a period of 32 years. Our data cover the entire technological life cycle, from emergence to saturation, of the first biotechnologies [14]. Accordingly, the data provided us with a unique opportunity to study the role of interfirm cooperation in development success and product sales resulting from the first two biotechnologies (i.e., recombinant DNA technology and monoclonal antibody technology).

3.2 Theory and hypotheses

3.2.1 Interfirm cooperation for new products and revenues

Given the various types of interfirm relationships, three distinct dimensions of interfirm cooperation are defined— that is, clusters, alliances, and M&As—and analysed in the context of the exploration and exploitation framework [157]. These two concepts of innovation not only require different structures, processes, strategies, capabilities, and cultures but also appear to have different impacts on firm performance [158]. These differences may be especially applicable in the context of the biotech and pharma industries [159, 160]. The value chain in drug development encompasses the complete R&D process from the discovery phase to market approval [63]. *Figure 3.1* shows this value chain, along with investment phases and dimensions of interorganizational cooperation.

Figure 3.1 Dimensions of cooperation and exploratory and exploitative activities in the context of the biopharmaceutical Value Chain. (PoC, proof of concept; IND, investigational new drug; CTD, common technical document. Adapted from Pronker [63])



In this line of thought, it is plausible that cooperation within biotechnology clusters, that is, networks and relationships among similar companies, is mostly related to the earlier stages of the value chain and therefore of a more exploratory nature. The second dimension is more difficult to ascertain because there are various types of alliances occurring at different stages of the value chain. For example, upstream alliances (i.e., university–industry alliances) are related to earlier stages of the value chain. Therefore, in accordance with Rothaermel and Deeds[149], alliances can be both exploratory and exploitative, depending on the nature of the deal, the type of partner (e.g., upstream, horizontal, downstream), and the role of the company (i.e., technology supplier versus technology recipient). Acquisitions of biotech companies, however, are generally exploitative in nature because such take-overs are usually considered investments in R&D replenishment [72, 161, 162]. *Appendix A* provides an overview of insights gained from empirical analyses of independent variables related to our dimensions of interfirm cooperation. As shown in *appendix A*, the different dimensions of cooperation have been thoroughly analysed separately, but to the best of our knowledge never all together in relation to both the likelihood of product introductions and revenue from new products. In the following subsections, the three dimensions of cooperation are further elaborated, and several hypotheses are developed.

3.2.2 Dimension 1: Biotechnology clusters

In biopharmaceuticals, much innovation occurs in large firms whose locational criteria mainly reflect those of a cluster as an industrial complex, as described by Iammarino and McCann[66]. However, simultaneously, large firms within such clusters also rely heavily on science-driven biotechnology SMEs for innovation, which are mostly also geographically concentrated but correspond more closely to the "new social network" type of cluster, where knowledge is transmitted within cognitive networks [66]. In this study, the data cover both biotechnology SMEs and larger biopharmaceutical firms. Therefore, in this context, the definition of clusters in this study is primarily based on the geographic colocation of companies within an industrial complex, where knowledge spillovers are also created through social networks of the SMEs.

The colocation of biotechnology firms mainly occurs in close proximity to knowledge sources, such as universities and other research institutions [67, 136]. However, other actors also play important roles, together providing the infrastructure necessary for innovation and growth. Creating value by transferring technology and knowledge to the marketplace involves complex chains of interaction and transactions among venture capitalists, entrepreneurs, scientists, managers, and other actors. Establishing a biotech SME within such a cluster setting leads to interfirm cooperation as technical knowledge is transmitted through social networks creating knowledge spillovers that facilitate innovation and growth [66-68, 163]. Accordingly, Zeller[164] also states that acquiring and transferring tacit knowledge within biotech clusters occur through concrete practice and direct social contacts. Interactive learning and innovation processes occur in the context of relations among different actors—not only other biotech companies or pharmaceutical companies but also service suppliers, R&D institutes, universities, and often hospitals in the vicinity [68, 164]. In this sense, "innovation activities are undertaken in complex social networks, characterized by heterogeneous actors, multidimensional interactions, and multiple knowledge flows" [165(p. 232)]. Biotech clusters create regional infrastructures that support and promote

knowledge transfer, help solve problems, reduce the costs of innovation, and create capabilities for commercializing innovative technologies [166], ultimately resulting in regional innovation systems [67, 69, 70]. Consequently, one important benefit of establishing a start-up company within a "business community," such as a biotech cluster, is that the political and institutional support for building such a community reduces barriers to launching risky commercialization processes [164].

Apparently, both innovation and new product development as competitive variables are positively affected within a "cluster setting" [67]. Empirical studies have usually found such positive effects [114, 143-145]. Both Phene et al.[114] and Folta et al.[144] have demonstrated that clusters are positively associated with innovation, as measured by patents. Deeds et al.[143] have found that clusters positively affect new biotechnological product development, as measured by a combination of introduced products and products in development.

Although these arguments and results support predictions that the "cluster setting" has a positive effect on success in terms of the likelihood of a product introduction, there is a lack of empirical evidence suggesting that biotechnology companies in a cluster setting perform better in terms of product revenues. For instance, George, Zahra, and Wood[167] have found that links between firms and universities can enhance product development but have not found statistically significant differences in financial performance among firms with and without university linkages. Arguably, the relationship between cluster settings and firms' financial performance in terms of revenues from product sales is more complex than the relationship between cluster settings and innovation and new product development because a company's financial performance depends on more factors than innovative capability alone. While a cluster location may be beneficial for innovation, the location is probably not optimal from a sales perspective where logistic conditions are most important. Therefore, learning within clusters is mostly limited to R&D and does not extend to marketing and sales, for which biotechnology SMEs mostly rely on larger (bio)pharmaceutical partner firms.

Consistent with the arguments and empirical findings discussed above, the following hypothesis posits a positive relationship between the biotech "cluster setting" and the likelihood of product introductions (i.e., negative impact on risk). However, it has been recognized that this relationship may not be reflected in the revenues from product sales (i.e., there is no impact on return).

H1a: The biotechnology "cluster setting" is positively related to a biotechnology company's likelihood of ultimately introducing a biotechnological product.

H1b: The biotechnology "cluster setting" does not affect the revenues biotechnological companies earn from product sales.

3.2.3 Dimension 2: Strategic alliances

Biotechnology companies enter into strategic alliances for various reasons. An SME is predominantly motivated to enter into an R&D alliance to access the complementary assets and knowledge needed to commercialize its technology or product [168]. Alliances can involve a range of different types of deals and agreements (e.g., licensing, collaborative R&D, out- sourcing, joint ventures, technology transfer). As companies in this industry frequently involve themselves in alliances with other firms, this analysis is embedded in the context of "alliance portfolio theory." The existing literature contains different views of the definition of alliance portfolios [169]. In this study, the view of social network theorists[170, 171] is adopted because their view is most compatible with the first dimension of cooperation, discussing social and interorganization networks within biotech clusters. In this view, alliance portfolios can be defined as a focal firm's egocentric network (i.e., all of its direct ties with partner firms[169, 170, 172]). Undoubtedly, there is a direct relation between a firm's portfolio and its accumulated alliance experience [169, 173], which considering the complexity of alliance portfolios varies by partnership type [174]. According to Duysters and Lokshin [174], and Faems, Van Looy, and Debackere[175], alliance portfolios' impact on the innovative performance of firms tends to differ depending on the partnership type and the nature of the partner(s) involved. Accordingly, and also prevalent in other literature [146-150], an important distinction is applied, relating to alliance experience from the strategic perspective of biotech firms. Arguably, biotech firms have two alliance portfolios, one in which such firms partake as the technology source (i.e., *technology source alliances*) and another in which they do not (i.e., *non-source alliances*). Moreover, it is arguable that non-source alliances will mostly concern upstream alliances, wherein the company concerned sources the innovation central to the alliance from its upstream or horizontal partner, whereas technology source alliances will mostly concern exploitative downstream or horizontal alliances with similar or larger partners, in which the company concerned is the source of the innovation central to the alliance. Logically, these different types of portfolios will affect success measures, related to new product development, differently.

In our analysis, the focus lies on the effect of "technology source alliances" because those alliances may provide insights that are relevant to the commercialization strategies of companies aiming both to introduce product innovations and to profit from product sales. Although many alliances fail to produce their desired outcomes[176], they are mostly positively associated with product innovation[177, 178] and firm performance [76]. In particular, these effects have been found in the biopharmaceutical industry [79, 111, 149, 179]. According to Collins and Hitt[180], drugs produced by alliances are 30% more likely to succeed in obtaining a Food and Drug Administration (FDA) approval, and nearly one third of newly marketed biopharmaceutical products seem to be developed through alliances. Moreover, Oliver[181] has shown that alliances are essential for biotech companies to survive. The expertise and resources of pharmaceutical firms are often needed to reduce the risk of failure during downstream R&D phases [149, 150]. Following this rationale, it is arguable that a firm's decision to engage in a technology source alliance will positively affect its chances of successfully introducing a product several years later (i.e., it will negatively impact risk).

Fewer studies have examined the effects of strategic alliances on companies' financial performance. George et al.[148] have found that vertical alliances have a positive effect on net sales, but that other types of alliances (e.g., horizontal, knowledge generative, knowledge attractive) have no such effect. In their study, vertical links included outsourcing and distribution links, whereas horizontal linkages included joint R&D, technology transfer, patent swaps, and joint ventures that supplemented firms' technology bases. As these submeasures moderately resemble ours, one can expect a nonsignificant relationship between "technology source alliances" and revenues from product sales, but a positive effect of "non-source alliances" on returns. For the *total* number of alliances, a nonsignificant effect on returns is expected, consistent with a subsequent study by George et al.[167]. According to the arguments and empirical findings described above, our second hypothesis is as follows:

H2a: Engaging in a "technology source alliance" for product development positively affects the likelihood of a product introduction several years later.

H2b: Engaging in a "technology source alliance" does not affect revenues from biotechnological product sales.

3.2.4 Dimension 3: Acquisitions

The existing empirical evidence suggests that M&A of technological companies reduce the innovative performance of acquiring firms [77-79]. To the best of our knowledge, however, there is no previous literature that has studied the effects of acquisitions on the eventual success of individual R&D projects that originated within the target firm.

There are various arguments explaining why acquisition and post-acquisition integration processes are detrimental to target firms' innovation projects. As discussed above, drug discovery and development has become a science-based process in which much of the important work and relevant technologies now come from universities and biotech SMEs. This transformation has presented major challenges to the organization of the drug innovation process, which hitherto had been relatively internalized within large pharmaceutical companies [182]. In the context of the "capability theory of the firm," Coombs and Metcalfe[182] have explained that new, innovation-relevant capabilities have been created by the rise of new, innovative biotech SMEs, and that such firms' external capabilities must be coordinated with the traditional internal capabilities of large pharmaceutical firms. Moreover, as a result of M&A in general, and acquisitions of biotech SMEs in particular, large firms have been forced to combine these previously separated capabilities while simultaneously maintaining their effectiveness. James[151] has argued, based on several case studies, that combining these capabilities can sometimes prove to be extremely difficult. Inevitably, managers fail to detach themselves from the dominant logic of their own organizations, which structures the way in which they view integration opportunities [151, 183]. These effective, dominant logic practices are often ineffective and detrimental when applied to projects involving radical innovations [184]. Arguably, established firms' inability to detach from their dominant logic can cause incompatibility issues with the entrepreneurial spirit of nimble biotech SMEs. Therefore, it is probable that acquiring firms often fail to successfully coordinate and combine the necessary

capabilities, as discussed by Coombs and Metcalfe[182] and others [151, 185, 186]. In many cases, this might result in a failure to commercialize biotechnological innovation.

In addition, the motive for an acquisition can be an important determinant for successful commercialization. Many articles have mentioned the fact that larger pharmaceutical firms commonly adopt an M&A strategy toward biotech companies in an attempt to counter the still-growing pharmaceutical innovation deficit [5, 72, 74, 75, 94, 161, 162]. Most such articles have argued that this strategy has defeated its purpose. Pisano[187] explained that the rapid internalization of biotechnological R&D through acquisition is likely to be an undesirable model for organizational change. He argued that acquiring biotech SMEs is a particularly dangerous strategy when used to overcome weak internal capabilities. The acquisition of a biotech SME is only recommended after the established firm has accumulated significant in-house R&D experience [185, 187, 188]. In reality, target companies are often acquired for just one product, or a few products, from their pipelines [189], which often leads to patent shelving and the termination of other in-process R&D projects [190, 191]. These competitive or defensive motives for acquisitions have generally failed to support the retention and further development of acquired knowledge and innovation. In addition, managerial motives, such as personal gain, risk, and hubris, as opposed to economic motives of the firm, can play an important role in M&A and are negatively associated with M&A performance [192, 193].

It is also important to consider acquisition motives from the biotech company's perspective. Often, biotech firms benefit from being acquired by gaining access to downstream expertise, resources, and marketing and distribution channels for potential future product introductions [74, 161, 162]. Importantly, investors and venture capitalists are strongly focused on their return on investment, which can be provided by an exit such as being acquired by a larger firm [194, 195].

Arguably, it is likely that this complex web of combining firm capabilities and underlying motives negatively affects the commercialization process, and therefore its outcome in the form of biotechnological product introductions. However, acquisition effects on product sales are unclear. Arguably, by being acquired, a target firm's product innovation might have a wider reach through the acquirer's sales and distribution channels, which would otherwise have been unavailable. This would suggest that acquisitions have a positive effect on revenues from product sales. Conversely, because acquirers control sales and distribution channels, they might also gain a larger share of the sales of certain products at the expense of the target firms. Although this result might depend on the nature of an acquisition deal, it might negatively affect returns for the target firm. Therefore, it is expected that being acquired has a nonsignificant effect on revenues from biotechnological product sales for the target firm.

H3a: M&A have a negative effect on the likelihood of future biotechnological product introductions.

H3b: M&A have a nonsignificant effect on future revenues from biotechnological product sales.

3.3 Methodology

3.3.1 Sample

This study examines the effects of multiple variables related to interfirm cooperation on the success and performance of a panel of biotech and biopharmaceutical firms. The sample of firms was established by collecting data on patents related to the first two biotechnologies (rDNA and mAb). As thoroughly described in previous work *(chapter 2)*[14], the data were gathered from several patent databases using the AcclaimIP patent analysis software[x]. The acquired data were then checked for consistency with data from the World Intellectual Property Organization (WIPO)[xi], the United States Patent and Trademark Office (USPTO)[xii], and Thomson Reuters's Derwent Innovation Index[xiii]. Searching for patents with specific international patent classification (IPC) codes, namely *C07K16/**, *A61K39/** and *G01N33/53* for mAb patents and *C07K14/*, C12N15/** and *A61K38/** (but excluding *A01H5/*, C12N5/*, C12N15/29,* and *C12N15/82)* for rDNA patents, resulted in a total of 7,350 mAb patents and 9,111 rDNA patents [14]. Our search only included US patents to prevent overlap with patents filed in multiple countries. Nonetheless, our sample included both US- and non-US-based firms because companies often choose to file their patents in the US, among other countries, to take advantage of the vast US market [14, 119].

The panel data sample was limited to all companies that acted as the original assignees of at least five of the aforementioned collected patents for each technology (i.e., five mAb patents and five rDNA patents). Subsequently, large, multinational pharmaceutical and chemical corporations were excluded, primarily because this study focuses on the success and performance of biotech companies. This process resulted in a panel of 220 firms for 32 one-year periods (1980-2011), resulting in a total of 7040 firm-years. Of these firms, 106 were acquired during the studied period, and the companies in the sample engaged in a total of 3,729 'technology source alliances'. For our dependent variables (DV), we included 81 marketed biotechnological products, of which 50 were rDNA products and 31 were mAb products [14]. The panel dataset for the second DV was limited to 25 companies (i.e. 800 firm-years) that earned revenues from product sales and royalties. By introducing a time window of 5 years for certain variables the total number of firm-years was reduced to 5697 firm-years and 675 firm-years for the first and second DV respectively.

3.3.2 Measures

Dependent Variables. A firm's success is subject to broad interpretation; therefore, we defined two dependent variables. For the first set of regression models, we used 'product introductions' as the dependent variable. This binary variable is defined by whether a company, was involved in the development of a product that was introduced within a five-year period (t to t +5)[xiv]. Given the limited amount of introduced biotechnological products[14], measuring this variable for a one-year period alone renders a product introduction a rare event. By introducing a window of 5 years, we created an opportunity to

[x] www.acclaimip.com (by FreePatentsOnline)
[xi] www.wipo.int
[xii] www.uspto.gov
[xiii] www.thomsonreuters.com
[xiv] The models tested for (t to t+3), (t to t+4) and (t to t+6) produced similar results (results not shown).

assess the effects of independent variables on future product introductions. Furthermore, this window allowed time for the independent variables to affect product introductions. For the second set of regressions, we used 'revenues from product sales'. This variable is defined as a log transformation of the amount of revenues that firm *i* earned in year *t* from biotechnological product sales. Product data were collected by researching the literature and databases, including the Food and Drug Administration (FDA) database [xv], the FDA Orange Book, and the Medtrack database [xvi]. Noteworthy, the raw revenue data do not include royalty payments to the product originator, which in essence are a measure for returns as well. Considering, most royalty payments vary between 5% and 15% [64, 196, 197], we have added a 10% royalty over sales to product originator companies.

Inter-firm Cooperation. This concept is constructed using several variables that represent the aforementioned dimensions of cooperation. To generate the cluster variable, company location details were retrieved from several databases and websites (e.g., Businessweek.com, Bloomberg.com), and it was determined whether companies were established within renowned biotech clusters. The cluster variable is a dummy variable for whether a company was founded within a cluster (industrial complex) or not.[xvii] *Table 3.1* provides a list of biotech clusters, based on geographic location, that are included in our analysis. The data were collected from reports on biotech clusters [198, 199]. We choose to include the top 10 US clusters as ranked by the Jones Lang Lasalle Institute [199] as well as the largest European and Asian biotech clusters mentioned in this report [199]. The definition of major European clusters was verified using the Milkens Institute report [198]. *Table 3.1* provides the complete selection.[xviii]

The second dimension of cooperation is defined by means of three variables related to alliances. Models 1 and 3 (*tables 3.3, 3.4* and *3.5*) include a firm's total number of alliances as a variable. In models 2 and 4, we applied the distinction between types of alliances, as discussed above. All of the alliances of the 220 firms in the sample were categorized into two submeasures: (a) 'technology source alliances', representing the number of alliances, in which firm *i* was the technology source (i.e. supplier) of the alliance; and (b) 'non-source alliances', in which firm *i* did not act as the source of the alliance[xix]. Furthermore, for these variables, a time lag was introduced to assess the effect of previous alliances on future product introductions by creating stock variables over a five-year period (*t*-5 to *t*).

Similarly, for the third dimension of cooperation, a dummy variable was created, indicating whether the majority of the equity of firm *i* had been acquired by another company within the previous five years (*t*-5 to *t*). Furthermore, acquirers' location data were collected to create an additional interaction variable defined by whether an acquisition (between *t*-5 to *t*) occurred within one cluster.

[xv] www.fda.gov

[xvi] www.medtrack.com

[xvii] This definition avoids the problem of endogeneity that arises when firms that are close to a product introduction move to a successful biotech cluster.

[xviii] The analysis is also conducted using a smaller selection (i.e. the top 5 US clusters as ranked by Jones Lang Lasalle as well as 3 major European clusters and 2 large Asian clusters) as a robustness check. This provided similar results, although the positive cluster effect on product introduction likelihood loses its significance at the 1% level in all models.

[xix] For each alliance the deals & alliances database (medtrack.com) discloses which company was the product or technology 'source' and which company engaged as the partner.

Table 3.1 Biotechnology Clusters as Included in the Analysis, Organized by Country[a]

Country	Clusters
Canada	Quebec Cluster (Saint-Hyacinthe Technopole)
United States	Greater Boston/Cambridge
	San Francisco Bay Area/ Silicon Valley
	San Diego Biocluster
	Raleigh-Durham (Research Triangle Region)
	Philadelphia
	Suburban Maryland/ Washington DC
	New York/ New Jersey
	Los Angeles/ Orange County
	Minneapolis- St Paul
	Seattle
United Kingdom	Cambridge Cluster
Switzerland /Germany /France	BioValley Cluster
Germany	Munich Cluster (Biotech Region Munich)
France	Paris Biocluster (Genopole)
Spain	Barcelona Cluster (Biocat)
Denmark/Sweden	Medicon Valley
Sweden	Umea cluster (Biotech Umea)
Norway	Oslo Cluster (Teknopol)
Netherlands	Wageningen, Eindhoven (HTCE)
Belgium	Brussels, Ghent
Japan	Hokkaido Biotechnology Industrial Cluster Forum

Source: Milken Institute[198], Jones Lang Lasalle[199]
[a] The analysis was also conducted using a smaller selection (i.e. the top 5 US clusters as ranked by Jones Lang Lasalle[199] as well as 3 major European clusters and 2 large Asian clusters) as a robustness check. This provided similar results, although the positive cluster effect on product introduction likelihood loses its significance in all models.

Control Variables. Patent activity is included as a control because it represents innovative activity, which is expected to positively affect future product introductions [77, 200-202]. Again, a time lag of 5 years is introduced by creating a stock variable for patent activity. We consider a company's number of patents associated to a specific type of technology as a proxy for R&D investments aimed at products associated with this same type of technology, and thus assume that there is a linear relationship between patent activity within a certain technological domain and the likelihood of successfully introducing a product associated with that same technological domain.[xx] Age represents the second control variable and controls for overall firm experience. Although it is possible for younger firms to be governed by experienced management teams, we assume that more mature firms are more likely to introduce products[202] and generate more revenue. Third, we introduce a dummy variable for *'category big biotech'*, which is a control variable because larger biotech companies are on average more likely to introduce products and earn more revenue.

[xx] This is supported by the non-significant effects of the quadratic term for patent activity (*appendix C*)

3.3.3 Data analysis

The analysis proceeds in two steps. To analyse the effects of inter-firm cooperation on the successful development of newly introduced products, we estimate a set of logit regression models, including year dummy variables, on the full panel. Subsequently, the effects of interfirm cooperation on revenues from product sales are examined using a set of pooled Ordinary Least Square (OLS) regression models on a limited panel set of companies that earned such revenues. Again, year dummies are included in all models; in addition, the second set of models are tested both with and without firm dummies (*tables 3.4* and *3.5*). As set forth below, we specified two main models for both dependent variables:

$$\textit{Product Introduction} = \beta_0 + \beta_1(\textit{Cluster dummy}) + \beta_2(\textit{Technology source alliances}) + \beta_3(\textit{Non-source alliances}) + \beta_4(\textit{Acquired}) + \beta_5(\textit{Patent activity}) + \beta_6(\textit{Age}) + \beta_7(\textit{Category big biotech}) + \textit{Year Dummies} + \varepsilon_1,\ \varepsilon_1 \sim N(0, \sigma_1^2)$$

$$\textit{Revenue} = \gamma_0 + \gamma_1(\textit{Cluster dummy}) + \gamma_2(\textit{Technology source alliances}) + \gamma_3(\textit{Non-source alliances}) + \gamma_4(\textit{Acquired}) + \gamma_5(\textit{Patent activity}) + \gamma_6(\textit{Age}) + \gamma_7(\textit{Category Big Biotech dummy}) + \textit{Year Dummies} + \varepsilon_2,\ \varepsilon_2 \sim N(0, \sigma_2^2)$$

As shown in the results (*tables 3.3, 3.4* and *3.5*), multiple variations of these models are tested. Note that the use of a (t to $t+5$) variable for 'product introductions' and several independent ($t-5$ to t) stock variables (e.g., Alliances, Acquired, Patent Activity) created a time window of 10 years. As shown in *figure 3.1*, independent variables such as alliances and acquisitions mostly occur during the clinical phases, which have a total duration of 6-8 years [59, 109, 203]. The use of these time windows gave us the opportunity to measure effects of independent variables within the past five years on the likelihood of a product introduction in the next five years.

3.4 Results

The results are derived from the analysis of a panel data set of companies that owned a minimum of five patents related to both rDNA technology and mAb technology over a period of 32 years (1980–2011). This period covers the life cycles of the respective biotechnologies (rDNA and mAb)[14]. With respect to the products examined in this study[14], a distinction between product originators and introducers is made. *Figure 3.2* shows this difference between categories of companies based on firm size and type. This difference clearly illustrates the relevance of technology/R&D transfer through alliances and acquisitions. Moreover, the figure shows big pharma's investments in biotechnology, as these firms have marketed twice the amount of drugs they have discovered.

Table 3.2 shows the descriptive statistics. The control variables are mutually correlated and correlated with most independent and dependent variables. This is not surprising because most of the variables can be indicators of a firm's innovative activities and/or performance. Being acquired seems to correlate with most of the variables except for patent activity, which is surprising because a firm's patents should logically make it a better candidate for acquisition. However, this difference might relate to the quality, rather than the quantity, of a firm's patents. Technology source alliances also seem to be positively correlated with most variables except for being acquired; however, one would expect a positive correlation because most acquisitions are preceded by such alliances [71].

Figure 3.2 Originators versus introducers of market-approved biotechnological products, illustrating technology/R&D transfer through alliances and acquisitions.
(Big Biotech: Genentech, Amgen, Biogen Idec, Novo Nordisk, Medimmune, Centocor;
Big Pharma: J&J, Pfizer, Roche, GSK, Novartis, Sanofi-Aventis, AstraZeneca, Merck, Abbott, Bayer, Schering, Eli Lilly, BMS; Other mostly concern small biotech companies)

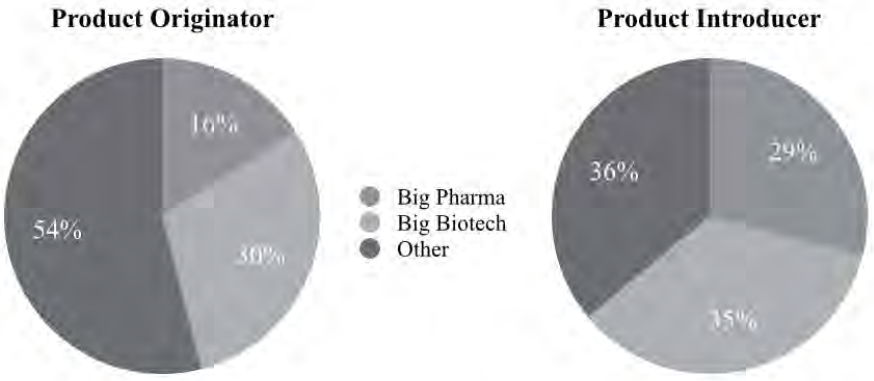


Table 3.2 Descriptive Statistics[a]

Variable	Mean	S.D.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. Product [b]	0.01	0.09	1									
2. Revenue [c]	0.19	1.08	0.25**	1								
3. Cluster [b]	0.55	0.50	0.05**	0.09**	1							
4. Alliances [c]	0.35	0.68	0.14**	0.25**	0.28**	1						
5. Technology source alliances [c]	0.22	0.51	0.12**	0.15**	0.26**	0.90**	1					
6. Non-source alliances [c]	0.21	0.50	0.16**	0.31**	0.21**	0.88**	0.61**	1				
7. Acquired [b]	0.01	0.10	0.04**	0.06**	0.05**	0.03**	0,02	0.04**	1			
8. Patent activity [c]	0.25	0.50	0.13**	0.18**	0.19**	0.34**	0.29**	0.30**	0,01	1		
9. Age [c]	1.82	1.44	0.07**	0.17**	0.49**	0.33**	0.27**	0.30**	0.57**	0.26**	1	
10. Category big biotech [b]	0.03	0.16	0.27**	0.47**	0.08**	0.25**	0.17**	0.29**	0,02	0.25**	0.12**	1

[a] n=7040

[b] These are binary variables

[c] These variables are log transformations

** Statistically significant at the 1% level.

3.4.1 Main effects

Tables 3.3, 3.4, and *3.5* contain the results of the regression analyses. First, the logit regression models (*table 3.3*) show the effects of interfirm cooperation on product introductions. The subsequent pooled OLS regression analyses (t*ables 3.4* and *3.5*) examine revenues from product sales as the DV, without (*table 3.4*) and with (*table 3.5*) firm dummies.

The results show support for H1a, as new product introductions are positively associated with the biotechnology cluster setting. However, the results show a negative relationship between the cluster setting and returns in the analysis of product revenues (*table 3.4*, H1b). H2a is also supported: technology source alliances with larger companies predict a higher probability of a successful product introduction several years later. However, "technology source alliances" also appears to have a negative effect on revenues gained from product sales (*tables 3.4* and *3.5*, H2b). Conversely, it seems that engaging in "non-source alliances" has the opposite effect; such alliances increase the likelihood of failure during product development but positively influence revenues from product sales. Finally, H3a, which predicts that being acquired negatively affects future product introductions, is supported in the first analysis (*model 1*; *table 3.3*). However, in *model 2*, the acquisition effect is negative, but not significant. *Tables 3.4* and *3.5* show that being acquired has a nonsignificant, negative effect on returns, consistent with H3b.

Considering the control variables, patents seem to be positively associated with both product introductions and revenue. Both firm age and the category dummy for big biotech companies are positively related to product introductions but are not related to revenue from biotech product sales.

Table 3.3 Logit Regression Models for Product Introduction[a]

Variable	Model 1	Model 2	Expected Sign
DV: Biotech Product Introduction (*t* to *t*+5)			
Category big biotech	9.33*** [2.19]	10.08*** [2.22]	
Age	1.02*** [.308]	.923** [.320]	
Patent activity (*t*-5 to *t*)	.733*** [.187]	.618*** [.190]	
Cluster	1.83** [.700]	1.53* [.719]	H1a (+)
Number of alliances (*t*-5 to *t*)	.390* [.170]	---	
Technology source alliances (*t*-5 to *t*)	---	1.08*** [.270]	H2a (+)
Non-source alliances (*t*-5 to *t*)	---	-.571* [.241]	
Acquired (*t*-5 to *t*)	-.902* [.439]	-.718 [.439]	H3a (-)
Constant	-18.14*** [1.72]	-17.44*** [1.78]	
Chi2	113.96***	113.52***	
McKelvey & Zavoina's R^2	.274	.269	
n = 5697			

[a] Year dummies are included in all models. Standard errors in brackets.

*Statistically significant at the 5% level.

