International Journal of Drug Research and Technology

Available online at http://www.ijdrt.com

Research Article

A Quantitative Prioritization and Barrier Analysis of Biotechnology fields and Therapeutic areas: A Venture Capital Perspective

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ABSTRACT

Biotechnology ventures highly depend on venture capital during early stages. Therefore, insights into investment priorities of venture capitalists can be valuable for bioentrepreneurs. This study presents a systematic prioritization analysis of venture capitalists' investment priorities in terms of biotechnologies and therapeutic areas, as well as associated investment barriers. By means of 21 qualitative interviews and 81 quantitative questionnaires with venture capitalists, the paper shows that venture capitalists seem to be considering cell- & gene therapy technologies as future disrupters in terms of innovation and economic development. The 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.

Keywords: Investment; Venture capital; Biotechnology; Bioentrepreneurship; Investment priorities; Investment barriers; Therapeutics; Technology ; strategy; Start-ups; Entrepreneurship.

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 (Colombo, *et al.*, 2010). 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 (Fernald, *et al.*, 2014; Fernald, *et al.*, 2013; Amir-Aslani and Negassi, 2006; Schweizer, 2005; Drews, 1998; Drews and Ryser, 1996). 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 (Bains, *et al.*, 2014), early (clinical-) stage biotechnology companies have historically been driven by substantial risk capital from venture capitalists (VCs; Lee and Dibner, 2005; Bradford, 2003). 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 (Pronker, *et al.*, 2011) and new product development costs of $0.8-$1.3 billion (Fernald, *et al.*, 2014; DiMasi and Grabowski "Cost of R&D," 2007; Drews, 1998). 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. Thus, venture capital is the prime source of funding for biotechnology ventures during the start-up and growth phase of the technology transfer gap (Festel and Cleyn, 2013).

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 (Knockaert, *et al.*, 2010; Cumming, 2007), and of those, most VC funding goes to research-driven university spin-off companies (Ortin-Ángel

and Vendrell-Herrero, 2010), while ventures that have spun out from corporate institutions perform below average in terms of VC exit performance (Streletzki and Schulte, 2013). Thus, VC plays a crucial role in the development of new firms in new markets (Wright, *et al.*, 2006; Von Burg and Kenney, 2000); 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 (Colombo, *et al.*, 2010).

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 (Fernald, *et al.*, 2015; EY 2013), 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 (Florida and Kenney, 1988), which is true for biotechnology in particular (Niosi and Banik, 2005; Welpe and Kollmer, 2006). VCs, as technological gatekeepers, accelerate the process of technological change (Fernald, *et al.*, 2015; Florida and Kenney, 1988) and in essence determine the supply of innovation for larger firms in the industry. This is illustrated by the fact that trade sales or acquisitions of biotechnology firms have become the most preferred exit-strategies for VCs (Giniatullina, *et al.*, 2013; Behnke and Hültenschmidt, 2007).

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 disease 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.

Background

Investment priorities

Research prioritization is an effective way of identifying research opportunities within a specific context that are needed most (Weenen, *et al.*, 2014). 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 (Weenen, *et al.*, 2014; Viergever, *et al.*, 2010; Sibbald, *et al.*, 2009; Ghaffar, 2009; Nuyens, 2007; Fleurence and Torgerson, 2004). As Weenen, *et al.*, (2014) 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 (Dehzad, *et al.*, 2014; Weenen, *et al.*, 2013). 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 (Dehzad, *et al.*, 2014; Weenen, *et al.*, 2013; Hadjimanolis, 2003).

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; Weenen, *et al.*, 2013; Hadjimanolis, 2003).

Methodology

The methodology in this study is based on previously developed methods of prioritization (Weenen, *et al.*, 2014; Weenen, *et al.*, 2013; Balabanova, *et al.*, 2011; Viergever, *et al.*, 2010) 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 (van der Valk, Moors and Meeus, 2009; OECD 2005; WHO: ICD-10; Giniatullina, *et al.*, 2013). 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.

