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Entrepreneurship in biotechnology: The case of four start-ups in the Upper-Rhine Biovalley

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Abstract

This paper explores entrepreneurship in biotech through the in depth analysis of four new ventures located in the Upper-Rhine Biovalley. One of the strengths of this paper is the presence of both successful cases of entrepreneurship and of cases of failures. This gives the opportunity to discuss the role of several factors on the performance of a new biotech venture. Three points particularly comes out of this study: The importance of public science, without which new biotech firms could hardly exist; the role of the patent system, the importance of which we link to the business model adopted by the firm; and the importance of collaborations, which we study through the concept of distributed entrepreneurship.

Keywords: Intellectual property rights, patents, science, distributed entrepreneurship, collective invention
JEL classification: D2, O3

1. Introduction

This paper was written in the framework of the Keins (Knowledge Based Entrepreneurship: Innovation Networks and Systems) project, which aims at "examining the relevance, features and developments of knowledge based entrepreneurship in Europe"[1]. This project is organised in two phases: In a first one, early case studies are conducted in order to identify preliminary hypotheses, which can then be tested in more depth in the second phase by using quantitative studies. This paper is part of the early case studies.

We describe and analyse the specific case of four start-ups[2] located in the Alsatian side of the Upper-Rhine Biovalley. For each firm we gathered in depth information about the genesis of the

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This work is also part of another project, specifically dedicated to DNA vaccine, called MIDEV and financed by the CNRS – INSERM - MiRe – DREES in the frame of the program "Sciences biomédicales, santé et société".
[1] The Keins project specifically aims at departing from the traditional approach of entrepreneur as an individual and isolated hero (the Schumpeterian mark I view, 1911) in order to focus on the importance of networks and institutions (such as universities and public research organizations) in the entrepreneurship process.
[2] One of the four firms we analyse is not really a firm in the sense that the project of creation of a venture aborted before the firm was founded.

firm, its history and the characteristics of the founders. Based on those four cases we aim at identifying variables that might help to understand entrepreneurship in biotech.

The field of biotechnology is appropriate to study knowledge based entrepreneurship since during the last two decades there has been an upsurge of new firms, "growing in the world from nothing in the mid seventies to several thousands nowadays" (Zucker *et al.*, 1998; Hemphill, 2003). In the case of France, the number of creation of biotech firms is also increasing, from fewer than 10 new firms per year a decade ago, to more than 30 nowadays (Mangematin *et al.*, 2003). Furthermore, it is undisputable that those new firms are knowledge based since biotechnology is widely acknowledged as a science-based and even a science-driven sector (Cohen *et al.*, 2002). Another interesting feature of biotech is that new firms are almost always pure cases of entrepreneurship, in the sense that they are new technology based firms. Firms are built upon the use of a new technology or the production of a new product. They usually do not use generic technologies already widely developed elsewhere. Hence, we dismiss here of the problem of knowing whether or not the creation of a new firm can really be considered as a case of entrepreneurship (Metcalfe, 2004).

To understand in details the process of entrepreneurship it is necessary, at least in a first step, to enter inside the black box. In this sense, an in depth analysis of the process of creation of four start-ups should bring interesting insights. Former studies on entrepreneurship showed that, even though the personal characteristics of the founder cannot be neglected to understand entrepreneurship, the latter is most of all a "systemic phenomenon driven by complementarities between technological, market and institutional opportunities" (Radosevic, 2005). Those elements are sometimes also defined as the "entrepreneurial climate", which represents the constellation of factors that determine entrepreneurial activity in an economy (Tamvada, 2006). Specifically, we aim here at exploring the role of variables such as the personality of the founder, the scientific community, public go-between institutions, inter firm collaborations, patents, etc., in the entrepreneurship process in biotech.

In order to recount the history of the foundation of each of our four cases we used different information sources. First of all we collected information through in depth interviews (at least three hours of interview) with one of the founders of each firm. Those interviews were semi-directive and aimed at analysing the evolution of firms through time, the factors that seemed important to determine this evolution and the strategies of the decision makers. They enabled us to gather precious information about the genesis of the new venture, the characteristics of the founders and the trajectory of the firm after it had been erected. Those interviews have been completed by email or telephone exchange in May 2006. The second source of information that has been exploited is the answers to a postal survey sent to all Biovalley R&D companies (see below) in 2004 and focused on firms' patenting and partnering activities[3]. This study provides

[3] We e-mailed a questionnaire, addressed either to the CEO, the R&D director or the intellectual property director of the company. We received 18 exploitable answers. This questionnaire included three main parts: One related to general information about the firm, such as the age of the company, its activity, its type, the total number of employees, the number of employees with a PhD, the function of the respondent, etc. The second part aimed at gathering information related to firms' patenting strategy. We questioned firms about the number of patents they held, their main motivations for applying for a patent, the main deficiencies they attribute to the patent system, the methods they used to prevent imitation, etc. The third part aimed at gathering information related to firms' set of R&D collaborations. We questioned firms about the number of R&D partnerships they had been engaged in over the

information about collaboration and patenting strategies of 18 biotech firms of the Upper-Rhine Biovalley. Finally, additional, complementary information has been gathered via public sources on the Internet and via queries in patent databases.

Our four firms are all part of the French side of the Upper-Rhine Biovalley network, which was founded in 1996. It is a trinational network strategically located in the Upper-Rhine region, which extends over northwest Switzerland, South-Baden in Germany and Alsace in France. This network gathers approximately 650 partners, of which 124 are considered as being firms doing R&D (other members are services and consulting companies, supply companies and public research institutions). Of those firms 56 are located in France but only 24 are considered as new biotech firms, the other being more traditional SMEs or subsidiaries of big-pharmaceutical companies[4]. Among those 24 firms, our four firms have been selected according to specific criteria: To be able to make some comparisons we selected young firms (founded between year 1999 and 2001), hosted by the local incubator and involved in the domain of human health that is the dominant model of the Upper-Rhine Biovalley, which has recently been selected as a "Pôle de compétitité innovation thérapeutique". Hence, we believe that those four cases may reflect some aspects of the situation of the Biovally. Yet, to dismiss all criticisms related to possible bias and lack of representativeness, we insist on the fact that our purpose is not to propose general conclusions, which is anyway contradictory with the method of case study, but only to raise testable hypotheses.

The first section describes each of the four cases. It is based on the interviews with the respective founders of the firms. Specific emphasis is put on the characteristics that seemed important to understand the genesis of the venture. We tried in this section to keep only with facts, i.e. to dismiss as much as possible our own interpretation. Then in the second part we propose a synthesis of those four cases and we try to infer characteristics that count to explain entrepreneurship in biotech[5]. We insist on three points: The role of public research, which appears as central in all four cases; the importance of patents to launch a new biotech business in the domain of drug development; the role of collaborations that we analyse through the notion of distributed entrepreneurship.

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last three years, the types of the partnership, the types of the partner, the terms of the collaboration and the purpose of alliances.

[4] Data for year 2004. For further information see the Biovalley website: www.biovalley.com. This amount of 24 firms can be compared to the total number of new independent biotech firms in France. According to Catherine *et al.* (2004) estimations are converging around 200 independent biotech companies.

[5] Ideally we aim at identifying features that help to explain why entrepreneurs in biotechnology succeed or fail. Yet, it must be kept in mind that it is difficult to speak about success in the case of biotechnology start-ups. These are young firms and it is obviously not because they were still alive by the time we did the inquiry (which means that they were for most of them 5 or 6 years old) that they are a success. In this sense, here success means rather "still alive at the time of the inquiry" or "no failure for the moment".

