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How do university IPRs and R&D funding mechanisms affect innovation performance in the healthcare biotechnology industry? Evidence from Europe and the USA

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List of abbreviations

IPRs	Intellectual property rights
R&D	Research and development
IPO	Initial public offering
NIH	National Institutes of Health
FDA	Food and Drug Administration
NME	New molecular entity
VC	Venture capital
M&A	Mergers and acquisitions

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Abstract

This paper analyses determinants of innovation performance in the healthcare biotechnology industry to develop propositions for the future development of this growth-accelerating sector. We use empirical data to point to specific differences in this domain between Europe and USA. We build from a body of literature investigating the historical development of the industry, its expansion to new entities and new scientific fields and the role of different sources of funding of biomedical commercialization process. We use the theory of innovative enterprise and the "maximizing shareholder value" concept to elucidate determinants of biotechnology innovation performance. Our findings point to the weaknesses of the highly monetized US business model given the tendencies of the European biotechnology industry to emulate this model. We provide implications directed to facilitating sustainable growth of the sector.

INTRODUCTION

Recently, an increasing research interest has been directed to the healthcare biotechnology industry because it has been seen as an important driver of economic growth *(1)*. In this industry, new value is created through a lengthy, costly and risky process of research and development (R&D), clinical trials, regulatory approvals and final commercialization of findings. The success of this process depends on valuable inputs provided by key stakeholders – universities, venture capitalists, pharmaceutical firms, governments and emerging firms *(2)*. Previous studies of the determinants of innovation performance in biotechnology, although substantial, have mostly been devoted to investigating collaborative networks and spatial dimensions of innovation *(1, 3)*. Table A1 in appendix of the paper summarizes the key findings in this research area. We outline key dependent variables analysed and pertinent findings.

In this paper, we extend the existing research on biotechnology innovation by focusing on three groups of factors that have been suggested in prior research as important: university-derived intellectual property rights (IPRs), public investments into knowledge base at universities and other research institutions and commercialization funding mechanisms.

There are two main contributions of the study. First, in order to develop an overall overview of driving forces of innovation performance in healthcare biotechnology, we compare the dynamics in the US and the European biotechnology sectors. Our comparative analysis is conceptually grounded in neoclassical financial theory and the theory of innovative enterprise *(4)*. The predominant neoclassical financial theory assumes shareholder value maximization as a guiding principle in doing business while technologies and market conditions are given constraints in the system. The newer theory of innovative enterprise builds on the resource-based view foundations to propose that enterprises actively use R&D investment strategy and organizational structure to transform technological, market, cognitive, and behavioural conditions to generate performance outcomes, such as innovations. It offers an alternative, critical view on innovation creation, by investigating how the capital markets have profiled strategic priorities of biotech companies *(5)*. The rationale for choosing these two divergent theories in the comparative analysis is to allow for the conjecture that each highlights a specific aspect of the biotechnology business development, while applied together, they contribute to a better understanding of the whole process. We make contribution by using the two theories as complementary views in assessing how university-generated intellectual property rights, public investments into knowledge base and business funding mechanisms affect biotechnology innovation performance.

Second, in this study we combine findings from the neoclassical financial theory and the theory of innovative enterprise with statistical data in comparing the US and the European biotechnology industries. Although the widely accepted US biotechnology business model was questioned after the collapse of speculative markets in the financial crises of 2001 and 2008-2009, recently there have been clear tendencies to emulate the US model in the European biotechnology industry. By identifying key determinants that drive and motivate the biotechnology innovation performance, we develop specific managerial implications regarding success factors of companies that compete in European environments.

The paper is structured as follows. We begin by a short overview of the emergence of biotechnology industry. We review the impact of intellectual property rights on commercial exploitation of inventions, taking into account both the growing interest in the academic institutions' role in this process and ongoing debates concerning its wider repercussions for the progress of science. We continue by focusing on the role of knowledge base investments in biotechnology innovation. Finally, we provide an overview of commercialization funding mechanisms and compare the US and the European healthcare biotechnology industries through the conceptual lenses of the neoclassical theory and the theory of innovative enterprise. The paper concludes by discussion of our main findings and implications to practitioners.

THE EMERGENCE OF BIOTECHNOLOGY INDUSTRY

Biotechnology industry emerged in the USA in the late 1970s, preceded by the discovery of the double helix in 1953. It quickly spread to the UK, continental Europe and Asian-Pacific nations. Healthcare is a specific domain of research within biotechnology. It is based on complex macromolecules (recombinant proteins, genetically engineered vaccines; therapeutic monoclonal antibodies; and nucleic acid based therapeutics) derived from recombinant DNA technology, cell fusion, or processes involving genetic manipulation *(6)*. What makes healthcare biotechnology industry different from others is strong reliance on resources of multiple parties in commercializing the life science research results. The focus of this study is on the specific healthcare segment of biotechnology industry.

The reasons for the commercial attractiveness of the healthcare biotechnology industry are multiple: first, innovative technologies of genetic, protein, and cell and tissue engineering hold great promise in many biomedical application areas. Venture capitalists originally considered the biotechnology industry to have both attractive market potential and lasting importance *(7)* due to steadily aging population and expected increasing demand for age-related pharmaceuticals and therapeutics. Also, large pharmaceutical companies are less effective innovators than biotechnology firms due to spending more money on R&D, yet putting fewer drugs into the pipeline and thus, biotechnology companies help fill the need for innovation *(8)*. The interests of investors in the biotechnology industry have in the past decade shifted from genomics, proteomics and bioinformatics companies towards companies that can produce therapeutics, as opposed to those offering tools and databases *(7)*. In this respect, recent years have also been marked with the shift of interest from small-molecule "blockbuster" therapeutic products towards niche products, including orphan drugs (drugs which target rare diseases) and vaccines for developing countries, based on recombinant proteins, monoclonal antibodies and stem cells technologies *(9)*.

As shown in Table 1, in 2010 Europe had more biotechnology companies than the United States. However, the United States had almost as twice as many publicly listed companies; more than twice as many employees, spent more than three times more on R&D and generated three times as much revenue in total *(10)*. According to the same report *(10),* "commercial leaders" (companies that had 2009 revenues exceeding US$500 million) in the USA had positive net income, whereas the other companies mostly had negative income; however, the latter had higher growth rates (13%) when compared to the former (9%). Interestingly, the commercial leaders increased R&D spending by 7% in the respective period, while the other companies reduced R&D by 1%. Thus, emerging companies, which have historically been a vital source of innovation, started decreasing their R&D expenditures. In Europe, both commercial leaders' and other companies' growth was 12%; however, both groups increased R&D expenditures (commercial leaders for 7% and other companies for 4%).

TABLE 1

Overview of the US and European healthcare biotechnology in figures, 2009-10.

	USA (US$b)			Europe (US$b)			Croatia (US$b)		
	2010	2009	% change	2010	2009	% change	2010	2009	% change
Public company data									
Product sales	52,6	48,1	9%	n/a	n/a	n/a	0,015	0,029	-47%
Revenues	61,6	56,2	10%	17,26	15,40	12%	0,016	0,029	-43%
R&D expense	17,6	17,1	3%	4,51	4,29	5%	n/d	n/d	n/d
Net income (loss)	4,9	3,7	33%	(0,61)	(0,62)	-2%	(0,002)	(0,001)	-63%
Market capitalization	292,0	271,6	8%	78,89	62,94	25%	n/d	n/d	n/d
Number of employees	112.200	106.600	5%	49.060	48.660	1%	344	360	-4%
Financings									
Capital raised by public companies	16,3	13,5	21%	2,47	2,78	-11%	n/d	n/d	n/d
Number of IPOs	15	3	400%	10	3	233%	0	0	0%
Capital raised by private companies	4,4	4,6	-3,2%	1,36	1,05	29%	n/a	n/a	n/a
Number of companies									
Public companies	315	314	0,3%	172	167	2%	1	1	0%
Private companies	1.411	1.389	2%	1.662	1.675	-1%	1	1	0%
Public and private companies	1.726	1.703	1%	1.834	1.842	-0,5%	2	2	0%

*The data for Croatia are also shown, for illustrative purposes.
Source: Adapted from Ernst & Young (10), Croatian Competition Agency (11), EuropaBio (12) and Venture Evalutation (13)

At the same time, net income increased for the commercial leaders, while for the other companies it continued decreasing.

