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"The role of ERC Funds schemes and their effects in the technology transfer process: a case study on team dynamics and collaborations between startups and industries".

Relatori:
Prof. Emilio Paolucci
Prof. Valentina Cauda

Candidati:
Giorgia Di Trapani (258309)
Greta Gasperoni (267858)

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1 Introduction

Technology transfer is the process that disseminate technology from a person to another and between universities, governments and industries. It has been used for a long time until now, but in the last years the volume of researches has increased while the number of projects successfully exploited in the market haven't, leading to the need to rethink the process itself.

In this Thesis we are going to analyze the technology transfer process from universities to the market, the actors that can help or operate it and the main variables that can lead to success or failure when a Research-Based Invention (RBI) needs to become an innovation, that is the economic exploitation of an invention.

In particular, we are going to focus on the biomedical and the pharmaceutical industries, a field in which innovation has three specific conditions: a high level of uncertainties that leads to a high technological risk, enormous costs associated to the development of a new drug or treatment and long time - often over 10 years - before *eventually* getting a payback.

We will try to give an answer to the following questions: is it possible to solve these issues within the academic environment? Which business models or incentives are used to create start-up or spin-off in this field and what is their impact? Finally, based on our experience and a practical example on a team of researcher and entrepreneurs of Politecnico di Torino, we will try to give some suggestions on how these models can be improved.

2 Technology Transfer

In the field of scientific research and industrial fields open to technological innovation, we often hear about Technology Transfer (TT): the process of disseminating technology from the person or organization that owns or holds it to another person or organization. These transfers may occur between universities, businesses and governments and could be either formal or informal.

Transfer of technology could be horizontal or vertical: it is horizontal when knowledge within a company or organization moves from one area to another. It is vertical whenever there's a net **change of goals**: from pure research to market applications, when it accesses to the potential for commercialization of technology. In this work we're going to focus on the latter, analyzing how to make the "jump" from academic to market easier for research-based inventions (RBI).

TT is therefore an **open innovation methodology**, composed of a set of activities that aim to transfer knowledge (technology, skills, manufacturing methods, production standards and services) from the world of scientific research to the market.

2.1 Open innovation

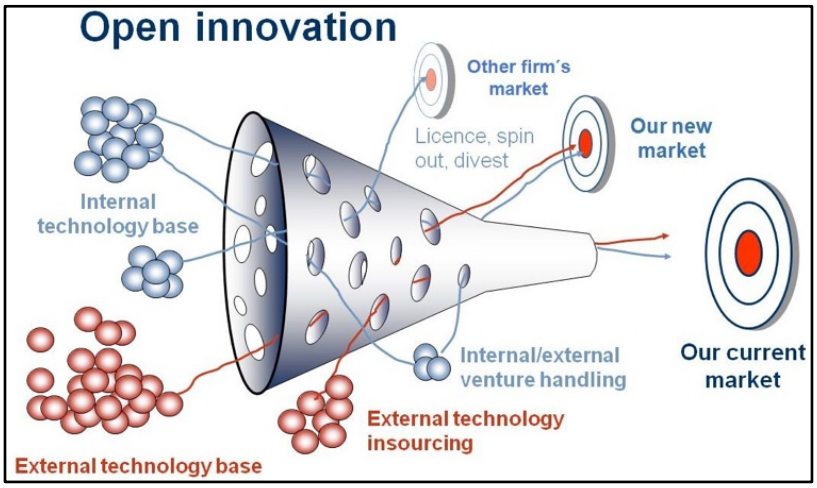

Figure 2.1: Open innovation funnel.

Open innovation is a strategic approach adopted by many companies in the last twenty years in order to create more value and to better compete on the market. It was theorized in 2003 by Henry Chesbrough, and it consists in using not only internal ideas and resources, but also ideas, solutions, technological resources and skills coming from outside the company (startups,

universities, research institutions, suppliers and consultants). Therefore, the company can access the innovations available on the market and integrate them with its business model. This process also allows a faster time to market, or a shorter time to move from the stage of product or service conception to its production (Chesbrough, 2003). These two qualities can be really helpful in some context such as biotech, where time to market is extremely long due to deep researches and strict regulations.

According to Chesbrough's scheme, the most competitive companies are not those who produce the best innovations within, but those who manage to create innovative products and services modulating at best what can be derived from players outside the company perimeter. The concrete ways in which open innovation is done are call for ideas, inter-company agreements, collaboration agreements with start-ups, hackathon or acquisitions.