2. Four cases to apprehend entrepreneurship in biotech

2.1 *Firm A*[6]: *"Success story … without the happy end"*

Firm A is a start-up founded in January 1999 by a Strasbourg CNRS researcher, following a collaboration with Aventis (now Sanofi-Synthelabo). It is therefore an academic spin-off. The story of *Firm A* starts like a success story. It raised many hopes and obtained easily important funding, which first led to a rapid evolution of the society. In 2001, i.e. only two years after its foundation, *Firm A* had been able to raise 30 million euros in two rounds of venture capital[7]. The firm grew rapidly from 26 employees in 2001, 46 in 2003 and according to the business plan an expectation of 100-150 employees in 2006. After 18 months the firm had its first product in pre-clinical trials, which is remarkably quick for a start-up.

The strategic focus upon which *firm A* is based is the discovery and development of novel medicines and drugs derived from the biological and chemical diversity of insects. The world of insects represents indeed the largest and probably most diversified reservoir of native substances with pre-determined pharmacological activity, giving an extraordinary potential for the discovery of novel medicines in many areas of unmet needs including antibiotic treatments. A focus was put specifically on the immune response developed by insects. In complement to the development of new drugs *Firm A* also built highly chemo-diverse libraries of small molecule compounds with applicability to many therapeutic fields. When it was founded, *Firm A* was the sole firm on this niche.

Unfortunately the society collapsed at least as rapidly as it had progressed and came to bankruptcy in 2005. Apparently financers had loss their hope in the society, which implies that *Firm A* was unable to raise more funds to pursue the research projects. This remarkable case study is therefore interesting since it reflects in itself the story of most biotech firms during the last ten years: hopes, easy funding before the high-tech bubble, quick growth (but usually without turnover), difficulty to raise funds after year 2003 and finally bankruptcy. More specifically it emphasises the versatility of financers who first agree to provide huge amounts of money and five years later refuse to reinvest. It also reflects the lag between the time horizon of research (at least 10 years) and the time horizon of venture capitalists (funds are usually allocated for approximately 5 years).

Let us now turn to the detailed story of the foundation of the company. The creation of *Firm A* is the outcome of a long process that started 20 years ago with the first research carried out in the CNRS lab of the founder (a world leading team in the Institute of Molecular and Cellular Biology in Strasbourg) in collaboration with a local start-up on the immune properties of insects. Already at this time the founder wanted to create a venture since the financial endowments in the academia was not sufficient to cover the needs for his research. We find here a recurrent motivation of academic scholars to engage in industrial projects: The absence of public funds and the rigidity of their allocation. Scholars may therefore be more likely to find funds and freedom within a private company than within the public research system. Yet the project did not succeed

[6] To respect the willingness of the interviewed founders, we do not disclose the name of the companies.
[7] This amount must be compared with the average amount raised in France, which stands approximately from 1 to 4 million euros per round (« guide du financement des entreprises de biotech »).

at this time (mainly for technological and market reasons but also for more unpredictable ones[8]). A second industrial R&D collaboration occurred some time later with a US partner. This time the association failed because the partner was managing an entry on the stock market, which did not allow it to focus on new projects. A third collaboration occurred with the French firm Rhone-Poulenc (which was later bought out by Aventis). This third collaboration succeeded on several points. It provided financial resources to the academic lab and it led to several patents in the nineties for which the lab was mentioned as the inventor and the firm as the owner[9].

It is this third collaboration that led to the creation of *Firm A* in 1999. For strategic reasons Rhone-Poulenc did not intend to use the technology and agreed to give access to its patents to the new-founded firm for free (in exchange it entered the capital of the new company). The good relationship between the academic lab and the industrial partner is very important to explain the genesis and the initial success of the project. It implies, for instance, that the new venture was able to obtain the patents on which it could build its initial development for free, which is central for a new firm that does not have important initial funds. More importantly, the creation was fostered by the arrival of a researcher who was back from a two years post doc in the US and who played a central role in the creation. He worked in the CNRS team of the founder and when the latter asked him to take the project of the start-up in charge, he immediately accepted. For him the start-up offered a research opportunity without any equivalent in the public, where the budgets are low and the organisation too codified and rigid. It is almost impossible for a young researcher to build his own team to work on a new project. Furthermore, the French legislation (with the law on innovation enforced in 1999) facilitated the passage of public researchers to the industry: It offers the possibility for public researchers to engage in industrial activities while keeping their status as civil servant during six years, which means that if the industrial project fails the researchers can return to academia without any damage. This system provides powerful incentives for academic scholars to found start-ups.

To complete the organisation of the new venture, *Firm A* also needed to hire a manager endowed with strong experience in the industry in order to take care of the business aspects of the project. Indeed, although the founder contributed to provide a solid scientific guarantee, scientific excellence is most of the time not sufficient to launch a new venture. Entrepreneurs must also prove that they are capable to handle the business side of their project, which is often not the case of academic scholars. This business credibility is essential to be able to raise funds and to obtain the trust of the investors. *Firm A* dealt with this problem by associating to the project a manager specialised in the launch of new biotech firms. This manager remained two years in the firm and was then replaced in 2001 by another CEO also endowed with a strong experience in the industry (more than 20 years). This double direction (CSO and CEO), which is common in the biotech sector, is a necessary condition in order to raise funds and to attract venture capital firms.

[8] The person in charge of the project within the partner's organisation died, which had a negative influence on the continuation of the collaboration. This point illustrates the many unpredictable things that may play positively and / or negatively on the success of a project.

[9] It is interesting to notice that such practices, where the public organisation abandons the full ownership to the industrial partner, are more controlled today. French universities have all developed technology transfer offices that manage interactions with industries and usually insist on co-ownership of patents. Yet this practice was common in the past. It is one of the purposes of the Keins project to estimate how many patents have been invented by French academic scholars, which should give an idea of the exact role of French public research for industrial innovations.

The company was therefore founded in 1999 and hosted by the local incubator in Strasbourg. As described above, it first experienced a quick growth and was able to raise important amount of money before going bankrupt in 2005.

The story of *Firm A* emphasises several elements that may help to understand entrepreneurship in biotech: A first feature is related to the importance of informal personal relationships and to the charisma of the founder. The latter was a famous researcher who developed during his career many relationships with industrialists and financers. His "know-who" was then useful to convince Aventis Crop-science to enter into the game, to find adequate collaborators and most of all to convince financers to invest. A second element deals with the importance of developing links with other organisations. The foundation of *Firm A* is a collective process that involved many partners: The CNRS, Aventis, Venture capitalists and local institutions such as ANVAR and the local incubator. The case also emphasises the role of the patent system for new start-ups since the creation of the start-up is directly linked to the exclusive licensing of several patents from Aventis Cropscience. Those patents proved very important to give credibility to the new firm. During its short life *Firm A* pursed an intense patenting strategy, which enabled it to gather a small patent portfolio of more than 15 patents[10].

To conclude with this case, let us try to propose a likely explanation of the failure of *Firm A*. The project on which the company was erected, although very promising in the long run, was too far from the market to be undertaken by a private firm. It was still a research program rather than an industrial project likely to yield money on a short spell of time. And, as stressed by Nelson (1959), although firms often undertake basic research and universities often do applied research, public research organisations have a comparative advantage in basic research as compared with private companies. In this sense the research undertaken by *Firm A* has still to be matured within the public sphere before being industrialised again, maybe in several years.

2.2 *Firm B*: *"Simple, sober and efficient (… until now)"*

Firm B is a biopharmaceutical company focused on the discovery and development of innovative treatments for psychiatric disorders such as schizophrenia, depression or anxiety. The company was founded in 2000 by three persons and is currently based in Mulhouse. Today it has two compounds in clinical trials phases II and I and several compounds in pre-clinical trials. It has about 40 employees, has been able to raise quickly important amount of money and has applied for several patents recently. The future of the company is considered with optimism since it is located on a promising market (psychiatric diseases), which should sharply develop in the future, and it has a pipeline of new compounds that have the potential to overcome the limitations of current drug therapies. In 2005 the company was selected as one of the top 100 (including 19 biotech firms) most promising (i.e. best-performing and innovative) high-tech private companies of Europe.