** Statistically significant at the 1% level.

*** Statistically significant at the .1% level.

Table 3.4 Second stage Ordinary Least Squares Regression Models (without Firm Dummies)[a]

Variable	Model 1	Model 2	Expected Sign
DV: Revenue from Biotech Products			
Category big biotech	2.38** [.906]	1.91** [.726]	
Age	-.232 [.303]	-.135 [.248]	
Patent activity (*t*-5 to *t*)	.484 [.253]	.522* [.246]	
Cluster	-1.14* [.506]	-.858 [.477]	H1b (□)
Number of alliances (*t*-5 to *t*)	-.151 [.192]	---	
Technology source alliances (*t*-5 to *t*)	---	-.831** [.305]	H2b (□)
Non-source alliances (*t*-5 to *t*)	---	.680* [.286]	
Acquired (*t*-5 to *t*)	-.106 [.516]	-.255 [.522]	H3b (-)
Constant	5.66*** [1.05]	4.87*** [.968]	
R^2	.5441	.5912	
n = 675			

[a] Year dummies are includååed in all models. Standard errors in brackets.

*Statistically significant at the 5% level.

** Statistically significant at the 1% level.

*** Statistically significant at the .1% level.

Table 3.5 Second stage Ordinary Least Squares Regression Models (with Firm Dummies)[a]

Variable	Model 3	Model 4	Expected Sign
DV: Revenue from Biotech Products			
Age	-.572 [.376]	-.381 [.324]	
Patent activity (*t*-5 to *t*)	.430 [.283]	.484* [.282]	
Number of alliances (*t*-5 to *t*)	-.074 [.202]	---	
Technology source alliances (*t*-5 to *t*)	---	-.799** [.330]	H2b (□)
Non-source alliances (*t*-5 to *t*)	---	.706** [.281]	
Acquired (*t*-5 to *t*)	-.170 [.532]	-.093 [.504]	H3b (-)
Constant	4.97** [1.83]	4.28** [1.55]	
R^2	.6812	.6982	
n = 675			

[a] Firm dummies and year dummies are included in all models. Standard errors in brackets

*Statistically significant at the 5% level.

** Statistically significant at the 1% level.

*** Statistically significant at the .1% level.

3.4.2 Additional analyses

In addition to the main effects shown in *tables 3.3*, *3.4*, and *3.5*, the regression analyses, including interaction terms, are conducted to assess interaction effects between the different dimensions of cooperation on our DVs (*appendix b*). These results include a few interesting findings. First, it seems that the interaction effect of the cluster dummy and technology source alliances, in addition to the interaction effect of the dummy for acquired firms and technology source alliances, are positive (negative) in the binary product introduction regression (revenue regression), suggesting that the risk-return trade-off especially holds for firms in a cluster that are acquired and engaged in technology source alliance agreements with other firms. Second, the interaction effect of acquired and non-source alliances remains negative for both DVs, whereas the main effect of non-source alliances is positive in the revenue regression. This might indicate that when firms acquire companies from which they sourced technologies, it reduces the returns that the firms receive from the eventually marketed products. Third, the "acquired within cluster" variable is significantly positive for the second DV (*appendix b; table a2*), suggesting that the normally nonsignificant effect of being acquired on returns becomes positive once the acquiring firm resides in the same biotech cluster.

Furthermore, regression analyses with quadratic terms are included to assess whether or not certain main effects are nonlinear (*appendix c*). In the product introduction regressions (*appendix c; table a5*), no nonlinear effects are found. In the revenue regressions, however, a U-shaped effect for the number of alliances is found, which appears to be caused by a U-shaped effect of non-source alliances. The minimum of this U-shape is reached around one alliance, suggesting that returns grow nonlinearly when the number of (non-source) alliances is two or more.

3.5 Conclusions and discussion

This study shows that strategic alliances involve a risk-return trade-off. Increased biotech company involvement in alliances, in which they supply the technology involved, decreases risk by increasing the likelihood of future product introductions. However, biotech companies earn lower returns when their products are developed through such alliances. In addition, we show that a similar trade-off exists for biotech clusters, as they positively affect product introductions, but have a negative effect on returns. Acquisitions, however, negatively affect the likelihood of introducing biotechnological products, but have no effect on revenues gained from such products.

The results show that, in general, alliances are positively associated with product introductions, which seems to be caused by the strong positive effect of technology source alliances, indicating that biotech companies' collaborations related to their technologies or products reduce the risk of failure during development. The consequential risk reduction is a common motivator for biotech companies to engage in such alliances [110]. The second set of analyses show that technology source alliances negatively and significantly affect revenues from product sales. This can be explained as products derived from such alliances are usually marketed by the technology recipient firm, which consequently earns a larger share of revenues from product sales. Moreover, it seems that of those companies that managed to successfully introduce products, the ones that did not develop their products through a technology source alliance earned more revenue from sales. Thus, a biotechnological product developed in-house generates greater returns for the respective company, but as shown, that company faces significantly higher risks and failure rates.

In contrast to technology source alliances, "non-source alliances" of biotech companies negatively affect the chances of introducing a product several years later. Although these results seem to contradict the existing literature [150], other empirical evidence supports these findings. For example, George et al.[148] have found that knowledge-attracting and knowledge-generative alliances have significant, negative effects on marketed products. Moreover, the variable "non-source alliances" includes strategic alliances that are not related to new product development. Engaging in a large number of such alliances might deteriorate a firm's focus on new product development, which could explain the negative effect on the introduction of new products. In the second set of models, non-source alliances are found to positively affect earned revenue from biotechnological product sales. This finding again implies that the technology recipient firm (i.e., non-source) in a technology alliance earns a larger share of the revenue from sales following a product introduction. The fact that technology source and non-source alliances are found to have opposite effects validates our premise of a risk-return trade-off for technology alliances.

The results show a similar risk-return trade-off for companies residing within clusters. Informal cooperation within a biotech cluster positively affects the likelihood of a product introduction, suggesting that it decreases risk in product development, which supports the beneficial factors of residing within a cluster. In the trade-off, however, companies established within such a cluster seem to earn lower returns from products that make it to the market. Undoubtedly, this is correlated with the similar effects of technology source

alliances. This correlation is also supported by the negative interaction effect of the cluster variable and technology source alliances on returns (*appendix b; table a2*).

For the third dimension, there are several arguments explaining the unfortunate effects of acquisitions on new product development in the studied sector. As discussed in the existing literature, previously dominant technologies in the pharmaceutical industry have become obsolete due to the rapid rise of science-driven biotechnologies during the 1980s and 1990s, thereby reducing the value of pharmaceutical firms' existing competences [162, 182]. Therefore, "biotechnology is a dramatic case of competence-destroying innovation" [204(p.368)]. Ironically, since the rise of biotechnology, established firms that exist by virtue of previously dominant technologies have begun to massively acquire biotechnological innovation to counter the pharmaceutical innovation deficit [5, 63]. In the regression models for returns, "being acquired" has no significant effects on revenues from product sales. However, these effects are negative, which may suggest that the negative effects on returns of being acquired slightly outweigh their positive effects, but not enough to sort a significant negative effect.

3.5.1 Strategic and managerial implications

This study shows that governance structures play an essential role in interfirm cooperation with respect to successful product commercialization. Our empirical findings have several implications for both leaders of biotech SMEs and managers at established firms. For biotech companies, the chances of a successful product introduction appear to be positively affected within a "cluster setting". Therefore, leaders of biotech companies do best to establish themselves in such an environment, but keeping in mind that this decision might influence the returns from products that are successfully launched. In addition, engaging in technology source alliances with larger (pharmaceutical) firms facilitates access to and benefits from the expertise and resources needed for downstream clinical R&D and commercialization. Such alliances significantly reduce the risk of failure during development, albeit at the expense of expected future revenues from sales. Nevertheless, during and after such collaborations, SMEs can optimally benefit from upfront, milestone, and royalty payments, depending on the value of their innovation, their IP position, and the nature of the deal.

Obviously, at an early stage, biotech SMEs need to focus on upstream R&D activities. At a later stage, after one or more successful product introductions, companies can choose one of two strategic options. First, they can focus on engaging in technology source alliances, which will increase the likelihood of additional product introductions and increase the company value for an eventual exit strategy. As a second strategic option, biotech companies can focus on developing new products in-house to maximize revenues from future product sales and simultaneously engage in "non-source alliances" further downstream to maximize revenue from future and existing biotechnological product sales.

There are also implications for larger firms when acquiring and exploiting externally sourced innovation. Established firms gain from biotechnological innovations by engaging in "non-source alliances," as opposed to acquiring biotech companies. This conclusion corresponds to that of Markides[205], who has suggested that established firms should

concentrate on their strengths instead of exploiting and attempting to create disruptive innovation. In this industry, established pharmaceutical firms are good at downstream R&D, marketing and commercialization, and consolidating young markets into large, mass markets. Correspondingly, instead of allocating valuable resources to acquiring and attempting to grow new, innovative businesses, they should aim to create and sustain a network of what Markides[205(p. 24)] describes as "feeder" companies. Biotechnological platforms can then be scaled up once their derived applications are ready for market consolidation. The study shows that by clustering feeder companies, as described earlier, an additional beneficial effect on new product development can be obtained.

3.5.2 Limitations and further research

Two limitations of this study point to future research opportunities. First, our large sample size made it difficult to deconstruct some variables into additional submeasures. It was possible to distinguish between technology source alliances and non-source alliances. However, further categorization of the alliances variable might provide additional insights. Different types of alliances (e.g., in- and out-licensing, collaborative R&D agreements, joint ventures) might have sorted different effects with respect to biotechnological product development and product sales. With respect to our results on acquisitions, future research could address categorization related to types of acquiring firms and assess which types are predominantly responsible for the negative effects of acquisitions. Additionally, future studies could account for post-acquisition integration measures to gain insights into optimizing integration and exploitation processes (see Puranam et al.[152]; Ranft and Lord[153]).

Moreover, it is possible that the second DV, revenues from product sales including 10% in royalty payments, is not always equal to the financial success of a biotech company. The main reason for this is that most biotech companies that indirectly introduce a product through alliances or acquisitions have made financial deals with their partners related to other forms of cash flow, in addition to royalties (i.e., upfront payments, milestone payments) [137, 139, 206]. Given the large sample size, it was fairly difficult to retrieve this financial data. This limited us to assessing the effects on income from revenue and royalties of introduced biotechnological product sales.

Certainly, the significant results of this single study do not provide conclusive evidence, and additional research is needed to examine in greater detail the link between biotech company success and governance structures in interfirm cooperation. However, the results clearly show that from a biotech firm's perspective, engaging in technology source alliances is a superior strategy for successfully commercializing biotechnological product innovations than being acquired by a larger (pharmaceutical) firm.

Appendices

Appendix a. Literature overview interfirm cooperation

Table a1. Literature overview of interfirm cooperation

	Study	Research sample/Data	Design and Independent variables	Dependent variables	Findings/Key Insights
Dimension 1: Clusters	**Deeds et al.[143]; (Journal of Business Venturing)**	Publicly held pharmaceutical and biotechnology companies.	Geographic location in cluster areas in the US; Research team capabilities; Strategic Alliances; R&D Management capabilities	New product development; measured by both marketed products and products in development.	"Location has a significant and positive impact on a firm's new product development. Specifically, a firm located in an area with a higher concentration of biotechnology firms has a significantly higher number of products completed or in trials than those located in areas with lower concentrations. However, when at the high end of the concentration the negative impact of competition for resources appears to have an impact and actually decreases the firms ability to develop products." "Close proximity of organisations with similar interests promotes the natural exchange of ideas through both formal and informal networks established among the organizations" " Firms which are located close to other firms in the same industry will reap benefits from knowledge spillovers, specialized suppliers, and labor pooling, but the results also indicate that there is a point at which competition for resources within a given geographic location interferes with a firm's ability to develop new products."
	Stuart & Sorenson[145]; (Research Policy)	Biotechnology firms.	Geographic proximity to establised biotech firms; Sources of biotechnology expertise; Venture capitalists	Location-specific founding rates and (financial) performance of biotechnology firms.	"The form of social capital most valuable in the resource mobilisation process is to a large extent a geographically localised currency" " According to our results, the most advantageous locations for new biotech firms provide access to an extensive technical workforce, but do not present intense local competition from nearby biotech firms." "the competitive effect of being located in a densely populated biotechnology cluster impacts poorly funded startups most strongly." "the faculties of leading universities in the biotech-related sciences establish more new biotechnology firms when only a few biotech companies operate in the immediate vicinity of their universities."
	Phene et al.[114] (Strategic Management Journal)	Patent data from US Biotechnology industry	Technological space; Geographic origin.	Breakthrough innovation, measured by patent citations (binary variable)	"Exploration across geographic or technological neighborhoods can be valuable in achieving breakthrough innovations"; "technological distance of knowledge does not assure its utility; rather, it is the interaction of technological space and geographic origin that enables firms to create breakthrough innovations. Technologically distant knowledge has a significant impact on breakthrough innovation only if it is from the same national context."
	Folta et al.[144] (Journal of Business Venturing)	Private and public US biotechnology firms	Cluster size; Cluster growth	Firm performance (five measures): Discontinuance; IPOs; Private equity offerings; patents; strategic alliances.	"Economies of agglomeration benefit firms in their ability to innovate through patenting, attract alliance partners, and attract private equity partners." "At the same time, marginal benefits to cluster size decline as clusters get large, clearly suggesting that diseconomies of agglomeration may play an important role when clusters exceed about 65 firms"; " the marginal benefit to being in a cluster is increasing at a decreasing rate"
	Ahrweiler et al.[165] (Journal or Product Innovation Management)	Knowledge-intensive industries	Simulation of innovation networks with and without university agents. University-industry linkages	Innovation diffusion and collaborative arrangements in innovation networks.	"University-industry links improve the conditions for innovation diffusion and enhance collaborative arrangements in innovation networks."

Dimension 2: Alliances	**George et al.[148] (Journal of High Technology Management Research)**	Biopharmaceutical firms	Alliance portfolio characteristics (Horizontal/vertical alliances and generative/attractive alliances)	Innovative performance (products on market), financial performance (revenue), and absorptive capacity	The results highlight the differential effect of the portfolio characteristics on performance. Vertical alliances rather than horizontal alliances increase the probability of bringing a product to market. "Horizontal alliances are positively related to patents (innovative capability), whereas vertical alliances are negatively related to patents. Also, vertical alliances are positively related to performance, whereas horizontal alliances are not significant predictors of company performance."
	George et al.[167] Journal of Business Venturing)	Publicly traded biotechnology companies	Business-university alliances	R&D expenses, innovative output, financial output	Companies with university linkages have lower R&D expenses while having higher levels of innovative output. However, companies with university linkages do not achieve higher financial performance than similar firms without such linkages.
	Rothaermel & Deeds [149] (Strategic Management Journal)	Biotechnology firms	Exploration alliances; Products in development; and exploitation alliances.	Products in development; Exploitation alliances ; and Products on the market	"We found support for an integrated product development path leading from exploration alliances, via products in development and exploitation alliances, to products on the market." "As a technology venture grows, it tends to withdraw from this product development path to discover, develop, and commercialize promising projects through vertical integration."
	Danzon et al.[111] (Journal of Health Economics)	Pharmaceutical and biotechnology firms.	Overall and Therapeutic experience; Diversified experience across therapeutic areas; Scope; Co-development alliance	Drug development phase completion	"Products developed in an alliance tend to have a higher probability of success, at least for the more complex phase 2 and phase 3 trials, particularly if the licensee is a large firm." "The evidence on effects of alliances tends to confirm the direct evidence from the economies of experience measures: experience increases the probability of success for late stage trials, whereas it is not necessary for the simpler, phase 1 trials. These productivity-enhancing effects of alliances with large firms dominate any lemons or moral hazard effects."
	Rothaermel & Deeds [150] (Journal of Business Venturing)	Biotechnology firms	Upstream, horizontal, and downstream alliances from the perspective of the biotech firm.	New product development.	"The biotech fi rms' limited capability for alliance management is exhausted the fastest with upstream alliances, followed by horizontal, and then by downstream alliances, in this order." "Consequently, firms can afford to engage in more horizontal alliances compared to upstream ones and can manage an even greater number of downstream alliances"
	Stuart et al.[207] (Research Policy)	Biotechnology firms	Upstream alliances; and affiliated scientists' networks	Revenue generating down-stream alliances	"(i) firms with multiple in-licensing agreements are more likely to attract revenue-generating alliances with downstream partners; however, (ii) the positive relationship between in-licenses and downstream alliances attenuates as firms mature, and (iii) the diversity and the quality of the academic connections of firms' principals influences their chances of successfully acquiring commercialization rights to scientific discoveries in universities." "Biotechnology firms with strong academic connections (but, not necessarily academic founders) are ideally suited to capitalize on the business model of brokering university technology."
	Sherwood & Cavin [146] (Journal of Product Innovation Management)	Firms engaged in technology transfer; partnerships with universities	Trust, familiarity with partner, familiarity with technology, alliance experience, use of formal collaboration teams, and technology experts' communication.	Technological knowledge acquisition success	"the results emphasise the importance of three factors to knowledge acquisition success: (1) the trust exhibited by the knowledge- seeking party in the knowledge source; (2) partner familiarity; and (3) the partners' technology experts' communications." Both parties should consciously strive, through substantive and symbolic actions, to create a trusting relationship and partner familiarity is needed to build partner trust. In addition, the employment of communications channels that offer the knowledge-seeking party unobstructed, timely, and complete access to the technology of the knowledge source party should be a communications objective, and this may be most easily accomplished by creating strong communications linkages between the parties' technology experts.
	Un et al.[178] (Journal of Product Innovation Management)	Manufacturing firms	R&D collaborations with universities, suppliers, customers, and competitors.	Product Innovation	"R&D collaborations with suppliers have the highest positive impact on product innovation, followed by collaborations with universities. Surprisingly, R&D collaborations with customers do not appear to affect product innovation, and collaborations with competitors appear to harm it." "These findings indicate that ease of knowledge access, rather than breadth of knowledge, appears to drive the success of R&D collaborations for product innovation."

	Van Beers & Zand [208] (Journal of Product Innovation Management)	12,811 innovating firms, based on data from the Dutch Community Innovation Survey	The diversity of different kinds of partners in R&D cooperation	Innovation performance	"Functional diversity leads to a variety of knowledge intake and synergetic effects necessary to develop and commercialize novel products. Geographical diversity results in successful adaption of existing products to different local requirements such as technical standards, market regulations, and customer preferences. The organizational determinants of both kinds of partner diversity are prior experience, patenting, and information technology infrastructure." "The observed effects of partner diversity on innovation performance are more profound in high-technology and knowledge-intensive industries because of higher degrees of product complexity, market volatility, and riskiness/uncertainty of innovation projects in these sectors."
Dimension 3: Acquisitions	**Ahuja & Katila[154] (Strategic Management Journal)**	Acquiring firms in the chemicals industry	Technological acquisitions, acquisitions in which technology is a component of the acquired firm's assets, and non technological acquisitions" acquisitions that do not involve a technological component.	Innovation performance	"Within technological acquisitions absolute size of the acquired knowledge base enhances innovation performance, while relative size of the acquired knowledge base reduces innovation output. The relatedness of acquired and acquiring knowledge bases has a nonlinear impact on innovation output. Nontechnological acquisitions do not have a significant effect on subsequent innovation output.within technological acquisitions absolute size of the acquired knowledge base enhances innovation performance, while relative size of the acquired knowledge base reduces innovation output. The relatedness of acquired and acquiring knowledge bases has a nonlinear impact on innovation output. Nontechnological acquisitions do not have a significant effect on subsequent innovation output." "From the acquisition selection standpoint this research suggests that a balance on both size and relatedness of acquisitions is favored."
	Hagedoorn & Duysters [156] (Technology Analysis & Strategic Management)	Companies in the international computer sector.	Relatedness in M&As (technological; similar size; R&D intensity)	Technological performance	"M&As can contribute to improving the technological performance of companies in a high-tech environment. However, it has to be stressed that both the organizational and the strategic fit of the companies involved in these M&As are crucial for the technological success of M&As." "The successful integration of other companies in a familiar environment and the search for new opportunities through M&As are both mentioned in that context as major mechanisms in a two- fold strategy to improve technological performance. The relevance of market relatedness of M&As stresses the importance of uncertainty reduction by means of integration of companies that are active in similar sectors and that have some similarity in terms of product- markets"
	King et al.[78] (Strategic Management Journal)	93 studies with 852 effect sizes with a combined size of 206.910 observations	Meta-analyisis of Empirical studies of acquiring firms.	Financial performance (e.g., abnormal returns with multiple event windows, return on assets (ROA), return on equity (ROE), return on sales (ROS)).	"Acquisitions either have no significant effect or a modest negative effect on an acquiring firm's financial performance in the post-announcement period." "This may lead one to conclude, for example, that acquisition is not the best means by which to access and profit from valuable resources existing in other, external businesses."Until researchers can provide managers better guidance on how value can be created through M&A activity, the apparent bias for external growth over internal growth likely will continue to result in disappointing performance outcomes."
	De Man & Duysters [76] (Technovation)	30 studies on alliances and 15 studies on M&A	Review of Empirical studies of acquiring firms and alliance partners	Innovation	"Alliances increase the innovativeness of firms. There are some conditions that enhance this effect, like similar knowledge backgrounds of the partners, a higher level of alliance capability and more intense relationships. Alliances involving public support or a public partner do not increase innovation, although they do lower the cost of innovation." M&A have a neutral or negative effect on innovation; M&A may lead to some scale economies thereby lowering the cost of innovation; well managed M&As and M&As among related firms outperform poorly managed M&As and diversifying M&As, respectively." "Overall conclusion: alliances are outperforming M&As in terms of their effect on innovation. Except for the possibilities offered by M&As to reap some economies of scale in R&D, alliances outperform M&As on almost each conceivable point."

Cloodt et al.[77] (Research Policy)	Acquiring firms in four major high-tech sectors.	Non-technological M&As; Technological M&As.	Post-M&A innovative performance	"Non-technological M&As appear to have a negative impact on the acquiring firm's post-M&A innovative performance. With respect to technological M&As, a large relative size of the acquired knowledge base reduces the innovative performance of the acquiring firm. The absolute size of the acquired knowledge base only has a positive effect during the first couple of years after which the effect turns around and we see a negative effect on the innovative performance of the acquiring firm. The relatedness between the acquired and acquiring firms' knowledge bases has a curvilinear impact on the acquiring firm's innovative performance. This indicates that companies should target M&A 'partners' that are neither too unrelated nor too similar in terms of their knowledge base."
Danzon et al.[74] (Managerial and Decision Economics)	Pharmaceutical and biotech firms	Excess capacity on merger activity and merger activity on performance	Mergers; Firm performance	"Firms with a low Tobin's *q*; hence with low expected earnings growth, are more likely to acquire another firm." "Large firms that merged experienced a similar change in enterprise value, sales, employees, and R&D, and had slower growth in operating profit, compared with similar firms that did not merge. Thus mergers may be a response to trouble, but they are not a solution." " For small firms mergers appear to be primarily an exit strategy for firms that are in financial trouble, as measured by low Tobin's **q**; few products and low cash–sales ratio. Because most of these small firms do not have marketed products, this financial trouble is more likely caused by unobserved R&D shocks rather than excess capacity due to patent expirations."
Demirbag et al.[155] (Multinational Business Review)	Pharmaceutical firms	Comparative Analysis of Pre-M&A versus Post-M&A performance	Research productivity, ROI, and profit margin	"Relying on three measures of evaluating M&A performance, it has been noted in general that no value creation was realized in our sample M&As in terms of research productivity, return on investment, and profit margin"

Appendix b. Additional analyses; interaction effects

Table a2. Logit regression models for interaction effects on product introduction[a]

Variable	Model 5	Model 6
DV: Biotech product introduction (*t* to *t*+5)		
Category big biotech	9.38*** [2.08]	11.04*** [2.19]
Age	.94** [.313]	.856** [.321]
Patent activity (*t*-5 to *t*)	.757*** [.190]	.598** [.196]
Cluster	1.56* [.715]	1.65* [.762]
Number of alliances (*t*-5 to *t*)	.618* [.242]	---
Technology source alliances (*t*-5 to *t*)	---	.518 [.349]
Non-source alliances (*t*-5 to *t*)	---	.211 [.350]
Acquired (*t*-5 to *t*)	-.369 [.726]	-.961 [.776]
Acquired within cluster (*t*-5 to *t*)	-.073 [.861]	-.572 [.877]
Cluster * Alliances (*t*-5 to *t*)	-.013 [.012]	---
Cluster * Technology source alliances (*t*-5 to *t*)	---	.043 [.024]
Cluster * Non-source alliances (*t*-5 to *t*)	---	-.062* [.026]
Acquired * Alliances (*t*-5 to *t*)	-.036 [.021]	---
Acquired * Technology source alliances (*t*-5 to *t*)	---	.148** [.877]
Acquired * Non-source alliances (*t*-5 to *t*)	---	-.112* [.049]
Constant	-17.66*** [1.73]	-17.30*** [1.77]
Chi2	112.46***	110.38***
McKelvey & Zavoina's R^2	.274	.27
n = 5697		

[a] Year dummies are included in all models. Standard errors in brackets.

*Statistically significant at the 5% level.

** Statistically significant at the 1% level.

*** Statistically significant at the .1% level.

Table a3. OLS regression models for interaction effects on revenue (without firm dummies)[a]

Variable	Model 5	Model 6
DV: Revenue from biotech products		
Category big biotech	2.45** [.927]	1.45 [.808]
Age	-.360 [.299]	-.242 [.243]
Patent activity (*t*-5 to *t*)	.515* [.244]	.616** [.235]
Cluster	-1.07* [.470]	-.599 [.442]
Number of alliances (*t*-5 to *t*)	.014 [.255]	---
Technology source alliances (*t*-5 to *t*)	-	-.488 [.395]
Non-source alliances (*t*-5 to *t*)	-	.777* [.323]
Acquired (*t*-5 to *t*)	-.374 [.666]	-.322 [.669]
Acquired within cluster (*t*-5 to *t*)	1.73* [.845]	1.91* [.773]
Cluster * Alliances (*t*-5 to *t*)	-.012 [.019]	---
Cluster * Technology source alliances (*t*-5 to *t*)	-	-.079** [.028]
Cluster * Non-source alliances (*t*-5 to *t*)	-	.018 [.019]
Acquired * Alliances (*t*-5 to *t*)	-.045** [.019]	---
Acquired * Technology source alliances (*t*-5 to *t*)	-	-.123** [.048]
Acquired * Non-source alliances (*t*-5 to *t*)	-	-.037* [.016]
Constant	6.12*** [1.06]	4.99*** [.954]
R^2	.5646	.6450
n = 675		

[a] Year dummies are included in all models. Standard errors in brackets.

*Statistically significant at the 5% level.

** Statistically significant at the 1% level.

*** Statistically significant at the .1% level.

Table a4. OLS regression models for interaction effects on revenue (with firm dummies)[a]

Variable	Model 7	Model 8
DV: Revenue from biotech products		
Age	-.656[.368]	-.456 [.303]
Patent activity (*t*-5 to *t*)	.467[.280]	.547* [.277]
Number of alliances (*t*-5 to *t*)	-.017[.203]	---
Technology source alliances (*t*-5 to *t*)	---	-.833** [.312]
Non-source alliances (*t*-5 to *t*)	---	.824*** [.251]
Acquired (*t*-5 to *t*)	.502[.502]	.550 [.565]
Acquired*Alliances (*t*-5 to *t*)	-.042*[.017]	---
Acquired *Technology source alliances (*t*-5 to *t*)	---	**-.099*** [.047]
Acquired *Non-source alliances (*t*-5 to *t*)	---	-.033 [.017]
Constant	5.57***[1.21]	4.39*** [1.01]
R^2	.7035	.7143
n = 675		

[a] Firm dummies and year dummies are included in all models. Standard errors in brackets

*Statistically significant at the 5% level.

** Statistically significant at the 1% level.

*** Statistically significant at the .1% level.

Appendix c. Additional analyses; quadratic terms

Table a5. Logit regression models for product introduction with quadratic terms[a]

Variable	Model 9	Model 10
DV: Biotech product introduction (*t* to *t*+5)		
Category big biotech	9.30***[2.12]	9.49*** [2.07]
Age	1.05**[.308]	.967**[.330]
Patent activity (*t*-5 to *t*)	1.35[1.29]	1.66[1.30]
Patent activity squared (*t*-5 to *t*)	-.289[.628]	-.509[.635]
Cluster	1.44[.738]	1.40*[1.50]
Number of alliances (*t*-5 to *t*)	1.97*[1.54]	---
Number of alliances squared (*t*-5 to *t*)	-.765[.754]	---
Technology source alliances (*t*-5 to *t*)	---	1.37[1.50]
Technology source alliances squared (*t*-5 to *t*)	---	-.145[.738]
Non-source alliances (*t*-5 to *t*)	---	.282[1.48]
Non-source alliances squared (*t*-5 to *t*)	---	-.385[.725]
Acquired (*t*-5 to *t*)	-.957*[.446]	-.778[.444]
Constant	-18.32***[1.67]	-17.42***[1.87]
Chi2	114.53***	104.87***
McKelvey & Zavoina's R^2	.270	.265
n = 5697		

[a] Year dummies are included in all models. Standard errors in brackets.

*Statistically significant at the 5% level.

** Statistically significant at the 1% level.

*** Statistically significant at the .1% level.

Table a6. OLS regression models (without firm dummies) with quadratic terms[a]

Variable	Model 9	Model 10
DV: Revenue from biotech products		
Category big biotech	2.20** [.858]	1.70* [.717]
Age	-.075 [.280]	.089 [.220]
Patent activity (*t*-5 to *t*)	-1.05 [1.03]	-1.13 [.957]
Patent activity squared (*t*-5 to *t*)	.750 [.505]	.824 [.471]
Cluster	-.982* [.496]	-.929* [.447]
Number of alliances (*t*-5 to *t*)	-3.34* [1.35]	---
Number of alliances squared (*t*-5 to *t*)	1.59* [.754]	---
Technology source alliances (*t*-5 to *t*)	---	-.567 [.885]
Technology source alliances squared (*t*-5 to *t*)	---	-.142 [.495]
Non-source alliances (*t*-5 to *t*)	---	-3.06* [1.49]
Non-source alliances squared (*t*-5 to *t*)	---	1.86* [.818]
Acquired (*t*-5 to *t*)	-.032 [.493]	-.778 [.444]
Constant	5.45*** [.977]	4.66*** [.895]
R^2	.5603	.6063
n = 675		

[a] Year dummies are included in all models. Standard errors in brackets.