Most European biotechnology companies are micro or small, research-intensive firms, smaller than their US counterparts. We argue that such differences are partially due to a significantly greater availability of risk capital and debt provision in the USA as well as a longer tradition of the US biotechnology and venture capital industry. Also, the lower availability of venture capital in Europe than in the USA has largely been due to the under-development of European stock markets that would list the young entrepreneurial firms, and consequently, a lack of "exit strategy" possibilities for investors in firms *(7)*.

Based on the in-depth review of literature on driving forces of innovation in the healthcare biotechnology industry we identified three gaps in the existing body of knowledge. Little is known about how intellectual property rights system facilitates innovation performance *(14)*. Intellectual property rights (in what follows IPRs) have gained particular attention in the literature on biotechnology innovation after they have been widely used in new areas of scientific discoveries – life forms (such as genetically modified organisms) and new actors (academic and other non-profit research institutions). However, studies that explore how patenting activities at academic institutions produce innovations yield mixed findings. Most of the studies implicate that "locking up" of an increasing number of upstream life science inventions in patents negatively affects scientific progress and innovation *(15, 16, 17, 18, 14, 19)*. These findings allude to potential deficiencies in the present IPR system as an innovation-driving force at universities.

Although it is believed that innovation in the biotechnology industry is facilitated through public investments into knowledge base at universities and other research institutions, there is only limited evidence in support of this assumption *(20)*. Toole *(20)* points to the scant empirical verifications and finds that basic research funded by the US National Institutes of Health (NIH) has a significant and economic effect on the pharmaceutical innovation in the form of entry of new therapeutics to the market.

Finally, only few studies try to capture the relationship between funding mechanisms and innovation performance in healthcare biotechnology industry *(5, 21, 22)*. Most of them build on the fact that biotechnology companies have been characterized by the overall lack of innovations entering the market and subsequent profitability, and at the same time "bubbling" capital injections, predominantly in the USA over the past decade *(23)*.

TABLE 2

Ownership of IPRs at European universities.

Country	Institution	Inventor	Country	Institution	Inventor
Austria	□ (2002)		Italy		□ (2001/2005)
Belgium	□ (1997/98)		The Netherlands	□ (1995)	◊
Czech Republic	□ (1990)		Norway	□ (2002)	
CROATIA	□ (1996)		Poland	□ (2000)	
Denmark	□ (2000)		Slovak Republic	□ (2000)	
Finland	□ (2007/2010)	◊	Slovenia	□ (2006)	
France	□ (1982)		Spain	□ (1986)	
Germany	□ (2002)	◊	Sweden		□ (1949)
Greece	□ (1995)	◊	Switzerland	□ (1911)	
Hungary	□ (2006)		United Kingdom	□ (1977/1985)	

□ Ownership assignment of inventions.
◊ Inventor ownership is assigned on certain types of inventions.
In brackets: years in which last change in regulation took place.
Source: Adapted from Geuna and Rossi (26)

THE ROLE OF UNIVERSITY-ASSIGNED INTELLECTUAL PROPERTY RIGHTS IN BIOTECHNOLOGY INNOVATION PERFORMANCE

The adoption of the Patent and Trademark Amendments of 1980 in the USA (Bayh-Dole Act) is historically viewed as an event that marked the beginning of the global upsurge of knowledge and technology transfer activities from academic and other non-profit research institutions to the business sector. The Bayh-Dole Act gave non-profit institutions and small businesses the privilege to retain the property rights to inventions deriving from the state-funded research and hence relaxed government control over the commercial use of the results of publicly-funded research *(22)*.

This new legislation was later adopted in most countries in Europe *(24)*, although not with the same clarity: whereas in the USA ownership of university-generated IPRs obviously belongs to the university, some countries in Europe (for example, Austria, Denmark, Finland, Germany and Norway) traditionally had the so-called professor privilege, which gives university employees the IPRs to their inventions. Even though most of these countries in the 1990s and 2000s changed their legislation by assigning ownership to the university (see Table 2), university ownership has usually been weakly enforced, thus in reality leaving the decision on ownership to be negotiated *(25)*.

The expansion of proprietary interests and commercial considerations to new actors and new scientific fields *(27)* has been evaluated as desirable and appropriate for both the academic and the biotech industrial partners. The benefits include the expansion of basic research funding sources, less strict borders between basic and applied research and facilitated transfer of knowledge that supports the creation and growth of new technology firms *(28)*. It was argued that many state-funded inventions would be left unexploited unless the conditions for the transfer of intellectual property were made less restrictive *(22)*.

The most important challenge associated with the current IPR regime relates to patenting and exclusive licensing of fundamental technologies or upstream discoveries with broad application in life sciences. Dasgupta and David *(15)*, Murray and Stern *(19)* and others argue that such practices can restrict, and not stimulate future innovation, measured by the number of new useful products for human health. With an increasing body of upstream knowledge covered by patents, they claim, the costs of research increase, access to technologies is hindered and free flow of scientific knowledge needed for subsequent research becomes compromised. What is more, these changes can lead to redirection of research efforts towards other priorities. This concern has been captured in the phrase "the tragedy of the anti-commons", which has been used extensively to point to the problem of existence of multiple holders of rights to separately patentable inputs which combined form one product or resource *(16)*. Exclusive licensing of broadly useful patented research tools seems to be particularly problematic from the social welfare perspective. If a single patent holder exploits the invention himself exclusively, it limits new entrants who would compete to produce more efficient and cheaper medicines *(22),* leaving the research and commercial potential of an upstream discovery in subsequent research largely unexploited. Alternatively, society benefits more if such discoveries are made broadly available *(29)*.

Other challenges related to the expansion of IPRs and commercial activities at academic institutions are discussed by Henderson and colleagues *(17),* Kenney and

Patton *(30)* and others. These authors argue that legal systems introduced to encourage academia-industry knowledge transfer indeed increased the number of university-assigned patents in the USA. However, one of the consequences of the increased demands for patenting is a growing number of low quality or commercially irrelevant patents in hands of university technology transfer offices.

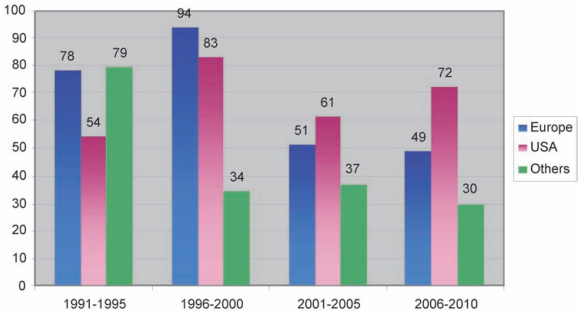
Building from these findings we contend that the change in the IPR regime towards patenting of life forms and university-assigned patenting has facilitated technology transfer from universities to the private sector, mostly through the creation of new biotechnology companies. What is more, the strong dependence of the healthcare biotechnology sector on science base, manifested primarily through monetization of IPRs *(5, 23)*, has increased its attractiveness to venture capitalists and private equity investors. Since the development of new biopharmaceutical products is a lengthy and unpredictable process, the biotechnology sector has usually been marked as critically dependent on the enforcement of patents as a means of protecting the future economic returns of inventions. However, we find that despite the positive impact on industry expansion, the new IPR regime does not necessarily increase biotech innovative performance (see Table A2 in Appendix for the summary of key findings in the literature). In this sector, IPRs are used by new companies to attract established companies, which in return enter into alliances with them or acquire them. IPRs thus enable young companies to send positive signals to investors, which are essential to obtain funding or quickly exit to capital markets through initial public offerings (IPOs), despite the fact that they typically lack products close to the market. This widely accepted operating principle may not go along with increased innovation performance. Indeed, recent studies show that strong intellectual property protection is a weaker determinant of successful development of innovative products than innovative capabilities of biotechnology firms to translate new technologies into innovative products and processes *(14)*. The critical importance of patents as a means of providing market advantage declines with the longer product development timelines, due to their limited term. This poses the need for development of capabilities of companies to absorb new technologies and to transform them into innovative products and processes. In addition, it was shown that the change in the IPR regime towards patenting of life forms and university patenting leads to "locking up" of an increasing number of broadly used inventions in patents, not necessarily commercially valuable. This increases the costs of subsequent research and potentially restricts innovation.