The project on which the company was erected is simple: To combine competences in drug discovery and clinical trials in order to accelerate the time needed to bring a new drug on the market. To put it differently, the objective of the company is to ensure a rapid transfer of compounds from their discovery to clinical trials phase IIb and then to sell or licence them. *Firm*

[10] Unfortunately, we have not been able to discover what happened to those patents after the bankruptcy.

B core competences are therefore not based on a new technology or a product but rather on a new type of organisation that enables the company to decrease the time needed to bring promising compounds to clinical trials phase III and with much lower attrition rate than industry standards. Apparently the organisation of *Firm B* enables the company to save time and money. To do this, *Firm B* relies on its privileged links with public research, which brings its scientific competences in the process of discovering rationally new promising compounds, and on its competences related to pre-clinical trials and to the first stages of clinical trials. At its very beginning *Firm B* was therefore a virtual company that selected new compounds and then subcontracted the pre-clinical and clinical trials to other firms[11]. Another important activity of *Firm B* is to survey the portfolio of other companies in order to identify promising compounds that would not be used by those companies and to buy them. This has allowed them to acquire the currently most promising compound of the company in-licensed from Janssen Pharmaceuticals (Johnson & Johnson) and that is now in clinical trial phase II.

Let us now turn to the story of the foundation of the company: Before all, the creation of *Firm B* relies on a long collaboration (and even friendship) between two of the co-founders, one specialised in drug discovery and one in clinical trials. The first one is a CNRS research director at the faculty of pharmacy of the Université Louis Pasteur (Strasbourg 1) and medicinal chemist specialised in neuroscience. During his career he has developed a strong experience of patenting and of collaboration with industry. The second one is a psychiatrist working for a company specialised in clinical trials on diseases of the central nervous system. Since each of them occupies a position at one extreme of the chain that leads to a drug (from basic research and drug discovery to clinical trials) they decided to associate their competences in order to develop an organisation that would optimise the time from drug discovery to market. A third person, who had developed a strong experience in the pharmaceutical and biotechnology industry, was then associated to the project to take care of all the managerial and financial aspects (he became the CEO of the company).

The company was therefore founded in September 2000 and benefited from the help of the local incubator that hosted it in its building in Strasbourg. It is only in February 2004 that the company moved into new headquarters in Mulhouse. Since is creation *Firm B* has experienced a constant progression. In November 2000 the company obtained a first financing of 7,6 million euros which enabled it to start on a solid basis. In August 2002 a second round of financing of 20 million euros was successfully closed. Finally, in December 2004, a third round of financing of 31,5 million euros was completed. Since 2000, *Firm B* has therefore been able to raise more than 55 million euros, which reflects the steady trust granted by the financers to the project. Beyond the amount of the funding, what is really remarkable is that *Firm B* was able to raise funds at a time (year 2004) when financers were very pessimistic and usually refused to engage in early projects. *Firm B* is one of the sole French Start-ups that was able to raise an important amount of money in 2004. Among others, the new company relied at its beginning on several innovating

[11] Yet, in 2003 *Firm B* absorbed a local company founded in 1996 and specialised in pre-clinical trials, which means that firm *B* is now able to do pre-clinical trials themselves. The buyout is not a denial of the prime strategy of *Firm B* as a virtual society but rather results from an unexpected opportunity that the society decided to seize. The company that was acquired, as a subcontractor doing pre-clinical trials, was one of the main partners of *Firm B*. It experienced difficulties and the integration within *Firm B* was one of the sole opportunities for the company to pursue its activities. The integration was facilitated by the strong complementarities between the two societies.

projects that resulted from the past collaboration among the co-founders. Quickly it applied for several patents and, most of all, in May 2002, *Firm B* in-licensed ocaperidone, which was a product that the company believed to be promising but was not exploited by the owner. The first results about this compound that is now in clinical trials phase II were released in 2005 and are promising. As it is now the company is looking for a big pharmaceutical company to absorb it or to develop a partnership.

At this stage it is not possible to predict the future of the company and to evaluate its chances of success but we can nevertheless raise some points that seem to have played an important role in the creation and the early success of the company[12]. First of all, the strong relationship between the founders played here a key role, which emphasises the importance of informal relationships and networking. Second point, this case stresses the core role of science in biotechnology. A recurrent point that has been raised all along the interview is that *Firm B* is strongly dependent on its relationship with ULP and CNRS, which provide new promising compounds to be tested as well as the scientific credibility of the project. Third point, the role played by public institutions and most notably the incubator. Fourth, the role of patents: When it was created the company did not hold any patents but quickly applied for two patents based on the former researches of its two co-founders. Therefore, if *Firm B* was founded without any patent *ex ante*, they quickly realised the importance of patents, which are central in the business of *Firm B* (basically to buy projects at early stages of development and to sell them at later stages): without patents there is almost no trade possible. Fifth, the initial organisation of the firm was based on a double direction with a CEO and a CSO. This leads to our last point, which is the strong experience and charisma of the three founders.

2.3 *Firm C*: *"An Embryo that never developed"*

Firm C is not properly a firm. It is only a project of a firm that never really started for several reasons that we develop below. *Firm C* is a project of a start-up carried-on by a single founder in the domain of functional proteomics. The objective of the company was to develop a database of interactions among proteins. To this purpose, *Firm C* applied for a patent over a technique of identification of those interactions (phage-display technique[13]). The advantage of this technique is that it reduces greatly the time to identify relevant proteins for specific uses because it allows simultaneous tests of interactions among different proteins. In short, *Firm C* aimed at becoming a producer of information (i.e. research tools) to be used by other firms engaged in life science. Potential customers are: Big-pharmaceutical firms for their activities of screening of new compounds, producers of bio-chips, Public research centers for their research on metabolism and biotech start-ups engaged in molecular interactions. At the time of the foundation, *Firm C* had only one competitor engaged in the same activity.

[12] To temper a little bit the optimism that may come out of this presentation, it is worth mentioning that the most important steps are still ahead. The company is fragile and depends strongly on the results of the clinical trials of its compound and most notably the one in phase II. Bad results would for sure announce the end of the society in a more or less short spell of time.

[13] Phage display is a powerful technique for identifying proteins or peptides that bind to particular molecules of interest. Antibody phage display has become a popular method for identifying and selecting novel molecules for therapeutic and diagnostic drug development. Screening large populations of antibody molecules with phage display can rapidly identify which individual antibodies bind to selected targets (http://www.xoma.com/technologies_for_licensing/antibody_phage_display.jsp)

Firm C is a corporate spin-off in the sense that it was initiated by an employee working for another firm. The idea of the project dates back to June 2000. The founder was a technician working for Transgene (where he spent 8 years), which offered a stimulating research environment. Employees were encouraged to participate in conferences, to interact with universities, etc. Following one of those conferences on phage-display and an ensuing in-depth discussion with a Transgene expert, the founder decided to engage in this project and to apply for a patent that would cover this new technique. His motivation to found a new venture was apparently not related with money. It had more to do with Schumpeter mark I type of motivations: the willingness to build something, to launch a new business. Most of all, it seems that the founder had understood that in its former company most favourable positions would always be offered to employees more qualified and that his progression within the hierarchy would be difficult due to his lack of university background[14].

Transgene, which might become a user of the technique once the latter would be operational, did not intend to explore it at this time. Hence, they did not deter the project and agreed to abandon any right over the future patent. With the help of the local biotech network (Alsace Biovalley), which provided technical and financial expertise as well as contacts with relevant institutions, a French patent application was completed in March 2001[15,16]. At this early stage the project did benefit only marginal financial support: A grant of 6,000 euros from Alsace Biovalley. Nevertheless it benefited from other kinds of support, such as the right to enter the local incubator (usually limited to public research valorisation) at the end of year 2000. The help of incubators is important since it gives scientific credibility to the project, especially to attract funds[17]. Furthermore it provides assistance to develop the project in more depth, which enabled the founder to prepare a business plan and a market study to submit to financers and to partners. It is also important to stress that during year 2001 the founder decided to quit his former company to be able to spend more time on his project.