*Statistically significant at the 5% level.

** Statistically significant at the 1% level.

*** Statistically significant at the .1% level.

Table a7. OLS regression models (with firm dummies) with quadratic terms[a]

Variable	Model 11	Model 12
DV: Revenue from biotech products		
Age	-.298 [.348]	-.073 [.292]
Patent activity (*t*-5 to *t*)	-.957 [.992]	-1.09 [.939]
Patent activity squared (*t*-5 to *t*)	.676 [.494]	.788 [.475]
Number of alliances (*t*-5 to *t*)	-3.68* [1.45]	---
Number of alliances squared (*t*-5 to *t*)	1.79* [.736]	---
Technology source alliances (*t*-5 to *t*)	---	-.725 [1.05]
Technology source alliances squared (*t*-5 to *t*)	---	-.054 [.574]
Non-source alliances (*t*-5 to *t*)	---	-2.98 [1.55]
Non-source alliances squared (*t*-5 to *t*)	---	1.85* [.844]
Acquired (*t*-5 to *t*)	-.170 [.533]	-.235 [.504]
Constant	4.36*** [1.02]	3.97*** [.897]
R^2	.6939	.7130
n = 675		

[a] Firm dummies and year dummies are included in all models. Standard errors in brackets

*Statistically significant at the 5% level.

** Statistically significant at the 1% level.

*** Statistically significant at the .1% level.

Chapter 4

THE MODERATING ROLE OF ABSORPTIVE CAPACITY AND THE DIFFERENTIAL EFFECTS OF ACQUISITIONS AND ALLIANCES ON BIG PHARMA FIRMS' INNOVATION PERFORMANCE

Abstract

In the context of increased pharmaceutical innovation deficits and big pharma blockbusters' patent expirations, this study examines the moderating role of firms' absorptive capacity in external innovation activities of big pharma firms. The study indicates a rising interest of big pharma in acquisitions of and alliances with biotechnology companies. Unfortunately, this increased interest is not reflected in the number of new drugs generated by big pharma. We find that acquisitions of biotech companies have negatively affected big pharma firms' innovation performance on average but these acquisitions might have a positive effect at higher levels of acquiring firms' absorptive capacity. Moreover, also acquisitions of pharma companies and alliances with biotech companies only have a positive effect on innovation performance at sufficiently high levels of absorptive capacity. The moderating role of absorptive capacity implicates that a tight integration of internal R&D efforts and (unrelated) external knowledge is crucial for harnessing complementarity effects.

Fernald, K.D.S., Pennings, H.P.G., van den Bosch, J.F., Commandeur, H.R. and Claassen, E.

4.1 Introduction

The pharmaceutical industry is one of the most research-intensive industries, with average new product development (NPD) trajectories of 11.9 years [58, 109]. For the past decade the industry has been coping with a growing "productivity gap" [12] or "productivity paradox" [4], which is generally described as a decrease in new products launched versus an increase in research and development (R&D) expenditures [14]. These increased expenses appear to be related to an increasingly rigid regulatory environment and higher quality demands [209, 210]. In addition, patent expiry on numerous blockbuster drugs, also referred to as the "patent cliff", and consequent generic competition is currently affecting the industry, eroding $Billions in annual sales [96]. Although the decrease in pharmaceutical productivity is controversial [210], the combination of challenges that are involved has serious ramifications for maintaining the industry's margins and double-digit growth rates of past decades [211]. These rates are still incorporated into the growth expectations of shareholders and can be maintained only with an annual launch of at least two new 'blockbuster' drugs [4].

An important strategy that has been used over the past two decades to address thinning pipelines involves mergers and acquisitions (M&A) [72, 73]. *Figure 4.1.* shows the consolidation of big pharma, with 32 incumbent firms in 1990 merging to 12 firms in 2013.

Together, these firms have generated more than 60% of the combined global pharmaceutical sales over the past decade (see *figure 4.2*). According to Danzon et al.[74] and Frantz[75], M&A appear to be a response to the expected patent expirations and gaps in a firm's product pipeline. However, this consolidation strategy has had little effect, as M&A do not appear to create or destroy value [72]. Nonetheless, since the 1980s, pharmaceutical firms have employed this M&A strategy with respect to biotechnology small- and medium-sized enterprises (SMEs) in the hopes of countering innovation deficits [5, 94].

The current innovation challenges have coincided with the considerable rise of new sources of innovation for pharmaceutical firms. The biotech 'revolution', which began in the 1970s [17], has significantly affected the radical innovation process within the industry. This rise of scientific drug discovery, spurred the origination of highly innovative and specialized biotechnology-driven firms [212].

Figure 4.1 Big pharma consolidation; M&A that led to the current 12 largest pharmaceutical firms (source: SDC Platinum Database (ThomsonReuters))

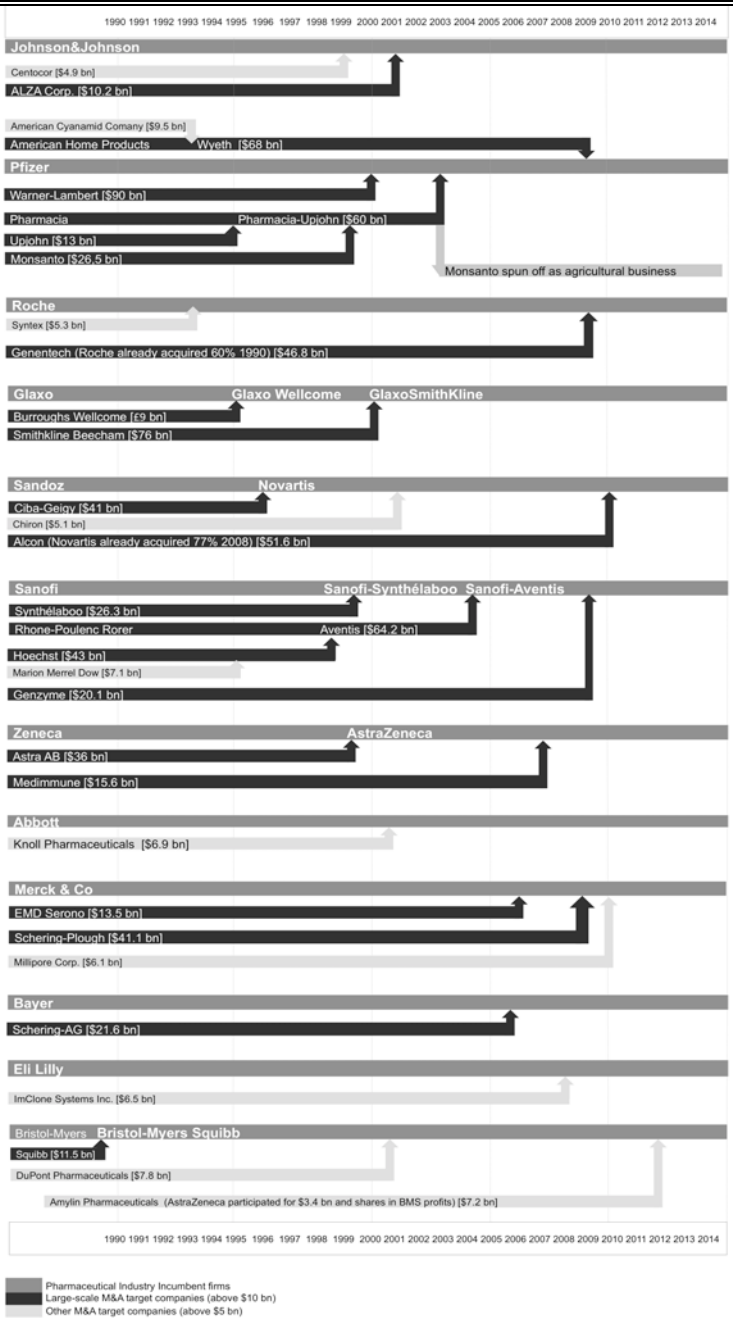
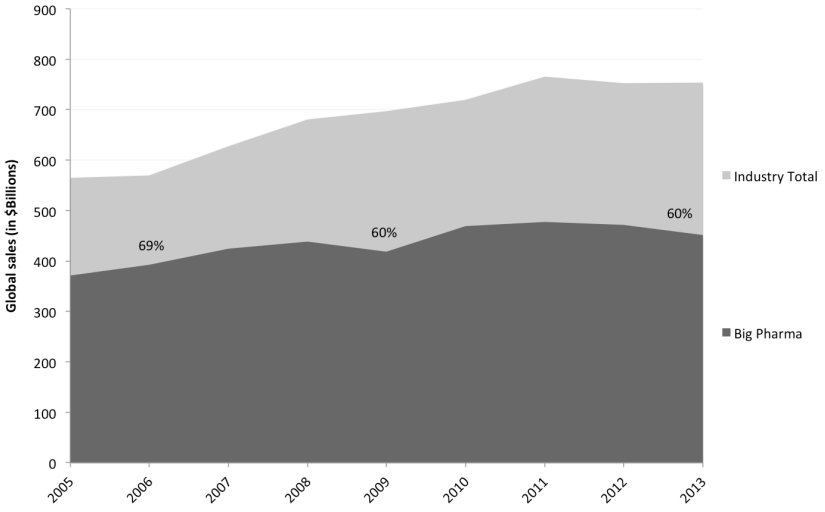


Figure 4.2 Global pharmaceutical sales (in $Billions); Showing the proportion of global sales of big pharma firms as illustrated in *figure 4.1* compared to global industry sales
(source: EvaluatePharma; Datastream (ThomsonReuters))



Biotechnology as a new source of external innovation was expected to be the answer to the challenges that the pharmaceutical industry is currently confronted with [16]. This development resulted in a continuous trend in the formation of new pharma-biotech collaborations and acquisitions of biotech SMEs [13, 213](*figure 4.3* and *4.4*). However, the coincidence of the incumbent firms' focus on external sources of innovation, the considerable rise in R&D expenditures, and the stagnant pattern of newly developed drugs (i.e. productivity paradox), does raise questions regarding the effects of external innovation from biotechnology SMEs on incumbent pharmaceutical firms' innovation performance.

The (bio)pharmaceutical industry is a prime example where technologically unrelated innovation sources are used to replenish incumbent firms' R&D pipelines, making it ideal to investigate differential effects of related and unrelated acquisitions and alliances on firms' innovation performance. By establishing a framework based on the innovation activities of incumbent pharmaceutical firms, this study uniquely aims to explore effects of related and unrelated sources of innovation, accessed through alliances and acquisitions, on firms' innovation performance. Moreover, the aim is to show the moderating role of absorptive capacity, measured as internal R&D, in these effects, identifying either complementarity or substitutability between big pharma firms' internal and external R&D activities.

4.2 Theory and hypotheses

In the context of open innovation[6] and exploration and exploitation[157] as it applies to the (bio)pharmaceutical industry[159, 160], three important innovation activities are internal R&D efforts, engaging in alliances, and engaging in M&A.

In the pharmaceutical industry, several types of M&A are prevalent, which include but are not limited to: large-scale mergers between pharmaceutical firms (e.g., Glaxo Wellcome merging with Smithkline Beecham to form GlaxoSmithkline in 2000 and Sanofi merging with Aventis in 2004), large-scale biotech mergers (e.g., Biogen and Idec merging in 2003) and acquisitions of biotech SMEs[13] on the one hand, and acquisitions of pharmaceutical companies on the other hand. It is apparent that pharma companies are related to big pharma firms, in terms of knowledge, technologies and NPD, whereas biotech companies are unrelated to the incumbent pharma firms.

Incumbent (pharma) firms and biotech companies make alliance and acquisition deals to reach their respective goals. Biotech companies want to ensure their short-term survival by accessing financial resources, sharing the high risks associated with drug development and ultimately gaining market access. In contrast, pharmaceutical firms intend to select product candidates with blockbuster potential to fill gaps in their pipeline [162, 214]. Although the blockbuster model is being increasingly questioned by firms themselves [4], the strong focus on the short-term commercial exploitation of high-potential products appears to resonate in the strategies of firms. As a result, firms generally target profitable or later clinical stage biotech companies. Although early stage companies are less expensive to acquire, they are typically more distant from becoming profitable and thus are less appealing [215]. The targets also tend to be acquired for only one or a few products from their pipeline [189], resulting in a frequent write-off of acquired in-process R&D.

4.2.1 External innovation activities and innovation performance

Alliances generally seem to outperform acquisitions when it comes to effects on a firm's innovation performance [76]. Where overall effects of alliances are often positive [111, 177, 179], the effects of acquisitions are mostly neutral or negative [76]. Effects of acquisitions appear to be more negative when acquirers and targets have more diverging knowledge bases or are more dissimilar in size [156]. So, especially for unrelated acquisitions, where the assimilation and application of newly acquired knowledge are likely to be resource consuming and can be counter-productive [216], the effects are found to be negative [77, 154, 217, 218].

Compared to acquisitions, different dynamics play a role in alliances, and hence different management capabilities are needed to adequately exploit innovation accessed through strategic alliances [219]. Alliances are often engaged prior to M&A [71], presenting the opportunity of 'cherry-picking' at a relatively low cost before committing to all assets of a target company [76, 220]. However, the extent to which alliances have positive effects on innovation performance is highly dependent on various factors, such as the relatedness of the knowledge bases of involved firms, the intensity of collaboration, and optimal alliance networks [76, 77]. Especially relatedness may be an important factor and positive effects of

alliances may be greater for related alliances as opposed to unrelated alliances. Distinguishing between biotech and pharma alliances, Deeds and Hill [177], however, find no significant differences in innovation performance between both types of alliances.

4.2.2 The moderating role of Absorptive Capacity

A firm's internal R&D investments is considered to be a proxy for its absorptive capacity [221-223] and appears to be a contingency variable that critically influences the relationship between external R&D strategies and innovation performance [224-226]. In particular R&D acquisitions are complementary innovation activities at higher levels of internal R&D investments, while at lower levels, internal R&D and acquisitions turn out to be substitutive strategic options. This might especially be true for related acquisitions as literature typically suggests that creating economies of scale and scope require a high level of technology- and market-relatedness [76, 227]. Accordingly, Zahra and Hayton[222] find positive significant interaction effects of related acquisitions and absorptive capacity on both firms' ROE (return on equity) and revenue growth. Building upon these arguments, we derive the following hypothesis:

H1a: Absorptive capacity has a positive moderating effect on the relationship between pharma acquisitions and big pharma firms' innovation performance.

Pisano[187] explained that the rapid internalization of biotechnological R&D through acquisitions is likely to be an undesirable model. He argued that acquiring biotech SMEs can be particularly dangerous when used to overcome internal deficits. Acquiring biotechnology companies is only recommended after sufficient accumulation of in-house R&D experience [185, 187, 188]. Correspondingly, Miyazaki[228] has reported negative effects in high-tech industries when firms choose between either high levels of internal R&D (i.e., 'making') or external growth strategies involving M&A (i.e., 'buying').

Although, as H1a suggests, complementarity between internal and external R&D often depends on relatedness [76, 227, 229], positive, but mostly non-significant, interaction effects of internal R&D activity and unrelated knowledge acquisitions have been found as well [222, 230]. In such cases, innovation management requires a tight integration of internal and external knowledge to capture the positive effects each innovation activity has on the marginal return of the other [229]. It seems that increased absorptive capacity (i.e. internal R&D) could positively moderate the effects of unrelated acquisitions on firms' innovation performance. As such, the following hypothesis is suggested:

H1b: Absorptive capacity has a positive moderating effect on the relationship between biotech acquisitions and big pharma firms' innovation performance.

A very fundamental difference between alliances and acquisitions lies in the degree of ownership between the parties involved. While larger firms can play a dominant role, the ownership of external R&D remains with the other firm, resulting in a lack of ownership advantages that could be essential to create complementarity between internal and related external R&D. The choice between internal R&D and related alliances is influenced by whether they are complements or substitutes which, ultimately, rely on whether synergies

exist between them[231] and the R&D governance mode choice appears to be an important contingent variable in this regard [232]. Due to a higher degree of separation in terms of ownership and governance between internal R&D and external alliances, firms are more likely to choose M&A over alliances with increased relatedness [232]. In this context, related alliances and internal R&D might even be substitutable, so that the marginal benefit of pharma alliances could decrease with higher levels of internal R&D investments. While Zahra and Hayton[222] find a positive moderating role of absorptive capacity on financial effects of related alliances, Berchicci[233] find a substitution effect between a firm's internal R&D capacity and external R&D through licensing, alliances and technology agreements with other firms. Given these mixed findings, we do not expect to find similar effects on firm's innovation performance and formulate the following hypothesis.

H2a: Absorptive capacity has no moderating effect on the positive relationship between pharma alliances and big pharma firms' innovation performance.

The effects of unrelated alliances on firms' innovation performance, on the other hand, could be enhanced by firms' absorptive capacity. Laursen[234] explains that the inherent tensions and conflicts between exploratory and exploitative activities may call for organizational separation of these activities within firms. Perhaps a higher degree of separation in governance between the (more exploratory) activities of biotechnology firms and the (exploratory and exploitative) activities of pharmaceutical firms can result in increased complementarity effects on innovation when internal pharmaceutical R&D interacts with biotech R&D through strategic alliances. Correspondingly, Lavie et al.[235] explain how inter-organizational R&D alliances may involve varying degrees of basic research and incremental development in which they recognize intermediate activities that combine new knowledge development and the leveraging of prior knowledge. Increased internal exploratory R&D might enhance effects of partnerships with unrelated innovation on a firm's innovation performance. This corresponds with positive and significant empirical findings from existing literature[222, 223, 230], offsetting possible negative effects from opportunism in unrelated alliances. Considering this, the following hypothesis is suggested:

H2b: Absorptive capacity has a positively moderating effect in the relationship between biotech alliances and big pharma firms' innovation performance.

4.3 Methodology

In this study, we collect data related to all incumbent pharmaceutical firms, together known as big pharma. As shown in *figure 4.1*, these firms are: Johnson & Johnson, Pfizer, Roche, GlaxoSmithKline, Novartis, Sanofi-Aventis, AstraZeneca, Abbott, Merck & Co (and Schering), Bayer, Eli Lilly, and Bristol-Myers Squibb. We examine the effects of alliances and acquisitions that occurred between the period from January 1990 to December 2013.

4.3.1 Measures

Innovation Performance – Abundant previous studies have used both input measures (e.g., R&D expenditures) and output measures (e.g., product introductions) to study innovation performance. According to De Man and Duysters[76], output measures are expected to provide the most accurate measure of innovation performance when estimating the effects of M&A. Accordingly, an output measure was used for the analysis in this study.

The Center for Drug Evaluation and Research (CDER) [xxi] distinguishes eight different chemical classes of new drug approvals (NDAs), of which the first class concerns new molecular entities (NMEs) [xxii]. This class has been used in the literature as a measure for pharmaceutical innovation performance [72, 236-239]. In addition, products generated by biotechnologies such as recombinant DNA technology are registered as Biologic License Applications (BLAs), governed by the Center for Biologics Evaluation and Research (CBER) [xxi]. The total number of NMEs and BLAs generated by the big pharma firms and their subsidiaries during the studied period, as depicted in *figure 4.1*, was used as the dependent variable in this study. The data was obtained from the online databases of the FDA, CDER, and CBER [xxi].

NMEs and BLAs generated by firms prior to their merger were included in the analysis. NMEs and BLAs generated by subsidiaries that remained active were only included after the respective acquisition, and only if the subsidiary also engaged in alliances and acquisitions prevalent in our dataset. Subsequently, we excluded NMEs and BLAs with the same name, applicant and approval date as a previous one. These occur due to multiple registrations according to different dosages or delivery methods. A total number of 318 NMEs and BLAs were included in the analysis. The focus was on US approvals because the USA is the largest market for pharmaceuticals and biotech products and accounts for more than 50% of global pharmaceutical sales [240], and any firm that generates new drugs would take advantage of this market.

Acquisitions – From ThomsonReuters SDC Platinum M&A database[xxiii], an initial total number of 1,205 mergers and acquisitions was gathered. This dataset was analysed per entry in order to properly categorize and include or exclude individual acquisitions. As

[xxi] www.fda.gov

[xxii] The class of NMEs is defined as drugs that contain an active moiety that has never been approved by the FDA or marketed in the US.

[xxiii] http://thomsonreuters.com/products_services/financial/financial_products/a-z/sdc/; consisting of a partial database for M&A and one for Alliances.

discussed earlier, this study does not focus on large-scale M&A, as depicted in *figure 4.1*; therefore, these were excluded from the analysis, and all minority stake acquisitions were also excluded. Subsequently, it was determined whether acquisitions were directly relevant for NPD, possibly leading to either an NME or a BLA. On the basis of this premise, acquisitions of (research) services companies and medical devices/diagnostic product companies were excluded from the analysis.

The remaining acquisition targets were subsequently categorized either as being biotechnology companies or pharmaceutical companies. This categorization was mainly based on the respective target company's lead product(s) in development. Information from the deal synopsis as included in the database was used in combination with additional searches for company websites and profiles on websites (e.g. Bloomberg's businessweek.com). The criteria used for distinguishing pharma companies from biotech companies resemble those described in existing literature [149, 241-243]. Targets were considered to be pharmaceutical companies if their products (in development) mainly concerned small molecule drugs and/or the companies used more traditional drug discovery methods for lead generation. For biotech targets, consistent with the works of Chiaroni et al.[212] and Chiesa and Chiaroni[241], we identified different types in our dataset. We only included Chiesa and Chiarioni's[241] description of "core biotech companies", which include "product biotechs", "drug agent biotechs", and "platform biotechs". Targets were considered to be biotech companies if their products (in development) concerned products of biotechnologies (e.g. recombinant proteins, antibodies) or platform biotechnologies (relating to gene therapy or cell therapy, for example). After these exclusion steps a total of 568 acquisitions were included in the analysis, of which 290 acquisitions of pharmaceutical companies (i.e. *Pharma Acquisitions*) and 278 acquisitions of biotechnology companies (i.e. *Biotech Acquisitions*).

Alliances – With the first inquiry, a total of 2,878 alliances were extracted from ThomsonReuters SDC Platinum alliances and joint venture database[xxiii]. This dataset was again analysed per entry, using similar exclusion criteria as described above. First, the type of alliance was considered and 'alliances for services', 'out-licensing', 'marketing alliances', 'out-sourcing', and 'manufacturing alliances' were excluded from the analysis. As a consequence, only 'joint ventures' (JVs), 'in-license deals', 'funding of external R&D projects', and 'collaborative R&D agreements' were included, if these were considered to be directly relevant for NPD (i.e. marketing or manufacturing JVs were also excluded). In addition, these latter set of alliance types with (research) services and medical devices/diagnostic product partners were also excluded from the analysis, as such partners were again not considered to be directly relevant for NPD.

The remaining alliances were further categorized based on the alliance partner being either a biotechnology partner or a pharmaceutical partner. For this categorization the same criteria as described for the acquisition targets, were used. Similarly, this categorization was also based on the deal synopsis as provided by the SDC Platinum database or, if necessary, on additional online data. After these exclusion steps a total of 1,270 alliances were included in the analysis, of which 552 alliances with pharmaceutical companies (i.e. *Pharma Alliances*) and 718 alliances with biotechnology companies (i.e. *Biotech Alliances*).

Absorptive Capacity (ACAP) – As stated by Zahra and Hayton[222], several measures for absorptive capacity have been used in the literature, but the most popular measure is R&D spending, as a firm's internal R&D is the foundation of its absorptive capacity[221]. Similarly to Lin et al.[223], we used a relative measure for R&D intensity, which was generated by dividing the R&D expenditures by the sales of the respective firm. Both data on firms' R&D expenditures and sales was collected from ThomsonReuters' Datastream[xxiv] and these measures were added together for merged firms prior to their merger. The role of *Absorptive Capacity* was assessed by estimating effects of interactions with the acquisitions and alliances variables on firms' innovation performance. For the main affects this measure for R&D intensity was included as a control variable in models without firm dummies.

Size – Firms' size was included as a control variable, measured by the number of employees. This data was also obtained from Datastream[xxiv]. In the analysis a log transformation of this variable was generated.

4.3.2 Models and analysis

For the regression analyses, a panel dataset was used to estimate effects on the dependent variable, $Innovation\ Performance_{it}$ for firm i in year t. Independent variables were generated by creating stock variables for the measures as described above for firm i over the period from year t to $t\text{-}5$, hereby creating a time lag of 5 years [xxv]. This time lag was introduced to estimate the lagged effects of our independent variables, considering companies' stage in product development. A longer time lag would lead to a larger decrease in the number of observations.

First, the main effects were estimated with a Poisson regression with robust standard error (SE) corrections, with and without firm dummies, including $Absorptive\ Capacity_{i(t - t-5)}$ and $ln(Size)_{i(t - t-5)}$ as control variables (results shown in *tables 4.2* and *4.3*).

Subsequently, the moderating role of absorptive capacity was explored with a Poisson regression of the same models including interactions of absorptive capacity with the acquisitions and alliances variables, using the same time lags of 5 years (results shown in *table 4.4*). By using dummy variables, we control for time-specific and firm-specific effects. The hypotheses were tested using the following model (results shown in *table 4.4*):

$$Innovation\ Performance_{it} = \alpha + \beta_1 ACAP_{(t - t-5)} + \beta_2 ln(SIZE)_{i(t - t-5)} + \beta_3 Pharma\ Acquisitions_{i(t - t-5)} + \beta_4 Biotech\ Acquisitions_{i(t - t-5)} + \beta_5 Pharma\ Alliances_{i(t - t-5)} + \beta_6 Biotech\ Alliances_{i(t - t-5)} + \beta_7 ACAP * Pharma\ Acquisitions_{i(t - t-5)} + \beta_8 ACAP * Biotech\ Acquisitions_{i(t - t-5)} + \beta_9 ACAP * Pharma\ Alliances_{i(t - t-5)} + \beta_{10} ACAP * Biotech\ Alliances_{i(t - t-5)} + \varepsilon$$

[xxiv] http://thomsonreuters.com/datastream-professional/

[xxv] Similar but more non-significant results were found using time lags of 4 and 6 years, (results not shown).

4.4 Results

4.4.1 Acquisitions and alliances

Over the studied period of 24 years (1990-2013), we do not observe a rise in the total number of acquisitions. However, pharmaceutical acquirers seem to have shifted their focus, with respect to the type of acquisition targets they acquire. *Figure 4.3* shows an increase in *Biotech Acquisitions* and a decline in *Pharma Acquisitions,* as percentages of total acquisitions that were considered to be directly relevant for NPD. This trend supports the notion of increased investments in biotech by big pharma firms.

Regarding the total number of alliances, we observe a decline, decreasing from an annual average of 220 between 1990 and 1995 to an annual average of 55 between 2008 and 2013. Similar to the patterns regarding acquisitions, the results show that over the past 24 years, firms have developed an increasing preference for collaborations in which they gain access to biotech products and platform technologies (*figure 4.4*). This result is not surprising, as many acquisitions, especially small-scale acquisitions, are preceded by alliances and collaborations [71]. These trends regarding acquisitions and alliances correspond to the trends that have been reported in other studies [13, 213].

Figure 4.3 Trends in externally acquired knowledge and assets through acquisitions by big pharma firms between 1990 and 2013. Showing the acquisitions of 'Pharma' targets and 'Biotech' targets as a percentage of included acquisitions (Source: SDC Platinum Database (ThomsonReuters))

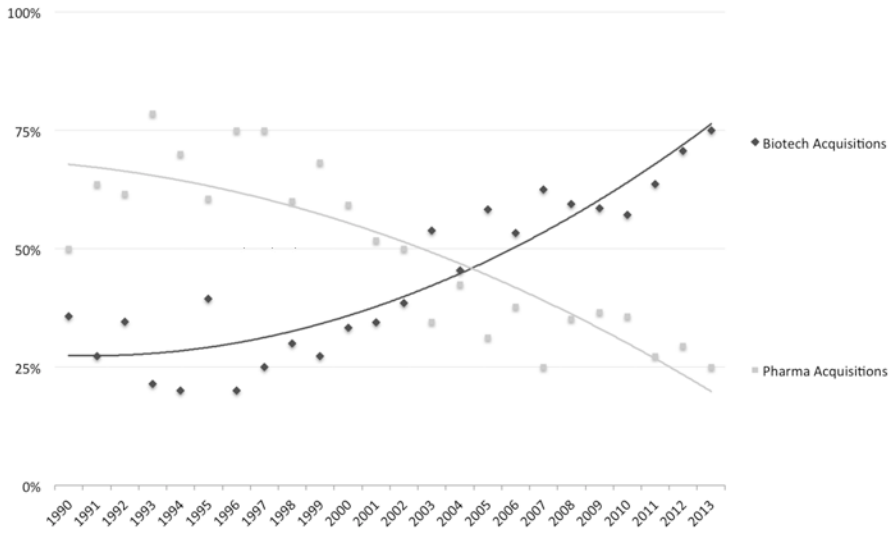
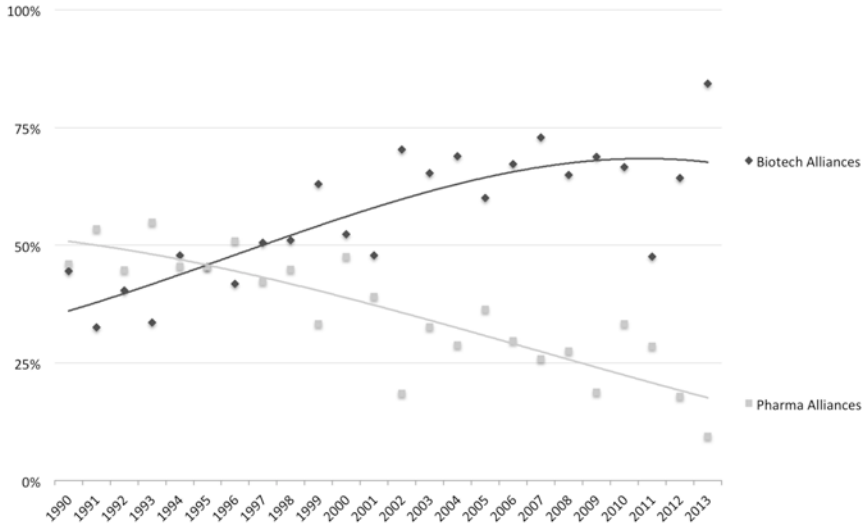


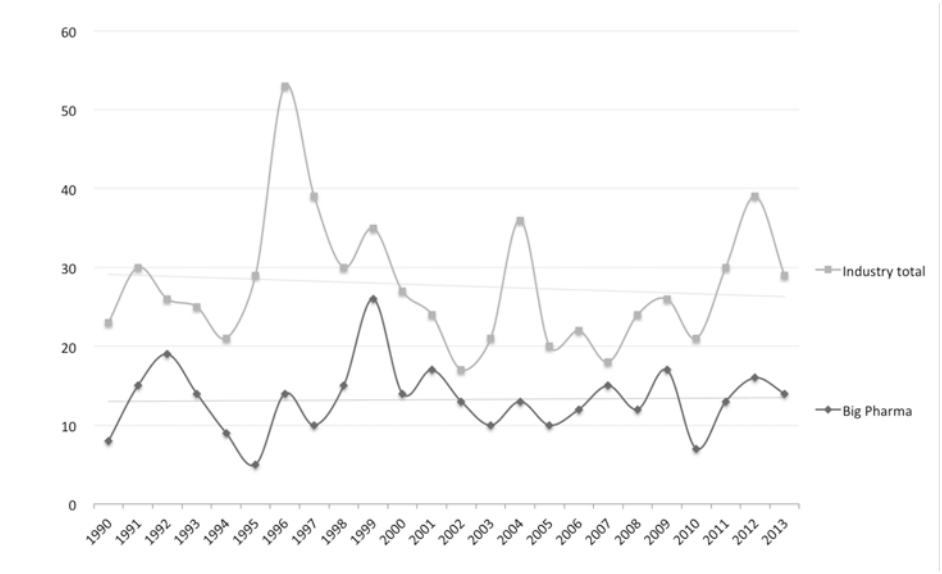
Figure 4.4 Trends in externally acquired knowledge and assets through alliances of big pharma firms between 1990 and 2013. Showing access to knowledge/assets in alliances with 'Pharma' companies and 'Biotech' companies as a percentage of all studied alliances (Source: SDC Platinum Database (ThomsonReuters))



4.4.2 Innovation performance

The total number of NMEs and BLAs generated by big pharma was used as the measure for innovation performance of these firms. In correspondence with existing literature [16, 17, 210], these measures show a rather static pattern for both big pharma and the entire industry.