Research subjects

A search query in ThomsonReuters SDC Platinum VentureXpert database 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.

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. 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 (van der Valk, Moors and Meeus, 2009, OECD, 2005).

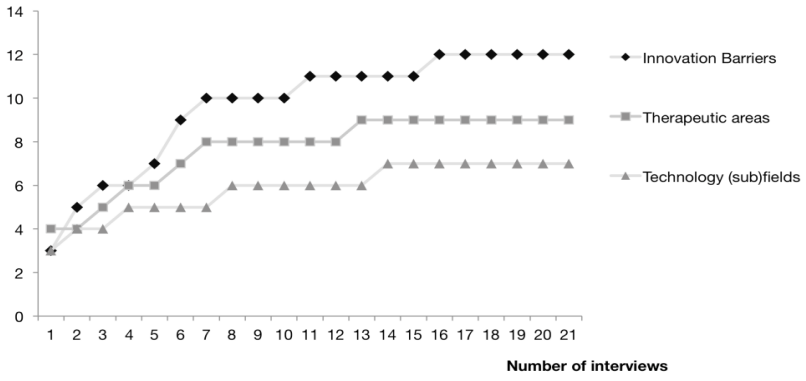

Figure 1. Saturation curves of the identification of therapeutic areas, technology fields and investment barriers, during interviews with 21 life sciences venture capitalists.

In addition, investment barriers specifically related to technologies and therapeutic areas as discussed in the interviews were identified. Saturation curves of therapeutic areas, 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 1). In total 21 interviews were conducted.

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 platinum1 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 (Pronker, *et al.*, 2015; Weenen, *et al.*, 2014; Dehzad, *et al.*, 2014; Weenen, *et al.*, 2013; Balabanova, *et al.*, 2011;

Viergever, *et al.*, 2010), 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 (Dehzad, *et al.*, 2014; Weenen, *et al.*, 2013).

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

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, r1/2/3 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 1 and 2).

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.

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 2, oncology as a therapeutic area received the highest investment priority by far; this is consistent with our previous research (Fernald, et al., 2015). 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.

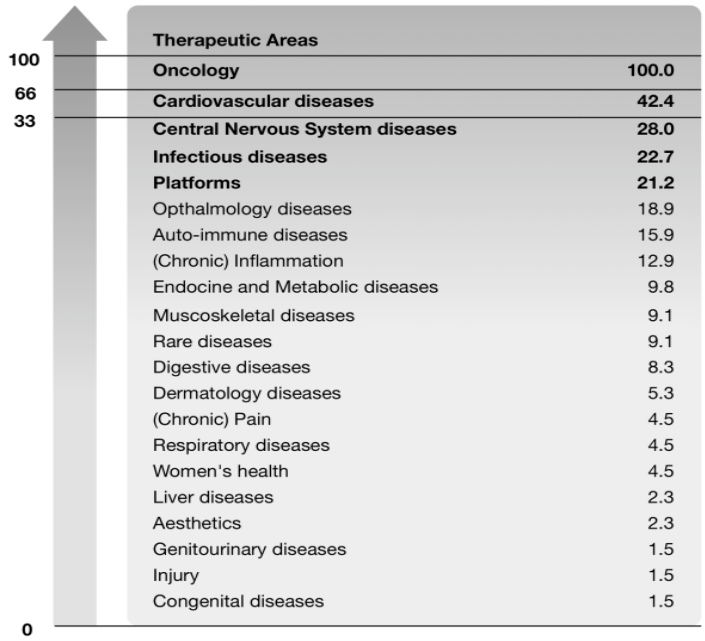

Figure 2. Therapeutic area ranking according to weighted scores divided in three priority groups: Low: 0-33; Medium: 34-66; High: 67-100.

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.

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 3a** shows the VCs' investment preferences for pharmaceuticals, medical technology, or biotechnology, which is quite evenly distributed and consistent with previous analyses (Fernald, *et al.*, 2015). 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 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.