Despite the numerous benefits, its implementation is taking place gradually and not everyone has fully understood the effectiveness of this tool yet.

2.2 Linear model of innovation

The linear model of innovation, in contrast with open innovation, is a simplistic way to explain how the product development process works and which actors are involved at any phase. Innovation is described as a linear process, a flow along a predetermined path. The main flaw of this models is the lack of feedback loops and information flows from the sales sector or end-users. All of these, however, are fundamental forms of feedback for the evaluation of performance, the subsequent steps to be taken in the process and in the identification of the competitive position on the market.

The first step in this model is the basic research, that is the pure discovery with no specific application. After that we have the applied research, the activity that leads to invention of a new technology and therefore a demonstrator to prove the viability. When moving into product development, the focus shifts from the technology characteristics to the commercial attractiveness and industrial viability, and it's important to define a price and a possible margin. Usability, safety, production, product certifications are then taken into consideration.

Product development could be split in a precompetitive and a competitive stage. The discriminating element is that the former stage leads to prototypes that do not have commercial value, while the latter leads to the actual product that will be launched on the market.

The innovation process is always long and risky, especially in its earlier phases, but some industries are riskier than others due to the intrinsic characteristics of the technology. That's why private sector companies do not usually finance basic or applied research: the economic returns are not guaranteed and are often too far in time. This situation represents a market failure, and governments are called to step in and provide public funding of the activities that private actors would not invest in, supporting the early stages of the innovation process by direct or grant-based financing to universities and research centers (Cantamessa & Montagna, 2016).

2.3 Technology Readiness Level

Technology transfer is strictly linked to the concept of technological maturity, known as Technology Readiness Level (TRL), this scale was originally defined by NASA in the 1990's as a means for measuring or indicating the maturity of a given technology. The TRL spans over nine levels as follows:

Table 2.1 TRL Descriptions

TRL Level	Description
TRL 1	Basic principles observed
TRL 2	Technology concept formulated
TRL 3	Experimental proof of concept
TRL 4	Technology validated in lab
TRL 5	Technology validated in relevant environment (industrially relevant environment in the case of key enabling technologies)
TRL 6	Technology demonstrated in relevant environment (industrially relevant environment in the case of key enabling technologies).
TRL 7	System prototype demonstration in operational environment
TRL 8	System complete and qualified
TRL 9	Actual system proven in operational environment (competitive manufacturing in the case of key enabling technologies; or in space).

Typically, many products go through the various stages of the TRL scale in their life cycle. It is possible that iterations will be needed between various TRL levels, especially during the development phase, although not limited to that. The TRL is perceived as an effective way to indicate the development stage of a given technology or product.

2.4 The supply chain in Technology Transfer

The activity of creating an idea (or an intellectual property) and the subsequent phase of technology transfer, as we have said, are rather complex processes. A certain number of subjects are part of it, which form a real supply chain. The **main goal is to make technology accessible to all people**, through a path characterized by a starting point (research), an arrival point (the market) and a series of intermediate stages (the supply chain of TT), in which different actors are involved.

The first section of the technology transfer path is occupied by **research institutions**, that are engaged in research and development every day. Within these institutions (such as the universities) different categories of people are involved, often classified according to the employment contract (employees, researchers, project collaborators, PhD students but also undergraduates). All these figures can be inventors and have to deal with significant problems concerning the protection of the intellectual property that they may generate.

Another relevant subject in the technological transfer process is made by the **companies**. They carry out research activities within their teams, establishing partnership with other companies or with research entities.

At the same time, companies can be the financiers of research projects, implementing - for example - open innovation paths, looking for the technological innovation they need outside the company perimeter. Furthermore, companies are the main purchasers of technology deriving from public bodies. For all these reasons, they represent an indispensable subject for completing the technology transfer process.

Founders, the third link in the chain, are indispensable, since the research activity can be carried out either with the research body's own resources or with external resources. In the latter case, the lenders can be both public (mainly through tenders) and private (companies, banks, funds, business angels). In the field of public funding, among others, in recent years **European funding** has become increasingly important.

2.5 Bridging academia and industry, an important challenge

Despite incentives to move research into production, the practical aspects are sometimes difficult to perform in practice. Using TRL as a criterion, research tends to focus on TRL 1–4 while readiness for production tends to focus on TRL 7 or higher. Bridging TRL-4 to TRL-6 has proven to be difficult in some organizations, and therefore it represents an important gap to fill, commonly called the "valley of death", since many technologies reach a medium level and then die (Rossini, 2018).