Figure 4.5 Output in terms of NMEs and BLAs produced by the big pharma versus the industry as a whole. These results represent the output NMEs and BLAs from the 12 largest pharma firms and the output of the industry as a whole based on all drugs approved by the FDA (Source: CDER (Center for Drug Evaluation and Research) and FDA (Food and Drug Administration))



Based on these numbers big pharma accounts for close to 50% of all NME approvals over the studied period of 24 years (1990-2013) [xxvi]. Considering the vast increases in R&D spending, these results are considered representative for the productivity gap as described in literature [4, 14, 244, 245].

4.4.3 Main effects

The descriptive statistics for all variables are provided in *table 4.1*. We observe an expected positive correlation between the control variable, *Size,* and the dependent variable, *Innovation Performance*. In addition, *Size* correlates with all acquisitions and alliances variables, which is not surprising as larger firms would also be able to engage in more acquisitions and alliances. Interestingly, there is no significant correlation between

[xxvi] As shown in *figure 4.2*, these big pharma firms accounted for more than 60% of total pharma sales over the past decade.

Absorptive Capacity (i.e. R&D intensity) and *Size* or *Innovation Performance.* And, *Innovation Performance* only correlates with *Acquisitions* and *Pharma Acquisitions*, in addition to *Size*, while *Absorptive Capacity* only correlates with *Acquisitions*, *Biotech Acquisitions* and *Pharma Alliances*.

Table 4.1 Descriptive statistics[a]

Variable	Mean	S.D.	Min.	Max.	1	2	3	4	5	6	7	8
1.Innovation performance	1.1	1.22	0	6								
2. Size [b]	11.33	.558	10.1	12.6	.222*							
3. Absorptive Capacity	.139	.058	.052	.422	.084	.072						
4. Acquisitions	2.13	2.07	0	9	.190*	.440*	.157*					
5. Pharma Acquisitions	1.01	1.34	0	6	.179*	.397*	-.015	.751*				
6. Biotech Acquisitions	.965	1.21	0	7	.095	.275*	.267*	.740*	.165*			
7. Alliances	4.77	4.61	0	30	.077	.168*	-.137	.169*	.196*	.049		
8. Pharma Alliances	1.92	2.51	0	17	.064	.170*	-.181*	.133*	.230*	-.030	.875*	
9. Biotech Alliances	2.49	2.4	0	15	.077	.154*	-.038	.185*	.120*	.132*	.826*	.492*

*Correlation is significant at the 5% level (2-tailed).
[a] *n= 228*
[b] Log transformation

Table 4.2 displays the main effects without the use of firm dummies. Here, we show that the control variable *Size* is positive and significant in our models. In addition, *table 4.2* shows that *Absorptive Capacity* (i.e. R&D intensity) has a positive but non-significant effect on the innovation performance of big pharma firms, which provides empirical support for the innovation paradox that is described in the literature [4].

Table 4.2 Main effects on big pharma firms' innovation performance (without firm dummies)[a]

Variable **DV: Innovation Performance**	Model 1		Model 2	
Size (*t*-5 to *t*)	.353**	[.134]	.310*	[.138]
Absorptive Capacity (*t*-5 to *t*)	.776	[1.05]	.809	[1.09]
Acquisitions (*t*-5 to *t*)	.021	[.011]	-	
Pharma Acquisitions (*t*-5 to *t*)	-		.021	[.015]
Biotech Acquisitions (*t*-5 to *t*)	-		.024	[.020]
Alliances (*t*-5 to *t*)	.008*	[.004]	-	
Pharma Alliances (*t*-5 to *t*)	-		.015	[.012]
Biotech Alliances (*t*-5 to *t*)	-		.009	[.012]
Constant	-5.15**	[1.76]	-4.73**	[1.81]
Adjusted R^2	.12		.12	
n = 228				
Log pseudolikelihood	-414.97		-412.67	

[a] Year dummies are included, and most are not significant (not shown).
* Statistically significant at the 5% level.
** Statistically significant at the 1% level.
*** Statistically significant at the .1% level.

Table 4.3 Main effects on big pharma firms' innovation performance (without firm dummies)[a]

Variable **DV: Innovation Performance**	Model 1		Model 2	
Size (*t*-5 to *t*)	-.594*	[.255]	-.694**	[.258]
Absorptive Capacity (*t*-5 to *t*)	-3.14	[2.09]	-3.55	[2.17]
Acquisitions (*t*-5 to *t*)	-.051**	[.016]	---	
Pharma Acquisitions (*t*-5 to *t*)	---		-.039	[.022]
Biotech Acquisitions (*t*-5 to *t*)	---		-.043*	[.019]
Alliances (*t*-5 to *t*)	.011**	[.004]	---	
Pharma Alliances (*t*-5 to *t*)	---		.029***	[.008]
Biotech Alliances (*t*-5 to *t*)	---		-.008	[.010]
Constant	7.76*	[3.35]	8.97**	[3.41]
Adjusted R^2	.23		.24	
$n = 228$				
Log pseudolikelihood	-358.78		-358.25	

[a] Year dummies and firm dummies are included, and most are not significant (not shown).
* Statistically significant at the 5% level.
** Statistically significant at the 1% level.
*** Statistically significant at the .1% level.

Table 4.3 displays the main effects estimated with the Poisson regression analysis[xxvii] for the same models, including firm dummies. Overall, acquisitions negatively affect the innovation performance of big pharma firms. This effect can be primarily attributed to the negative effect of *Biotech Acquisitions* as opposed to *Pharma Acquisitions*. These findings are consistent with the literature. *Pharma Acquisitions* also appear to be negative but are non-significant, which supports the notion that technologically related acquisitions are more beneficial for a firm's innovation performance than unrelated acquisitions.

In contrast to acquisitions and as expected, main effects of alliances positively affect innovation performance, primarily because of the positive and significant effect of *Pharma Alliances*, again illustrating the benefits of relatedness. There appears to be a negative but non-significant relationship between *Biotech alliances* and *Innovation performance*. Nevertheless, alliances with biotech partners outperform acquisitions of these companies and may, therefore, be a more preferred strategy, in particular when considering the moderating effects of firms' absorptive capacity.

[xxvii] A negative binomial regression analysis provided near identical results, as the standard deviation and the mean of the dependent variable are similar in magnitude (results not shown).

4.4.4 Interaction effects

The moderating role of *Absorptive capacity* is shown in *Table 4.4*. Although the interaction effect with acquisitions is not significant, it is positive, while the main effect is negative and significant. *Absorptive capacity* seems to predominantly moderate the effects of related acquisitions, given that the interaction with *Pharma acquisitions* is positive and significant, which provides empirical evidence for H1a. On the other hand, the interaction with *Biotech acquisitions* is positive but not significant, suggesting that absorptive capacity does play a moderating role here, neutralizing the negative main effect of biotech acquisitions. However, this effect is not significant, providing insufficient support for H1b.

For alliances, overall, *Absorptive capacity* seems to negatively moderate their positive main effect. However, this seems to be caused by a stronger negative and significant interaction effect of *Absorptive capacity* and *Pharma alliances*, while the interaction of *Absorptive capacity* and *Biotech alliances* is positive and significant. These results do not support H2a, which anticipated a neutral interaction effect of internal R&D with *Pharma alliances*; but they do support H2b, as the sign of the interaction between internal R&D and *Biotech alliances* is positive and significant.

Table 4.4 Interaction effects on big pharma firms' innovation performance[a]

Variable **DV: Innovation Performance**	Model 3		Model 4		Expected Sign
Size (*t*-5 to *t*)	-.650**	[.252]	-.576*	[.261]	
Absorptive Capacity (*t*-5 to *t*)	-2.34	[3.85]	-8.51*	[3.46]	
Acquisitions (*t*-5 to *t*)	-.060*	[.030]	-		
Pharma Acquisitions (*t*-5 to *t*)	-		-.089*	[.039]	
Biotech Acquisitions (*t*-5 to *t*)	-		-.080**	[.030]	
Alliances (*t*-5 to *t*)	.026***	[.008]	-		
Pharma Alliances (*t*-5 to *t*)	-		.110***	[.022]	
Biotech Alliances (*t*-5 to *t*)	-		-.052*	[.022]	
ACAP * Acquisitions (*t*-5 to *t*)	.143	[.170]	-		
ACAP * Pharma Acquisitions (*t*-5 to *t*)	-		.568**	[.220]	H1a (+)
ACAP * Biotech Acquisitions (*t*-5 to *t*)	-		.274	[.173]	H1b (+)
ACAP * Alliances (*t*-5 to *t*)	-.152*	[.063]	-		
ACAP * Pharma Alliances (*t*-5 to *t*)	-		-.758***	[.177]	H2a (□)
ACAP * Biotech Alliances (*t*-5 to *t*)	-		.405*	[.172]	H2b (+)
Constant	9,10**	[3.20]	8.70**	[3.35]	
Adjusted R^2	.28		.29		
n = 228					
Log pseudolikelihood	-386.64		-381.67		

[a] Year dummies and firm dummies are included, and most are not significant (not shown).
* Statistically significant at the 5% level.
** Statistically significant at the 1% level.
*** Statistically significant at the .1% level.

4.5 Discussion

4.5.1 Conclusions

In this study we show that increases in the number of acquisitions of biotech companies have negatively affected big pharma firms' innovation performance. However, we also show that the level of these firms' absorptive capacity, which is characterized by a relative measure for in-house R&D investments, is a contingency variable that critically influences the relationship between some external innovation activities and big pharma firms' innovation performance. In particular, acquisitions of both pharma and biotech companies are complementary innovation activities at higher levels of absorptive capacity[xxviii], whereas the general effects of these acquisitions appear to be negative. Noteworthy, pharma acquisitions outperform biotech acquisitions in this regard, illustrating the known influence of technology- and market-relatedness. In addition, we show that the same complementarity exists between biotech alliances and absorptive capacity, while pharma alliances' main effect is positive but these alliances turn out to be substitutive strategic options at higher levels of absorptive capacity.

Given the current innovation deficits big pharma is confronted with, this study indicates that big pharma firms may have neglected internal R&D efforts because of the promising expectations of the biotech revolution. Apparently, firms have relied on biotech companies for innovation and may have underestimated the need for an emphasis on internal R&D, absorptive capacity, and post-acquisition integration. We show that optimal gain from external technologically unrelated innovation, either through acquisitions or alliances, is contingent upon these closely related constructs; and when underemphasized, effects of engaging with external biotech innovation can be detrimental to a pharmaceutical firm's innovation performance.

Although literature mostly attributes the M&A strategy of incumbent firms to their drying pipelines and need for innovation, the negative main effects of biotech acquisitions could also be explained by differences in acquisition motives. Schweizer[162] indicates that M&A strategies certainly differ and that an understanding of the motives behind them is important for the successful implementation of different types of acquisitions. Moreover, Ahuja and Katila[154] acknowledge that technological reasons do not motivate all acquisitions. Other motives may include the desire to obtain access to distribution channels, to gain entry into new markets, or to obtain financial synergies or market power [154]. Furthermore, Ahuja and Katila[154] argue that such acquisitions cannot be expected to improve an acquiring firm's innovation performance. Moreover, R&D replenishment in the short-term or other short-term motives, such as the ability to enter new biotechnology markets or enhance short-term competitive advantages, could be driving the spur of acquisitions of biotechnology companies, which could not reasonably be expected to resort real benefits to innovation performance.

[xxviii] Threshold at ACAP > 0.16 ($p < .000$) for pharma acquisitions and at ACAP > 0.29 ($p < .005$) for biotech acquisitions.

Where general effects of acquisitions on innovation performance are mainly negative, effects of alliances are mainly positive. Alliances with either related or unrelated partners may be subject to differences in tensions between, for example, vigilance and trust, control and autonomy, design and emergence, innovation and replication, and exploration and exploitation, referring to dialectical theory [246-248]. Such tensions can strengthen an alliance and increase its likelihood of success; however, they can also lead to alliance instability and consequent negative effects. These tensions could thus influence internal R&D processes and, consequently, the interaction effects with internal R&D intensity on a firm's performance. In this regard, technology relatedness seems to be an important factor as higher levels of absorptive capacity (i.e. R&D intensity) are complementary with biotech alliances but substitutable with pharma alliances.

A related explanation for the negative interaction effect of alliances with pharma companies is that a large number of such partners could lead to more interference and reconciliation issues regarding strategy and thus internal R&D processes. Governance mode choice in interfirm cooperation[25, 232] may be important here as well as, in contrast, interaction effects of pharma acquisitions and absorptive capacity are positive. Perhaps this difference can be attributed to potential ownership advantages of acquirers during acquisitions and post-acquisition integration, where the acquirer exerts a more dictating role, fitting the acquired assets into its own strategy and R&D focus.

4.5.2 Implications

For future pharmaceutical productivity and business model innovation [249], it is essential that acquired biotechnology companies, once integrated, form a complementary force with internal pharmaceutical R&D efforts, even when companies are acquired for reasons other than R&D replenishment and NPD. Other researchers have concluded that focusing either on accumulating internal R&D but not exploring external opportunities or on continuously acquiring but not assimilating new knowledge will negatively affect innovative performance [228, 250]. A delicate balance must be found between the 'make' and 'buy' strategies [228], and ideally a focus on both is most beneficial as capabilities associated and developed by putting effort in the 'make' increase absorptive capacity necessary to optimally leverage the 'buy' [188]. In addition to a balance between 'make' and 'buy', a similar balance between 'make' and 'collaborate' is equally important and may vary for different types of partners and targets. Thus, a tight integration of externally acquired knowledge and internal R&D efforts is crucial for harnessing potential complementarity effects [229]. This encompasses an important firm level implication regarding R&D management, emphasizing the importance of this integration, especially with respect to technologically unrelated companies. For affairs with related companies, firms are best to focus on gaining governance control over external R&D through acquisitions as this can work complementary to internal R&D efforts. Without such control, this cooperation with external related companies will be substitutable with internal R&D efforts.

Fetterhoff and Voelkel[251] describe the management of open innovation activities in the context of biotechnology by proposing a five stage value chain: 1) 'seeking' opportunities, 2) 'evaluating' the market potential of an opportunity, 3) 'recruiting' potential partners, 4) 'capturing' value through rapid commercialization, and 5) 'extending' the innovation (i.e.,

working collaboratively to generate additional innovation and develop collaboration beyond the life cycle of a given product). From the firm perspective, this five stage process represents a process of integrating external exploratory innovation, adequately exploiting that innovation, and eventually further 'extending' the innovation in an exploratory manner. Fetterhoff and Voelkel[251] state that each stage offers an opportunity for value creation but also presents unique challenges requiring specific capabilities. Examining the results of this study, we suggest that large pharmaceutical firms often do not possess such specific capabilities. Moreover, pharmaceutical firms might not complete this value chain through the final step of 'extending' externally acquired innovation. Generating additional innovation beyond the life cycle of one or a few products requires exploratory capabilities and increases the value of the initially acquired innovation[251].

The results in this study do not imply that firms should make fewer investments in biotechnologies. On the contrary, we believe that investment in and adequate exploitation of biotechnologies holds the future for pharmaceutical productivity, innovation and growth. As stated by Dhankhar and Evers[211], pharmaceutical firms must identify ways to spend less and achieve more. However, we suggest that it is unwise to fully rely on acquiring biotechnology innovation alone, while neglecting to continuously invest in internal exploratory R&D activities [188], needed for increased absorptive capacity and post-acquisition integration capabilities. Investing in biotechnology requires a long-term perspective that includes future internal exploration and that will not be successful if the post-acquisition integration process is predominantly focused on short-term innovation boosts and short-term profits. The motives behind acquisitions and alliances are important, as they may function as a predictor of the success of an acquisition or alliance and of whether such activity will positively affect innovation performance.

4.5.3 Limitations and further research

Our results should be interpreted with caution in view of the limitations of this study. Although the trends that are identified in our study are consistent with global industry trends, this study was conducted using data of the largest pharmaceutical firms of the past decades, which makes it difficult to generalize these results and conclusions throughout the industry, including smaller (bio)pharmaceutical firms. However, the purpose of this study was to investigate the processes pertaining to large incumbent pharmaceutical firms. Additional data related to smaller firms would have increased the amount of data but could have also obscured the effects that are mostly associated to big pharma firms' conduct of business. Furthermore, our dataset is quite substantial, as the big pharma firms account for more than 60% of global pharmaceutical sales over the past decade (see *figure 4.2*) and have produced close to 50% of all approved NMEs and BLAs between 1990 and 2013.

Another limitation of this study is the extent to which we defined our categories. Perhaps additional categorization would reveal more nuances; for example, different therapeutic areas or types of products may be associated with different effects on innovation. In addition, in this study we used but one variable that could moderate general effects of acquiring innovation, while additional variables could also play an important role herein (e.g. measures for alliance or acquisition experience).

Noteworthy, this study was limited to analysing a specific industry with a high-risk profile that is increasingly dependent on innovation from a still upcoming industry. As such, similar effects might be apparent in other industries with similar characteristics. Further research could examine such industries in a similar way to assess this. Another avenue of further research could be to study innovation performance from the perspective of the acquisition target, in this case the biotechnology company (for example see: Fernald et al.[25]), as most related research has focused on the incumbent firm's perspective. Additional further research could include assessing, in detail, the determinants of the absorptive capacity of firms, and the necessary capabilities of optimal post-acquisition integration.

Finding a direct relation between innovative input and trends in output remains difficult. However, by implementing time lags of up to five years in the models, we have been able to measure significant differences in the effects of acquisitions and alliances on innovation. As data from before 1990 was not included, this study does not allow for an accurate measurement of long-term effects beyond five years. However, we show that acquiring biotechnology companies will not solve the innovation deficit in the next five years without continuous development of internal R&D.

Chapter 5

I. VENTURE CAPITALISTS AS GATEKEEPERS FOR BIOTECHNOLOGICAL INNOVATION

Abstract

Venture capitalists (VCs) aim at trade sales as a preferred exit-strategy for biotechnology companies they invest in. Therefore, VCs pay close attention to the wishes of larger (bio)pharmaceutical acquirers. In this study we explore VCs' behavior and strategies by analysing the technology fields and therapeutic areas in which they are invested most and which yield the highest relative returns by means of trade sales. The data show that VCs are by far most invested in oncology and this is also an area in which relatively high returns are realized. Regarding other areas, VCs could balance their average investment valuations more in correspondence with what acquirers are willing to pay. In addition, VCs have predictive insight in the types of technologies that do well and they seem to employ a strategy focused on both short-term and long-term success. They are investing most in small molecule drugs and protein/peptide therapeutics, which both yield high returns, followed by DNA/RNA technologies which underlie the possibilities of personalized medicine. We conclude that VCs act as technological gatekeepers because they are predicting long-term cure and care macro-trends.

Fernald, K.D.S., Hoeben, R.P.N. and Claassen. E.
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5.1 Introduction

Venture Capital (VC) is the primary source of funding for biotechnology ventures, with annual VC financing of biotechnology quadrupling in ten years from $2 billion in 1999 to $8 billion in 2008 [252, 253]. Since this 2008 high, annual VC financing has been relatively stable at $5.5 billion.

From an investor's perspective biotechnology start-ups are considered to be high-risk investments [64]. On the flipside, VC firms can reap returns of five to ten times their initial investment when portfolio companies are successful, as measured by an initial public offering (IPO) or a trade sale (i.e. acquisition) [254]. In light of recent merger and acquisition (M&A) trends in the (bio)pharmaceutical industry related to innovation deficits and the productivity paradox[25, 161], most biotechnology companies are currently built with a trade sale in mind as a preferred exit [255]. Not surprisingly, venture capitalists (VCs) pay close attention to the wants and needs of larger (bio)pharmaceutical firms [255]. However, the taste of big pharma can change over time - even within the average three to five years between investment and exit. For this reason, when it comes to investment decisions and valuations, VCs rely on their own intuition and market intelligence, in addition to the declared wants and needs of big pharma.

In a sense VCs are the drivers for technological change within a given industry, and the biotechnology industry in particular. They act as "technological gatekeepers, accelerating the process of technological change" [27]. By their investment decision-making, VCs set the tone for the entire life sciences market, essentially generating the supply of innovation to big pharma and the market in general. Considering multiple factors influencing investment decisions, it is imperative for both investors and bio-entrepreneurs to gain insight in global biotechnology investment strategies. Not only for deciding whether or not to get involved in new life sciences opportunities, but also to use this information in negotiating company valuations, business planning and raising capital.

Therefore, this study aims to distil global investment strategies of VCs by analysing the distribution and extent of investments with respect to therapeutic areas and technology fields. Furthermore, these areas and fields are analysed in terms of exit potential and relative returns on investment (ROI), which are based on trade sale multiples.

The aim is to explore the therapeutic areas and technology fields in which VCs are invested most and whether that corresponds to where they realize the highest relative returns. Therefore, a total of 2,639 life sciences companies receiving VC backing between 1999 and 2013 are analysed to identify the most popular areas and technology fields for investment and acquisition. In addition, the average investment amounts and average trade sale transaction values are analysed by technology field and therapeutic area of the lead product(s) to gain insights in investments and show what acquirers are willing to pay for different types of companies. Finally, the average trade sale multiples are calculated in order to evaluate relative success rates of VC investments per technology field and therapeutic area. From the results an overall investment strategy is interpreted that is useful

to investors and entrepreneurs in considering their engagement in new life sciences opportunities.

5.2 Methodology

An initial dataset was developed, containing early stage investments in life sciences ventures between 1999 and 2013 based on data extracted from ThomsonReuters' SDC Platinum VentureXpert database (official database of the National Venture Capital Association; NVCA). A total of 2,639 dataset entries were analysed individually to determine the companies' main technology field and therapeutic area focus. Subsequently, medical technology/devices (medtech) companies and service-oriented companies were excluded from the dataset, resulting in a total of 1,217 small molecule and biotechnology ventures that received their first investment round between 1999 and 2013. Of those 212 companies were acquired later on and for these, additional data on transaction details have been gathered from the ThomsonReuters' SDC Platinum VentureXpert M&A database and news reports, to calculate the average trade sale values and multiples.

5.2.1 Biotechnology fields

Based on 21 exploratory interviews with VCs and literature [256, 257], a classification of technology fields is used. The categorization of individual companies is based on in-database and online company descriptions as well as companies' lead products in development. In addition, the Cooperative Patent Classification (CPC) codes were analysed, if available and as provided by Espacenet (worldwide.espacenet.com), of respective companies' patents to verify our categorization. First medical technology (devices), small molecule drugs, and biotechnology are separated. Medical technology companies are excluded from further analysis and Biotechnology is further categorized in biotechnology fields (DNA/RNA; Proteins/peptides; Cell/tissue engineering; Gene/RNA vectors; Targeting/delivery; Bioinformatics; Nanobiotechnology; and Glycobiotechnology), depending on the technology used for the respective company's lead product(s) (*table 5.1*). Note that some companies may focus on combinations of technologies, so the illustrated data will add up to more than 100% of actual funding.

Table 5.1 Overview of Biotechnology fields

Biotechnology Field	Biotechnology Subfield
DNA/RNA Technologies	
	Genomics/pharmacogenomics
	Gene probes/DNA markers
	Genetic engineering
	DNA/RNA sequencing/ synthesis/ amplification
	RNAi/siRNA (inhibiting gene function)
	Gene expression profiling/Antisense technology
Proteins/peptides and other large molecules	
	Engineering of proteins and peptides/ recombinant proteins
	Proteomics
	(Monoclonal) Antibodies
	Subunit/VLP vaccines
	Protein isolation and purification
	Peptide/protein sequencing/ synthesis
	Signalling Analysis (of cytokines, chemokines, transcription factors, cell cycle proteins, and neurotransmitters)
Cell and tissue engineering technologies	
	Cell therapy (including Immunotherapy)
	Tissue engineering (including tissue scaffolds and biomedical engineering)
	Cellular fusion
	Embryo manipulation
Gene and RNA vector technologies	
	Gene therapy
	DNA vaccines
	Viral vectors
Drug targeting/delivery technologies	
	Proteins
	Liposomes
	Micelles/dendrimers
	Inorganic/biodegradable
	Nanostructures
Bioinformatics (ICT applications in life sciences)	
	Construction of databases on genomes
	Modelling complex biological processes (including systems biology)
Nanobiotechnology	
Glycobiotechnology	

Based on 21 exploratory interviews with venture capitalists and literature. [256, 257]

5.2.2 Therapeutic areas

Based on the WHO ICD-10, literature [255], and declared investment interests in 21 exploratory interviews with VCs, a full range of therapeutic areas is used for analysis. Again the classification of backed companies was based on their lead product(s) in development. Ultimately the 15 most invested areas are included in the analysis. Note that some companies may focus on combinations of technologies, so the illustrated data will add up to more than 100% of actual funding.

5.2.3 Limitations

While our analysis aimed to be a systematic, bias-free, review of life sciences VC investments and average trade sale multiples, several limitations apply. First, our dataset is in essence a data sample as we are unable to ensure that the collection of relevant data is 100% complete. While we are confident that the large majority of early stage life sciences

investments is included in our dataset, we cannot claim a 100% coverage of all deals, as the search criteria might have excluded deals that should have been included or the ThomsonReuters SDC Platinum VentureXpert database, which is based on self-reported data, might not include all existing deals. Second, the categorization process was conducted using several indicators to assess technology fields and therapeutic areas, namely lead products and programs, company websites and profiles, and CPC codes. Although two researchers conducted this process separately, some cases are still open to interpretation and for others limited information was available. Nevertheless, we are confident that most VC backed companies were categorized correctly. Third, of approximately 37% of trade sales, transaction values were not disclosed. Therefore, the average trade sale valuations as used for the analysis are also based on a sample of trade sales and we do not claim to cover 100% of all existing data. Fourth, the dataset included global data, and differences between geographic regions were not analysed. Such differences may provide additional insights and could be an avenue of further research. Finally, this study does not aim at uncovering absolute returns for VCs in biotechnology as we focus on trade sales as successful exits and do not include losses or other gains VCs have made with their investments. Further research may attempt to reveal general results of VC investments in biotechnology. However, this study aims at comparing general VC investments in technology fields and therapeutic areas with realized trade sale multiples in those fields and areas.

5.3 Results

The majority of backed companies concerned medtech companies (965) followed by biotechnology companies (813) and small molecule drug companies (456). VC financing, however, is almost equally distributed over these three fields of technology, with biotechnology taking the upper hand (36%). Thus, small molecule drug companies receive the highest average investment per company ($48.6 million), followed by biotechnology companies ($32 million) and medtech companies ($25.7 million). The total amount of $26 billion invested in biotechnology is distributed among several biotechnology fields as specified in *table 5.1*.

5.3.1 Technology fields

As shown in *figure 5.1*, almost half (43%) of VC investments in biotechnology has been invested in companies focusing on proteins/peptides, which include products and technologies such as recombinant proteins, monoclonal antibodies, recombinant subunit and virus like particle (VLP) vaccines, peptide therapeutics, engineered enzymes, and proteomics. Subsequently, 29% has been invested in DNA/RNA technologies mainly involving genomics and pharmacogenomics; gene probes and DNA markers; sequencing, synthesis and amplification of DNA/RNA, RNAi and siRNA gene regulation therapeutics; and gene profiling and antisense technology. Following these two subfields, which are undoubtedly most popular, 9% of VC financing of biotechnology companies involved cell/tissue engineering technologies, which include (stem) cell therapy (immunotherapy); tissue engineering; cellular fusion and embryo manipulation. Thereafter, 5% concerned gene/RNA vector technologies, involving gene therapy; vector vaccines and DNA

vaccines. Another 5% has been invested in drug targeting and delivery (encapsulation) technologies using proteins; liposomes; micelles/dendrimers; inorganic, biodegradable structures; and nanostructures. As such there is overlap with nanobiotechnology, in which 4% of VC biotechnology funds has been invested. The remaining 5% was invested in bioinformatics (4%), involving IT as a basis for new diagnostics and therapeutics; and glycobiotechnology (1%), which involves the synthesis of glycolipids and glycoproteins. Moreover, 21% of backed biotechnology companies focused on molecular diagnostics technologies, mostly within the subfield of DNA/RNA. In total $ 4,6 billion has been invested in biotechnology related diagnostics companies (*figure 5.1*).