The described findings suggest some deficiencies in the present IPR system as a biotech innovation-driving force in the USA and Europe. In the final section we propose several solutions that, we argue, might overcome the problems related to misaligned interests of academic researchers-inventors, universities, technology transfer offices and licensees-biotechnology companies.

THE ROLE OF PUBLIC INVESTMENTS INTO KNOWLEDGE BASE IN BIOTECHNOLOGY INNOVATION

Biotechnology requires both the support of large and small enterprises that supply the critical inputs required in commercializing the industry's high-quality health products at low unit costs and a unique knowledge base that depends on intense interactions among scientists in research institutes and business enterprises *(22)*. Despite the fact that many scholars acknowledge the importance of public investments into science base at universities and other research-performing organisations for biotech innovation performance *(31)*, very few have shown empirical evidence in support of this claim *(20)*. An overview of the key studies investigating this relationship is provided in Table A3 in Appendix. The results generally indicate a high reliance of the biotechnology industry on public science. A particularly challenging discussion is presented by Angell *(32)*, who finds that more than one-third of the medicines marketed by big "pharma" are either licensed from universities or small biotech companies and that those few therapeutics that are truly innovative are usually based on taxpayer-supported research done in non-profit academic medical centres or at the National Institutes of Health. Furthermore, Stevens and colleagues *(33)* find that 9,3% of medicines approved by the US Food and Drug Administration (FDA) in the last 40 years were discovered by public sector research institutions. According to this view, the bearers of innovative activities in healthcare biotechnology are institutions funded by governments, which implies that biopharmaceutical companies overstate the development costs of new medicines, and consequently, product prices. However, one must not neglect the fact that a substantial part of experiments required to develop the efficient medicine, including the clinical trials, is done by the private sector.

In what follows, the US and the European practices of public investments into life science base are compared. The US National Institutes of Health (NIH) have been the major and, historically viewed, stable provider of funding for basic biomedical research at academic research laboratories, government research institutes and small businesses worldwide. Unlike venture capital and stock market investments, which have fluctuated widely from year to year, NIH funding increased in nominal terms in every single year from 1970 to 2009, except for a small decline in 2006 *(22)*. In 2011, NIH provided funds for more than 40.000 competitive research grants and more than 325.000 research personnel at more than 3.000 research institutions and small businesses *(34)*. In 2007, the investments by NIH represented 27% of the total biomedical research expenditures in the USA, making it the second largest contributor to biomedical research, next to industry (58%) *(35)*. These investments are indispenswable for the development of biotech industry knowledge base and consequently, responsible for venture capital and public equity flows into the sector *(22, 36)*.



Source: Adapted from Berghmans (37)

Figure 1. *Overview of NME approvals in the USA, Europe and other countries (includes Japan and Canada), 1991-2010.*

Unlike in the USA, in the European Union (EU) there is no single major public provider of funding of biomedical research. The majority (85%) of public funding is provided by various national funding organisations, while the remaining 15% is funded at the supranational level. The European Commission complements national policies primarily through its Framework Programmes (FP) and the European Research Council (ERC). In addition to the fragmented research, another difference from the USA refers to the concentration of funding in only a few countries, like Germany, France, UK or Finland *(37)*. Moreover, the major part of R&D funding in Europe is for "top-down" activities, whereas the USA favours "bottom-up" investigator-initiated research *(38)*. In Table 3 we compare Europe and the USA with respect to public investments in biomedical research. The figures show the lead of the USA over Europe. Looking at the time trends, the investments in Europe have mostly steadily grown between 1995 and 2007; however, an overall increase of 170% over that period was not sufficient to match a much stronger growth in the USA *(37)*.

Taken altogether, the healthcare biotechnology sector highly depends on public investments into knowledge base. Since the private sector needs a rapid return on invested capital, it cannot afford to support basic research. NIH, the European Commission and other governments' agencies worldwide thus produce a broad portfolio of fundamental discoveries, which provide pharmaceutical and biotechnology companies with expanded opportunities to transform these into diagnostic and therapeutic products. We have also discussed how very few studies have empirically assessed the actual impact of public investments into science base on biotechnology innovation performance. The most often used indicator of innovation performance is the number of approvals of new molecular entities (NMEs). Until the end of 1990s, the European biopharmaceutical industry was the major global developer of NMEs. As shown on Figure 1, the USA has taken the lead in the past decade, with 47,68% of all NME approvals in the period from 2006-2010 as compared to Europe's 32,45% *(37)*.

Another interesting trend that can be observed from Figure 1 is the decreasing number of total NME approvals over the past 15 years. Thus, the increase in funding levels was not accompanied by an increase in approvals of molecular entities, including medicines *(35)*. One explanation for this trend is the increasing cost and complexity of research, accompanied by increased regulatory requirements *(10, 37)*. Others find that research productivity should not be measured solely by the number of NME approvals, since broader factors, such as lower death rates, longer life expectancy and improved quality of life, are also relevant consequences of biomedical research investments *(35)*.

THE ROLE OF COMMERCIALIZATION FUNDING MECHANISMS IN FOSTERING BIOTECHNOLOGY INNOVATION

This section investigates the impact of funding mechanisms deployed by the US and the European healthcare biotechnology companies on innovation performance in the sector. The review addresses two periods: the period of dramatic increases in investments in the biotechnology industry and the period of rapid loss of trust of investors in this sector.

Triggers to the biotechnology "boom" and relations to innovation

Before and during 2000s, healthcare biotechnology industry in both the USA and Europe was characterized by a "boom" in investments, primarily from venture capital (VC) firms and R&D alliances with established pharmaceutical companies. In the period between 1999 and 2010, the largest jump in the level of investment occurred in 2000 in relation to 1999, amounting to 273% in the USA and 525% increase in Europe *(10)*. These substantial investments were present despite the fact that the industry mostly lacked market-ready products and profitability, with the exception of few commercially successful companies, such as Amgen and Genentech in the USA *(23)*. Following the literature review we identify two major explanations for this phenomenon: existence of initial public offerings (IPOs) and use of stock-based executive compensations.

First, IPOs have had two primary roles in the biotechnology industry: first, to quickly and lucratively attract funds for further therapeutic development *(42)*, and second, to provide venture capitalists and pharmaceutical companies with the opportunity to exit from their investments, often with a considerable return, without having to wait for product regulatory approvals and market entry *(22)*. It is known that the development of new medicines requires a process that can take up to 20 years, with highly uncertain prospects for success *(22)*. In contrast to the direct private investment in innovation, which involves facing technological, market and competitive uncertainty, and where "patient capital" is needed from investors, public shareholders' investments have been characterized by "short-termness", or need for financial liquidity. The

TABLE 3

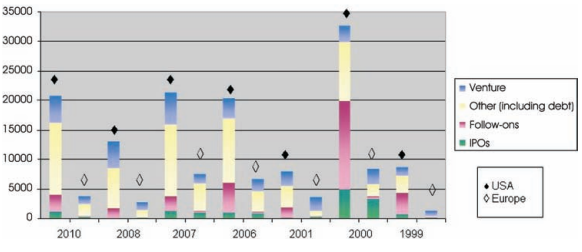
Public investments in biomedical research in the USA and Europe.