The reasons of this phenomena can be various, among them there's a lack of communication between academia and industry: the work style, culture and mentality are different and for academics is hard to address properly the industrial challenges. On one hand it could be useful to test a technology on the market in the early stage, so that mistakes can be avoided or addressed immediately, on the other hand, rushing prototypes into production can be costlier and time consuming than expected.

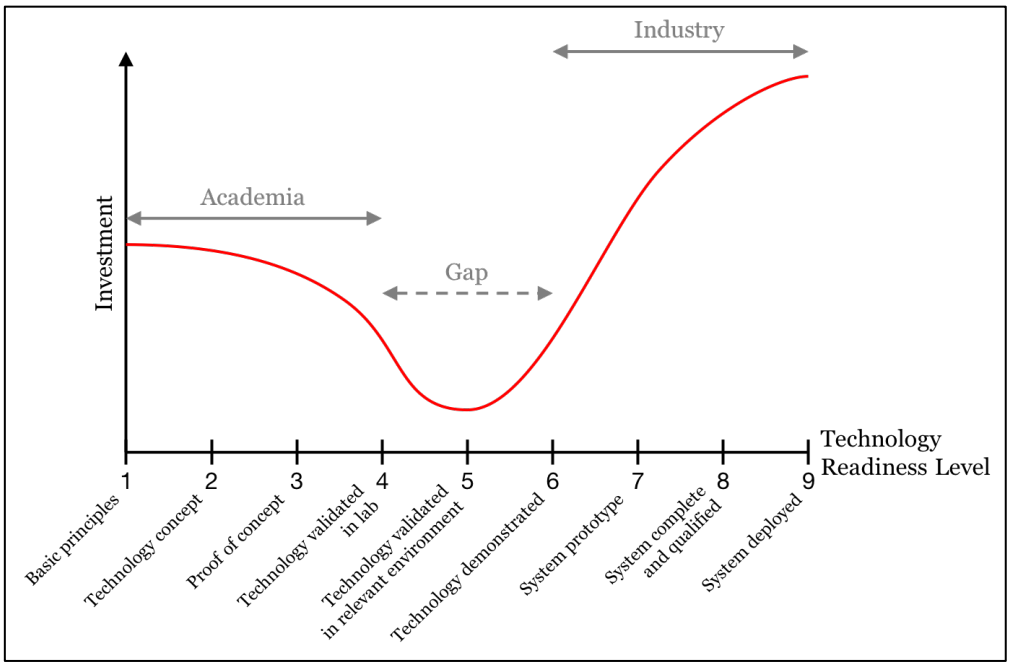

Figure 2.2 Gap in TRL between academia and industry.

2.6 Partnership intermediaries

Academic entities and governments have a **key knowledge-generating role in the innovation process**, particularly in the pre-competitive phase of product development, whose end-products are prototypes that do not have commercial value.

2.6.1 The role of the government

In general, governments can provide an economic and institutional environment that supports or hinders innovation. For instance**, the U.S. government's annual budget funds over $100 billion in research and development activity** (Sargent, 2018), which leads to a continuous pipeline of new inventions and technologies from government laboratories.

Governments do not usually act in the last phase of product development because risks are low and markets are usually able to work properly. Nevertheless, governments can have a strong impact on this phase too (Cantamessa & Montagna, 2016) through **taxation, labor and bankruptcy laws**. In fact, a **favorable environment** can increase the potential returns on the investments made and lower the loss of value. Moreover, a dynamic and highly competitive economy will be likely to increase demand for the products and services that are being proposed by innovating firms. Finally, governments can provide generic infrastructure, such as highways and telecommunication networks that lowers the cost and increases the effectiveness of business activities, thus making it easier for private firms to invest in innovative projects.

2.6.2 The hard relationship between university and industry

Relationships between university and industry have many positive effects, among which giving extra financial support to university and increasing the speed of technology transfer. These interactions create a virtuous cycle by improving the productivity of the academic research in terms of papers and patents and therefore increasing visibility and reputation.
Although these good points, we also have some cons. First, universities get the financial support from the industries, but they do not benefit enough of the industrial competencies. Moreover, some of the cooperation models (including licensing of intellectual property, performing contract-based research and undertaking government-funded research projects jointly) may generate conflicts of interests: industries, indeed, tend to push researchers through applied-research project rather than base-research because their goal is the commercial exploitation of the invention (Triulzi, et al., 2014).