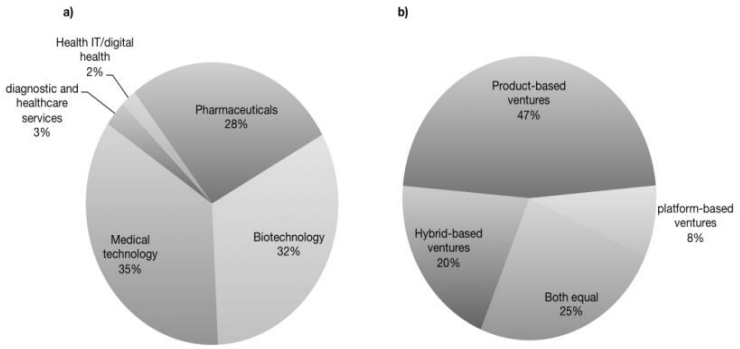

Figure 3. VC investment preferences in terms of technology types (a) and product-based vs. platform-based ventures (b).

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.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.

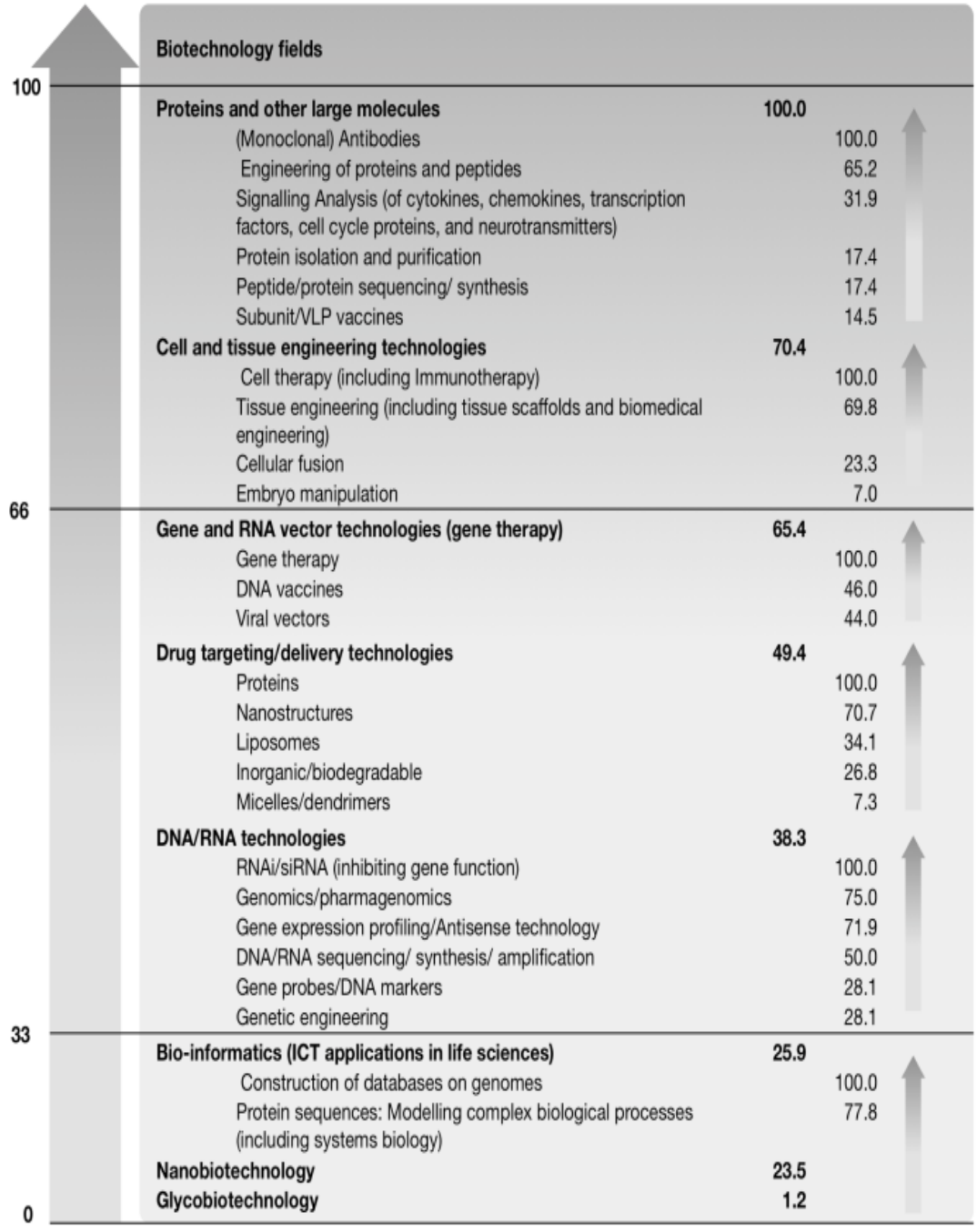

Figure 4. Technology ranking according to weighted scores divided in three priority groups: Low: 0-33; Medium: 34-66; High: 67-10

The results of this prioritization are shown in Figure 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 ground breaking technologies VCs are investing in.

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.

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 1. Shows the results for the therapeutic areas and Table 2 shows the results for the technology 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

Table 2. Relative ranking of associated investment barriers for the top 3 biotechnology fields

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 forms 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 ground breaking 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 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, and High).