Figure 5.1 VC investments ($M) per technology field and per biotechnology subfield (a); and VC investments ($M) per technology field and date of first round
Note: Hypothetical future investments are included, as a subset of companies backed since 2009-2013 will most likely receive later stage financing in the near future. For illustration purposes, an estimated 15% is added. This percentage is based on average later stage funding of companies initially backed in previous periods (Source: ThomsonReuters' SDC Platinum VentureXpert Database, company websites, worldwide.espacenet.com)

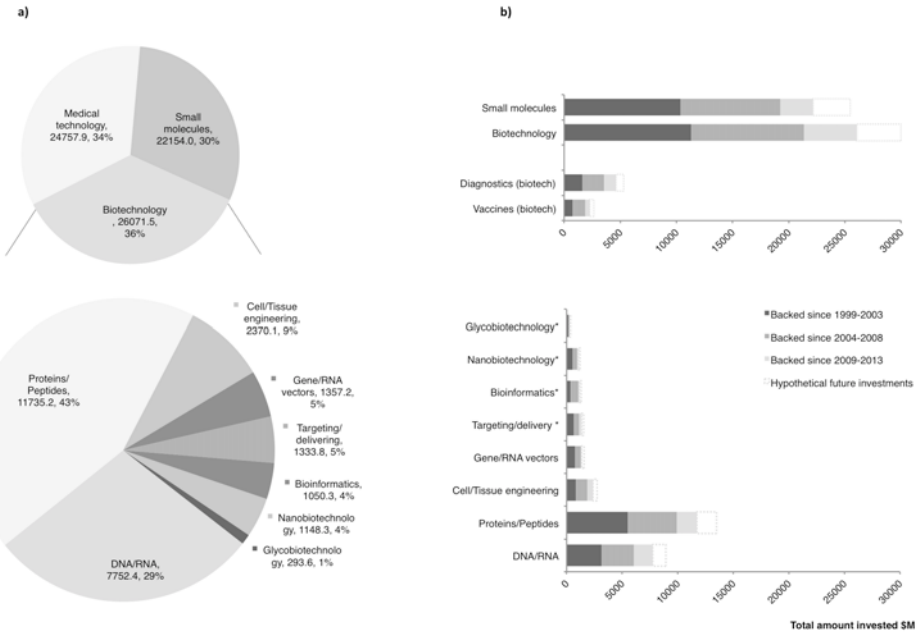
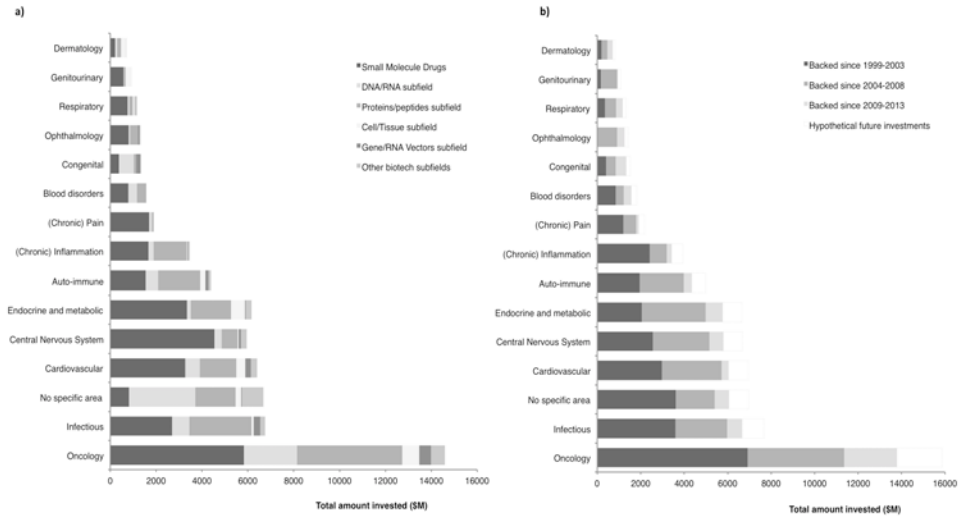


Figure 5.2 VC investments ($M) per therapeutic area and technology field (a); and VC investments ($M) per therapeutic area and date of first round (b)
Note: Hypothetical future investments are included, as a subset of companies backed since 2009-2013 will most likely receive later stage financing in the near future. For illustration purposes, an estimated 15% is added. This percentage is based on average later stage funding of companies initially backed in previous periods (Source: ThomsonReuters' SDC Platinum VentureXpert Database, company websites)



5.3.2 Therapeutic areas

Figure 5.2 shows that 29% ($13.8 billion) of all small molecule and biotechnology investments have been in companies that focused on oncology, making it by far the most invested therapeutic area (*figure 5.2*). The following five most invested areas are infectious diseases ($6.7 billion), platform technologies, defined as 'no specific area' ($6 billion), cardiovascular diseases ($6 billion), central nervous system (CNS) indications ($5.8 billion), and endocrine and metabolic diseases ($5.8 billion).
Not surprisingly, small molecule drugs are mostly invested in when targeted on a specific disease area and not often when developed as platforms (*figure 5.2a*). They are mostly focused on CNS, pain, oncology, endocrine and metabolic diseases, and cardiovascular diseases. However, it seems that different biotechnology subfields are used for a wide variety of therapeutic areas (*figure 5.2a*). Proteins/peptides are developed mostly for treating oncology, infectious diseases, inflammation, auto-immune diseases, and endocrine and metabolic diseases, while DNA/RNA includes many discovery and diagnostics technologies, which seem to be mainly developed for oncology, platforms, and for congenital diseases. Furthermore, cell therapy and cell/tissue engineering is used most for oncology and endocrine and metabolic diseases, while gene therapy and vectors are mainly focused on oncology, infectious diseases, cardiovascular diseases, and auto-immune diseases. This data seem quite accurate considering advances such as immune cell

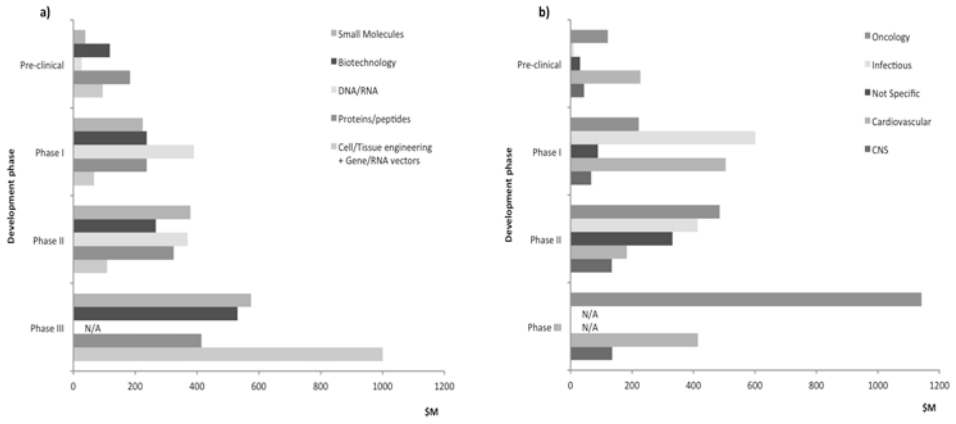
modifications (cell therapy/immunotherapy) to treat cancer and the use of vector- and DNA vaccines for infectious diseases [258-260].

5.3.3 Trade sales

As IPOs and more so trade sales are the most important denominators for success from an investor's perspective the dataset includes which companies went public and which ones have been acquired. Of the 1,217 small molecule and biotechnology companies backed between 1999 and 2013, 212 have been acquired and 132 went public. Of those that were acquired, subsequent data was collected on the transaction values, if disclosed, and the clinical development phase of the respective company's lead product. This data was collected from ThomsonReuters' SDC Platinum M&A database (thomsonreuters.com/sdc-platinum), clinicaltrials.gov, company websites and additional webscraping of business websites (e.g. businessweek.com). Average trade sale transaction values are plotted per development phase for different therapeutic areas and technology fields (*figure 5.3*).

The average trade sale valuations of companies in different development phases vary amongst therapeutic areas and technology fields, suggesting different risk profiles. Strikingly, trade sale valuations of oncology focused companies increase substantially with each development phase, whereas those of cardiovascular diseases or CNS show different patterns. In *figure 5.3b*, the complexity of newer technology fields (e.g. cell therapy and gene therapy) is represented by relatively low trade sale valuations of such companies up until phase III clinical trials. Yet, when phase III is reached, the value of such companies increases substantially, illustrated by the acquisition of Biovex by Amgen in 2011. Small molecule drugs, however, as a more classical technology field, show a more predictable and stable path as average trade sale valuations of small molecule drug companies increase more gradually with each development phase. The same holds true for proteins/peptides.

Figure 5.3 Average trade sale prices ($M) per therapeutic area (a) and per technology field (b), for each phase in clinical development (Source: ThomsonReuters' SDC Platinum VentureXpert and M&A Databases, company websites, clinicaltrials.gov)



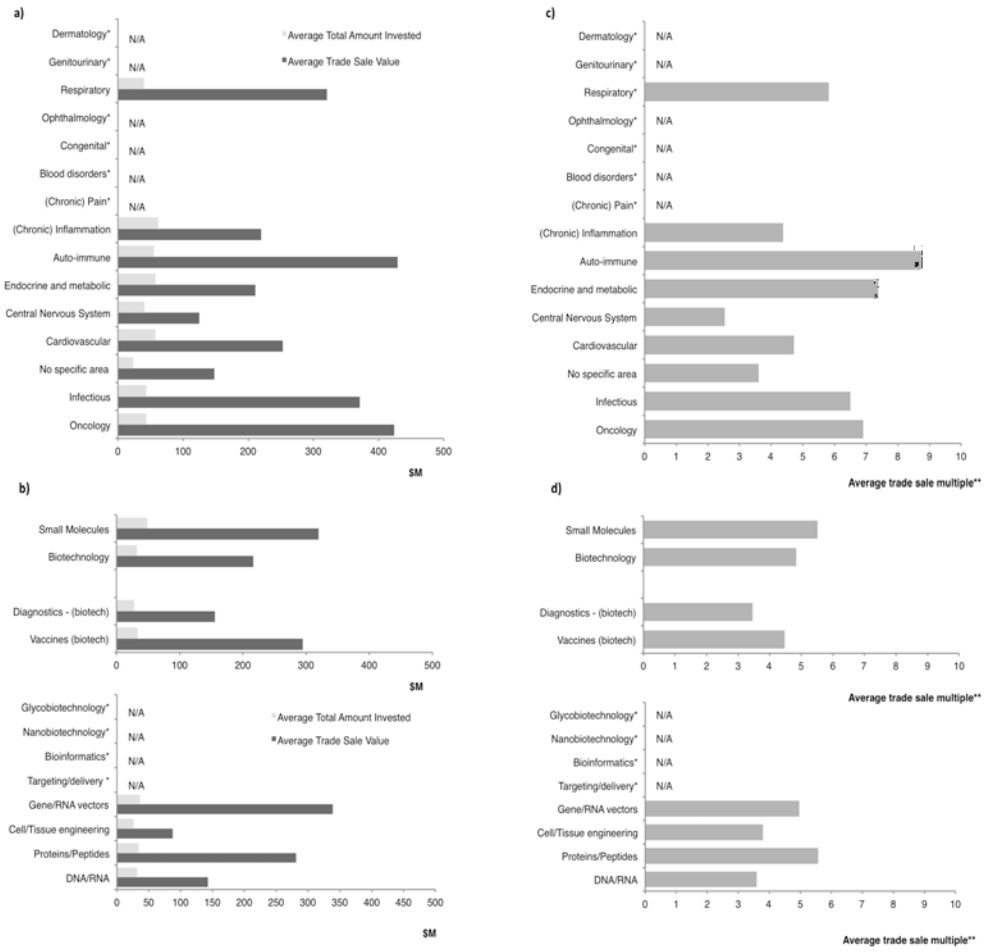
5.3.4 Deal values and multiples

Arguably, there are various ways to evaluate the success of individual investments and of investments over categories. In order to review patterns between where VCs invest the most and where they earn the most, the average trade sale values and the average total amounts invested in companies are evaluated per therapeutic area (*figure 5.4a*) and technology field (*figure 5.4b*). In addition, for the VC backed companies in our dataset that have been acquired, the trade sale multiple was calculated for each individual acquisition to determine the average trade sale multiples, again per therapeutic area (*figure 5.4c*) and technology field (*figure 5.4d*).

As shown in *figure 5.4a*, average trade sale transaction values are highest for auto-immune diseases ($430 million) and oncology ($424 million), followed by infectious diseases ($371 million). Interestingly, this top three of therapeutic areas for acquirers is different from the top three areas based on average VC investment values. Per company VCs have invested most, on average, in (chronic) inflammation ($62 million), endocrine and metabolic diseases ($58 million), and cardiovascular diseases ($58 million). Auto-immune diseases comes fourth for VCs with an average total investment amount per company of $55 million, while it seems to be the first area for acquirers. Moreover, average trade sale transaction values for different therapeutic areas seem to have a much wider range (from $125 million to $430 million) than the average total VC investments per therapeutic area ($40 million for CNS to $62 million for inflammation).

The average multiples, however, are highest for auto-immune diseases (8.7), endocrine and metabolic diseases (7.4), oncology (6.9), and infectious diseases (6.5). Of these the first two are also in the top four of areas that receive the highest average investments from VCs. The second highest multiple has been realized in endocrine and metabolic diseases, while the difference between average VC investment and average trade sale value for this area is not very large ($58 million versus $211 million). This suggests that the successful exits have come from relatively lower investments in this area. For all other areas, the average trade sale multiples are quite consistent with the average trade sale values, confirming little differentiation of average VC investments with regards to therapeutic areas.

Figure 5.4 Average trade sale price ($M) and average total investment amount ($M) per therapeutic area (a) and per technology field (b); and average trade sale multiples per therapeutic area (c) and per technology field (d)
* Too few or no trade sales to calculate appropriate average (N/A).
** Trade sale multiple = (Trade sale value)/(Total amount invested in acquired company).
(Source: ThomsonReuters' SDC Platinum VentureXpert and M&A Databases)



For the technology fields, an overall difference in average VC investments is shown between biotechnology ($32 million) and small molecule drugs ($49 million). The biotechnology subfields subsequently range between $26 million for cell/tissue engineering to $36 million for gene/RNA vectors, with $32 million for DNA/RNA and $34 million for proteins/peptides in between. This suggests that VCs undoubtedly expect most from the technology field of small molecule drugs, especially when also considering the total amount invested in this field (30% of all funds; *figure 5.1*). Although high expectations for this field are justified by the corresponding average trade sale value ($320 million) and

multiple (5.5), similar trade sale multiples have been realized for the biotechnology subfields proteins/peptides ($ 282 million; 5.6) and gene/RNA vectors ($339 million; 5.0). The average trade sale values for the subfields DNA/RNA and cell/tissue engineering are much lower ($143 million and $87 million respectively). However, the average multiples for these fields are relatively close (3.6 and 3.8), suggesting that the successful trade sales resulted from relatively lower investments in these fields. This is especially true for the DNA/RNA subfield, considering the average VC investments in this field ($32 million), which is the same as the average for the entire biotechnology field. Moreover, the total amount invested in DNA/RNA technologies is high (29% of all biotechnology investments) relative to what big pharma is willing to pay for these technologies. This suggests a notable interest of VCs in the DNA/RNA technology subfield.

The average multiples in the technology fields as shown in *figure 5.4d* show less variation (4 - 6) than those in the therapeutic areas (3 - 9; *figure 5.4c*). VCs, thus, seem to be better at anticipating returns within technology fields and adjusting their investment allocation accordingly, than doing the same for the various therapeutic areas.

5.4 Conclusions

We conclude that VCs act as technological gatekeepers because they are predicting long-term cure and care macro-trends. They have formidable predictive insight in the types of technologies that do well. However, in terms of therapeutic areas, VCs can balance their average investment valuations more in correspondence with what big pharma is willing to pay. We set out to distil global investment strategies of VCs by analysing the distribution and extent of investments with respect to technology fields and therapeutic areas. It seems that VCs employ a strategy focused on both short-term and long-term success. On the one hand they play it safe, minimizing risk by investing most in small molecules and proteins. On the other hand, they are investing heavily in DNA/RNA technologies, which as a field seem to be underperforming (*figure 5.4b*, *d*). As VCs and bio-entrepreneurs build for big pharma, the blockbuster business model directly affects new venture financing by VCs for the short term. However, VCs are also rebelliously investing for long-term cure and care macro-trends, as they invest in biotechnologies that underlie the possibilities of personalized medicine.

For therapeutic areas, a discrepancy between variation in average VC investment amounts and variation of average trade sale transaction values is illustrated by an imbalance in average multiples (3 – 9). Acquirers seem to attach greater importance to differentiating between therapeutic areas than VCs do, resulting in unnecessary overinvestment in one area versus potential underinvestment in another. As VCs are essentially building for big pharma, they, their investors and bio-entrepreneurs would benefit from a portfolio balanced more in correspondence with what pharma is willing to pay. Doing this can in turn lead to more predictability and consistency of average multiples over the therapeutic areas. However, success ratios between therapeutic areas may be more susceptible to rapid changes than technology fields, making prediction difficult. Many VCs might therefore be investing quite opportunistically with less distinction per therapeutic area.

With regards to technology fields, there seems to be a macro investment strategy that appears to focus both on short-term and long-term success. For the short-term, VCs are investing heavily in small molecule drug companies with a relatively higher average investment valuation. In addition, within biotechnology they are investing most in the proteins/peptides subfield (43% of all biotechnology investments), while keeping their average investments relatively low. This conservative risk-averse strategy corresponds with pharma's blockbuster business model as small molecules and proteins/peptides are the only type of products that can become blockbusters (in the form of new molecular entities and biologicals) [14]. This strategy has resulted in average multiples of around 5.5 for both these technology fields. However, VCs have invested less in the gene/RNA vectors field, while there have been some tremendous recent successes in this field.

In addition to the conservative investment strategy tailored to pharma's business model, VCs have also invested a large proportion (29%) of biotechnology funds in the DNA/RNA technology field. The DNA/RNA field includes the technologies required for realizing the potential of personalized medicine, which has been claimed to be the future of medicine, promising to significantly increase the quality of healthcare [261-263]. Here, we find evidence that despite the low average multiple and average trade sale valuation for this field, VCs are embracing their role as technological gatekeepers. They are investing in this field and thereby the future, while a proven business model for personalized medicine that could be equally lucrative as the blockbuster model is still lacking now.

For other investors and VCs with less experience investing in life sciences, a similar investment strategy is recommended. Moreover, we believe it to be wise to evaluate the therapeutic areas new ventures are focusing on, with respect to both an appropriate match with technology types and relative ROI rates. It is however noteworthy that VCs evaluate companies on a case-by-case basis and employ strict criteria for their investments (e.g. competition, regulations, reimbursement, management team, financials) irrespective of therapeutic areas or technology fields. Notwithstanding, oncology, infectious diseases and auto-immune diseases seem to be the most interesting therapeutic areas to invest in, considering investment amounts, average trade sale valuations and average multiples.
In the current investment climate, bio-entrepreneurs can increase chances of being funded by combining a focus on radical innovation within technology fields with blockbuster potential with a focus on therapeutic areas where investors can realize relatively high multiples. When developing technologies underlying personalized medicine and diagnostics, where the blockbuster model is not applicable, it is imperative that entrepreneurs focus on business models for generating income during (early) development stages, ensuring survival whilst cure and care macro-trends continue towards a personalized and patient-centered approach.

II. BIOTECH TRADE SALE RETURNS ON VENTURE CAPITAL – 2010-2014

Fernald, K.D.S. and Claassen. E.
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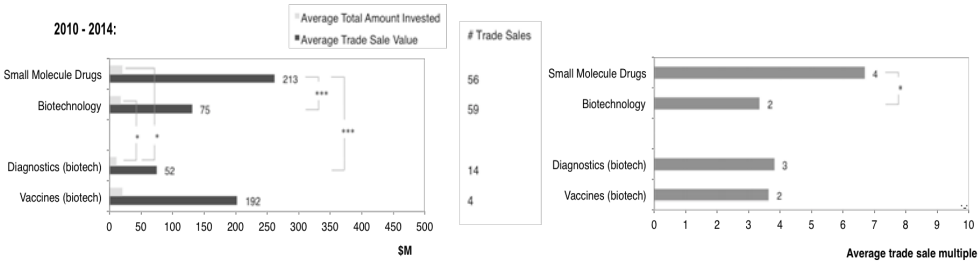
Over the past decades venture capitalists (VCs) have invested heavily in early-stage biotechnology companies[252]. Acquisitions (i.e. trade sales) of these companies have become the preferred exit-strategy for VCs [255], as big pharma has been increasingly acquiring innovative biotech companies [25]. Here, we present an analysis of trade sale returns based on investment and acquisition data of VC-backed biotech and pharmaceutical companies over the past five years. Companies acquired between 2010 and 2014 are categorized by their lead product(s) in development; categories are based on exploratory interviews with VCs and literature [255, 257].

The field of biotechnology contains companies that focus on: DNA/RNA technologies, including molecular diagnostics and nucleotide therapeutics; protein/peptide therapeutics; cell and tissue engineering therapies; gene/RNA vector technologies/therapies; delivery technologies; bioinformatics; nanobiotechnologies; and glycobiotechnologies. Diagnostics refers to the subset of companies that develop molecular diagnostics or biomarkers; and vaccines encompass companies that develop recombinant protein vaccines/sub-unit vaccines, virus-like particle (VLP) vaccines, vector vaccines or DNA vaccines. Finally, companies that develop small molecule drugs are separated from biotechnology companies.

As shown in *figure 5.5*, trade sales of small molecule drug companies have benefited VCs most over the past five years. Big pharma firms remain most interested in small molecules, resulting in higher average trade sale values ($p < .001$) and multiples ($p < .05$) of these companies compared to biotechnology companies. Furthermore, although not significant, the difference between trade sale values of biotechnological diagnostic and vaccine companies illustrates a difference in valuation of DNA/RNA technologies (average of $83M) versus biotechnological products such as protein therapeutics (average of $195M) or cell- & gene therapies (average of $276M). VCs, however, seem to be aware of this difference and invest accordingly, resulting in comparable multiples (*figure 5.5*).
Interestingly, in terms of total investment amounts, VCs have invested more in biotechnology ($3,945M) than in small molecules ($2,117M). Furthermore, from *figure 5.5* it seems that VC investment amounts land in a specific range, which is most likely due to a maximum VCs can afford to invest in ventures before undermining the multiple on their return. Moreover, the average investment amounts suggest that VCs valuate diagnostic companies ($11M) lower than small molecule - ($20M; $p < .05$), biotechnology - ($18M; $p < .05$), or vaccine companies ($21M; *N.S.*). The lower average investment amount for diagnostic companies is probably due to shorter development timelines before a profit can be realised. Diagnostic ventures need less money to achieve results faster, however, the

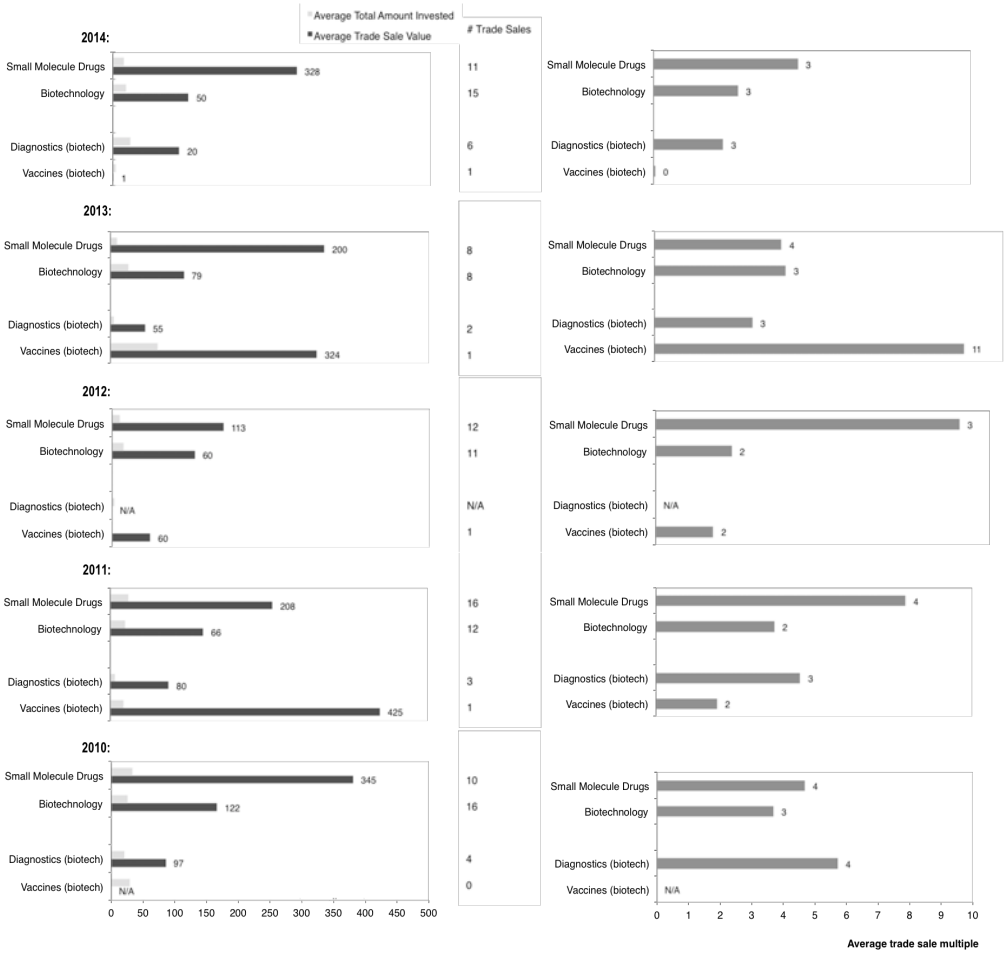
returns are smaller as well, resulting in similar, and sometimes even marginally better, multiples.

Figure 5.5 Trade sale returns of VC-backed biotech and pharmaceutical companies acquired between 2010-2014, categorized by lead product(s) in development
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
Note: The medians of trade sale values and multiples are included as data labels. Investment data is based on a total of 324 early stage biotechnology companies that received their first investment round between 2010-2014. Trade sale data is based on a total of 115 VC-backed companies that were acquired between 2010-2014, and only contains those of which the values have been disclosed (71%). Outliers of transactions above $1 billion or with multiples above 100x have been excluded from the analysis. The average trade sale multiple is calculated as the average trade sale value divided by the average total known amount invested in each acquired company (Source: ThomsonReuters' SDC Platinum VentureXpert Database (National Venture Capital Association (NVCA) Database)



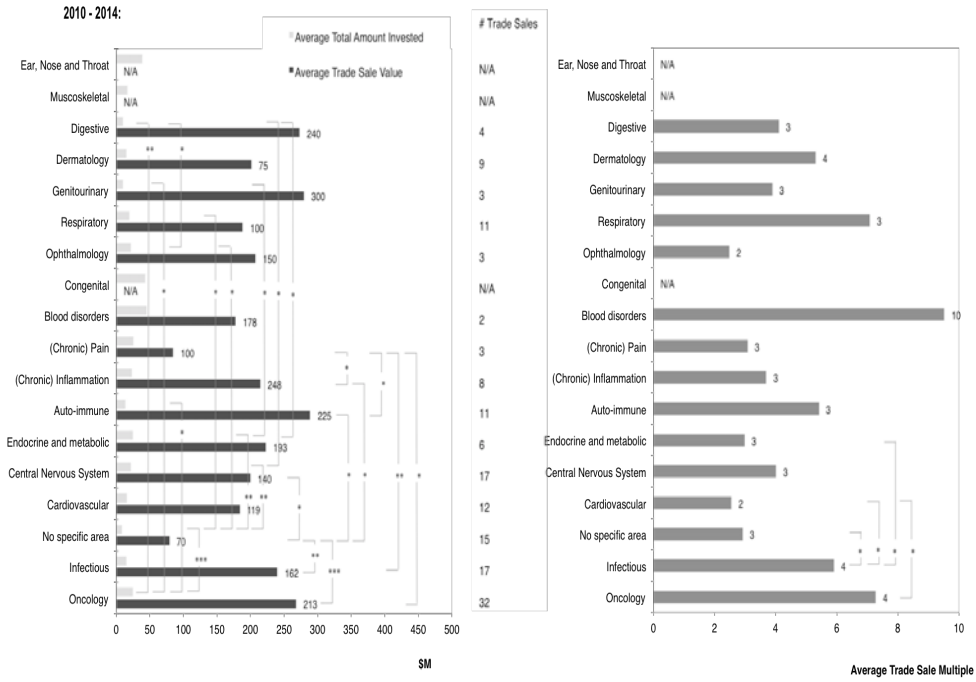
In *figure 5.6*, several outliers are revealed, as the data is presented for each year, separately. Overall, small molecule drug companies outperform biotechnology companies in each year. However, in 2012, the average trade sale value of small molecule drug companies is relatively low, also resulting in a below average multiple. This may give the impression that there is more variation in small molecule company trade sale values over the years, however, it is likely due to fewer larger deals occurring in that year. For the field of vaccines it seems like there is even more variation over the years, but this is likely due to the overall lower amount of trade sales in vaccines. The multiple for biotechnology companies is high in 2012 due to the acquisition of Epitomics Inc. Furthermore, there are two outliers of trade sale multiples in 2012 and 2011 that influence the overall average for small molecule drug companies. These were realized in the acquisitions of Boston Biomedical Inc. and Graceway Pharmaceuticals LLC, respectively. Above average multiples were also realized in the acquisitions of: a vector-based vaccine company, Okairos AG in 2013; a cellular and molecular diagnostics company, Diagnostic Hybrids Inc. in 2010; and a small molecule drug company AkaRx Inc. in 2010. This last acquisition also explains the outlier of blood disorders in *figure 5.7*, which can be attributed to chance because there are but two acquisitions in this area. Similarly, the Okairos AG acquisition in 2013 (*figure 5.6)* was the only one in the field of vaccines that year.

Figure 5.6 As for *figure 5.5* but includes separate analyses per year.