	USA	EU	CROATIA*
Major public provider of funding	National Institutes of Health (NIH)	No single major provider: – national organisations (85%) – EU (15%)	Ministry of Science, Education and Sports
Health R&D expenditures in the non-profit sectors, PPP US$b (2007)	32,0	20,3	0,045
Budget for health of the major public provider of funding, US$b (2011)	30,7 (NIH)	0,86 (European Commission)	0,044
% of public funding going to biomedical research (2011)	50%	30%	10%
% of GDP committed to public funding of health research (2008)	0,222%	0,054%	0,069%

* The data shown for Croatia refer to 2009.
Source: Adapted and compiled from Wiecek (39), Berghmans, *et al. (37),* the European Public Health Association *(40)* and the Croatian Bureau of Statistics *(41)*

operating principle becomes speculation, which produces gains for investors based on their assumption of existence of "greater fools", who will remain ready to buy the over--priced shares on the market. The accumulation of innovative capabilities is here set aside since more effort is often devoted to reaching an IPO than to commercialization *(42)*.

Second, in the USA, stock markets for new technologies have had longer tradition and higher relevance than in Europe. Only minorities of European companies have managed to access stock markets, primarily through IPOs *(12)*. Even though the share of IPOs in the total European biotechnology financing rarely exceeded 15%, in 2000 it was almost 40%, compared with the US 15% in the same period *(10)*. Figure 2 shows the extent and distribution of biotechnology financings in the USA and Europe in selected years over the period between 1999 and 2010. In addition to the significant difference in the level of financing, the USA and Europe differed in the relative importance of funding mechanisms. While "other" sources, mostly debt, dominated in the USA, in Europe venture capital generally had the highest relative importance. Moreover,



Source: Adapted from Ernst&Young (10).

Figure 2. *Overview of biotechnology industry financings in selected years (USA and Europe).*

secondary ("follow-on") stock offerings on the public markets were common in the USA and rare in Europe.

Although underdeveloped, fragmented, illiquid and without the necessary support structures *(43),* stock markets were a playground for speculations in Europe. Cooke's *(44)* analysis of top European biotechnology companies pointed to unusual difference between valuation (market capitalization) and their much lower turnover, which was assigned to the speculative confidence of stock market investors in the industry characterized by non-profitability of the majority of its enterprises. Similarly, in her case study of Swedish biotechnology companies, Nilsson *(45)* reported much stock speculation and value fluctuation for some of the companies due to limited patience of stock market investors, which led to a stance that it might have been wiser to postpone going public until agreements with established pharmaceutical companies had been reached. The result of such an approach are loss-making biotechnology companies on the stock market, with strong research results, alliances with large pharmaceutical firms, or products going through clinical trials, using stock market valuations to ensure the expansion of firm activities *(46)*. Both in Europe and in the USA, speculative stock markets have been highly sensitive to media news and expectations at every stage of the product development process, and particularly concerning the results of the clinical trials of potential therapeutics *(5)*.

The second explanation for the occurrence of substantial investment capital in the biotechnology industry can be related to the exercise of executives' stock-based compensations. This practice stems from the USA and was gradually expanded to non-executive employees, as an instrument to attract highly skilled personnel to high-tech start-up companies *(42)*. The European legal and tax systems discouraged stock options until the beginning of the 21st century *(44)*. However, empirical

evidence shows that stock-based compensations to executives and employees are at present regularly exercised also in Europe *(47)*. As discussed by Casper, and Kettler *(46)*, the legalization of stock options as performance incentives in the UK has been as dangerous as stimulating, since they are highly dependent on the stock price of public companies and lowering of stock prices may motivate entrepreneurial scientists to seek performance rewards in established pharmaceutical companies, rather than in biotech companies. Moreover, Lazonick and colleagues *(22, 47)* argue that stock-based compensations can stimulate stock manipulation through buybacks due to their short-term orientation, and in that way challenge the extent of investments of biotechnology companies in generation of innovative products. Specifically, by making resource allocation decisions in a way that productive resources are not developed or utilized, but deployed to make primarily personal gains, top managers may jeopardize new value creation and long-term stability and growth of their companies.

In summary, IPOs and stock-based executive compensations mechanisms largely facilitated the industry attractiveness regardless of its overall lack of products close to the market and subsequently, lack of profitability.

Triggers and consequences of the burst of the "biotechnology bubble"

This section identifies two major origins of the burst of the "biotechnology bubble": substantial dependence of the industry on speculative stock markets and inadequate expertise of investors.

The first cause of sharp decreases in investments in the biotechnology industry is the dependence of companies on stock markets for funding commercialization-related activities. The finance-driven innovation model *(21)* mostly disregards the need of the biotechnology industry for "patient" capital as the main motivation of investors remains a quick exit from their investments through speculations and securing of gains in the short term. This leads to discrepancy between the companies' value on the stock markets and actual performance, which disrupts the long-term sustainability of the industry. Although specific for the USA, the reliance on speculative stock markets has been present in Europe as well. One illustrative example is British Biotechnology, formerly Europe's largest biotechnology company in terms of market capitalization and R&D costs, which experienced a stock market decline of $2 million in 1997 because of delays in gaining approval for its two leading products. This event highly affected the level of confidence of the European investors in the sector *(44)*. Following the crash of NASDAQ at the beginning of the 21st century, many European stock markets collapsed *(47)*. For example, the German *Neuer Markt* collapsed after only five years of existence, after it had lost 96% of its value in two years *(8)*. The facilitated access to stock markets is therefore estimated as positive with respect to necessary fund raising, but it can also be problematic for companies without capacity to meet expectations and cause dissatisfaction on the stock market, which easily spills over to other biotechnology firms notwithstanding their performance, as it occurred in 2001 and 2008 (Table 4). Investors in the biotechnology industry were then no longer motivated to invest because of weaker exit opportunities and IPOs seriously decreased *(7, 22)*.

The second cause of the lost trust in the biotechnology industry was more dominant in Europe than in the USA. It springs from the lack of industry expertise of investors. The Critical I study of biotechnology in Europe *(12)* discusses Europe's "localized and inward-looking" investors and not sufficiently mature industry to attract debt finance for growth-by-acquisition strategy of the US biotechnology industry. Moreover, venture capitalists are evaluated as investors that inhibit innovation, because of their weak specialization, or support of too many companies with insufficient funding. This is closely related to the fragmentation of the European venture capital industry *(43)*, not only in countries with no tradition in biotechnology entrepreneurship, such as Portugal, Spain and Italy, but also in mature ones, like Germany *(46)*.

Funding crises produced the following effects: increased concentration of funding, change in investment targets, more prominent role of the public sector, increasing share of debt financing, and cost-cutting. First, increased concentration of funding in a smaller number of companies is observed both in the USA and in Europe. In 2010 in the USA, top 20% companies in raising funds received 82,6% of capital (compared to 78,5% in 2009 and 68,7% in 2005), whereas the bottom 20% of companies raised only 0,4% of funds (compared to 0,6% in 2009). Moreover, funding often represented reinvestments in existing portfolio companies rather than in new ones *(10)*. The rising unevenness in funding allocation distribution is expected to result in the return to quality, at the expense of the number of IPOs, but with larger amounts of funds on average raised than had been the case in the period of a "boom" *(42)*. Thus, restrictions in the access to funding forces companies to focus their resources to a more narrow set of technologies. They are required to concentrate on achieving short-term milestones to satisfy their investors, which have become more careful in assessing regulatory and commercial risks earlier in a product's development cycle. Short-term milestones enable the VC investors exiting earlier even in the period of higher caution and higher selectivity of IPO investors, preferably through mergers and acquisitions (M&As), which may not always be in the interest of a company *(10)*.