Therapeutic areas			**Technology fields**	
Barrier	WR		Barrier	WR
Efficacy issues in trials	100		Complicated technology	100
Intricate pathology	87		Validation issues	62.7
Regulatory barriers	77.6		Regulatory barriers	53.3
Competition	70.2		Efficacy issues of technology in trials	50
Finance barriers	69.6		Competition	49.3
Difficulty to carry out clinical trials	56.5		Finance barriers	43.3
Issues obtaining reimbursement	37.3		Return on investment/business model	33.3
Prices of therapy/product	32.9		Manufacturing issues	32.7
Changing strategies of acquirers	26.1		Prices of therapy/product	32
Small patient groups	19.9		Time consuming R&D	31.3
Risk/Safety	19.3		Difficulty to carry out clinical trials	26
Time consuming R&D	18.6		Wrong timing (too early or too late)	14
Wrong timing (too early or too late)	14.9		Risk/Safety	11.3
Barriers to collaborate (with academia or industry)	9.3		Issues obtaining reimbursement	10.7
Lack of preclinical support (validation)	3.7		Changing strategies of acquirers	8.7
Ethical barriers	1.9		Ethical barriers	4.7
			Barriers to collaborate (with academia or industry)	2.7

Table 3. Relative ranking of associated investment barriers for therapeutic areas and technology fields