Once the patent application was completed, *Firm C* really started to exist and could try to approach financers and partners (without patents the society cannot really exist since there is nothing tangible to propose to partners). The business plan established for the company was based on a realistic scenario: Low initial investments, expectation of reasonable benefits already after the third year of activity and the hiring of only 7 employees. Hence, according to this roadmap, *Firm C* had to find funds and a scientific partner endowed with a strong reputation. Yet, despite an association with a university professor in pharmaceuticals located in the Netherlands, *Firm C* failed to raise more money either from venture capital firms, from business angels or

[14] A feature that played a central role in the story of *Firm C* is that the founder was not entitled with a university PhD. Originally he had a BTS, which means in the French system that he is a technician and not an engineer or a doctor. Furthermore, during the 8 years spent in Transgene he attended at the same time a university training that provided him with an MBA.

[15] Due to a lack of financial resources *Firm C* did not use its priority right to apply for patents in other countries than France.

[16] During the interview the founder stressed the importance of the assistance he received from the incubator and the IP firm to complete the drafting of the patent application.

[17] Yet, incubators remain most of all units of valorisation of public research. For outsiders (i.e. non public researchers) it is harder to benefit fully from this support. This remark of *Firm C* founder is consistent with the importance of informal relationship for entrepreneurs in biotech. Formal support is worth less if it is not accompanied by informal links.

from public institutions. Finally, at the end of year 2002 (2 years after its beginning) the project to create a new firm was abandoned and the priority of the founder was redirected towards a more modest objective: To sell his patent in order to be reimbursed for all the expenditures he had engaged during the project[18].

This story of a failure is nevertheless very instructive to understand entrepreneurship in biotech. Putting aside the eventuality that the project was just unworkable and doomed to fail one can stress the following points to explain the failure: First of all, scientific credibility and the reputation of the founder are central. In the case of *Firm C*, the founder did not have any network to mobilise either in the scientific or in the business communities. He did not have a PhD, did not work in a prestigious university and had no real experience of management. Even in the case of a promising project this lack of experience and credibility can easily explain the reluctance of partners and financers to participate. Had the founder been from a prestigious research team with links with other start-ups, it is likely that he would have been able to gather more funds.

Another feature that emerges from this failure deals with the professional situation of the founder. It suggests that corporate spin-offs not explicitely backed by the mother firm are confronted with more difficulties than academic spin-offs. In the case of *Firm C*, the founder had to deal with a precarious and uncertain personal situation. He was finally obliged to quit his former firm a few months after the beginning of the project, which does not provide good conditions to ensure the success of a young venture (he did nevertheless find another job a few months after he stopped his project). Conversely, as already discussed above, had the founder been a civil servant working for a public research center he would have been able to quit his function and to be reintegrated in case of failure. This provides steadier situations that especially allow entrepreneurs to mature their projects and to manage the time dimension differently. In the case of *Firm C* it is certain that time was a central factor. The project needed to be launched quickly, which may have affected its quality.

Finally, a peculiar point may also explain the failure to raise funds at that time: The lack of ambitions of the project. Contrary to traditional economic theory, it seems that in the economics of biotech, the higher the amount requested the more financers are willing to invest. This can be explained by the lack of scientific competences from the financers, who are therefore unable to assess the true value of the project, and by their willingness to "dream" (this was emphasised in all four interviews). Hence, realistic projects may eventually be penalised as compared with other less realistic but more ambitious ones. Yet, in the case of *Firm C* it is doubtful that had the project been more ambitious, financers would have invested in it.

2.4 *Firm D*: *"cautiously but surely"*

Firm D was founded in 2001. It is focused on the development of reagents for intracellular delivery of biomolecules. In clear, the company develops and commercialises chemical based vectors that serve to transfer genes or other bio-molecules (proteins for instance) within cells in-vivo or in-vitro. Compared to viruses, which are usually used to this purpose, chemical based vectors provided by *Firm D* have several advantages. Among others, they do not trigger undesired side-effects and they experience a lower failure rate.

[18] Unfortunately we have not been able to find out whether or not the founder succeeded in selling his patent.

Before going in more depth into the history of the company, it is important to understand that transfection, the business in which *Firm D* is actively engaged, is central to the future development of the biotech sector. Gene therapy has raised huge hopes in the past but due to several negative and unexpected results during clinical trials it is now in a dead-end. Scientific and technological problems as well as a negative perception by the general public prevent financers from investing in the sector. It is widely acknowledged among scholars that one of the major issues for leading gene therapy out of the crisis it encounters actually is related to the vectorisation of the gene into the cell. This emphasises the importance and the potentialities of the research led by *Firm D* should they prove to be workable.

Firm D stems from a mixed team from the world of science and of industry. It was founded by the association of a CNRS research director with a person who had an experience in industry and who became the CEO of the company (she is still the CEO today). The CNRS research director wanted to valorise one of his patents (owned by the CNRS), which was not used by any firm at the time. This valorisation was of course not possible within the public domain. It is important to note here that it is not only a matter of money or of freedom of research that induced him to found *Firm D* but also the willingness to make research undertaken in the public domain useful to the general public (to remove them from the shelves).

Everything happened very rapidly after the meeting of the two co-founders: The firm was founded in January 2001. It had been licensed two exclusive patents from the CNRS, which soon started to yield some money. Furthermore, in June 2001 *Firm D* raised 600,000 euros after the first round of financing which, coupled with the revenues of the exploitation of the CNRS licences, contributed to ensure the financial viability of the project. Those funds were accompanied by several public subsidies. Public institutions not only provided funds but also supported the project by hosting the company in the local incubator. It is only recently (in June 2004) that the society left the incubator to new buildings near Strasbourg. In July 2004 a second round of financing still consolidated the firm by yielding 2 million euros. Furthermore, in 2002 *Firm D* was awarded ISO 9001: 2000 quality management system certification, which is an element worthy to emphasise since it is rather rare for biotech firms that are usually satisfied with GMP norms.

The growth of the firm since its foundation has been constant: From 4 employees in 2001 it has grown to about 20 employees now and displayed a turnover of 750,000 euros in 2003 and 797,000 euros in 2004. This turnover is still expected to increase in the following years due to an important and ambitious strategy of distribution all around the world (see below) and of dissuasion against piracy[19].

One of the most interesting element of *Firm D*'s case is related to the strategy adopted by the firm since its beginning: Contrary to many other biotech start-ups, *Firm D* has adopted a mixed business model, i.e. a strategy of development that relies on a coupling of risky research investments (which can lead to important profits in the long run) with the sales of vectors to other research companies (which ensure a part of the financing of the firm's research). Thus *Firm D*

[19] One of the main concerns of *Firm D* is to enforce its patent rights on its vectors, which is usually very difficult in the case of process innovations.

plays on two sides: (i) Commercialisation of reliable vectors and (ii) Active participation in ambitious research programs to find treatments to diseases such as cancer or Aids.

(i) First of all, *Firm D* has developed a wide network of distributors all around the world to ensure the commercialisation of its vectors. As a first step the firm therefore strongly relies on the exploitation of the initial CNRS patents. Yet, distribution cannot be done independently from research since according to the specific needs of each customer the relevant vector may change. Hence, *Firm D* does not provide a single vector but adapts its vectors according to the specific needs of the customer. Potential customers are all types of organisations that carry on research in life science and that need to transfer bio-molecules within cells (among others for clinical trials). This can be either big pharmaceutical and biotech firms (that need vectors during clinical trials among others) or public research centers that need vectors to carry on their researches. The relevance of the distribution policy of *Firm D* is illustrated by its trade with foreign firms. In 2004, 70% of the turnover was realised with foreign firms. This strategy focused on intermediary products and services explains the low financial need of *Firm D* as compared to other firms involved in drug development.