Second, another effect of the burst of the "bubble" is refocused investors' preference towards investments of lower risk. An example is their preference for late-stage clinical trials rather than for discovery of therapeutics. According to Dorsey and colleagues *(35)*, such practice is accompanied by a more frequent purchasing of small biotechnology firms by large pharmaceutical companies as an alternative to in-house investing to early stage, discovery research. This trend is problematic because higher risk investments are essential to fill the gap between government-sponsored research and commercial research.

Third, public sector takes a bigger role in industry financing, particularly in Europe. By launching new national and supranational funding and fiscal initiatives *(43)*, the governments aim to bridge biotechnology financing gaps. Moreover, recent initiatives in frame of the European Framework Programmes for Health recognize the deficiencies of the generalist measures and recognize the need for a narrower-scope specialized approach in defining funding priorities.

Fourth, identified consequence of the burst of the biotechnology "bubble" is increasing importance of debt financing, specifically in the USA. Even though the most recent industry reports show that in 2010 biotechnology companies managed to attract amounts of funding similar to those raised during the "boom" preceding the second crisis *(10)*, this recovery mostly came from debt funding of mature profitable companies, to refinance existing debt and for stock buybacks and acquisitions. If these funding sources are excluded, "innovation capital" raised by US companies was in fact in decline by 21% in 2010.

Finally, a very frequent effect of the crisis, both in the USA and in Europe, is cost-cutting, primarily in R&D expenditures. In 2009, 64% of US companies and 55% of European companies decreased their R&D spending. With this step, restructuring of the companies with a subsequent negative impact on employment becomes apparent and future innovation in the form of new products in the pipeline becomes compromised *(43)*. According to a report published in Nature Biotechnology *(48),* those companies that increase their R&D expenditures explain their strategy of constant product innovation as indispensable to survive, in particular in a time when a significant number of marketed products are losing patent protection.

The evidence presented in this section indicates that not all commercialization funding mechanisms increase biotech innovation performance. This primarily refers to stock-market-related practices that foster short-term gains of executives and investors and thus disregard the need of the biotechnology industry for "patient" capital.

We find that the European biotechnology industry has been largely following the US practice, driven by stronger performance of the latter in terms of R&D expenditures, patented inventions, revenues and new molecular entity approvals. Second, a thorough analysis of the industry dynamics revealed the deficiencies of the present IPR system tailored to boost the exploitation of academic research results, a decrease in the "innovation capital" levels and industry innovative performance (measured by the number of new molecular entities) despite the increased overall funding levels, and the fragility of the finance--driven business model in both regions observed. This suggests that the present "shareholder value-oriented" system may not be compatible with the long-term sustainability of the biotechnology industry.

INNOVATION IN THE US AND THE EUROPEAN BIOTECHNOLOGY INDUSTRY: A COMPARATIVE ANALYSIS

We compare the US and the European industries using the neoclassical financial theory and the theory of innovative enterprise to propose an overview of driving forces of innovation in healthcare biotechnology. In specifics, we critically compare the US and the European practices with respect to innovation determinants identified in this paper: university-generated intellectual property rights, public investments into knowledge base and commercialisation funding mechanisms.

The main characteristic of the neoclassical financial theory is that it takes market price signals and shareholder value maximization as guiding principles in doing business, while it treats technology and market conditions as exogenous factors. In contrast, the theory of innovative enterprise builds on the resource-based view roots and treats technology, market and other conditions as dynamic, transformable, endogenous factors. It further argues that innovative capacity to create new products and processes is what drives innovations and economic growth *(4)*. The innovative performance depends on "organisational integration" of participants in a specialized division of labour, who collaborate toward the achievement of common goals, "strategic control" in executive-made resource allocation decisions, and "financial commitment" of resources to sustain the innovation process until it can generate viable products that can produce financial returns *(49)*.

By selecting these two theories as a framework for our analysis, we recognize that although the neoclassical financial theory is commonly accepted in modern theory and practice, it mostly does not consider the role of different in-house and environmental conditions that have been shaping innovation performance in the healthcare biotechnology industry. The theory of innovative enterprise is relevant because it combines theory and history in investigating how conditions such as financial markets or government investments impact strategic priorities of biotechnology companies *(5)*. Applied together, these two theories provide a crucial contribution in understanding why biotechnology evolved into a "shareholder value--oriented" industry and how this dominant practice has been affecting the industry innovative performance. Methodologically, we perform this critical comparison by combining empirical evidence from the US and the European settings with theoretical discussions on the role of university IPRs, public investments into knowledge base and commercialisation funding mechanisms in stimulating innovation performance. The results are summarized in Table 5 below (refer to Table A4 in Appendix for a more detailed overview).

As discussed in the table, the neoclassical theory promotes broad university patenting as a means of securing optimal innovation performance and maximisation of investor rewards while the theory of innovative enterprise evaluates broad IPRs and exclusive licensing as harmful in regards to efficient exploitation of inventions

TABLE 4

Capital raised in the biotechnology industry in USA and Europe, 2000-10 (US$m).

		2010	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000
IPOs	**USA**	1.097	697	6	1.238	944	626	1.618	448	456	208	4.997
	Europe	219	137	100	978	905	1.066	484	42	191	280	3.294
Follow-ons	**USA**	2.971	5.165	1.715	2.494	5.114	3.952	2.846	2.825	838	1.695	14.964
	Europe	207	792	40	263	279	377	273	584	65	171	499
Other	**USA**	12.242	7.617	6.832	12.195	10.953	6.788	8.964	8.306	5.242	3.635	9.987
	Europe	2.044	1.845	1.245	4.714	3.452	1.493	2.183	1.708	236	908	1.983
Venture	**USA**	4.409	4.556	4.445	5.464	3.302	3.328	3.551	2.826	2.164	2.392	2.773
	Europe	1.355	1.049	1.368	1.606	2.006	1.895	2.017	1.226	1.768	2.250	2.670
TOTAL USA		**20.719**	**18.035**	**12.998**	**21.391**	**20.313**	**14.694**	**16.979**	**14.405**	**8.700**	**7.930**	**32.721**
TOTAL Europe		**3.825**	**3.823**	**2.753**	**7.561**	**6.642**	**4.831**	**4.959**	**3.561**	**2.260**	**3.609**	**8.447**
TOTAL USA + Europe		**24.544**	**21.858**	**15.751**	**28.952**	**26.955**	**19.525**	**21.938**	**17.966**	**10.960**	**11.539**	**41.168**

Source: Adapted from Ernst&Young (2011)

in subsequent research. According to the latter theory, biotech enterprises should instead focus on development of innovative capabilities and academic institutions in both regions reconsider their "patent-as-much-as-possible" policies. Next, unlike the neoclassical theory, which views public investments into science base as market failure correction mechanisms, the theory of innovative enterprise acknowledges the vital role of government basic research funding and subsidies in stimulating the development of the US and European biotech industry. Both theories acknowledge that commercial success is boosted by opportunities for accessing high-risk finance and attracting and motivating entrepreneurial scientists and managers *(46)*. So far, the US companies have been more successful in translating research into biopharmaceutical end products than EU companies *(50)*. However, both in the USA and in Europe there has been a dominant stance on the side of investors that the most favourable way to maximize the shareholder value in the short-run is "selling to revenue-hungry pharmaceutical companies that have to complement their internal R&D efforts by looking externally for breakthrough innovations and products, rather than by pursuing high risk R&D" *(10)*. According to the theory of innovative enterprise, the consequence of this strategy is an increasing gap between the high values announced and the funds actually deployed for development and utilization of productive resources to increase innovative performance.