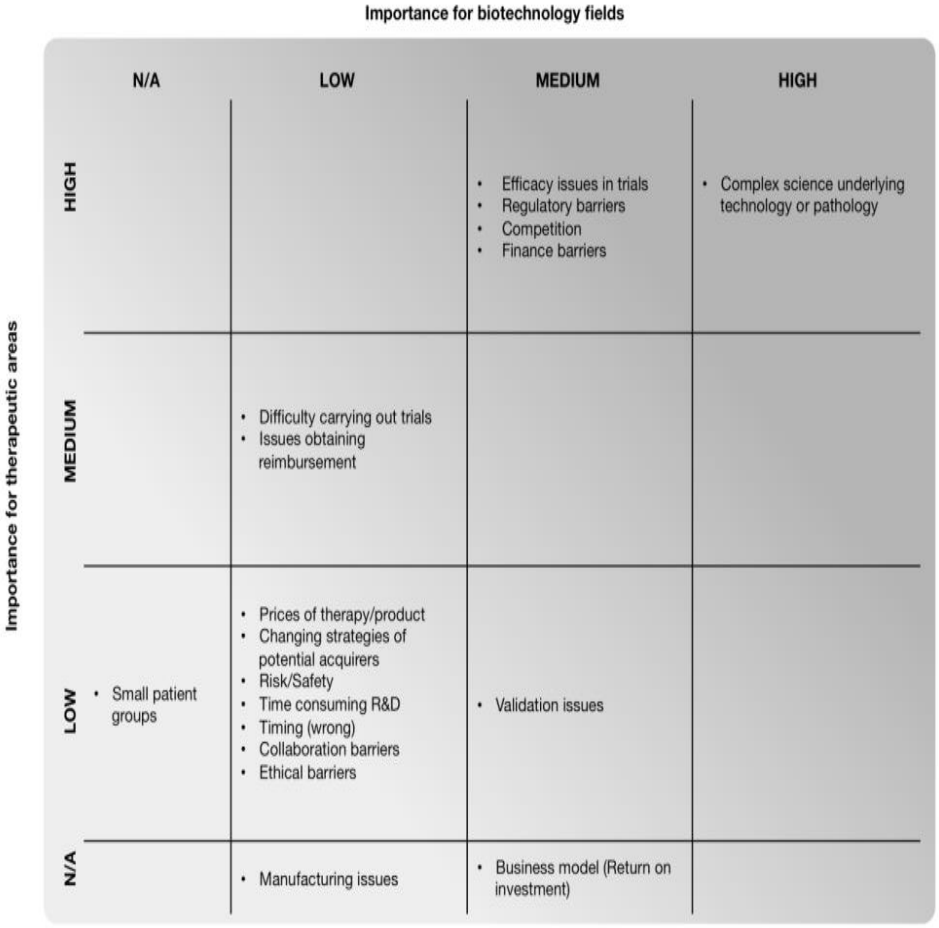

Figure 5. Matrix of investment barriers for therapeutic areas and technology fields divided in priority groups: Low: 0-33; Medium: 34-66; High: 67-100.

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, and 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.

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 (Fernald, *et al.*, 2015; Florida and Kenney, 1988) 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 (Fernald, *et al.*, 2014)

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.

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 (Fernald, *et al.*, 2015) Substantial amounts of investments in oncology drug development over previous years (Fernald, *et al.*, 2015; DiMasi and Grabowski, 2007) may have been influenced by the fact that the antibody market is heavily focused on oncology (among others; Pavlou and Belsey, 2005). 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 (Fernald, *et al.*, 2015). 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.

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 (Fernald, *et al.*, 2013; Pavlou and Belsey, 2005). 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%; Fernald, *et al.*, 2015). Therefore we can conclude that VCs' high prioritization and investments suggests that they still expect sufficient future economic development within this field. However, the second highest prioritized field mainly focused on promising advances in the cell therapy subfield involving technologies that are currently still in clinical research stages. Whereas, the third highest prioritized field, mainly due to gene therapy, has been promising for a while, but has only recently made it through clinical trials and onto the market (UniQure's Glybera®; Moran, 2012; Büning, 2013).

Considering the limits of technological development and a potentially imminent innovation cliff for protein related technologies (Fernald, *et al.*, 2013), 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 (Weenen, *et al.*, "PhD diss." 2014, 123-128; Fernald, *et al.*, 2013; Asthana, 1995). Gene therapy, for example, has been suggested to be a future disrupter of the protein therapeutics market (Datamonitor, 2013). 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 (Fernald, *et al.*, "VCs as gatekeepers"; Davis, *et al.*, 2009; Sander, 2000). 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 (Fernald, *et al.*, "VCs as gatekeepers"). Correspondingly, in our previous research we concluded that VCs invest in these DNA/RNA technologies for long-term cure and care macrotrends. 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.

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.

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, and High). Although this approach was

adopted from literature (Weenen, *et al.*, 2014; Balabanova, *et al.*, 2011), 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 (Giniatullina, *et al.*, 2013).

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.

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Cite This Article: Fernald KDS, Janssen NM, Claassen E (2018) "A Quantitative Prioritization and Barrier Analysis of Biotechnology fields and Therapeutic areas; A Venture Capital Perspective." ***International Journal of Drug Research and Technology*** Vol. 8 (3) :137-165.

INTERNATIONAL JOURNAL OF DRUG RESEARCH AND TECHNOLOGY