The analysis indicates that VCs have benefited most in the area of oncology, followed by infectious -, auto-immune - and central nervous system diseases. Furthermore, the analysis shows that big pharma's predominant blockbuster paradigm guides their acquisition preference and therewith their innovation demand. Surprisingly, VCs predict the corresponding innovation supply and act as visionary technological gatekeepers[27], building for big pharma [255].

Figure 5.7 As for *figure 5.5* but includes analysis for therapeutic areas



As a bioentrepreneur it is important to adjust both short-term and long-term strategies to VC investment preferences, which are largely determined by big pharma acquisition preferences[26]. VCs are in many cases foreseeing technological developments and investing accordingly. Generally speaking, bioentrepreneurs should present to VCs with a history of exits at similar or higher multiples as shown here. Furthermore, this data is relevant for governmental subsidy and grant providers and fund-to-fund managers of larger healthcare funds that invest in life sciences private equity.

Chapter 6

A QUANTITATIVE PRIORITIZATION AND BARRIER ANALYSIS OF BIOTECHNOLOGY FIELDS AND THERAPEUTIC AREAS; A VENTURE CAPITAL PERSPECTIVE

Abstract

Early stage research and development in the biotechnology industry requires significant risk capital investments, which are mostly provided by venture capitalists that invest for high returns. As biotechnology ventures highly depend on this capital during early stages, insights into investment priorities of venture capitalists is valuable for entrepreneurs. In this study, a systematic prioritization analysis has been conducted to determine venture capitalists' investment priorities in terms of biotechnologies and therapeutic areas, as well as associated investment barriers. 21 qualitative interviews were conducted and 81 quantitative questionnaires were completed by venture capitalists. We show that venture capitalists seem to be considering cell- & gene therapy technologies as future disrupters in terms of innovation and economic development. Our analysis further reveals several niches of technology - therapeutic area combinations with high venture capital attractiveness, namely: protein technologies, cell therapy & gene therapy technologies for oncology, cardiovascular and central nervous system diseases. It also reveals high-prioritized investment barriers specific to these technologies and therapeutic areas, which mainly concern the complexity of the science underlying the respective technology or pathology, efficacy issues in trials, regulations, competition, and finance. Overcoming high-prioritized barriers for specific niches of technology-therapeutic area combinations could significantly increase venture capital attractiveness.

Fernald, K.D.S., Janssen, N.M. and Claassen, E.

6.1 Introduction

In high-tech industries young innovative ventures have become a major source for the development of new radical technologies and more generally for economic growth and competitiveness [82]. For the pharmaceutical industry, biotechnology ventures have even become the predominant source of innovation as large incumbents have increasingly turned to alliances with- and acquisitions of biotechnology companies to replenish R&D pipelines and counter innovation deficits [5, 14, 15, 25, 94, 214]. In contrast to established firms, young innovative ventures are mainly concerned with early stage research and development (R&D) and are often not in a position to generate revenue. This negative cash-flow position makes it far more difficult for smaller ventures to obtain external financing, and these ventures therefore rely mostly on risk capital investments.

While there have been trends of biotech start-ups adapting towards additional funding opportunities[264], early (clinical-)stage biotechnology companies have historically been driven by substantial risk capital from venture capitalists (VCs)[252, 254]. This capital is used merely to fund the early clinical stages, after which an exit for the respective VC becomes apparent. This is mainly due to the relatively lengthy and expensive R&D trajectories within this industry, with an average total duration of 11.9 years[58] and new product development costs of $0.8-$1.3 billion [25, 59, 94]. As such, the final phases of clinical R&D are most often funded by large incumbent (bio)pharmaceutical firms through alliances and acquisitions. These incumbents will typically get involved after successful phase II clinical trials, as they are far more risk-averse [15]. Thus, venture capital is the prime source of funding for biotechnology ventures during the start-up and growth phase of the technology transfer gap [265].

Moreover, high technology and research-driven ventures have mostly been the focus of VCs that prefer pre-seed, seed and early stage investments. In fact, most VC firms are involved with technology investments[85, 86], and of those, most VC funding goes to research-driven university spin-off companies[87], while ventures that have spun out from corporate institutions perform below average in terms of VC exit performance [266]. Thus, VC plays a crucial role in the development of new firms in new markets [80, 81]; and fostering the creation of VC industries is even considered to be a necessary preliminary step to support the generation of innovative high-growth ventures and thus to stimulate innovation, economic growth and regional competitiveness [82].

There have been substantial VC investments in biotechnology and VC funding of biotechnology firms has continuously increased until 2008 and has remained at the $5.5 billion per year level onward [26, 253], However, an overview of investment priorities in terms of technologies or disease areas is lacking in literature and in the market. For a large part VCs are drivers of technological innovation and of the formation of high technology innovation clusters [27], which is true for biotechnology in particular [267, 268]. VCs, as technological gatekeepers, accelerate the process of technological change [27] and in essence determine the supply of innovation for larger firms in the industry[26, 28]. This is illustrated by the fact that trade sales or acquisitions of biotechnology firms have become the most preferred exit-strategies for VCs [255, 269].

Therefore, an overview of early stage VC investment strategies and priorities in terms of technologies and therapeutic areas can be valuable in shedding light on where to expect most future innovation and economic development. Moreover, insights in issues that may keep VCs from investing in certain technologies or diseases areas may be equally important. Such insights can be the basis of a competitive advantage in business planning, fundraising and attracting investors for new biotechnology ventures. Thus, there is an obvious need to systematically assess biotechnology and disease priorities for investors and what keeps them from investing in them. Consequently, the aim of this study is to evaluate investment priorities of VCs in terms of therapeutic areas and technology fields as well as associated investment barriers by means of qualitative interviews and quantitative questionnaires. VCs were interviewed about therapeutic areas and technologies and related potential investment barriers, and were asked to rank these in a questionnaire. This study provides novel insights into the perspective of VCs on investing in biotechnologies and therapeutic areas.

6.1.1 Background

Investment priorities – Research prioritization is an effective way of identifying research opportunities within a specific context that are needed most [270]. As such, a similar process of prioritization can be used to identify investment opportunities from the perspective of investors within a specific industry context. Several prioritization processes have been conducted and described in literature, particularly in the context of health [270-275]. As Weenen et al.[270] explain there is no absolute standard or best practice for conducting prioritization research as the context of the research may vary. Therefore, in this study the method as described in literature has been adapted to rank investment priorities and associated investment barriers from a VC perspective. The aim of this process is to develop a relative ranking list of technology fields and therapeutic areas and not to define an absolute cut-off point beyond which therapeutic areas or technology fields are considered to contain only less interesting investment opportunities. This exercise rather produces a generalized representation of which areas and fields might contain the most interesting investments opportunities looking forward, providing the opportunity to look for niches in the market.

Investment barriers – The analysis of innovation barriers along the value chain of new product development does not only provide insight in the innovation process but is also a first step in accounting for these barriers and overcoming them [276, 277]. In this study we are looking at the early stages in the value chain of biotechnological product development, in which technology based ventures are receiving seed or start-up funding from VCs. The innovation barriers that we are looking for and are attempting to prioritize are in fact barriers for VCs to invest in specific technologies or therapeutic areas. In this context, we therefore refer to them as investment barriers. From a more theoretical perspective we can also refer to them as relative exogenous barriers, as they selectively affect companies within this specific sector but are exogenous to any portfolio company in question [276-278].

As clarified in literature, barriers can be endogenous or exogenous to a respective firm and, in addition, can be relative or general. General barriers affect all types of companies, while relative barriers are only apparent in certain industry sectors or only apply to certain types

of companies. Furthermore, endogenous barriers can directly be attributed to the respective firm (e.g. lack of capabilities or resources), whereas exogenous barriers are caused by factors external to the firm in question (e.g. governmental barriers, financial barriers) [277, 278].

6.2 Methodology

The methodology in this study is based on previously developed methods of prioritization[270, 271, 277, 279] and adapted to evaluate VC investment priorities in terms of technologies and therapeutic areas. In addition investment barriers related to specific technologies and therapeutic areas were identified and ranked as well. The multi staged process started with the identification of the most interesting therapeutic areas, technologies and investment barriers through exploratory interviews. Subsequently, complete collections of technology fields and therapeutic areas were developed by combining qualitative data from the interviews with literature [26, 255-257]. Thereafter, these collections of therapeutic areas, technology fields and related investment barriers were systematically prioritized by means of an online questionnaire. In addition, the study includes evaluation of VCs' opinions regarding investments in orphan diseases and product- versus platform-based ventures as well as the importance of the interests of potential pharmaceutical acquirers in making investment decisions. This could provide insights in the extent to which VCs are influenced in their investment decision-making with regards to technologies and therapeutic areas.

6.2.1 Research subjects

A search query in ThomsonReuters SDC Platinum VentureXpert database[xxix] resulted in a total of 272 venture capital firms. The search criteria for this dataset were focused on the firm's preferred industry for investment (limited to: Biotechnology, Life Sciences, Medical Products/Diagnostics/Therapeutics/Health, and Pharmaceuticals), and the preferred investment stage (limited to: Seed, Start-up, Early Stage, and Balanced). From this dataset, one hundred executive members of the included firms were selected to participate in the semi-structured interviews. This was a random selection, taking position and experience of the participants into account.

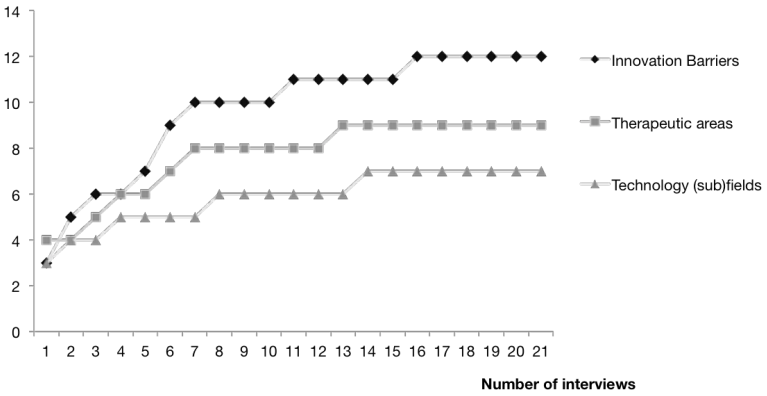
6.2.2 Exploratory interviews

The selected participants were initially contacted by e-mail, informed of the nature of the study and invited to participate. A semi-structured format was used, by taking participants through a standardized set of questions[xxx]. Therapeutic areas that were mentioned, were further specified by asking for indications during the interviews. Similarly, technologies were specified by asking for explanations. By means of theme coding, the technologies were categorized using an overview of biotechnology fields adapted from the literature [26, 256, 257]. In addition, investment barriers specifically related to technologies and therapeutic areas as discussed in the interviews were identified. Saturation curves of therapeutic areas,

[xxix] SDC Platinum VentureXpert Database by ThomsonReuters Financial www.venturexpert.com
[xxx] Interview questions available upon request

technology (sub)fields and investment barriers ensured a most complete set of answers, thereby increasing content validity of the questionnaire. Saturation of therapeutic areas, technology fields and investment barriers for both, as mentioned by the VCs was reached after 16 interviews (*figure 6.1*). In total 21 interviews were conducted.

Figure 6.1 Saturation curves of the identification of therapeutic areas, technology fields and investment barriers, during interviews with 21 life sciences venture capitalists



6.2.3 Questionnaire design and analysis

The aim of the questionnaire was to prioritize the main technology fields and therapeutic areas for VC investment, along with prioritizing the main barriers related to these, as identified during the interviews. Using the original dataset of VC firms, extracted from SDC platinum[xxix] and additional webscraping of firms' websites, 614 individuals were successfully approached, 91 questionnaire responses were realized and data from 81 respondents was included in the analysis, as some failed to complete the questionnaire or provided insufficient data (13% response rate). The anonymous online questionnaire was created and distributed through the online web survey program SurveyMonkey. VCs that did not respond to the initial survey received a follow up phone call or e-mail 1.5 weeks later to increase response rates.

The questionnaire contained mainly closed questions, with some allowing for qualitative answers to be added. Several demographic questions (e.g. age, title, position, country, experience) were followed by a few general questions regarding investment preference. The rest of the questionnaire was dedicated to systematically ranking therapeutic areas and associated investment barriers as well as technologies and associated investment barriers.

Prioritization – Both technology fields and therapeutic areas were prioritized by means of the questionnaire, in which VCs were asked to prioritize the three most important, ranging from 1 to 3 (1 being the highest priority, representing a weight of 3). The prioritization process was based on prioritization methodologies as described in existing literature[270, 271, 276, 277, 279, 280], and adapted to fit the scope of this research. Each score was multiplied by the respective weight (3, 2, or 1). The sum of these weighted scores reflects the total weighted score of the respective technology field or therapeutic area. A relative measure for the weighted ranking was used for comparison, by dividing the score by the highest ranked area or field. As such, the following equation was used to rank technology fields and therapeutic areas as well as related investment barriers [276, 277]:

$$WR = \frac{((n_{r1} * 3) + (n_{r2} * 2) + n_{r3}) * 100}{((n_{r1} * 3) + (n_{r2} * 2) + n_{r3})_{HR}}$$

Where WR is the Weighted Rank of the respective field, area or barrier, n is the number of times this area, field or barrier was chosen, $r_{1/2/3}$ is the respective rank that was chosen, and HR is the Highest Ranked area, field or barrier.

Regarding the technology fields, participants were also asked to prioritize technology subfields for any technology field that they included in their top three. In addition, participants were asked to rank the investment barriers specifically for each therapeutic area and each technology field that they included in their top three, effectively prioritizing barriers six separate times (for three therapeutic areas and for three technology fields). As such, the barriers are ranked for each technology field and therapeutic area separately (*tables 6.1 and 6.2*).

6.3 Results

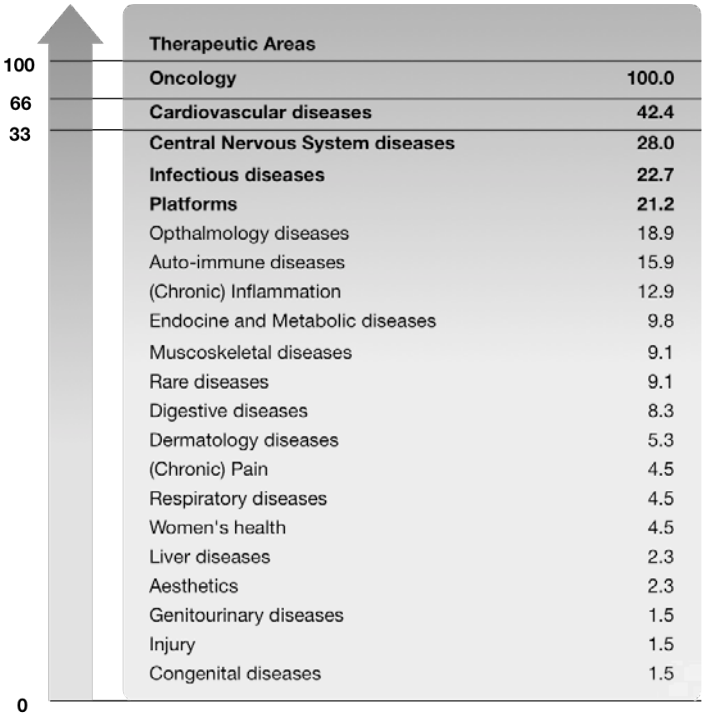
With the questionnaire a response rate of 13% was reached, with a total of 91 respondents. As some participants failed to complete the questionnaire or provided insufficient data, responses from 81 participants were used for the analysis. In terms of further descriptive data, 58% of respondents was a partner at their firm, and 74% fulfilled an executive or management position; the average experience in life sciences venture capital was 12.5 years; 59% of respondents lived and worked in Europe, 38% in North America, and 3% in the Asia/pacific region; and 35% was 55 years of age or older, 48% was between 40 and 54 years of age, and the remaining 17% was younger than 40 years of age.

6.3.1 Therapeutic areas

While 56% of respondents declared themselves to invest opportunistically, 80% deemed the respective therapeutic area to be (very) important when considering investments in early stage ventures. In terms of ranking, respondents were asked to prioritize their top three therapeutic areas from an investor perspective. As shown in *figure 6.2*, oncology as a

therapeutic area received the highest investment priority by far, which is consistent with our previous research [26]. Cardiovascular, central nervous system, and infectious diseases are the following investment priorities for VCs, followed by companies that develop platforms applicable to multiple therapeutic areas. In addition, the majority (62%) of VCs declared to have an interest in investing in orphan diseases. Respondents were also asked whether opportunities in orphan diseases would increase or decrease in the future, and 52% of VCs is expecting an increase in orphan disease opportunities, while 17% expects a decrease.

Figure 6.2 Therapeutic area ranking according to weighted scores divided in three priority groups: Low: 0-33; Medium: 34-66; High: 67-100

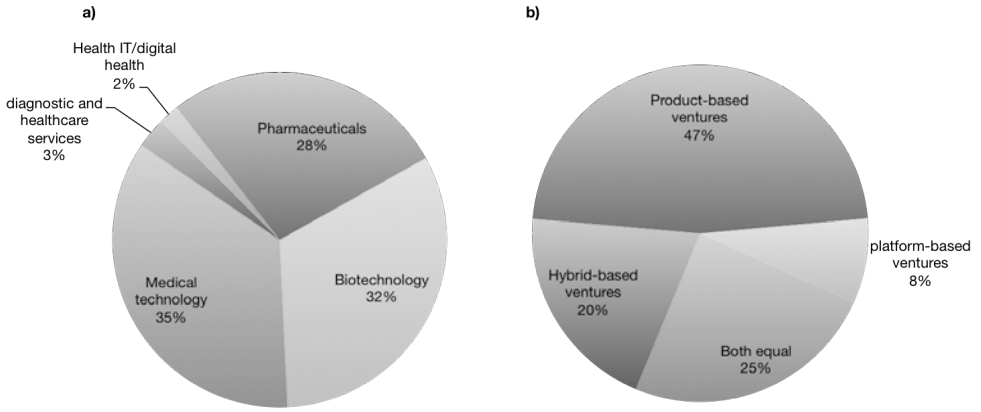


6.3.2 Technology fields

Similar to therapeutic areas, technology fields were considered to be (very) important factors in investment decisions, as indicated by 75% of the respondents. Although one of the respondents made clear that "there are no a priori considerations in terms of technology fields". Another respondent mentioned that "the importance of areas and fields really is based on market demands" and that "there has to be a significant unmet need in the area or field".

Notwithstanding, the results show a clear distribution of VCs' investment preference when it comes to technology types and fields. *Figure 6.3a* shows the VCs' investment preferences for pharmaceuticals, medical technology, or biotechnology, which is quite evenly distributed and consistent with previous analyses [26]. Respondents were also asked to declare their preference for portfolio companies in terms of products versus platforms, and the results show that product-based ventures are most popular amongst VCs (*figure 6.3b*). Moreover, in the interviews, respondents indicated that moving one product forward is often an important validation for the technology platform from which it is derived. For this reason many VCs focus either only or partially on products first, causing the percentage of VCs investing in platform-based ventures alone to be relatively small.

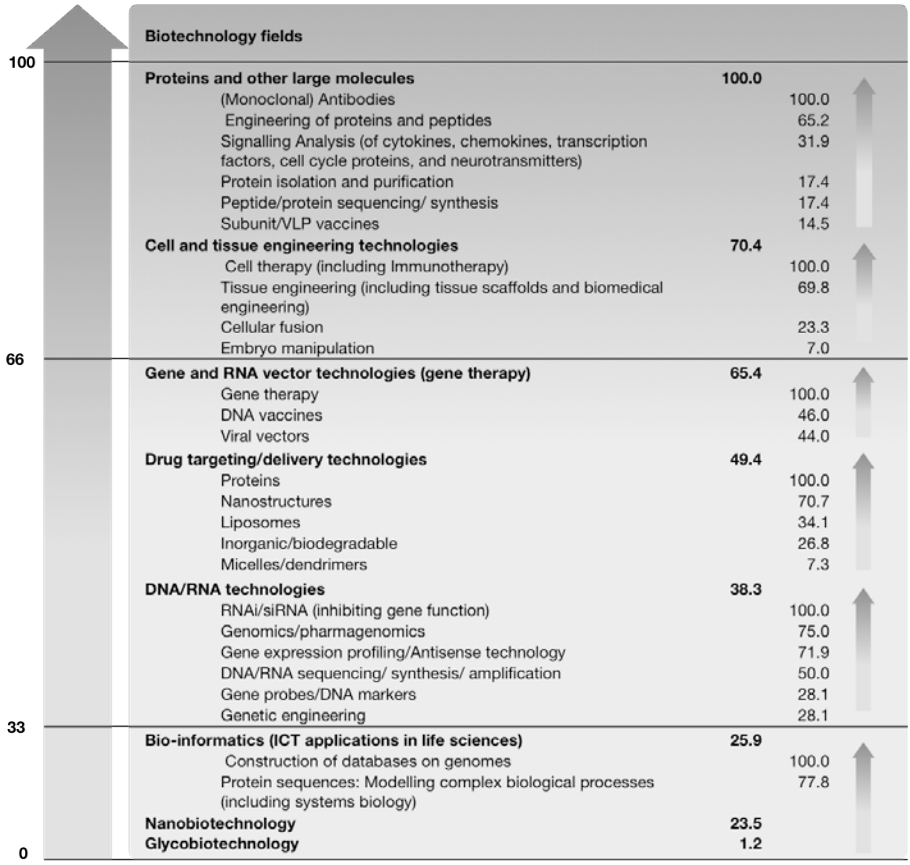
Figure 6.3 VC investment preferences in terms of technology types (a) and product-based vs. platform-based ventures (b)



Subsequently, respondents were asked to prioritize their top three technology fields within the field of biotechnology and were then asked to prioritize specific technology subfields for each field included in their top three. The results of this prioritization are shown in *figure 6.4* according to their weighted ranking score into three priority groups. Consistent with previous research, proteins/peptides as a field is considered to be of highest investment priority, in which (monoclonal) antibodies and recombinant proteins are leading. This is not surprising, considering the fact that all biological products, as approved by the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA), are derived from this technology field.

The second priority group contains the fields 'cell and tissue engineering technologies' led by cell therapy (immunotherapy), and 'gene and RNA vector technologies' led by gene therapy. Correspondingly, gene therapy and cell therapy were also mentioned most often during the interviews as being the most groundbreaking technologies VCs are investing in.

Figure 6.4 Technology ranking according to weighted scores divided in three priority groups: Low: 0-33; Medium: 34-66; High: 67-100



6.3.3 Investment barriers

The barriers are ranked in relation to both the top three therapeutic areas and the top three technology fields. Respondents were asked to rank the barriers as identified in the interviews for each therapeutic area and technology field that they included in their top three, separately. *Table 6.1* shows the results for the therapeutic areas and *table 6.2* shows the results for the technology fields.

Table 6.1 Relative ranking of associated investment barriers for the top 3 therapeutic areas

Therapeutic area	WR	Associated barrier ranking	WR
Oncology (*n*=48)	100	Efficacy issues in trials	100
		Intricate pathology	86.4
		Competition	54.2
Cardiovascular (*n*=21)	42.4	Regulatory barriers	100
		Competition	68.2
		Finance barriers	54.5
Central Nervous System (*n*=19)	28.0	Intricate pathology	100
		Efficacy issues in trials	84.6
		Finance barriers	50

n represents the number of respondents that included the area in their top three

Table 6.2 Relative ranking of associated investment barriers for the top 3 biotechnology fields

Biotechnology field	WR	Associated barrier ranking	WR
Proteins/peptides and large molecules (*n*=32)	100	Competition	100
		Complicated technology	90
		Finance barriers	86.7
Cell and tissue engineering (*n*=24)	70.4	Complicated technology	100
		Validation issues	95.8
		Efficacy issues of the technology in trials	62.5
Gene and RNA vectors (*n*=22)	65.4	Complicated technology	100
		Validation issues	56.7
		Regulatory barriers	50

n represents the number of respondents that included the field in their top three

For the therapeutic areas it seems that most barriers are related to efficacy issues in trials, the complexity of the illness itself, regulations, competition and finance issues. However, the analysis shows an important difference between the three highest prioritized therapeutic areas. Namely that for oncology and CNS diseases, efficacy issues in trials and the pathology itself form the strongest investment barriers, while regulations seem to form a crucial barrier for cardiovascular diseases. As made clear by one of the respondents, regulatory issues represent a weighty barrier for VCs, causing them to "under invest in for example cardiovascular diseases and over invest in other areas such as oncology". In addition, competition seems to be an important issue as well for companies focusing on oncology.

Similarly, investment barriers for the second and third highest prioritized technology fields, which mainly revolve around cell therapy and gene therapy, concern the complexity of these technologies and validation issues for underlying technology platforms. As specified during interviews "validation of technology platforms is shown by taking one product forward". Thus, it seems that there are many instances in which it is difficult to further develop a product candidate from gene therapy and cell therapy platforms. However, exits (e.g. trade sales) have also been mentioned as validation indicators for technology platforms, suggesting that this may also be more difficult to realise for these groundbreaking technologies. Furthermore, showing the efficacy of cell therapy products in trials seems to be difficult as well, while regulations are a larger concern for gene therapies in particular.

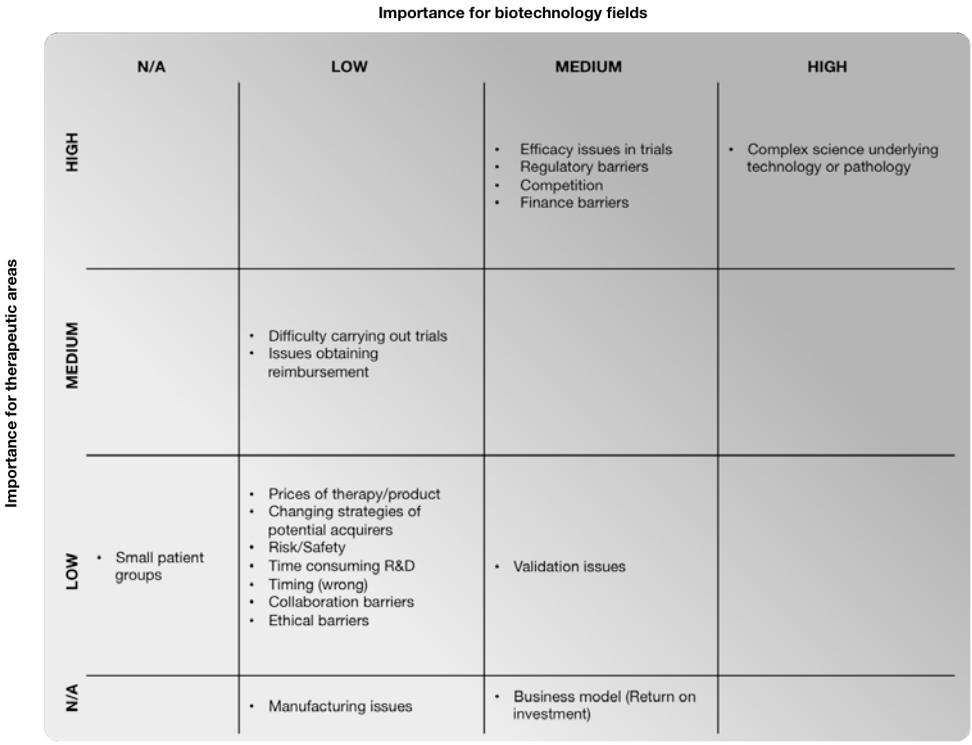
In *figure 6.5* we have included a general ranking of barriers over therapeutic areas and technology fields into a matrix, according to three priority groups (Low, Medium, High). Although this figure must be interpreted with caution because respondents were asked to rank the barriers per area and field, it does provide a general overview of the most common issues that keep VCs from investing in therapeutic areas or technology fields. It seems that overall; the most common investment barriers are associated with the complexity of the science underlying the technology or the pathology in question. In addition, efficacy issues in trials, regulatory issues, competition and finance barriers seem to represent significant obstacles as well. Overall, for biotechnology fields, validation of the respective technology is also an important issue from an investment perspective.

Table 6.3 Relative ranking of associated investment barriers for therapeutic areas and technology fields

Therapeutic areas	
Barrier	WR
Efficacy issues in trials	100
Intricate pathology	87
Regulatory barriers	77.6
Competition	70.2
Finance barriers	69.6
Difficulty to carry out clinical trials	56.5
Issues obtaining reimbursement	37.3
Prices of therapy/product	32.9
Changing strategies of acquirers	26.1
Small patient groups	19.9
Risk/Safety	19.3
Time consuming R&D	18.6
Wrong timing (too early or too late)	14.9
Barriers to collaborate (with academia or industry)	9.3
Lack of preclinical support (validation)	3.7
Ethical barriers	1.9

Technology fields	
Barrier	WR
Complicated technology	100
Validation issues	62.7
Regulatory barriers	53.3
Efficacy issues of technology in trials	50
Competition	49.3
Finance barriers	43.3
Return on investment/business model	33.3
Manufacturing issues	32.7
Prices of therapy/product	32
Time consuming R&D	31.3
Difficulty to carry out clinical trials	26
Wrong timing (too early or too late)	14
Risk/Safety	11.3
Issues obtaining reimbursement	10.7
Changing strategies of acquirers	8.7
Ethical barriers	4.7
Barriers to collaborate (with academia or industry)	2.7

Figure 6.5 Matrix of investment barriers for therapeutic areas and technology fields divided in priority groups: Low: 0-33; Medium: 34-66; High: 67-100



6.3.4 Importance of big pharma's interests

Other noteworthy findings mainly relate to the interests of (bio)pharmaceutical acquirers for VC investment decisions. Due to the fact that in most cases "pharma ultimately pays for the exits", as stated by respondents, their interests might be of great importance for VC investment decisions. However, as noted by one of the respondents this very much concerns the future interests of acquirers as "pharma strategy is subject to frequent change" and is mostly "dependent on changes in management and strategic direction, which are more profit-centred than focused on positively impacting health and well-being". It was also noted that "pharma rather is a follower than a leader when it comes to the next wave of game changing technologies". This corresponds with the idea that VCs fulfil a critical role as technological gatekeepers [26-28] and suggests that their intuition in terms of where the highest returns may be realised in the future could also be a strong influencing factor in making investment decisions. Thus, participants were asked which of the two they believed is more important for them when investing in early stage biotechnology ventures. Interestingly, the majority of respondents (84%) declared either that pharma's interest is

more important than VCs' intuition (42%) or that their intuition and pharma's interest are equally important (42%) when investing in biotechnology ventures. Thus, the results show that for many VCs, the interest of potential future acquirers is quite important for current investment decisions.