DISCUSSION AND IMPLICATIONS

The aim of this paper was to analyse the role of university-generated intellectual property rights, public investments into knowledge base and commercialization funding mechanisms in stimulating innovation performance in healthcare biotechnology industry. We focused our research on these three determinants of innovation performance following the in-depth literature review, which pointed to limited knowledge on key determinants that drive the development of this sector. In our analysis we directly compared the US and the European healthcare biotechnology industries, relying on conceptualization extended by statistical data. Our conceptual frameworks were two grounding theories, neoclassical financial theory and the theory of innovative enterprise, which were contrasted assuming the theoretical and practical dominance of the former and historical perspective of the latter in evaluating innovation-influencing factors in the biotechnology industry. In this concluding section, we summarize our findings and develop implications for practitioners and future research avenues.

Legislation regarding intellectual property rights was changed in order to allow universities and other entities involved in life science research to protect their discoveries by patents, initially in the USA and later in most countries in Europe. Evaluated as beneficial for commercial exploitation of university-generated research results, biotechnology venture creation and (particularly by neoclassical economists) necessary in order to protect the future economic returns of inventions, patenting with wide scope and exclusive licensing of upstream discoveries in this field was also discussed as harmful for future innovative output. This is primarily due to its blocking impact on efficient use of protected results in subsequent research. Even though the change in the IPR regime positively affected the extent of university patenting, it has also led to a lot of commercially irrelevant patents. Another deficiency in the present IPR system as an innovation-driving force is related to the substantial use of patents by new biotech companies to attract acquisitions by established companies, which enables them to quickly exit to capital markets, despite the lack of products close to the market. The theory of innovative enterprise argues that patents are a weaker deter-

minant of successful development of innovative products when compared to innovative capabilities to translate new technologies into innovative products and processes.

The theory of innovative enterprise also acknowledges that public investments into knowledge base at universities and other research institutions are indispensible for the development of innovative activities in the biotechnology industry and its competitiveness, as companies lack resources and often specific knowledge to invest in basic infrastructure and research projects aimed to reveal the fundamental mechanisms in molecular biology, which are in the background of discovery of any diagnostic tool or therapeutic agent. For that reason, companies rely on investments by governments, in the form of research grants through universities or direct grants to the company, as well as on knowledge available at academic and other non-profit research institutions. The US National Institutes of Health are the major provider of funding for basic biomedical research, not only in the USA, but also globally, while in Europe the majority of basic funding is provided at the level of member countries. Neoclassical theory also stipulates the importance of government investments into knowledge base; however, it argues that the reason for government involvement is related to the existence of market failures, which discourage biotechnology firms from funding their own research due to high risks and long terms specific for the industry and their inability to appropriate all the benefits.

Finally, the analysis of different mechanisms of funding of biotechnology commercialization process revealed that speculative stock markets attracted substantial funding flows into this sector in the USA, and less so in Europe, primarily through IPOs and exercise of stock-based compensations. Substantial investments were present due to quick exit opportunities for investors, and regardless of the fact that most companies involved were principally R&D companies, with the lack of profitability and virtually no products on the market. This, in practice still dominant business model, highly relies on the neoclassical financial theory and its emphasis on short-term maximisation of shareholder value in an industry characterized by long terms and high risks. However, it was questioned after the collapse of speculative markets in the financial crisis of 2008-2009, which largely affected the USA. The crisis affected European biotechnology industry as well, however, not only because of its attempts to emulate the US speculative stock markets, but also because of the generally weak expertise and fragmentation of investors, primarily venture capitalists. We concluded our analysis with the identification of effects of the funding crises in the USA and Europe, which include increased concentration of funding, change in investment targets, more prominent role of the public sector, increasing share of debt financing, and cost-cutting. Some of these effects, like increasing share of debt financing, cost-cutting and refocusing of investors' preferences towards investments of lower risk, were evaluated as unfavourable for the extent of future innovation.

Implications and future research avenues

Our study has indicated that the US biotech business model relies heavily on monetization of IPRs generated at academic institutions, government investments in high-risk research, public capital markets and financial institutions. Its European counterpart has been striving to emulate that model because of its better performance in most of the indicators. Yet, we also provided evidence that the financial markets-driven US sector impedes innovation performance due to its focusing on short-term financial gains, tied to stock-price fluctuations and stock-based compensations, in the industry which demands "patient" capital. This questions the long-term sustainability of the biotechnology industry and calls for several recommendations for enterprises that compete in the European environment.

First, most European countries have adopted their IPR legislations and technology transfer policies in line with the US example, driven by the quick expansion of the US biotech industry thanks to its excellent connections with the academic institutions, as generators of basic discoveries. However, since the conducted empirical studies revealed an increasing number of commercially irrelevant university-generated patents, we propose that European academic institutions should reconsider their present technology transfer policies: instead of "pushing" their technology transfer offices to patent as much as possible in a "monolithic way", universities should invest in developing effective pipelines for critical evaluation of potentially patentable inventions. In that way, they will reduce irrelevant activities in technology transfer offices; reduce the pressure on basic academic research and decrease the costs of legal services associated with IP protection (e.g., application filing, enforcement). On top of that, there have recently been attempts to propose alternative IPR regimes. These include the return to inventor ownership and compulsory non-exclusive licensing *(30, 35, 54)*. Recently initiated in the USA and already existing in Germany, compulsory licensing should enable innovative companies to receive a return on their investment in research. At the same time, users would have access to technology at reasonable prices.

Second, an area where the European industry should emulate the US biotechnology is bigger interrelatedness of basic science and clinical development, as proposed already by Owen-Smith and colleagues *(3)*. They showed that the US public research organizations and small biotechnology companies conduct decentralized R&D across multiple areas and stages of the development process, while Europe has regional specialization with a less diverse group of public research organizations working in a smaller number of areas, with a considerably more centralized funding within nations. Europe thus needs to make changes in the division of labour in order to support innovation.

Third, in order to encourage the sustainable development, the European biotech industry should invest more

TABLE 5

Innovation-influencing factors: a comparison of the US and the European biotechnology industries.