(ii) *Firm D*' strategy of cash –flow is coupled with a more ambitious one, focused on research. *Firm D* participates in several research projects (vaccine against Aids and Cancer) for which they provide the vector. For instance, recent clinical trials on bladder cancer carried out in the US and using a vector provided by *Firm D* gave very interesting results in phase I. Those investments in R&D determine the future value of the firm. Thus, the two strategies are in some sense complementary and ensure the viability of the firm over the long run. The revenues that stem from the sales of vectors finance in part the research program of the firm. The company invests about half its revenues in research and development. Those investments in R&D are necessary to develop constant improvement of existing solutions as well as original products.

Among the other elements that are worth mentioning in the case of *Firm D*, patents occupy a central place. The creation of *Firm D* is entirely based on patents held by CNRS and exclusively licensed to *Firm D*, which aimed first at exploiting those patents. Would not the CNRS have applied for patents it is likely that *Firm D* would not have been founded. A second very important element is the role of the scientific community. *Firm D* stems from the world of science and still interacts heavily with its former community. Public research is essential for *Firm D* at two levels: First due to its scientific excellence it is a partner that cannot be ignored by firms involved in ambitious research programs. Second, it is also a potential customer for *Firm D* since public labs are likely to need in their experiences the vectors produced by *Firm D*. Finally, a third element central to understand the creation of the venture consists in informal links among individuals. The two founders knew and appreciated each other long before the creation of the venture.

3. What can we learn from those cases?

Now that we have presented the history and the characteristics of the four firms, let us try to make a synthesis and infer some characteristics regarding entrepreneurship in biotech. This discussion, although based on detailed qualitative empirical findings, is necessarily a speculative one. Yet, several insights come out of our four cases. Overall, they allow emphasising three main

things about entrepreneurship in biotech: The central role of public research, the importance of patents and the importance of formal and informal links.

3.1 The key role of public research

One element put forward by all the four cases is the prominent role of public research for new biotech start-ups. Many new biotech firms stem from the academic community (are academic spin-off or at least are mixed structure from the academia and industry) and even for those that are not, it is central to establish strong links and to collaborate with public labs. This central role of public research in the development of the biotech industry was already emphasised by Zucker *et al.* (1998), who showed that in the US during the early days of the biotech industry, between 1976 and 1989, there was a strong positive correlation among the local presence of a university and the development of biotech start-ups.

Table 1: Synthesis of the four cases

	Year of foundation	Spin-off	Patent	Initial Organisation	Domain	Incubator
Firm A	1999	Academic	Yes	CSO+CEO	Human health	Yes
Firm B	2000	Mixed	Yes	CSO+CEO	Human health	Yes
Firm C	2001	Corporate	Yes	Single employee	Human health	Yes
Firm D	2001	Mixed	Yes	CSO+CEO	Human health	Yes
	Initial Financing	Scientific reputation	Formal collaborat°	Business Model	Informal network	Situation in 2006
Firm A	High	Very strong	Yes	Product - Drug LR	Developed	Bankrupt (in 2005)
Firm B	High	Strong	Yes	Product - Drug LR	Developed	Alive
Firm C	Low	Weak	Yes	Service SR	Pour	Bankrupt (in 2003)
Firm D	Modest	Strong	Yes	Mixed LR + SR	Developed	Alive

Our interviews especially stress the advantages that public researchers have to create their own venture. First, since biotech is a science based industry in which scientific knowledge is central and may provide firms with an important competitive advantage, it is obvious that researchers who work in centers of excellence are more likely to create a new venture because they possess the appropriate scientific knowledge. Biotech firms cannot be disconnected from science and usually good science is undertaken in public research centers. As scientists, public researchers have therefore a strong advantage to engage into new potentially valuable projects.

Another important feature is related to the risk supported by the researcher. It appeared all along our interviews that the French system, which enables public researchers to quit their employment for a time and to reintegrate it afterwards, provides a powerful incentive for public researchers to launch into new and risky businesses. As a comparison, a researcher working for a private company would have to quit his job definitely. Moreover, a maybe more important reason deals with the management of the time dimension. Being a public researcher enables the founder to mature his project whereas other researchers may have more difficulties to handle the time dimension of their project correctly.

These elements may explain why many biotech start-ups are academic spin-offs. Three firms out of the four we study are either academic spin-offs or have at least one founder from the academia. *Firm A* is an academic spin-off. *Firm D* and *Firm B* are mixed organisations stemming partly from the academia. Only *Firm C* does not come from public research and this seems to have strongly penalised its development. This is in line with other results from studies in France. To mention only one realised in the Paris region by Bellon and Plunket, in 2003, out of 64 biotech firms founded since 1990, 40 firms had at least one founder from the academia. Academic spin-offs represent therefore 2/3 of the new biotech firms. More specifically, 19 firms resulted directly from the public sector (INRA, CNRS, CEA, IP) and 21 had one public researcher among the founders (Bellon and Plunket, 2005). These statistics confirm the central role of universities in the technological process. This role had for long been denied, at least in Europe[20], but most recent studies that use more appropriate indicators tend to acknowledge the importance of public research organisation to produce technological knowledge[21].

Catherine *et al.* (2004) refined those results on the role played by scientists in the creation of new biotech ventures. Based on the analysis of 132 founders of 62 French biotech start-ups, they emphasised three points: First, they show that academic founders with a high level of academic production usually do not enter the new venture but have a part time or scientific advisor position. This situation is illustrated here with the case of *Firm A*, for which the founder did not become the CSO but delegated one researcher from his academic team. Second, they show that non scientific founders are more likely to have a position as CEO or in the top management, which again is consistent with our finding about the organisation of a biotech start-up with two heads: A CEO occupied by a person with a strong experience in industry and a CSO occupied by a scientists usually coming from the academia. Finally, they find out that more productive scientists tend to create riskier start-ups, which is also consistent with the case of *Firm A.*

A second element that comes out of our interviews and that support the centrality of public research is the importance for new ventures to collaborate with public research centers. The four firms interviewed acknowledged explicitly the importance of their collaboration with the academia. For instance, looking at the case of *Firm C*, it seems that a central reason to explain

[20] We can mention, for instance, the European research paradox which postulates that, as compared to the US, Europe would do efficient basic research but would be bad in transforming this research into industrial progress (see Dosi *et al.*, 2005, for an analysis of this paradox).

[21] In terms of patent applications, for instance, it was long considered that public research centers did not patent enough because the statistics considered the number of patents owned by public research organisation. Yet, it is much more appropriate to consider the number of patents invented by public researchers whether or not owned by public research institutions. By doing this, one can demonstrate that contrary to common belief public research is very active in terms of patenting (Verspagen, 2006).

why it has never been able to collect funds deals with the background of the entrepreneur who lacked a strong reputation within the scientific community. He was not part of the academic community and, although he had collaboration with a scientist from Holland, he had no collaborations with famous academic scientists. Had this founder been a doctor coming from university, or at least had he been endowed with a strong reputation within the scientific community, it is likely that it would have been easier for him to convince partners. The importance of developing links with science is also emphasised by the answers to our questionnaire, which showed that most of the new biotech firms in the Upper-Rhine Biovalley do collaborate with public labs[22] (Bureth *et al.*, 2005).

Why are collaborations with public research organisation important? First, collaboration with university is central to increase firms' reputation and to achieve scientific credibility. Here, collaborations essentially aim at increasing the firms' attractiveness for financers or potential partners. Star scientists among others, by their ability to bridge different communities, ensure to the entrepreneur the scientific visibility necessary in order to collect fund and to develop collaborations (Zucker and Darby, 1999).