A final noteworthy finding is that there are some VCs that try to avoid acquisitions as an exit because it "destroys value", as one respondent claimed that "companies should therefore not be built to sell to Pharma". Although many VCs do focus on acquisitions as preferred exit-strategies, there is literature that confirms the notion that acquisitions, in this field particularly, destroy value, including our previous research [15, 25].

6.4 Conclusions and discussion

This study shows that VCs seem to be considering cell- & gene therapy technologies as future disrupters in terms of innovation and economic development, and might be jumping the S-curve of technological development from protein therapeutics to cell therapy & gene therapy technologies. Our analysis further reveals several niches of technology - therapeutic area combinations with high VC attractiveness, namely: protein technologies, cell therapy & gene therapy technologies for oncology, cardiovascular and central nervous system diseases. It also reveals high-prioritized investment barriers specific to these technologies and therapeutic areas, which mainly concern the complexity of the science underlying the respective technology or pathology, efficacy issues in trials, regulations, competition, and finance.

In addition to the opportunity to aim for niches with high VC attractiveness, the study provides opportunities for entrepreneurs to create competitive advantages by finding ways to overcome these technology and therapeutic area specific investment barriers. Solving high-prioritized barriers for specific niches of technology-therapeutic area combinations could significantly increase VC attractiveness of new ventures.

6.4.1 Therapeutic areas

VCs prioritize oncology as the highest therapeutic area by far. The relatively large gap in prioritization between oncology and other therapeutic areas is fully in line with the amount of VC money invested in oncology, which is at least twice the average total amounts invested in other high-prioritized therapeutic areas[26]. Substantial amounts of investments in oncology drug development over previous years [26, 281] may have been influenced by the fact that the antibody market is heavily focused on oncology (among others)[282]. In addition, there are noteworthy differences between clinical R&D of oncology therapies, compared to other areas, which might contribute to the attractiveness of oncology for investors and entrepreneurs. For example, oncology therapies, with the exception of antibodies, are not usually tested on healthy subjects, effectively skipping phase I trials and testing for safety in phase II trials. Moreover, oncology therapies are always evaluated in addition to standard care and there is no use of placebos in oncology trials.

With regards to VC funding, oncology and the other four highest ranked therapeutic areas (cardiovascular diseases, central nervous system diseases, infectious diseases, and platforms) are identical to the top five therapeutic areas that have received the most VC funding over the past 15 years [26]. Although the order differs slightly, the total amounts invested in the four areas following oncology are very similar. The notable similarity between VCs' expressed interest and actual money invested, shows that VCs put their money where their mouth is when it comes to therapeutic focus.

6.4.2 Technology fields

As technological gatekeepers, VCs focus most on antibodies & protein technologies; cell therapy & cell/tissue engineering technologies; and gene therapy & vector technologies. The focus on protein technologies is evident, considering a track record of biologics that fit pharma's blockbuster business model (e.g. Genentech's Rituxan ®, Centocor's Remicade®). The focus on antibodies within this field is mainly due to the fact that antibodies and recombinant proteins dominate the biologics market [14, 282]. Moreover, this investment priority is fully consistent with previous research as proteins are also the most funded technology field over the past 15 years (43%) [26]. Therefore we can conclude that VCs' high prioritization and investments suggests that they still expect sufficient future economic development within this field. The second highest prioritized field, mainly revolves around promising advances in the cell therapy subfield, which, apart from Dendreon's Provenge®, involves technologies that are currently still in clinical research stages. Similarly, the third highest prioritized field has recently generated UniQure's Glybera® as the first approved gene therapy [38, 39].

Considering the limits of technological development and a potentially imminent innovation cliff for protein related technologies [14], VCs' second and third priorities might indicate that they are counting on these technology fields for disruptive innovation and that they are jumping the technology S-curve of proteins to cell- & gene therapy technologies. The concept of 'jumping the S-curve' relates to slowly abandoning one technology or market as it reaches its saturation phase while adopting a disruptive technology or market during its emerging or growth phase [14, 128, 283(p.123-128)]. Gene therapy, for example, has been suggested to be a future disrupter of the protein therapeutics market [284]. In this context, our study suggests that VCs seem to be considering cell- & gene therapy technologies as future disrupters in terms of innovation and economic development.

In contrast to therapeutic area priorities, there is a noteworthy discrepancy between prioritization and VC funding of technology fields. The allocation of DNA/RNA technologies at the bottom of the medium priority group is surprising, since it is the runner up field in terms of VC funding (29%). Moreover these DNA/RNA technologies form the basis of personalized medicine opportunities, which is a major trend in healthcare [26, 261, 262, 285]. The discrepancy between declared priority and relative amount of funding might be due to the relatively moderate to low returns that have been realized for this technology field [26]. Correspondingly, in our previous research we concluded that VCs invest in these DNA/RNA technologies for long-term cure and care macro-trends. However, from this study we can also conclude that although VCs invest heavily in DNA/RNA technologies, it does not have a high investment priority relative to proteins and, more importantly, to

technologies such as cell therapy and gene therapy. It may also be the case that there are simply less viable opportunities available in cell- & gene therapies, while VCs do perceive these to be higher investment priorities. This may explain the relatively lesser amounts invested in cell- & gene therapy technologies, in relation to their prioritization.

6.4.3 Niches and investment barriers

Insights from this study provide the opportunity to identify niches with high VC attractiveness and further increase this attractiveness by solving barriers that VCs associate with those niches. Generally, the highest prioritized investment barriers are associated to the complexity of the science underlying the respective technology or pathology, efficacy issues in trials, regulations, competition, and finance. However, the study mainly focused on the differences in prioritized barriers for different technology fields and therapeutic areas. Thus, for specific combinations of applying technologies within certain therapeutic areas, entrepreneurs have the opportunity to adjust their organizational strategy and activities in such a way so as to overcome related investment barriers or at least include them as risk parameters in their business planning. Hereby, entrepreneurs may transform barriers into opportunities and develop unique competitive advantages. For example, if one is developing a gene therapy for oncology, one may gain a competitive advantage by including solutions for regulatory issues that are specific for gene therapy technologies in their business planning; as well as any validation issues by demonstrating a sound proof of concept of the technology and the ability to move a specific product forward into clinical trials. They may also, for example, benefit from studying efficacy issues that occurred in other oncology trials that involved similar technologies. In contrast, addressing other issues may be more important in gaining a competitive edge when a venture is developing a new therapeutic protein for a cardiovascular disease. In this case, focussing on and planning for potential regulatory issues specific for cardiovascular diseases as well as milestone planning for financing of R&D will probably be more beneficial in convincing VCs to invest.

A noteworthy issue is the importance of the interests of potential future (bio)pharmaceutical acquirers from a VC perspective. This measure was included in the questionnaire to gain insight into the extent to which VCs are influenced in their investment decisions with regards to technologies and therapeutic areas. The results show that pharma's interests are considered to be either equally important or more important than VCs own intuition and thus are often quite leading. Therefore, pharma's interests may easily influence niches with VC attractiveness as identified in this study. Because pharma's interests are subject to frequent change, as stated by one respondent, it is imperative that entrepreneurs not only focus on these niches but also account for pharma's future interests. Vice versa, as technological gatekeepers, VCs in essence control the supply of innovation and therefore pharma's future interests may also depend on the investment decisions VCs make now. Especially when it comes to new waves of game changing technologies and radical innovation, pharma may rather be a follower than a leader, as claimed by one of the respondents.

6.4.4 Considerations and future research

There are several considerations that have to be taken into account when interpreting the results from this study. For the prioritization we used cut-off points to categorize fields, areas and barriers into priority groups (Low, Medium, High). Although this approach was adopted from literature [270, 279], it resulted in the allocation of a high number of therapeutic areas and investment barriers in the low priority groups. Thus, in future analyses in this context, cut-off points may be re-evaluated. In addition, the analysis required a total number of 49 questions in the questionnaire, which may have been considered as too many by potential participants. Nevertheless, we do not suspect that this might have led to sampling bias since we observed an appropriate distribution of demographic characteristics amongst respondents (e.g. age, geographic location). Therefore, the group of respondents was considered to be representative for life sciences VCs.
Future research may focus on investigating the technology S-curves of cell- & gene therapy technologies to identify current phases in technological and economic development of these technologies. This could also provide insights in whether VCs could indeed be jumping the S-curve of protein technologies. Evaluating these technologies a decade from now and comparison with VCs' current investment priorities as found in this study could subsequently provide insight into the predictive abilities of VCs in terms of innovation and economic development of technologies. In addition, the method of prioritization analysis used in this study may be applied to a wide range of interests across different disciplines and markets. Additional future research could aim at uncovering more in-depth knowledge about the underlying causes and opportunities associated to the investment barriers. This may be realized by conducting case studies of ventures with a specific technological focus. Another potential avenue of further research may entail a similar analysis targeting R&D-, alliances- or acquisition managers or directors at incumbent (bio)pharmaceutical firms as research subjects. A comparison of a prioritization of therapeutic areas, technology fields and associated barriers from that perspective could shed light on similarities and discrepancies between the VC perspective and acquirer perspective (see Giniatullina et al.[255]).

This study provides the first systematic prioritization of therapeutic areas, technology fields and investment barriers from a VC perspective. It provides unique quantitative findings that contribute to the knowledge about new ventures and investments in the biotechnology sector. Because VCs are considered to be technological gatekeepers, their perspective on investment priorities and barriers provides unique opportunities for entrepreneurs to create competitive advantages and look for niches with high VC attractiveness.

Chapter 7

CONCLUSIONS AND DISCUSSION

This chapter commences with a summary of the main conclusions of each study presented in this dissertation, and discusses how these contribute to existing literature. Subsequently, central challenges of the pharmaceutical industry are discussed in relation to the waves of biotechnological innovation, concluding that biotechnology has been underutilized by established firms due to their dominant logic and blockbuster paradigm. Hereafter, management implications are discussed and a trajectory of organizational innovation is suggested involving gradual changes and transition towards a prevention-based paradigm. This is followed by recommendations for a new organizational form that may better sustain and drive future waves of biotechnological innovation. This form is mainly based on differentiation regarding organization and governance of exploration and exploitation. Separation of these constructs based on required capabilities and the link between them through long-term alliances beyond single product development are both crucial to achieve sustainability. Finally, several avenues for further research are suggested, focusing on future development of exploratory innovation networks, the role of venture capitalists, long-term exploitation alliances and organizational transition, institutional factors that could accelerate adoption of new innovation, and the potential reconstruction of the value chain based on a prevention-based paradigm.

7.1 Summarizing conclusions and contributions

The studies in this dissertation reveal several important and contributing findings with regards to interfirm cooperation between biotechnology companies and established pharmaceutical firms. Furthermore, they reveal findings regarding investments, trade sale multiples and investment priorities and investment barriers, exploring a venture capital perspective. Here, the main conclusions from the individual chapters are summarized and their contributions to existing literature are discussed.

7.1.1 Technological development and interfirm cooperation effects

First, *chapter 2* thoroughly examines biotechnological development and adds a dimension to the innovation deficit problem of the (bio)pharmaceutical industry [4, 12, 63, 94, 96] by showing that the first wave of biotechnology has reached a stage of technological saturation. As explained in *chapter 1*, from its inception, biotechnology was expected to revolutionize pharmaceutical R&D; however, literature states that it has not met these expectations [1, 5, 16, 18]. Moreover, rDNA and mAb technologies, as the first wave, are the only ones that produced products, except for Provenge® and Glybera®. However, rDNA and mAb products have accounted for a mere 5% of total pharma sales[14] and will be in competition with biosimilars after patent expiry [286]. Given these insights, and considering *chapter 2* predicts imminent maturation and saturation of productivity, this first wave will surely not revolutionize pharmaceutical R&D. Therefore, later waves of biotechnological innovation will have to play a significant role in realizing the potential of biotechnology and meeting expectations. In addition to these insights being relevant for stakeholders, this chapter confirms that patent and patent citation analyses are an efficient method of technological forecasting, adding to innovation literature by building on existing research using similar methodologies [23, 283].

In *chapter 3*, we take a more in-depth look at the innovation system from a company-level perspective. Merging patent data with additional company specific variables (e.g. location, partnerships, deals) of its applicants resulted in a unique dataset providing the ability to study interfirm cooperation in relation to company success. In particular, the effects of three dimensions of interfirm cooperation – clusters, alliances, and acquisitions – on product introduction probability are examined. To the best of our knowledge, *chapter 3* presents the first study where this is done from the perspective of the technology supplier. It adds to existing empirical evidence, showing that cluster settings positively affect the likelihood that individual companies' will introduce new products and thereby stimulate innovation and economic growth [114, 144, 145, 165]. In addition, this chapter contributes to literature on strategic alliances[76, 146, 178, 208], regarding biotechnology[149, 150, 207], as it uniquely shows that these alliances involve a risk-return trade-off in biotechnological product development: on the one hand, engaging in alliances, as technology suppliers, decreases risk by increasing the likelihood of future product introductions; but, on the other hand, biotechnology suppliers earn lower returns after product introductions when these products are developed through alliances, as opposed to independently. Finally, this chapter provides empirical evidence regarding the destructive impact of being acquired on technology suppliers' productivity. It shows that acquisitions negatively affect the likelihood of

introducing biotechnological products, although they do not affect revenues gained from these products. This chapter therefore contributes to M&A literature in general[76], and relating to biotechnology in particular [74, 155].

In contrast, the perspective of established pharmaceutical firms and the dynamics of interfirm cooperation in relation to their innovation performance have been thoroughly examined in *chapter 4*. The study presented in this chapter shows that these incumbents, as literature suggests[75, 111], have been increasingly acquiring biotechnological companies to replenish R&D pipelines and counter their innovation deficits. However, these increases in the number of acquisitions of biotech companies have negatively affected firms' innovation performance. These findings contribute to existing M&A literature, in which there lacks consensus regarding the effects of M&A [76]. However, *chapter 4* also demonstrates that these negative main effects are moderated by firms' absorptive capacity as measured by internal R&D efforts, concluding that acquisitions of both pharma and biotech companies are complementary innovation activities at higher levels of absorptive capacity. Noteworthy, pharma acquisitions outperform biotech acquisitions in this regard, illustrating the known influence of technology- and market-relatedness[156, 218, 227]. These findings add to the existing body of knowledge concerning absorptive capacity in M&A literature[148, 188, 221-224, 229], as they uniquely show the differential effects of acquiring technology related and unrelated target companies. For alliances with biotech companies as a subsequent dimension of interfirm cooperation, the same complementarity exists at high levels of absorptive capacity. However, the study demonstrates that alliances with other, often smaller, pharmaceutical companies are substitutive strategic options at higher levels of absorptive capacity, while the main effect of pharma alliances is positive. Again, these differential effects increase our understanding of technology relatedness and absorptive capacity with regards to alliances. Moreover, *chapter 4*, as well as *chapter 3*, provide insights regarding the need for integration of internal exploratory and exploitative capabilities with external innovation to reach complementarity and thereby increase value [224, 225]. These insights are particularly relevant to open innovation literature [6, 7, 251, 287], exploration exploitation literature [149, 157-160, 188, 235] and literature that specifically focuses on ambidexterity in organizations [159, 288-291].

7.1.2 A venture capital perspective

Where *chapters 3* and *4* examine the dynamics relating to organization of R&D and biotechnological product development from a firm-level perspective, distinguishing between technology suppliers (*chapter 3*) and technology recipients (*chapter 4*); *chapters 5* and *6* build on the technological development analysis (*chapter 2*), as they focus on identifying ground-breaking biotechnologies that are relevant for the future, from the perspective of VCs. The first part of *chapter 5* evaluates VC investments in biotech companies and returns on these investments through trade sales (i.e. acquisitions). Investments in these portfolio companies, categorized by technology field and therapeutic area focus, based on their lead product(s), reveal VC preferences. The second part of *chapter 5* includes an analysis of trade sales between 2010-2014, showing that VCs have benefitted most in the area of oncology. Other beneficial therapeutic areas are infectious -, auto-immune -, and central nervous system diseases. As for technologies, small molecule drug companies outperform biotech companies as both trade sale values and multiples are

higher on average. As technological gatekeepers [27], VCs select the supply of future biotechnological innovation to meet the acquisition demand of established firms; and their preference may, therefore, have predictive value in light of development waves of biotechnological innovation. As such, this dissertation suggests the analysis of VC investments as a useful methodology to examine technological development in a given technology sector. Normally, forecasting and analyses of emerging technologies are conducted using patent data (*chapter 2)* [14, 23, 98, 99, 121, 283, 292], but a combination with VC investment data can shed light on which type of technologies are being picked up by the market. In this case, *chapter 5-I* shows that VCs focus on both short-term and long-term success: on the one hand they play it safe, minimizing risk by investing most in small molecules and proteins; on the other hand, they are investing heavily in DNA/RNA technologies, which underlie the possibilities of personalized medicine. In conclusion, *chapter 5* shows that big pharma's predominant blockbuster paradigm guides their acquisition preference and therewith their innovation demand; and that VCs predict the corresponding supply of innovation, acting as visionary technological gatekeepers, building for big pharma. Moreover, *chapter 5* shows that as technology gatekeepers VCs provide the foundation for new waves of biotechnological innovation. They are investing in technologies for current and future cure and care macro-trends while some of these technologies have not (yet) realized good returns through trade sales.

Correspondingly, *chapter 6* adds depth to the perspective of VCs by providing a thorough qualitative and quantitative prioritization analysis of technology fields and therapeutic areas, including associated investment barriers. The application of prioritization analysis in this field and to this particular group of research subjects contributes to- and validates this existing methodology as implemented by several researchers [270-275]. This chapter shows that venture capitalists are considering cell- & gene therapy technologies as future disrupters in terms of innovation and economic development, suggesting that they might be jumping the S-curve of technological development from recombinant proteins to cell- & gene therapy technologies. It further reveals several niches of technology - therapeutic area combinations with high venture capital attractiveness, mainly concerning protein technologies and cell therapy & gene therapy technologies for oncology, cardiovascular and central nervous system diseases. Furthermore, the chapter also reveals high-prioritized investment barriers specific to these technologies and therapeutic areas, which mainly concern the complexity of the science underlying the respective technology or pathology, efficacy issues in trials, regulations, competition, and finance. The chapter suggests that venture capital attractiveness can be increased by overcoming high-prioritized barriers for specific niches of technology and therapeutic area combinations.

The studies presented in *chapters 5* and *6* contribute to a better understanding of the role of VCs in the current 'science-business model'. They show that, with their unique competences, VCs have found a delicate balance between money, time and risk, fulfilling a crucial role in the biopharmaceutical value chain. While small biotech companies seek risk in early stage R&D, and established firms are risk-averse by investing and engaging in late stage R&D, VCs fill the gap of risk versus required capital, and connect supply and demand as risk-neutral investors. By investing in the right technologies and therapeutic areas, they foresee technology developments and big pharma's future innovation demand, while at the same time creating a technology push as visionary gatekeepers.

7.2 The blockbuster paradigm and biotechnological innovation

7.2.1 Pharmaceutical R&D and the first biotechnologies

Traditional pharmaceutical R&D is historically based on chemistry and has spun-off from chemical companies that produced dye-stuffs and plastics [1, 293]. Simultaneously, pharmacists who invented preparations and started to manufacture and sell them, were the founders of several companies that became today's established pharmaceutical firms [293]. Since 1935, sales of pharmaceuticals started growing to the benefit of these firms. The industry really took off after WWII, with an enormous increase in productivity [293], illustrated by a peak of NME approvals in the late 1940s [294]. However, from 1950 to the present, the number of NME approvals has remained constant [72, 294], with the exception of a large peak of approvals in 1996 [14].

During this period the blockbuster business model evolved with Tagamet becoming the first blockbuster drug in 1986 [295]. This model worked exceptionally well for chemical products and provided feasible and necessary R&D investments to produce next waves of blockbuster drugs [210]. Unfortunately, this paradigm created a virtual 'trap' as each new drug has to be more successful than the last to cover the increasing R&D investments, essentially driving R&D expenditures to record levels [14, 210]. In addition, since 1962, regulations for the testing of new drugs have gradually become stricter, resulting in a greater delay between discovery and marketing as well as increased costs. Moreover, from the 1980s, price pressures, increased competition of both first-in-class and generic drugs, market fragmentation, enormous rises in R&D expenditures, imminent patent expirations of existing blockbusters, and innovation deficits, presented themselves as challenging factors that affected profits and growth as productivity remained constant [5, 72, 94, 210, 296].

As discussed in *chapter 4*, industry consolidation increased with M&A as an attempt to cope with these challenges. Although M&A may seem beneficial as they often create economies of scale [74, 75, 162], the M&A strategy creates another virtual 'trap' where a firm needs to continue merging and acquiring to sustain innovation pipelines. Moreover, as we and others have shown, M&A often destroy value with regards to innovation and this strategy was rather a response to challenges than an adequate solution [25, 74]. Moreover, technology-relatedness and absorptive capacity play crucial roles in the relationship between M&A and innovation performance (*chapter 4*).

In this context, literature and studies presented in this dissertation suggest that the open innovation model has not been successful for pharma and biotechnology [1, 297]. The first biotechnologies have only generated products that fit the dominant logic[298, 299] of established firms' blockbuster model. Although some have become blockbuster biologics [33], it can be argued that the potential of these biotechnologies is restrained when subdued to the blockbuster business model.

Although this first wave will not revolutionize pharmaceutical R&D (*chapter 2*), early stage VCs are currently still prioritizing proteins and small molecule drugs highest (*chapter 6*). The main reason for this is that they still represent the technology fields with the

highest trade-sale returns (*chapter 5*). From this, it can be concluded that pharma's dominant logic and blockbuster model currently still dominate the industry. This remains a major issue, because it is fairly certain that the future biotechnological developments are not headed towards more products with blockbuster potential. In contrast, cure and care macro-trends are headed towards better diagnostics and highly complex targeted therapies and treatments that care for patients' individual unmet needs (i.e. personalized medicine).

7.2.2 Future biotechnological innovation and the current science-business model

As revealed in the study presented in *chapter 6,* cell- & gene therapies are prioritized second and third highest and perceived as the next groundbreaking technologies by VCs. These technologies will become increasingly relevant as firms seek opportunities for cures beyond palliative treatment regimens [300]. However, there are several hurdles, both technical and organizational, that have to be addressed. Most of these are revealed in *chapter 6* as VC investment barriers mainly include validation issues and efficacy issues in clinical development, regulatory issues, product prices, and manufacturing issues. Due to the high degree of complexity, meeting clinical end-points is an often-encountered challenge for these technologies. Furthermore, regulatory hurdles increase with the complexity of a technology, in particular with regards to classification of end products [301]. Finally, costs of production and delivery of cell- & gene therapies are significantly higher than standard therapeutics [300, 302], illustrated by Glybera®'s price tag of €1.1 million. Given these hurdles, the second wave of innovation involves a considerably different risk profile, and because its productivity curve is only just emerging, it is difficult to predict blockbuster potential of these therapies. Notwithstanding, VCs appear to be jumping the S-curve from proteins to gene- & cell therapy technologies (*chapter 6*).

Simultaneously, VCs are heavily investing in technologies that underlie personalized medicine, in line with cure and care macro-trends, although they have not made great returns from these investments in terms of trade sales (see *chapter 5*). There is no question that targeted therapies based on molecular diagnostics and personalized medicine can save more lives, increase quality of life, and can save a great deal of money [303]. Such outcomes are directly in line with the purpose of biotechnological innovation and will undoubtedly be realized by the third wave of innovation. These technologies provide the opportunity to customize treatment for patients, maximizing effectiveness whilst minimizing side effects.

However, the implementation of these technologies in global healthcare is inexcusably far behind the scientific possibilities due to several major hurdles that have to be overcome. Noteworthy, some of these hurdles are associated to interests of stakeholders other than the three perspectives evaluated in this dissertation (e.g. governments, insurance companies, healthcare providers). Most importantly, the possibilities of the third wave are in conflict with the obsolete blockbuster model of established pharmaceutical firms. From an economic perspective, this model focuses on as large and homogenous patient groups as possible, discouraging the development of diagnostics that identify subsets of patient groups that may be unreceptive to a given treatment [303]. Interestingly, this economic interest according to the blockbuster model is in direct conflict with the economic interest of health insurers in terms of cost-effectiveness. The larger the subset of patients for which

a companion-diagnostic may prevent the use of more expensive treatment, the more cost-effective this diagnostic product will be for health insurers [261, 285].

While health insurers may benefit enormously from the potential cost-effectiveness of companion-diagnostics and personalized medicine, the current reimbursement system disincentivises companies to develop these tests and physicians to use them. Companies have to go through great lengths to obtain reimbursement for innovative diagnostic products; and physicians are primarily rewarded for the procedures they execute, benefiting more from practicing trial-and-error medicine [303]. Finally, current regulations are also aimed at one-size-fits-all products as they require companies to conduct increasingly large and costly phase II and III clinical trials with considerably broad patient groups [261, 285, 303].

Thus, in the current environment, value slippage would occur for several stakeholders, providing little incentives for value creation in the long-term [304]. While the creation of value for patients due to personalized medicine technologies is clear, the value capturing for all involved stakeholders remains unclear and has yet to be organised properly. Several initial strategies that may lead to a situation in which all stakeholders may benefit from the third wave of innovation are mentioned as management implications in *section 7.3*.

7.2.3 Underutilized innovation

As introduced in *chapter 1*, an integrated 'science-business model' has evolved, which has allowed each of the stakeholders, studied in this dissertation, to capitalize on the first wave of biotechnological innovation. However, as discussed above and illustrated by the findings in this dissertation, the current organizational form turns out to be unsustainable to foster future innovation.

Chapters 5 and *6* show that VCs keep prioritizing and investing most in small molecule drugs and proteins, which fit the blockbuster model. This shows that, in essence, the entire innovation system is guided by established firms' dominant logic[298, 299]. Arguably, that influence has now become the main obstacle for the future of biotechnological innovation. The blockbuster paradigm, on which the value chain is based, cannot sustain future biotechnological innovation because the challenges cannot be solved with the same thinking that created them.

Moreover, as incumbent pharmaceutical firms lack innovation but have accumulated excess cash[74], they have increasingly acquired biotechnology companies during the past decades (see *chapter 4*). This acquired biotechnological innovation is integrated into the dominant pharma logic before it has a chance to develop independently. Therefore, from a technology development standpoint, new impulses of biotechnological innovation are continuously nipped in the bud as they are acquired prematurely.

In this context, it can be argued that the focus on blockbusters co-created the current result of biotechnology, which is disappointing due to unrealized expectations and potential (*chapter 2*)[2, 3, 5, 16-18, 94]. Therefore, a major conclusion from this dissertation is that biotechnology has been underutilized for the past decades because of big pharma firms' dominant logic and blockbuster paradigm [303]. It is not that biotechnology itself was not

enough to counter pharmaceutical innovation deficits, but it rather was the way in which established firms utilized biotechnology that has caused failure in realizing its potential. The combination of firms' short-term goals and focus on one-size-fits-all products has had a profound effect on science-based business and its current organizational form. If subjected to different organizational forms, business models, or even an adapted value chain, biotechnological innovation can still drastically improve the quality of medicine and global healthcare.

7.3 Management implications: towards organizational innovation

In general, the dominant industrial logic of a firm constitutes its business model [299, 305]. As Teece[305] explains, "business models must morph over time as changing markets, technologies and legal structures dictate and/or allow"; and sometimes this results in significant changes or even abandoning an existing business model entirely. In many cases this, therefore, also means that firms have to change their dominant logic in order to survive or thrive. For clarification purposes, Teece[305] explains that new organizational forms are important as a component of a business model. However, organizational forms are not business models. Here, several managerial implications are discussed, relating to the necessary organizational and institutional changes. The development of a new business model for this industry lies beyond the scope of this dissertation.

Pisano[2] states that throughout economic history, technological innovation and organizational innovation are interdependent and new organizational forms are invented to cater to specific economic issues and needs [2, 306]. Moreover, Teece[305] states that the creation of organizational forms are as – if not more – important to society and to the business enterprise, than technological innovation. He also argues that good business model design and implementation, combined with strategic analysis, are necessary for technological innovation to succeed commercially [305]. Therefore, the potential of biotechnological innovation can only be realized through complementary organizational, institutional and managerial innovation [2, 306]. Moreover, the fundamental issue(s) of the current organizational form, as described in the previous section, can only be overcome by such innovation based on different logic. This represents an evolutionary process, involving gradual improvement as well as leaps of- or abrupt improvement (i.e. nongradual evolution; saltation).

Arguably, gradual organizational improvements have to be implemented to enhance innovation performance within the current paradigm. Subsequently, a new organizational form has to evolve from a different paradigm as the blockbuster model has been proven to be unsustainable. This is a continuous process that includes an organizational transition phase, in which economic circumstances must be improved to gradually sustain future technological waves.

7.3.1 Gradual improvement

Starting with the current organizational form, the studies presented in *chapters 3* and *4* mostly focus on improving it. According to Pisano[18] there are a number of key elements that ought to shape a more suitable industry anatomy for biotechnological innovation, two

of which directly relate to the findings presented in these chapters. These two elements are critical in improving biotechnological innovation performance within the current organizational form.

Firstly, improved *vertical integration* is suggested, and *chapters 3* and *4* make considerable contributions to this notion within the context of the biopharmaceutical value chain. Because of their positioning in this chain, pharmaceutical firms have the potential to be exceptional integrators. However, radical changes in their dominant logic and conduct of business are required, before firms can realize this integration potential. It is argued that, internal processes will have to be restructured to adequately sustain externally acquired technological innovation [3, 18]. In this context, complementarity between internally derived innovation and externally acquired innovation through integration might significantly improve established firms' innovation performance *(chapter 4)*.

Secondly, fewer and longer-term alliances are suggested. *Chapters 3* and *4* consistently show that alliances outperform acquisitions when it comes to biotechnological innovation. For alliances, it is similarly important that they complement internal R&D, especially when the technological capabilities of both firms are less related (*chapter 4*). Arguably, a way of achieving this is to indeed focus on longer-term alliances that go beyond the scope of developing a single new compound or biologic [18]. Instead future alliances may focus on specific technologies, technology fields, therapeutic areas, or combinations thereof (*chapters 5* and *6)*. This, however, requires a shift in approach from focusing on large numbers to longer-term commitments, and might lead to more productive investments and thus sustaining more technological innovation.