Innovation-influencing factor	USA	Europe	Theoretical framework
University-generated IPRs	IPR laws boosted academic research exploitation *(22)*. Academic patenting increased, but its importance decreased *(18)*.	Most countries emulate the US Bayh-Dole Act *(24)*. High costs and heavy administration related to patenting impede innovation *(50)*.	**Neoclassical financial theory:** Without IPRs on publicly funded research, the innovative output will be suboptimal and innovators will be under-rewarded *(14)*. Broadening the scope is desirable – it maximises the reward to investors *(51)*. **Theory of innovative enterprise**: In the case of public research, the incentive in the form of IPR laws is not needed because invention has already been paid for *(14)*. With upstream discoveries, exclusive exploitation of a patent limits new entrants who would compete to produce more efficient and cheaper medicines *(22)*.
Public investments into knowledge base	Substantial government investment in knowledge base has financed US biotechnology and motivated equity investors throughout the history *(22, 32)*.	Biotechnology development is boosted through government-initiated technology transfer initiatives, seed funding schemes, and taxation schemes *(12)*.	**Neoclassical financial theory:** Government policy should be limited to market failure situations. One example is government funding of basic research, which overcomes the reluctance of firms to fund their own research because of their inability to appropriate all the benefits *(52)*. **Theory of innovative enterprise**: Governments have a critical role in developing the knowledge base indispensable for international competitiveness of biotechnology, through infrastructural investments that are of far too broad scope for companies *(42)*.
Funding mechanisms *Speculative stock markets* *– IPOs*	Industry funding mechanisms have been characterized by stock market investors investing in IPOs of R&D companies *(22)*	To a lesser extent than in the US, but equity investors are also motivated by speculative gains, extract value, even though the products are not yet market-close *(47)*.	**Neoclassical financial theory:** The healthcare biotechnology business model is financialized, shareholder distribution-oriented; products in pipeline and firms trade for shareholder value in speculative processes *(5)*. **Theory of innovative enterprise**: The extent of financial commitment required to sustain an investment strategy depends on the size of the investments in productive resources and duration of time required to generate financial returns *(49)*.
– Stock buybacks *Debt and venture capital* *Established pharma companies*	Stock-based compensations are regular *(47)*. Companies are supported by stock markets and financial institutions lending money secured only by stock. Debt funding dominates the sector. In order to maximize shareholder value, firms are typically acquired by big pharma, instead of pursuing high-risk R&D *(10)*.	The industry is not mature enough to attract debt finance for growth-by-acquisition strategy of the US industry *(12)*. Venture capital industry is fragmented, with weak specialization *(43)*. Companies mostly license out their inventions to big pharma, get acquired by US companies or move to the USA to access their markets and thus export value-creating R&D *(12)*.	**Neoclassical financial theory:** Short-term earnings per share and share price are the most important measures of corporate performance. Only shareholders are "residual claimants" as they do not have "guaranteed contractual stakes" *(42)*. By giving managers stock-based compensation, shareholders mitigate the principal-agent problem – ensure that managers allocate resources efficiently *(53)*. **Theory of innovative enterprise**: Shareholders are not the only "residual claimants" – state is also without guaranteed return on investment, to taxpayers *(42)*. Productivity problems of the US biotechnology industry were not due to a shortage of funding, but due to the highly monetized business model which undermines innovation *(22)*. Acquisitions of small companies by established pharma companies as a dominant business strategy prevent Europe from developing self-sustainable, larger biotech companies and endangers the extent of future innovation *(50)*. In both regions, this trend negatively affects the investments in early stage research by big pharma *(35)*.

effort in the direction of strategic selection of fewer funding priorities and long-term focus on therapeutic and diagnostic products that have the potential for viable commercial success *(55)*. An opportunity exists in the development of biosimilars (which assume an R&D-intensive activity, unlike the production of generic pharmaceuticals), due to the fact that the patent protection of many biotechnology medicines will expire in the forthcoming years. Developing treatments for conditions with very small patient populations, or rare diseases, represents an opportunity that has already been recognized on both sides of the Atlantic *(10)* as a response to the challenge of unsustainable "blockbuster" medicines. Such strategies should be accompanied by adequate policies, which would promote greater specialisation and the need for "patient" capital to venture capitalists and other types of investors. As discussed by Casper and Kettler *(46)* in their comparison of the US, UK and German settings, due to limited skills in technology transfer and bottlenecks in the supply of personnel in relation to the science base, UK was shown to be unsuccessful in emulating the US "high--return but high-risk radical innovation" model, despite the developed capital markets. In the same period, the German biotechnology sector benefited from the "long--term and incremental innovation" business models, by combining entrepreneurial endeavours with stable institutional frameworks featured by government incentives, regulatory labour laws and "stakeholder" supervision.

Finally, we point to some avenues for prospective research. Since there are still too few studies empirically assessing the impact of public investments into science base on innovation performance, we propose that future efforts should take this direction. Namely, it would be very interesting to investigate further why the most recent industry reports point to decreases in new molecular entity approvals despite the increasing R&D and commercialisation funding levels in both regions included in this study. Also, one limitation of this research is that it does not take into account the diversity of national biotechnology industries across Europe in assessing the determinants of innovative performance. Instead, the study deploys a "big picture" approach in comparing the two regions which represent the key global players in the biotech industry. Future research endeavours should consider the heterogeneity of European national IPR as well as R&D and commercialisation funding systems.

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APPENDIX

** Full references available from authors on request*

TABLE A1

Overview of key studies on networks and spatial dimensions of innovation in the biotechnology industry.

Important authors	Setting	Key findings	Dependent variable(s)
Shan, Walker and Kogut (1994)	USA	While cooperative agreements with large firms affect innovation output of small firms, the opposite is not the case.	– innovative output of start-ups – number of agreements with commercial firms
Powell, Koput and Smith-Doerr (1996)	USA	Innovation and growth in industries with a complex and expanding knowledge base are achieved through networks of learning.	– subsequent number and diversity of R&D ties – network position in terms of central connectivity – rates of firm growth
Deeds and Hill (1996)	USA	There is an inverted U-shaped relationship between the number of strategic alliances and the rate of new product development.	– rate of new product development
Owen-Smith et al. (2002)	USA and Europe	In contrast to the USA, public research organizations and small biopharmaceutical companies in Europe are regionally specialized, less diverse, working in a smaller number of areas, with a more centralized funding within nations and weaker integration of basic and clinical studies.	
George, Zahra and Wood (2002)	USA	Companies having alliances with universities have lower R&D expenses and higher levels of innovative output, but not necessarily higher financial performance than similar firms without such alliances.	– number of patents – number of products in the market – number of products under development
Owen-Smith and Powell (2004)	USA	Membership in a geographically collocated network of collaborations, centrality in a geographically dispersed network and dominance of public research organizations in a network positively affect innovation.	– number of patents assigned to corporations
Faems, Van Looy and Debackere (2005)	Europe, Belgium	Interorganizational collaboration positively affects innovative performance, but varies depending on the type of the collaborators.	– proportion of turnover attributed to new and improved products
Phene, Fladmoe-Lindquist and Marsh (2006)	USA	Technologically distant knowledge of national origin has a curvilinear effect and technologically proximate knowledge of international origin has a positive effect on breakthrough innovation.	– breakthrough innovations (patents with the highest number of citations)

TABLE A2

Overview of key studies on university-generated IPRs and innovation in biotechnology.

Setting	Authors	Study type	Key findings	Dependent variable(s)
USA	Dasgupta and David (1994)	Conceptual	Growing "privatization of the scientific commons" may endanger scientific and technological progress, particularly by restricting access to upstream discoveries that are essential for subsequent research.	
USA	Heller and Eisenberg (1998)	Conceptual	Commercialization of biomedical research can stimulate private investments in science, but it can also produce a "tragedy of the anti-commons", through a rise of fragmented and overlapping intellectual property rights. This is due to the high transaction costs of bargaining, heterogeneous interests among owners, and cognitive biases of life science researchers.	
USA	Henderson, Jaffe and Trajtenberg (1998)	Empirical	Explosion in US university patenting in the period from 1965 to 1992 has been accompanied by a decrease in their importance, measured by patent citations.	– patent importance – patent generality
17 OECD countries	Furman, Porter and Stern (2002)	Empirical	Variation in innovativeness across countries is due to differences in the level of R&D personnel and spending, extent of IP protection and openness to international trade; share of research performed by academia and funded by the private sector.	– number of "international patents"
USA	Nightingale and Martin (2004)	Empirical	The "biotechnology revolution" model of technological change along the innovation path from basic research to clinical development is not supported by the empirical evidence: R&D expenditures increased tenfold, while patenting output increased only sevenfold, and only a handful of new chemical entities were approved by the FDA over the period 1983–2003. The slowdown in innovation is explained by difficulties in keeping pace with the increasingly complicated new scientific and technological base.	
USA, Europe, Japan, India	Orsenigo, Dosi and Mazzucato (2006)	Conceptual	A tighter IPR regime does not automatically lead to an increase in innovative activities in the countries which introduced substantial institutional changes in the IPR systems.	
Nat Biotech articles and USPTO patents	Murray and Stern (2007)	Empirical	Patenting has a modest negative effect on free flow of scientific knowledge; citation rate for a scientific publication falls after formal IP rights associated with that publication are granted.	– number of forward citations

TABLE A3

Overview of key studies on public investments into knowledge base and biotech innovation.