Second, and most important, being involved with public researchers is essential to have access to relevant scientific knowledge. Universities are indeed important sources of scientific knowledge and developing links with public labs enable biotech firms to access this knowledge more easily. This explanation is in line with the analysis of Zucker *et al.* (1998), who attribute the central role of public research organisations during the birth of the biotech industry essentially to the tacit nature of the scientific knowledge (at least during the emerging phase of the industry): "We believe that at least for the first 10 or 15 years the innovations which underlie biotechnology are properly analysed in terms of natural excludable knowledge held by a small initial group of discoverers their co-workers and others who learned the knowledge by working at the bench science level with those possessing the know how. Ultimately this knowledge spreads enough to become part of routine science in the industry" (Zucker *et al.*, 1998). Hence firms need to collaborate with universities in order to access sticky knowledge on which they can base their development. The authors conclude by claiming that their finding: "provides new insights into the role of research universities and their top scientists as central to the formation of new high-tech industries".

This discussion about the role of tacit knowledge in determining the importance of public science leads us to a central hypothesis: For new biotech venture the importance of establishing links with public science would be correlated with the degree of emergence of the industry. The younger the industry the more important it is to be connected with public research centers in order to benefit tacit knowledge developed within the public sphere. Once the industry becomes stable, knowledge becomes more easily available, which decreases the importance of direct links with public science. In short, the central role of public science for new biotech venture in Europe would be due to the relative novelty of the sector and should decrease through time. The Upper-Rhine Biovalley, for instance, is an emergent cluster, which may explain the central role played

[22] The importance given to public research by firms in the Alsace Biovalley may be explained by the presence of the *Université Louis Pasteur*, one of the world leading universities in life sciences (Levy, 2005). It is possible that the presence of this university generates a bias and leads to overestimate the role of science in the Upper-Rhine Biovalley.

by the Université Louis Pasteur and the fact that our four firms mention the importance of establishing links with public science. Conversely, in the US the industry is older and clusters are usually already stable, which may trigger a relative decrease of the importance of public research centers. As explained by Zucker *et al.*, in the case of stable cluster, "knowledge spreads enough to become part of routine science in the industry", which decreases the importance of being connected with universities. This hypothesis, which must still be validated, is in line with the work of Cohendet *et al.* (2006). Those authors also stress the prominence of sticky knowledge during the first phase of an industry which, during the first years of an industry moves firms' strategic goal from logic of exclusion and protection (that are dominant in stable industry) to logic of collaboration and coordination.

3.2 Patents: Essential or not?

Another element that comes out from all four interviews is the major role played by the patent system within the process of creating the new venture. All four firms did hold patents. Furthermore, for three firms out of the four, patents were directly involved in the creation of the company. For *Firm D* and *Firm A* it is a patent transfer from a public research organisation to the new venture that ensured the foundation while for *Firm C* the patent application was the first and necessary step towards the creation. For those three firms it is likely that without patents there would have been no firm creation. Only for *Firm B* did a patent not precede the foundation but occurred some time after. Overall, patents are omnipresent within all four cases.

These results are in line with many empirical studies suggesting that the most important asset for entrepreneurship in biotech is patent and that without patents there would have few investments in biotech (Federal Trade Commission, 2003). The prominent role of patents in biotech goes back to the origin of the sector. There is indeed a strong correlation between the birth of the industry and important changes in patent laws, which suggests that patents played a central role in the birth and development of the biotech industry. It is possible that without the patent system the biotechnology revolution would not have reached the dimension it has nowadays. Two changes related to patent legislation may have encouraged the emergence of an industry in biotechnology: The Bayh-Dole Act in the United States[23] and the 1980 US Supreme Court decision *Diamond vs. Chakrabarty* (447 US 303, 1980), which in some sense allowed firms to patent living organisms[24].

[23] The Bayh-Dole act established in 1980 that US universities were allowed to apply for patents and most of all to own patents, even though the research that led to the patent had mainly been financed by public funds. Before this law, universities could apply for patents but those patents were then owned by the State, which made the incentives for universities to use the patent very low. The Bayh-Dole act was even reinforced in 1984, when it was decided that public research organisations were allowed to grant exclusive exploitation licences to firms in order to exploit public research, even though the latter was financed mainly with public money. Officially this law intended to spur the industrial exploitation of public research.

[24] In 1974, Dr Chakrabarty applied for a US patent on a genetically modified bacterium. His demand was first rejected, the court considering that living organisms were not patentable. However, the case was brought before the US Supreme Court, which decided in 1980, by 5 votes against 4, to validate the patent. It is therefore the highest court of the most powerful country in the world that decided that living organisms can be patented under some conditions. Since then, it is considered that "anything under the sun that is made [and not only invented] by the hand of man" can be patented. In France, pieces of the human organism, like genes for instance, cannot be patented as such but only if the applicant has identified a precise use for them.

Although it is unclear whether the Bayh-Dole really contributed to the tremendous upsurge of university patenting in the US (Mowery *et al.*, 2001 ; Mowery and Ziedonis, 2002; Sampat and Mazzoleni, 2002), in the specific case of life sciences, it is likely that this law had major consequences. Biotechnology is indeed a science-driven sector. Almost all the pioneer discoveries in this domain have emerged from public organisations. Furthermore, the industrial exploitation of this research (to turn them into marketable items) is an uncertain and costly activity. It is thus unlikely that entrepreneurs would have agreed to invest in this business without being protected by patents. By being public and thus available to everybody, public research in the field of biotechnology was of no interest for businessmen. The fact that they became patentable and that exclusive licences could be granted to entrepreneurs appeared therefore as a necessary step to launch the business in this industry. Without patents it is possible that much socially profitable research would have remained on the shelves of public labs.

In life sciences, and contrary to most other sectors, it has indeed been shown that patents are highly important to appropriate the returns of an innovation and to enhance incentives (Levin *et al.*, 1987; Cohen *et al.*, 2000; Combs and Metcalfe, 2002). Firms acting specifically in biotechnologies are usually small and young companies faced with high competitive pressures and thus they strongly rely on patents because they do not have any other tangible asset. Without patents those firms would have no guarantee to offer to potential partners and to financing institutions.

Biotechnology companies may apply for patents not only in order to exclude rival firms but also to facilitate collaborations and interactions (Bureth *et al.*, 2005). Patents are central instruments of coordination in an environment composed of multiple and heterogeneous actors and in which interactions are complex (Galambos and Sturchio, 1998; Thumm, 2001). Three types of actors perform research in biotechnology: New Biotechnology Firms (NBF), Public Research Centres (PRC) and Big Pharmaceutical Firms (BPF). Around them many other actors do not directly perform research but are involved in the innovation process, such as financing institutions, patent offices, consulting companies, etc. In such a context, patents are crucial in order to overcome the strongly differentiated bargaining power and the diverging incentive schemes of these actors. They are also a necessary condition to access the market since they reassure customers and partners and constitute the core of the negotiations with other actors. Furthermore, considering the multiplication of the players, patents (through the disclosure they entail) provide the possibility for entrepreneurs who founded start-ups and small size firms to signal competences and to facilitate the valorisation of complementarities, both in terms of financial and of technological resources (Pénin, 2005). Finally, patents allow the separation of inventors and exploiters of the innovation (separation of a market for ideas and a market for products), allowing gains in specialisation by the respective entities (Gans and Stern, 2003). In this context, the inexistence of patents would mean that the same entity would have to be both the exploiter and the inventor.

All the above arguments suggest that patents are essential for entrepreneurship in biotech. Yet, two comments may soften this conclusion: First, it is obvious that the fact that firms in the field massively apply for patents does not automatically imply that patents are sufficient to succeed in biotechnology. This is illustrated, for instance, by the case of *Firm C*, which although it had been granted a patent nevertheless went bankrupt. Patents alone do not necessarily open all the doors. Second, in apparent contrast with the above discussion, patent statistics indicate that many firms

active in biotech do not hold patents. For instance, a search on the INPI database (covering all European patent application) for all the firms identified in the Alsace Biovalley directory shows that most firms in this directory did never apply for a patent[25]. Only 8 firms out of the 24 new independent biotech firms in Alsace have applied for a patent.