Innovation performance can be enhanced by focusing on one common denominator for these two elements, which is 'extending' innovation in an exploratory way [251]. The scope in both vertical integration and strategic alliances has to extend beyond the development of a single product, hereby generating additional innovation and collaboration. This may stimulate technological innovation, albeit for initial steps within the current organizational form.

In addition, literature has provided several practical improvements that can be applied to the current R&D process. These may relate to: 1) reducing R&D costs by, for example, aggressive outsourcing, prioritizing activities that reduce risk of failure, or risk-sharing through collaborations [307-309]; 2) Reducing development times through 'novel parallel-development techniques' and selecting the right programs to accelerate [308]; 3) Shifting attrition of compounds to earlier R&D phases by improving decision-making in project suspension through better identification of promising compounds [308, 310, 311].

7.3.2 Organizational and institutional transition

In order to eventually sustain future biotechnological innovation, a number of previously described hurdles have to be overcome. Initial steps in organizational and institutional innovation can be taken during an organizational transition phase to gradually pave the way to sustainability. First, for cell- & gene therapy technologies, there is little doubt that the issues relating to complexity and validation will be overcome through technological

innovation. However, the managerial and organizational processes that have to be improved form a significant issue. With high production and delivery costs, these technologies will require novel manufacturing and operations processes that are not easily developed [312]. Therefore, in the near future, considerable organizational and managerial innovation is necessary to capture and deliver the value of this second wave of biotechnologies.

Regarding the third wave, accelerating the adoption and implementation of personalized medicine in global healthcare would save more lives, increase quality of life and save money[303]. Conflicting economic interests, however, are a major issue inhibiting this adoption. Initial steps towards aligning interests of pharmaceutical firms and health insurers may involve a renewed focus on patient outcomes and increased clinical value combined with innovative risk-sharing models for drug and diagnostic coverage, where reimbursement becomes contingent upon patient outcomes [285]. Initially, visionary companies and insurers may seek to form such agreements, for new promising diagnostic-therapeutic combinations to demonstrate both clinical effectiveness and cost-effectiveness. If this could lead to more companion-diagnostics being reimbursed, it would stimulate companies to develop them and physicians to use them.

In addition, it would be better if physicians were rewarded for accurate early diagnosis and prevention rather than the execution of medical procedures and treatments. There lies a large role for insurers and regulatory authorities to coordinate decisions and align the reimbursement process with the approval process [261, 285, 303]. A corresponding reform that might catalyse the adoption of personalized medicine would be stricter regulatory requirements for safety and efficacy so that companies would need companion diagnostics to comply – this may vary per therapeutic area. Simultaneously, the authorities would have to decide not to require the collection of clinical data on marker-negative patients, which would lower development costs. New drugs and biologics would then only be approved for marker-positive patients, enforcing physicians to use companion diagnostics before treating patients with state-of-the-art therapies.

Finally, established pharmaceutical firms may have to suffer more losses in terms of sales and profits in the short-term, as they slowly but increasingly adopt companion-diagnostics in clinical development, during this organizational transition phase. In the intermediate- and long-term, however, it will lead to a sustainable model for future technological innovation with increased sales and, more importantly, significant cost-reduction of clinical development[303]. Given the trends, as described throughout this dissertation, organizational transition is necessary for established firms to successfully partake in the potential future of prevention- and personalization- based medicine and healthcare.

7.3.3 Managing uncertainty of biotechnological innovation

As stated before, cure and care macro-trends are headed towards a paradigm focused on preventing disease instead of curing it [55, 261, 285, 303]. Moreover, individualization, customization and self-management in healthcare have become apparent trends [303, 313]. From a perspective of technology forecasting, this trend can be perceived when observing the technologies underlying the three waves of innovation, as described in this dissertation.

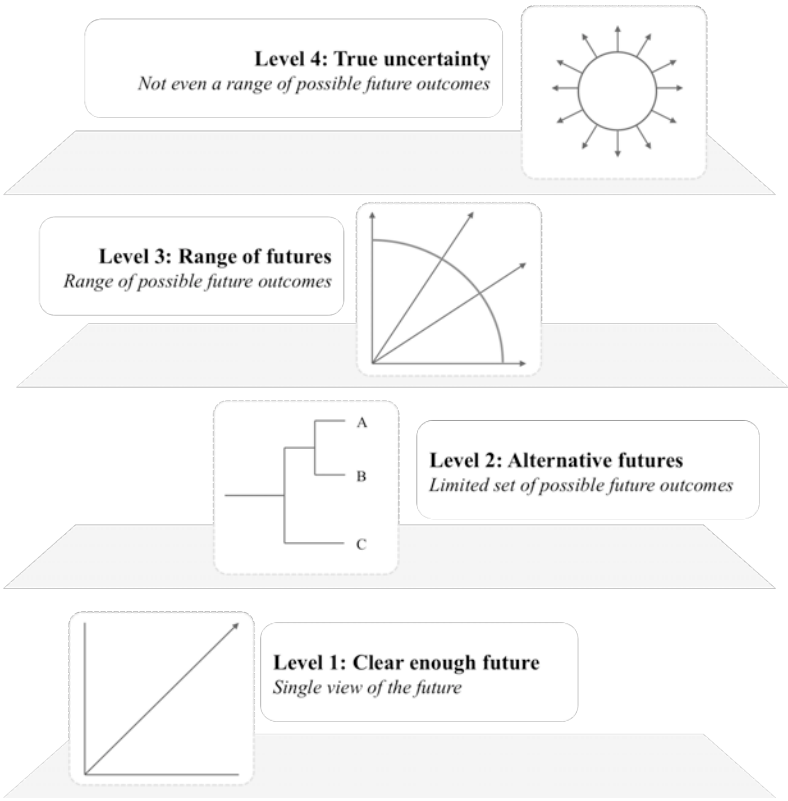
The first wave of biotechnological innovation has been utilized within the classic paradigm of curing large homogenous groups of patients from an industrial way of producing medicine (i.e. blockbuster model). In contrast, the third wave is generating better ways of early detection and diagnosis combined with personalization and customized treatment and a different paradigm is required to utilize this innovation. Moreover, such a paradigm requires different management tools, organizational principles and strategic approaches. While these are well developed within the classic paradigm, they have to be adapted or replaced to adequately sustain biotechnological innovation within a prevention-based paradigm.

In the context of organizational innovation, it is thus important to take incremental steps towards a prevention- and personalization- based model, and to, simultaneously, keep exploiting cures and medicine for homogenous patient groups. This will require management with dual strategies, distinguishing between the management of today's business and planning for the future [314]. It will further be necessary to experiment with combining different business models to develop ambidexterity and balance to adapt the scope of the firm.

Different technologies, as mentioned in *chapter 1*, are associated with different levels of uncertainty, as depicted in *figure 7.1* [21]. There have been various ways of conceptualizing uncertainty, and because it can be a major issue in blocking or delaying decision-making, it has been a thoroughly described concept in literature on decision-making [315-320]. Courtney et al.[21, 22] describe four different levels of uncertainty, with various management tools and strategic approaches adequate for each level. As different technologies are associated with different uncertainty levels, they also require different management tools and strategic approaches for optimal utilization.

The first biotechnologies are, presumably, associated with level one and level two uncertainty, mainly because the type of products and their success have been demonstrated (see *chapter 1* and *2)*. Moreover, the managerial tools and organizational principles of exploiting these technologies have been relatively well developed and implemented, as these products fit the existing pharmaceutical blockbuster model. Technologies of the second wave of innovation may be associated with more uncertainty (level two and three), as its products are still mostly in development and it remains difficult to predict their commercial success. Lastly, the third wave is mostly associated with level three and four uncertainty.

Figure 7.1 The four levels of uncertainty; a framework to determine the level of uncertainty surrounding strategic decisions (adopted from Courtney[21])



Noteworthy, level four situations are not static and usually migrate to one of the other levels over time. In case of dealing with this level of uncertainty, it is important for managers to focus on several pre-defined indicators and follow the market evolution to adapt their strategy[21, 22]. In addition, the fourth level of uncertainty is naturally associated with more possibility, for example in terms of industry divergence and convergence as industry boundaries may become blurred. This is, for example, already illustrated by the increasing importance of information technology (IT) as a complimentary technology in the third wave of innovation (e.g. bioinformatics, big data)[321, 322].

Thus, current management tools, organizational principles and strategic approaches associated with the blockbuster model may have to be adapted or replaced to deal with higher uncertainty and fit a prevention- and personalization- based model. In essence, the transition can be viewed as changing the model from 'mass production' (i.e. blockbuster drugs) to a 'mass customization' model (i.e. personalized medicine) [323], which usually requires significant change in internal processes. Although such significant change may be

expected, it is assumed that the current value chain, which is also based on the blockbuster model, will remain roughly the same. However, this does not necessarily have to be the case. A complete transformation in industrial logic and organization of science-based business, may also require an altered or replaced value chain framework designed from a prevention- and personalization- based paradigm.

Moreover, it is questionable whether the currently dominating incumbents will have the capacity to design and implement an alternative value chain based on a different logic. Like many traditional business models[305], the blockbuster model follows a mainstream, but obsolete, approach, where there is no need to worry about the value proposition for the customer. This is because new products are only approved after they have proven to be more safe and efficacious than the standard of care; and this in itself is the value proposition for patients. However, with the third wave of innovation, there is an additional value proposition as the treatment can be personalized based on a patient's specific needs. This provides opportunities for companies, and potentially even for new groups of commercial stakeholders aside from biotech companies and established firms. Existing research has argued that at times of radical technological change, new entrants often displace industry incumbents because their capabilities are rendered obsolete by such radical change, or because investing in the respective radical change may harm existing products and programs [324-327]. Ansari and Krop[328] discuss factors that influence displacement or survival of incumbents in the face of radical technological innovation.
Notwithstanding, it lies beyond the scope of this dissertation to assess which new entrants may seize a role in a prevention-based paradigm, or what an alternative value chain, based on a new paradigm, may look like. Therefore, the following section discusses recommendations, based on a transformation of science-based business within the context of the current value chain.

7.4 Recommendations: transforming science-based business

For a large part this dissertation deals with the predictability of future biotechnological innovation and in this section an attempt is made to recommend ideas for a new sustainable organizational form. Such a leap of improvement would only result from stakeholders abandoning the obsolete blockbuster paradigm and moving towards a diagnostic and prevention centred paradigm.

In terms of institutionalized innovation, regulatory-authorities would have to fully accept clinical research focused on subsets of patient groups based on biomarker and diagnostic programs, provided that these become mandatory companion-diagnostics in patient treatment. This will reduce R&D expenditures while enforcing the use of markers and companion-diagnostics before treatment. Furthermore, a functional healthcare system would need health insurers to reimburse value adding diagnostic-therapeutic combinations and reward physicians according to their ability to accurately diagnose and prevent disease, as opposed to rewarding them for carrying out treatment procedures [303].

Parallel to this, organizational innovation within the industry would have several implications. First, it can be assumed that the consolidation trend, as shown in *chapter 4*, will gradually continue, resulting in the remainder of a few large pharmaceutical multinationals. The continuation of this trend is, for example, illustrated by the recently alleged desire of Pfizer to acquire GSK, after abandoning its bid for AstraZeneca in 2014 [xxxi].

During the transition phase of shifting towards adopting diagnostics, some firms may successfully transform while others may fail. The transformation of firms that do survive would cause them to shrink in size due to initial declines in short-term profits and revenues. However, it would lead to increased sales and profits in the intermediate- and long-term[303]. Given the average duration of R&D trajectories[58], this may be estimated at 10 to 20 years from now. In this scenario firms have entirely abandoned the blockbuster model and have integrated the third wave of biotechnological innovation. However, out of necessity, they would have to concentrate most on their strengths [205] in late stage clinical development, manufacturing, operations, registration, marketing and distribution (see *chapter 4*). The result would be a polycentric model, in which several large firms would supply the market with novel diagnostics, therapeutics and therapies.

From here, internal R&D of these firms would be smaller and more exploratory to remain at the forefront of science and innovation. Rather than large R&D departments, firms would own independently operating business units[329] organized in a network, in which some units focus on specific technologies and others on specific therapeutic unmet needs. Through cooperation and exploratory alliances, multiple technological applications may be validated and developed for various indications. Furthermore, these networks would also include small entrepreneurial biotech companies that operate in a similar way, and be situated within various innovation clusters worldwide. Previous empirical evidence

[xxxi] nytimes.com; bloomberg.com

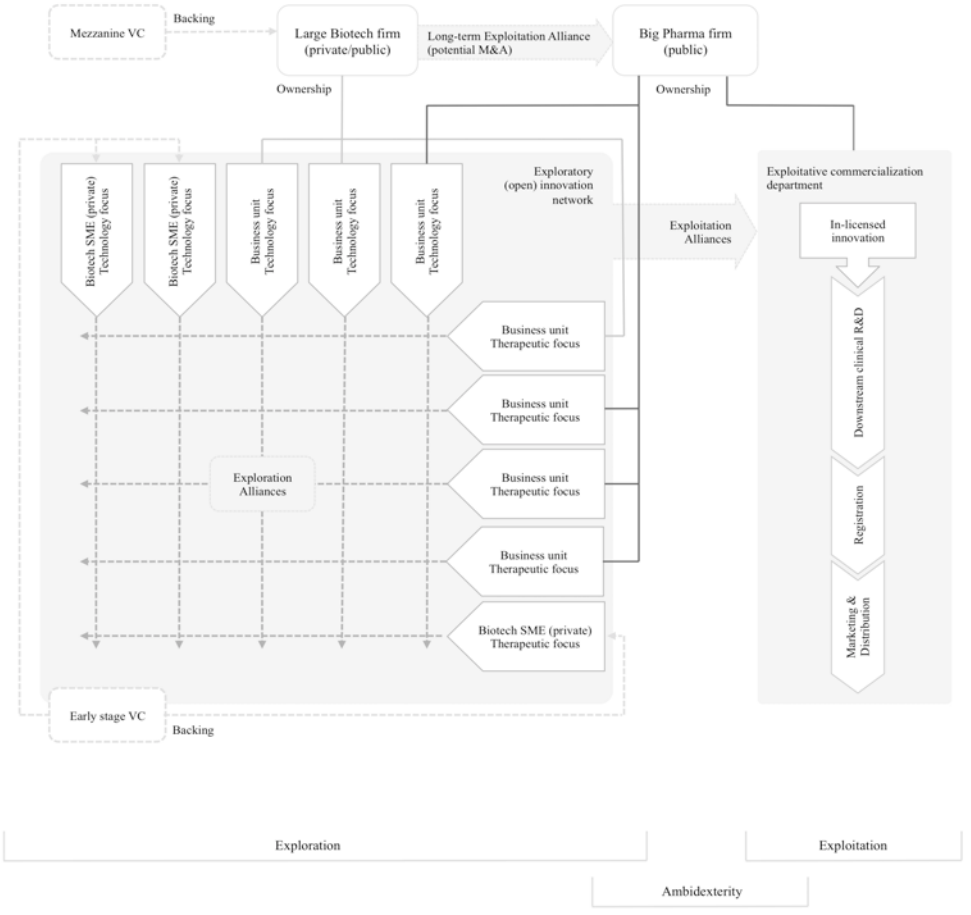
suggests that the locus of biotechnological innovation is found in networks of learning, rather than in individual firms[330]. Correspondingly, at this level, many exploratory alliances between biotech companies and independently operating business units would fuel the open innovation engine, and commercialization would only take place through long-term exploitative partnerships with commercialization departments, based on licensing and revenue sharing models. Instead of allocating valuable resources at acquiring and attempting to grow new businesses, established firms would co-create and sustain networks of entrepreneurial companies and independently operating business units, which may be (partially) self-owned. Acquisition would only take place at this level of exploration, provided that ownership would enhance complementarity between external companies and internal business units[229]. Thus, within the ownership of an established firm, exploration would have to become self-sustaining through partnerships with their own commercialization departments. Such an organizational form corresponds to the approach of differentiation, emphasizing the importance of separating smaller, decentralized, and more flexible organizational units that pursue exploration from larger, centralized ones that pursue exploitation [290, 331, 332]. As such, true ambidexterity will be embraced and biotechnology platforms can be scaled-up once their derived applications are ready for market consolidation.

This scenario implicates that biotechnology companies would represent a discovery industry solely focused on discovering new treatments and innovation, subsequently seeking exploratory alliances with business units owned by established firms. Biotechnology companies would be an essential part of such a new innovation system and through organic- or inorganic growth they may develop a similar organization of independently operating business units, partnering with one of the large established firms for late stage R&D and commercialization. This would be a long-term dedicated alliance through which multiple innovative products may reach the market. Following this growth-path and after several successful product introductions, these biotechnology companies may eventually go public. In contrast to the current model, in which biotechnology companies go public while their products are still in clinical development [18]. Moreover, larger scale acquisitions may also occur at this level, but would merely represent a change in ownership of an organization of independently operating business units. As such, it would be quite different from the current M&A model of established firms.

Finally, this new organizational form would provide a slightly different role for VCs and would increase the difference between VCs that prefer early stage investments and those that prefer mezzanine stage (i.e. growth- or late stage) investments. The former would invest in earlier stages of R&D, in which portfolio companies are aspiring partnerships with business units of established firms. Such VCs would focus on early stage acquisitions or trade sales to established firms or mezzanine stage VCs as appropriate exit-strategies. Noteworthy, these early stage VCs, would have to diversify more to account for the risk associated with earlier R&D stages. Furthermore, VCs that prefer mezzanine stage investments would primarily focus on biotechnology companies that either have a product in late stage R&D or have products on the market with established partners. Their portfolio companies would want to grow by developing their own organization of independently operating business units. An exit-strategy for such VCs would either be an IPO or large-scale acquisition by an established firm.

Arguably, the key of a new organizational form as described in this section is that exploration and discovery is organized and governed apart and differently from exploitation and commercialization. Differentiation of exploration units and exploitation departments, based on the required capabilities, is crucial to achieve sustainability [290]. Success would subsequently depend on the long-term exploitation alliances between the exploratory (open) innovation networks and exploitative commercialization departments. Although, such a new form is still based on the currently existing value chain, it may foster the realization of the potential of biotechnological innovation and thereby significantly improve global medicine and health.

Figure 7.2 Simplistic overview of a hypothetical transformed organizational form for science-based business



7.5 Suggestions for further research

Considering the described transformation of science-based business organization as a form to sustain and drive future biotechnological innovation, several avenues for further research are suggested. First, network analysis of exploratory alliances among biotech firms, particularly in an innovation cluster setting, could shed further light on how these can be structured[333, 334]; and whether a potential organization of independently operating business units, focusing on specific technologies or therapeutic unmet needs, has merit. Furthermore, firm-level alliance network-analysis may provide insight in how changes in network strategy can redirect an exploitation strategy towards an exploration strategy (see Dittrich et al.[335]). This could be valuable during organizational transition, if firms would start to adopt the earlier described explorative innovation network-approach.

Further network analysis regarding VC syndication in this context may provide additional insights [336, 337], particularly with regards to the role of VCs or VC syndicates in specific biotechnology innovation networks[338]. Moreover, considering VCs' crucial position in the current value chain, and assuming the continuation of the macrotrend towards individualized and prevention-based healthcare, the question arises whether and how the position of VCs would change and how they could adapt their unique competences to capture value in a new paradigm. More specifically, would they still be able to fulfil their role as gatekeepers building for big pharma? The answers to these questions highly depend on the effects the new paradigm may have on the anatomy, organization and value chain of science-based business. Additional further research regarding VC may focus on when and where biotechnology companies can best raise money for specific technologies and therapeutic areas, and whether correlations can be identified between different types of VC syndicates and different types of companies' ability to get funded. Furthermore, from a VC perspective it would be valuable to identify related independent variables and study their effect on VC success in terms of successful (trade sale) exits for this specific industry, building on existing research [339, 340].

Another angle for further research would be to aim at advancing insights and understanding of capabilities and processes for accurate integration of innovation through long-term exploitation alliances. Such capabilities and processes may slightly differ depending on the technologies in question, and may therefore be optimized as such. An additional, but perhaps more pressing issue would be the short-term returns for shareholders of established firms as these are likely to decline during an organizational transition phase, as described earlier. Further research could explore ways in which pharma firms can best approach this transition phase from a strategic and organizational perspective, anticipating inertia or relapses into their dominant logic[298, 299].

Additional further research could focus on elements that are external to the stakeholders studied in this dissertation, but could accelerate the adoption of personalized medicine in clinical development and healthcare in general. For example, Davis et al.[285] suggest how newly established government agencies that assess both clinical- and cost-effectiveness of novel diagnostics may catalyse this adoption. Moreover, regulatory authorities can play a critical role in establishing and enforcing policies that could incentivise companies to

incorporate diagnostics into clinical development and novel treatment regimens. During the past decade, initial guidelines for co-development of diagnostics and drugs have already been introduced[303] and further research may study their effects and barriers of implementation. Research regarding institutional elements that can play a catalysing role in the adoption of biotechnological innovation will be most relevant.

Finally, the most challenging avenue of research is in the area of further organizational innovation towards a prevention-based paradigm, mainly because it remains very difficult to predict what the effects will be and what successful organizational innovation in this context will look like. Further research may focus on rethinking the current value chain, approached from a personalization – and prevention-based perspective, as opposed to the current industrial cure-based paradigm. This may result in the attempt to design a new value chain framework and to study the implications of an alternate value chain for this industry. It may also explore the possibilities for entirely new groups of commercial stakeholders and their potential role in such a new value chain.
There remains much uncertainty in giving substance to the organizational and institutional innovation needed to sustain and foster the next waves of biotechnological innovation in medicine. But, given the insights gained from the studies presented in this dissertation, the necessity for organizational innovation has become evident.

Samenvatting

Het uiteindelijke doel van biotechnologische innovatie is het verbeteren van medicijnen en daarmee de gezondheid van mensen. Hier wordt fundamentele wetenschap gebruikt om nieuwe innovatieve diagnostische en therapeutische producten te ontwikkelen en daarmee de levens van patiënten wereldwijd aanzienlijk te verbeteren. Tegelijkertijd, is het doel voor drie verschillende groepen ondernemingen om winstgevendheid te genereren vanuit biotechnologische innovatie. Deze drie groepen zijn: ondernemende biotechnologie-bedrijven, investeerders en farmaceutische bedrijven.

In dit proefschrift worden samenwerkingen tussen bedrijven alsmede durfkapitaal investeringen geëvalueerd binnen de context van biotechnologische innovatie en op wetenschap gebaseerde bedrijfsvoering. Na de opkomst van biotechnologische innovatie zijn er een aantal veelbelovende golven van technologische ontwikkeling ontstaan maar tot nu toe, zijn de hoge verwachtingen van biotechnologie nog niet gerealiseerd. De onderzoeken in dit proefschrift hebben als doel om meer inzicht te krijgen in hoe meer biotechnologische innovatie de markt kan bereiken en welke biotechnologieën de productiviteit en de gezondheidszorg drastisch zullen veranderen. Gerelateerde processen worden onderzocht vanuit verschillende commerciële perspectieven (namelijk: biotechnologiebedrijven, grote farmaceutische bedrijven en investeerders). Hoofdstukken twee tot en met zes bieden diepgaande analyses van: Technologische ontwikkeling van initiële biotechnologische innovatie; De dynamiek van samenwerkingen tussen bedrijven en hoe biotechnologie bedrijven hun kansen op succesvolle product introducties kunnen vergroten; Hoe grote farmaceutische bedrijven deze dynamiek van samenwerking kunnen adapteren om hun productiviteit en innovatie prestatie te verhogen; En welke nieuwe velden van biotechnologische innovatie de toekomst van het ‘science-business model’ gaan vormgeven, vanuit een investeerders perspectief.

De eerste onderzoeken van dit proefschrift tonen aan dat allianties tussen farmaceutische bedrijven en biotechnologiebedrijven van positieve invloed zijn op innovatie. Anderzijds hebben overnames van biotechnologiebedrijven door farmaceutische bedrijven een negatieve invloed op innovatie. Verder blijkt er in het geval van allianties sprake te zijn van een risico-rendement trade-off in nieuwe productontwikkeling, voor biotechnologiebedrijven als technologie-aanbieders in deze allianties. Daarnaast blijkt uit de onderzoeken dat allianties met- en overnames van biotechnologiebedrijven complementaire innovatie activiteiten zijn bij een hoger niveau van absorptiecapaciteit.
Betreft durfkapitaal, blijkt uit de laatste onderzoeken van het proefschrift dat investeerders een cruciale rol vervullen in de biofarmaceutische waardeketen. Door te investeren in de juiste technologieën en therapeutische gebieden, anticiperen deze investeerders op de toekomstige vraag naar innovatie van farmaceutische bedrijven. Tegelijkertijd creëren durfkapitaal investeerders een technologie-push als visionaire poortwachters van innovatie. Tot slot wordt in dit proefschrift geconcludeerd dat de dominante logica en het ‘blockbuster’ paradigma van grote farmaceutische bedrijven de oorzaken zijn geweest van de onderbenutting van biotechnologische innovatie. Verder wordt een transformatie voorgesteld richting een nieuwe organisatorische vorm voor duurzame, op wetenschap gebaseerde, bedrijfsvoering en effectieve exploitatie van biotechnologische innovatie.

Summary

Improving medicine and health is the ultimate purpose of biotechnological innovation, where basic science is used to develop new innovative diagnostics and therapeutics to significantly improve the lives of patients worldwide. Concurrently, for three stakeholder groups the primary goal is to generate profitable business from biotechnological innovation. These stakeholders are 'entrepreneurial' biotech companies, venture capitalists and established pharmaceutical firms.

This dissertation evaluates interfirm cooperation and venture capital investments in the context of biotechnological innovation and science-based business. After the rise of biotechnological innovation, several promising waves of technological development have emerged but as of yet, the high expectations of biotechnology have not been realized. The studies in this dissertation aim to better understand how more biotechnological innovation can reach the market and which biotechnologies will revolutionize R&D productivity and global healthcare. Related processes are evaluated from different business perspectives (i.e. entrepreneurial biotech companies, established pharmaceutical firms and venture capitalists). The five research chapters offer thorough analyses of: Technological development of initial biotechnological innovation; The dynamics of interfirm cooperation and how biotech companies can increase chances of eventual product introduction; How pharmaceutical firms can adapt these interfirm cooperation dynamics to increase R&D productivity and innovation performance; And which new fields of biotechnological innovation may shape the future of the 'science-business model' from a venture capital perspective.

The first studies show that alliances between established pharmaceutical firms and biotech companies outperform acquisitions of biotech companies by such firms, as these acquisition negatively affect innovation performance. Furthermore, alliances involve a risk-return trade-off in new product development, for biotech companies as technology suppliers. Moreover, for big pharma, alliances with- and acquisitions of biotech companies are both complementary innovation activities at higher levels of firms' absorptive capacity. Regarding venture capital, the final studies show that venture capitalists fulfil a crucial role in the biopharmaceutical value chain. By investing in the right technologies and therapeutic areas, venture capitalists build for big pharma as they foresee big pharma's future innovation demand. Simultaneously, venture capitalists create a technology push as visionary technological gatekeepers. Finally, the dissertation concludes that big pharma's dominant logic and blockbuster paradigm have been the root cause of underutilized biotechnological innovation. It further proposes transformation towards a new organizational form for sustainable science-based business and effective exploitation of biotechnological innovation.

About the author

Kenneth Dimitri Satya-Graha Fernald was born on May 13th 1987 in Rotterdam, The Netherlands, and raised in Rotterdam and The Hague. He completed his pre-university education in the direction of Nature & Health in 2005, and obtained his Bachelor of Science (BSc.) degree in Biomedical Sciences in 2008 at the Vrije Universiteit Amsterdam. In 2010 he obtained his Master of Science (MSc.) degree (Cum Laude) in Management, Policy-Analysis and Entrepreneurship in Health & Life Sciences at the Vrije Universiteit Amsterdam, after which he started lecturing and laying the foundation for his PhD research at the Vrije Universiteit Amsterdam. In 2011, he started to pursue his PhD research under the supervision of Prof.dr. Eric Claassen and later also that of Prof.dr. Harry Commandeur and Prof.dr. Enrico Pennings, at which point the research was further conducted at the Erasmus School of Economics. The studies initially focused on interfirm cooperation with respect to biotechnological innovation in medicine and later on venture capital investments and the perspective of venture capitalists on biotechnological innovation in medicine. While conducting his research, Kenneth had the opportunity to work on several life sciences related consultancy and business development projects.

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THE WAVES OF BIOTECHNOLOGICAL INNOVATION IN MEDICINE

INTERFIRM COOPERATION EFFECTS AND A VENTURE CAPITAL PERSPECTIVE

Improving medicine and health is the ultimate purpose of biotechnological innovation, where basic science is used to develop new innovative diagnostics and therapeutics to significantly improve the lives of patients worldwide. Concurrently, for three stakeholder groups, the primary goal is to generate profitable business from biotechnological innovation. These stakeholders are 'entrepreneurial' biotech companies, venture capitalists and established pharmaceutical firms.

This dissertation evaluates interfirm cooperation and venture capital investments, aiming to better understand how more biotechnological innovation can reach the market and which biotechnologies will revolutionize R&D productivity and global healthcare. The first studies show that alliances between established pharmaceutical firms and biotech companies outperform acquisitions of biotech companies by such firms, as these acquisition negatively affect innovation performance. Furthermore, alliances involve a risk-return trade-off in new product development, for biotech companies as technology suppliers. Moreover, for big pharma, alliances with- and acquisitions of biotech companies are both complementary innovation activities at higher levels of firms' absorptive capacity.

Regarding venture capital, the final studies show that venture capitalists fulfil a crucial role in the biopharmaceutical value chain. By investing in the right technologies and therapeutic areas, venture capitalists build for big pharma as they foresee big pharma's future innovation demand. Simultaneously, venture capitalists create a technology push as visionary technological gatekeepers.

Finally, the dissertation concludes that big pharma's dominant logic and blockbuster paradigm have been the root cause of underutilized biotechnological innovation. It further proposes transformation towards a new organizational form for sustainable science-based business and effective exploitation of biotechnological innovation.

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The Netherlands

Tel. +31 10 408 11 82
Fax +31 10 408 96 40
E-mail info@erim.eur.nl
Internet www.erim.eur.nl