Setting	Authors	Study type	Key findings	Dependent variable(s)
USA; top 10 biotech countries	Zucker and Darby (1996)	Empirical	The larger the extent of collaboration of a company with star scientists, the bigger its success, particularly in the USA.	– products in development – products on the market – employment growth
USA	McMillan, Narin and Deeds (2000)	Empirical	Biotechnology industry relies on public science much more heavily than other industries, including pharmaceutical, for very basic scientific research.	– non-patent references (NPRs) on patents
France	Autant-Bernard (2001)	Empirical	Public research produces positive effects in increasing innovation level; however, the positive externalities are limited to geographic space.	– patents
USA	Gittelman and Kogut (2003)	Empirical	Publication, collaboration, and science intensity are correlated with patented innovations; there is a negative relationship between important scientific papers and high-impact innovations.	– cumulative forward citation frequencies to an individual patent assigned to firms
USA	Angell (2004)	Conceptual	A large part of the upfront search and innovation costs are borne by the public sector. Truly innovative therapeutics almost always originate from publicly funded laboratories.	
USA	Toole (2012)	Empirical	NIH-funded basic research and market size have an economically and statistically significant effect on pharmaceutical innovation in the form of entry of new medicines.	– number of new medicines (new molecular entities) applications

TABLE A4

Innovation-influencing factors: a comparison of the US and the European biotechnology industries.

Innovation-influencing factor	USA	Europe	Theoretical framework
University-generated IPRs	Regulatory changes associated with IPRs, in particular the Bayh-Dole Act, encouraged commercialization of federally funded research at universities and establishment of new biotech start-ups (Lazonick and Tulum 2011). Although university patenting increased, its importance, measured by patent citations, decreased (Henderson, *et al.,* 1998; Nightingale and Martin, 2004).	Most countries emulate the US Bayh-Dole Act (Geuna and Nesta 2006, Hall 2007). However, high cost and heavy administration of filing and defending patents are identified as factors that impede innovation (Jonsson 2007). Most countries introduced patent protection in pharmaceuticals later than the USA, which has been characterized by strong IP protection in this sector (Orsenigo, *et al.,* 2006).	**Neoclassical financial theory:** Patents on publicly funded research serve the purpose of creating markets for knowledge (Orsenigo, *et al.* 2006). IPRs are incentive to invest based on excluding access to information. Without IPRs, the innovative output will be suboptimal and innovators will be under-rewarded, because markets are highly competitive and information is perfectly appropriable – easily transmitted to those not paying for its use. Broadening the scope of patents is desirable, as it is imposing higher penalties for infringement and if successfully marketed, maximises the reward to investors in the form of income from licensing and royalties (Dempsey 1999). **Theory of innovative enterprise**: In the case of public research, the incentive in the form of IPR laws is not needed because invention has already been paid for, by the public (Orsenigo, *et al.* 2006). Information is a resource; innovation is not a bounded process, but involves many participants that interact in a learning process and that have limited knowledge and abilities (Dempsey 1999). IPRs are used by new biotech companies to attract acquisitions by established companies, which enables them to quickly exit to capital markets, despite the lack of products close to the market (Lazonick and Tulum 2011). Innovative capabilities of biotechnology firms to translate new technologies into innovative products and processes are a stronger determinant of successful new value creation than IPRs (Orsenigo, *et al*. 2006). In the case of upstream discoveries, exclusive exploitation of a patent limits new entrants who would compete to produce more efficient and cheaper medicines from subsequent discoveries (Lazonick and Tulum 2011).
Public investments into knowledge base	Continuous and substantial government investment in knowledge base and subsidies have financed US biotechnology and motivated equity investors throughout the industry's history (Angell, 2004; Lazonick and Tulum, 2011).	Biotechnology development is boosted through government-initiated technology transfer initiatives, seed funding schemes, and taxation schemes (EuropaBio 2006).	**Neoclassical financial theory:** A purely market relation produces the optimal situation and government policy should be limited to situations where market failures have developed. One such market failure demands government funding of basic research, which overcomes the reluctance of firms to fund their own research because of their inability to appropriate all the benefits (Salter and Martin 2001). **Theory of innovative enterprise**: Governments have a critical role in developing the knowledge base indispensable for international competitiveness of the biotechnology industries, through infrastructural investments that are of far too broad scope to be done by companies, and different incentives to companies for investment in innovation (Lazonick 2007).
Funding mechanisms The role of speculative stock markets IPOs	Industry funding mechanisms have been characterized by stock market investors investing in IPOs of not-yet-commercially-present companies (Lazonick and Tulum 2011).	Similar to the USA, although to a lesser extent, equity investors are motivated by speculative gains, extract value from companies, especially after the IPO, even though the products are mostly not yet close to the market (Lazonick and Sakinç 2010).	**Neoclassical financial theory:** The healthcare biotechnology business model is financialized, shareholder distribution-oriented; companies are investment portfolios of innovations where products in pipeline and firms trade for shareholder value in speculative processes (Andersson, et al. 2010). **Theory of innovative enterprise:** The extent of financial commitment required to sustain an investment strategy depends on the size of the investments in productive resources and duration of time required for those investments to generate financial returns (Lazonick 2011).

Innovation-influencing factor	USA	Europe	Theoretical framework
– Stock buybacks	Stock-based compensations to executives and employees are regularly exercised (Lazonick and Sakinç 2010).		**Neoclassical financial theory:** Short-term earnings per share and share price are the most important measures of corporate performance. Only shareholders are "residual claimants" as they receive returns only after all other stakeholders have received their "guaranteed contractual stakes" (Lazonick 2007). By giving managers stock-based compensation, shareholders mitigate the principal-agent problem – they ensure that managers have aligned interests with them and allocate resources efficiently (Jensen and Meckling 1976). **Theory of innovative enterprise:** Shareholders are not the only "residual claimants". State is one example of a "residual claimant" without guaranteed return on investment to taxpayers (Lazonick 2007). Strategic decision-makers allocate resources to financial interests using speculation and stock-based compensation, to increase stock price regardless of the effect on organizational learning that can result in a commercial product (Lazonick and Tulum 2011).
Other sources of funding: debt and venture capital	Companies are supported by public capital markets and financial institutions lending money secured only by stock (Ernst&Young 2011). Debt funding dominates the sector.	The industry is not mature enough to attract debt finance for growth-by-acquisition strategy of the US industry (EuropaBio 2006). Venture capital industry is fragmented, with weak specialization (EC 2009).	**Theory of innovative enterprise:** Productivity problems of the US biotechnology industry were not due to a shortage of funding, but due to the highly financialized business model which undermines innovation (Lazonick and Tulum 2011), as managers extract value; they don't create value by allocating resources to developing and utilizing productive resources (Lazonick 2011).
Other sources of funding: established pharmacompanies	In order to maximize shareholder value, companies typically become acquired by pharmaceutical companies, instead of pursuing high-risk R&D (Ernst&Young 2011).	Mature companies mostly license out their inventions to large pharmaceutical companies, get acquired by better funded US companies or move to the USA to access their product and financial markets and thus export value-creating R&D (EuropaBio 2006).	**Theory of innovative enterprise:** Pursuing acquisitions of small biotech companies by established pharmaceutical companies as a dominant business strategy prevents Europe from developing self-sustainable, larger biotech companies and endangers the extent of future innovation (Jonsson 2007). In both Europe and the USA, this trend negatively affects the investments in early stage research by pharma companies (Dorsey, et al. 2010).