To summarise, on the one hand there is a bundle of studies and theoretical elements that suggest that patents are essential for biotech entrepreneurs and, on the other hand, we have statistics that indicate that many firms considered as biotech do not apply for patents. How can we reconcile those two positions? One possible way, but this is purely speculative, is to distinguish between the different business models adopted by the firms. It may indeed be possible to draw an analogy with the software sector and the open source software movement, which has been well documented recently (Lerner and Tirole, 2001; Jullien and Zimermann, 2006). Literature about the Business models adopted by firms involved in the OSS movement shows that, whereas the underlying software is open source, i.e. anyone can view and copy it, firm's revenue is entirely based on the services that it provides complementary to the software such as installation, teaching manuals, teaching courses, customisation and security, etc. Firms that join the OSS movement usually make money by providing services associated with the software and not by selling the software, which therefore does not need to be protected.

This distinction between services and products may also be relevant to explain the differentiated use of patents in biotech. The importance that firms grant to patents may be related to the business model they adopt. Firms, such as firm *A* and Firm *B*, that are engaged into a product business model that consists in producing new drugs rely strongly on patents. Conversely, firms that are engaged into services (such as tests and clinical trials) or non drug products (such as diagnostic kits) may grant less importance to patents, since their core competence is mainly tacit. This hypothesis is partly illustrated by the case of *Firm D*: Although *Firm D* do hold patents and considers them as central, they also acknowledged in the interview that they could survive (at least for their strategy of vector commercialisation) without patents. In this case they would sell less vectors but they could still make money due to their technological excellence. This is clearly not the case of companies involved in drug production such as *Firm A* and *Firm B*, which rely heavily on patents. In conclusion, we have raised here an important hypothesis that is worthwhile going into in more depth: The way in which biotech firms rely on patents would depend on their business model, which explains why the extent to which firms rely on patents is very different across biotech firms and why, conversely to what is often argued, many biotech firms do not need patents.

3.3 Distributed entrepreneurship[26]

The phenomenon of entrepreneurship in biotech, with the multiplicity of small new ventures it has generated, has often been perceived as a renaissance (as compared with the big traditional

[25] Yet, our feeling is that many firms reported in the Biovalley directory as R&D firms are not doing research in biotechnology. Certainly some firms may be classified as doing research while they are just drug manufacturers or services providers.

[26] In this paper we use the expression distributed entrepreneurship to illustrate the fact that the entrepreneurial activity is not retained into the hand of a single individual but is distributed among across many institutions. Yet the economic and managerial literature proposes many different terminologies -such as distributed, dispersed, collective or diffused entrepreneurship- that are often used to refer to the same thing.

pharmaceutical companies) of the entrepreneur-hero that Schumpeter had in mind in his seminal book "Theory of Economic Development" (1911). To quote Radosevic (2005): The entrepreneur would be "a heroic almost Nietzschean type of lonely individual who faces resistance to innovation and who is driven by non utilitarian motives". In line with this description, biotech start-ups are usually founded by a small number of persons (often a single individual) who personally assume the direction of the project. Motivations of those founders, which are often not only profit oriented, and the recourse to credit to launch the business are also in line with Schumpeter's early view. Our four case studies, which all insist on the charisma and the experience of the founders, partly confirm this analysis. Our founders are all individuals endowed with a strong experience either scientific or managerial. Hence, according to this view, the revival of small business and self-employment world-wide may announce a reversal of the trend concerning the nature of entrepreneurship, from Schumpeter mark II (the managed economy that started at the turn of the 20th century, see Lamoreaux and Sokoloff, 2005) to Schumpeter mark I (an entrepreneurial economy).

Yet, this view of entrepreneurship ignores interdependences between the multiple actors of innovation. It comes from a deep misunderstanding of entrepreneurship in biotech, which is mainly a collective process that relies on the assembling of competences distributed across a large number of agents. The entrepreneur is not a single agent but belongs to a network and has to interact with other members to succeed in his enterprise. In short, the locus of innovation has shifted from individual organisations to networks (Freeman and Perez, 1988; Powell, 1996; Baum *et al.*, 2000). There is no reversal to Schumpeter mark I but rather the emergence of a new type of entrepreneurship that relies on the importance of networks and collaborations (Powell, Koput and Smith doerr, 1996).

Yet, if networks are the central drivers of innovation it does not mean that individual entrepreneurs play no role. They still need to develop specific competences, at least to ensure the creation of their network. In this sense, competences such as the ability to bridge different culture, open-mindedness, etc. may become central. Following Radosevic (2005), the entrepreneur must have the ability to set-up agreements among all interested parties (such as the inventor of the process, the partners, the capitalists, the suppliers, the distributors), to enlist cooperation of official agents, to put together adequate staff, etc. We have identified this competence (the ability to bridge different actors) in three interviews with founders. Only *Firm C* lacked it, which may provide the central explanation of its failure. This ability to bridge heterogeneous networks and persons may become far more important for entrepreneurs in biotech than scientific or managerial abilities.

To summarise, far from following the traditional Schumpeter mark I or II framework, entrepreneurship in biotech is a distributed process since, as put by Minkes and Foxall (2003, pp. 226): "The entrepreneurial spark will be found in more than one person and in more than one place". The entrepreneurial function is in some sense distributed among a wide number of individuals and institutions[27]. An important difference between this paper and former studies on

[27] Minkes and Foxall (2003) emphasise the contribution of Herbert Simon to the notion of distributed entrepreneurship. They consider that the seminal work of Simon regarding bounded rationality, dispersed knowledge and satisfactory choices contributed to question the hypothesis of 'the lonely captain on the bridge' and opened the door to distributed entrepreneurship.

distributed entrepreneurship is that the latter seem mostly to consider the function of entrepreneurship as being distributed across individuals within a given firm, while we would like to suggest in this work that it is distributed between different institutions. The locus of entrepreneurship cannot be limited to a single institution. Our four cases emphasise this distributed dimension of entrepreneurship by putting forward the role of formal alliances, informal relationships and public institutions that surround and assist the entrepreneur.

In biotechnology, beyond maintaining close relationships with public research and the scientific community, the importance of which were already emphasised in section 3.1, it is central for entrepreneurs to develop formal alliances with other players. Formal collaborations are necessary for small structure such as new biotech firms in order to access external knowledge, to outsource clinical trials or administrative tasks, to acquire specific inputs, to access the market, etc. Our interviews confirm that firms' development rests strongly on their networks of partners, such as other biotech firms, academic labs, consulting companies, suppliers, financers, public institutions, etc. Firms that cannot rely on such networks can hardly expect to succeed, as illustrated by the example of *Firm C*. Answers to the questionnaire we addressed to firms of the Upper-Rhine Biovalley also stress the importance of formal collaborations[28].

More generally, this need to contract alliances is observed in all the biotech industry. According to Hagedoorn (2002), the bio-pharmaceutical industry experiences since the end of the 1970s an extraordinary burst of technological inter-firm collaborations. In 1998, collaboration agreements contracted between biotechnologies and pharmaceutical companies represented approximately 30% of the total of the collaborations in all industries. This is in line with the analysis of McKelvey, who stresses that: "The small biotech start-up firms do not replace the pharmaceutical firms. They instead play a vital role as the link between on-going university science and pharmaceutical firms, where each actor has specialised knowledge and institutions relevant for producing specific kinds of knowledge relevant to innovations" (McKelvey, 1998, p. 166).

Yet, most usual partners of biotech start-ups in the Upper-Rhine Biovalley are public research organisations (which is acknowledged by most of the firms as the most central partner) and other small new biotech firms. Firms of the Upper Rhine Biovalley collaborate rarely with big-pharmaceutical firms. This comes out both from our interviews (none of our four firms collaborate with big-pharmaceutical companies) and from answers to the questionnaire.

This lack of collaboration with big-pharmaceutical companies is rather surprising since usually the latter are fully part of the story in entrepreneurship in biotech as indicated by statistics of collaborations above. Yet, it is likely to come from a discrepancy between research programs undertaken by new biotech firms and big pharmaceutical companies, which are positioned closer to the market and will agree to develop collaborations only with start-ups that have research close enough to the market. Since the Upper-Rhine Biovalley corresponds more to an emerging network and none firms of its is in such an advanced position, it is of few interest to big-

[28] Almost all the 18 firms that answered our questionnaire are involved in formal collaborations with other organizations. Only two firms out of the 18 report that they were not engaged in any R&D partnership within the last three years. Furthermore, firms are not involved in only a single collaboration but for most of them develop a web of partners.

pharmaceutical companies to collaborate with them. Conversely, in the US biotech firms may be closer to the market and therefore may be of more interest to big-pharmaceutical companies.

Formal collaborations are central but this does not mean that informal relationships among individuals are not. On the contrary, our interviews emphasise strongly the importance of informal contacts during the process of creating a new biotech venture. In the four cases informal contacts were central to explain the birth of the new venture. In the case of *Firm B*, for instance, it is the links and even the friendship among two of the cofounders that led to the new firm. Similarly, for *Firm A* it is a personal contact that enabled the founder to find his CSO. In the case of *Firm D* it is also informal contacts that led to the meeting of the two founders. Finally, the failure of *Firm C* can be explained by the lack of know-who of the founder, who was not endowed with a sufficient reputation, managerial as well as scientific, to attract partners.

Informal contacts are central first in order to get financing. Our interviews all indicate that beyond the scientific quality of the project or its feasibility, personal contacts with financers are necessary to attract funds. Second, informal links are useful to find collaborators willing to enter the project, i.e. they allow the founder to set up the team and to hire competent collaborators. It comes out of all cases that the composition of the double heading of the company (CSO and CEO) that is absolutely standard in biotech[29] was always operated through informal links. People meet each other and develop their informal network during conferences and professional meetings. Biotech in France is a small world where it is very difficult for outsiders to find collaborators.

More generally, it seems that informal contacts among scientists, industrials and financers are very important to ensure the coherence and the assemblage of complementary competences. Gittelman and Kogut (2003) have indeed showed with US data that the logic that drives science and industrial innovation are likely to be diverging. In order to overcome those conflicting logics go between actors, who are persons both entitled with a reputation as scientists and industrials and who have therefore developed an important informal network, are essentials. We find here an important justification for star scientists, who usually do not play an active role in a company, but essentially give an access to their know-who.

A last feature related to the collective nature of entrepreneurship in biotech is the important role played by public institutions, either to fund new projects at an early stage or to provide assistance and networking. Our four interviews acknowledge the importance of the incubator during the first stage of the project. It usually facilitates the creation of new ventures by hosting the company within its own building during the first years of the project, which helped resolving the problem of finding a place and of buying costly scientific equipments. First, it removes most of the financial burden and, second, it allows the entrepreneur to focus on the core of the project and not on peripheral details. Furthermore, incubators usually also provide assistance to the new venture. They help the founder to establish a business-plan, to build a relevant intellectual property right

[29] We already mentioned that biotech start-up almost all adopt a standard organisation composed of two heads: One chief scientific officer (CSO), in charge of scientific aspects, and one chief executive officer (CEO), in charge of managerial and business aspects. This standard organisation is essential in order to obtain financing. It came out of all our interviews that, although financers value highly patents and the credibility of the scientific project, they hardly agree to finance start-ups that do not have an experienced business officer (Powell *et al.*, 2002 ; Prevezer, 2001).

policy, and most of all they play a very important role as go between institution: they give more visibility and credibility to the project and they help the entrepreneur to find relevant partners and collaborators.

Other public institutions also play a role during the first year of a new company. Public institutions such as ANVAR in France can, for instance, distribute grants that, although modest, help to activate the project during its initial phase. Standard financial institutions indeed hardly agree to provide funds when the project is at an early phase, which means that entrepreneurs must use other sources of financing such as their own funds or the help of business angels. In this sense public institutions that provide money at an early stage are often necessary to launch projects that otherwise could never take off. Those institutions usually also do more than merely funding early projects. They send a signal of quality towards other actors of innovation. By helping the project they indicate that it may be feasible and promising.

To conclude this section, we discussed here the emergence of a distributed form of entrepreneurship in biotech. New biotech start-ups, although they rely heavily on the personality of their founder(s), are most of the time the outcome of a distributed process that involves many actors who need to develop tight interactions. They are not the fact of isolated individuals or organisations. An interesting issue is whether this feature is due to the emerging nature of the industry in France, which exacerbates the needs for collaboration and coordination (Cohendet *et al.*, 2006), or to the intrinsic nature of the sector. Comparison among the European case and the US, where the industry is much more mature, could bring an answer to this question. First results indicate that clustering and R&D collaboration are also central feature of biotech in the US. Aharonson *et al.* (2004), for instance, examine how industrial clustering affects biotechnology firms' innovativeness. They find that clustered firms are eight times more innovative than geographically remote firms, with largest effects for firms located in clusters strong in their own specialization.

4. Conclusion

This paper aimed at understanding the main features of entrepreneurship in biotech through a detailed analysis of the foundation of four start-ups located on the French side of the Upper-Rhine Biovalley. Our objective was to go into the black box in order to analyse the genesis of new biotech ventures. Hypotheses raised here should hence provide a good starting point for more quantitative research that will confirm or invalidate them.

The four firms we studied were founded between 1999 and 2001, developed different strategies and experienced divergent trajectories. One firm has never really been able to take off and went bankrupt two years after its foundation. Another firm raised many hopes, experienced a rapid growth and finally went bankrupt six years after it was erected. The third one also experienced a quick growth but is still alive at the present time, although its future is uncertain. Finally the fourth one adopted a less ambitious strategy based on short run cash-flows but it also seems to be more stable than the others.

Our analysis enabled us to stress several characteristics of entrepreneurship in biotech. A first insight deals with the motivations that drive the founders, at least when they come from the

academia. We have seen that those motivations are usually not directly based on money but on more complex mechanisms. Scientists may, for instance, want to foster the industrial exploitation of their research in order to make them benefit general public. Or they may want to increase research budget and achieve more freedom for their research. More generally, scientists may want to join industry because it often offers more opportunities than the public sector. Yet, we have also seen that this willingness to create a venture in order to pursue his research also entails risks. Projects that are too far from the market usually do not survive very long.

Beyond the motivations of the founders, we emphasised three broad points that appear as central within the entrepreneurship process: The role of public science, the role of patents and the collective dimension of start-ups' creation. First, biotech entrepreneurship in France cannot be understood without public science. Most new biotech firms are founded by public scientists and almost all biotech start-ups acknowledge strong links with at least one public lab. Second, for biotech firms involved in drug production, patents are highly necessary. New ventures cannot exist without a strong patent system. Third, the process of entrepreneurship in biotech is a distributed process in the sense that it does not rely on one single entrepreneur but on the assemblage of a mix of competences distributed over a wide range of individuals and organisations.

To conclude, we believe that a promising approach of entrepreneurship in biotech deals with the notion of distributed entrepreneurship. Entrepreneurship in biotech is never the fact of one single player, neither is it the fact of several firms that just share knowledge or other items. Rather, entrepreneurship arises in a collective network of heterogeneous actors, each of them acting on a fraction of the system but being inseparable from the other members, implying that the whole is worth more than the sum of each of its parts. Following McKelvey (1998, p. 168): "Entrepreneurship in modern economy is different because entrepreneurs can be distributed among a system of innovation rather than concentrated in one type of firm". In this sense, although there may be a leader who orients the project, each actor plays a role and it may be very damaging for the overall efficacy of the project to exclude some actors.

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