2.6.3 Biotech perspectives

Thinking about biotech research, this conflict of interests may be significant: in order to generate innovative solutions basic research is fundamental.

If all the biomedical and pharmaceutical researcher would have been driven only by profit, new treatments for rare or less-known disease would never have been developed, causing a failure in the innovation system. In many circumstances, indeed, market forces might not be able to select the projects that maximize social utility.
For instance, pharmaceutical companies are often criticized for working on lifestyle drugs addressed to rich countries, and not dedicating enough effort to develop potentially life-saving medicines for emerging countries or for orphan diseases[1], where the financial rewards might be lower.
In conclusion, even if debates and connections may have a positive impact, the traditional roles division and each actors' own identity and mission should be kept.

To avoid industry's control over research body and mitigate their negative effects, governments should increase the funding for basic research (Triulzi, et al., 2014). At the same time, to be more independent, academic organizations should raise entrepreneurial awareness and foster the creation of academic spinoffs based on internally developed technology or know-how. Nevertheless, creating a spinoff is not easy at all and some requisites are necessary in order to succeed: an engineering-based RBI (instead of a science-based one), a sufficiently high Technology Readiness Level (TRL) of the invention (best between 4 and 5) and the previous intention of the research team to set up a spinoff (Battaglia, et al., s.d.).

In Chapter 4 we are going to analyze in details other problems and conditions that characterize the biomedical startup funding system and we will show some initiatives that can mitigate the negative effects and determine the success of a biotech startup.

- **Good Reputation**: (of the startup, university or team members) can increase the value of the invention and make the startup noticed by companies and investors. It can be

[1] A disease that has not been adopted by the pharmaceutical industry because it provides little financial incentive for the private sector to make and market new medications to treat or prevent it. An orphan disease may be a rare disease (according to US criteria, a disease that affects fewer than 200,000 people) or a common disease that has been ignored because it is far more prevalent in developing countries than in the developed world **(Shiel, s.d.).**

obtained by patenting technologies, publishing on medical journals, taking part in events and competitions and also with good promotion and presentation (for instance a good website or a short presentation video).

- **Solid Funding**: essential to validate the technology. The initial test in vitro and in vivo must be carried out as soon as possible and should be conducted thinking about values, criterions and parameters that investors will want to see, keeping in mind defined goals and KPI to monitor.
- **Continuous Discussion with experts:** debate is fundamental to well structure the work and the testing procedures in order to better fit what companies will look for. Talking with experts and insiders may also help to find qualified personnel to add to the team.

2.7 The third mission

Universities have always had **Education** and **Research** as primary missions, but in the last decades things have changed and along with business, governments and societies, **universities had to adapt themselves and re-organize in order to link their activities with the socio-economic environment**. Internationalization has created new potential markets for students, alongside increasing access to research collaborators, but it opened universities up to competition with and comparison against institutions in other countries.

The commercialization of RBI developed by academic researchers has become a crucial mission for universities around the world, which are investing in the "third mission", through the creation of activities and transfer offices, with the provision of entrepreneurial training for scientists and the strengthening of industrial collaborations.

Despite these efforts, it has been recognized that universities are still facing significant gaps in the transfer of their RBI to industry. One of the main reasons for the persistence of these gaps is **the lack of appropriate investments and tools to support the development of basic research in applied research**.
Before reaching the market, the RBI require a **technology validation**: the implementation of a pilot that acts as a demonstrator of the technology for the market and, subsequently, the feasibility of the production of the RBI on a large industrial scale.

The funding constraints affecting these demonstrative steps, as scientists have internal funds to

complete these tasks and traditional investors are held well away from investing money in RBI, which are characterized by high risk and uncertainty.
For this reason, universities and governments have introduced specific policy initiatives to financially support the Scientist in the realization of pilot activities, just like the **programs proof of concept (PoC)**, that will be examined in depth in the following sections.

Nevertheless, this new mission still lacks an efficient and stable framework of relationships with the actors in their environment, particularly with firms. Initiatives such as the knowledge transfer offices (KTOs) try to create linkages between the academy and business, supporting spin-off and start-up creation, collaborative research projects, and industrial property rights registration and licensing. These new hybrid organizations gain new support schemes and instruments, from the regional scale to nation-wide initiatives or even at the international level. KTOs seem to have an important role in consolidating relations between researchers and entrepreneurs to ensure an alignment of interests, speeches and timings in order to promote an effective transfer of knowledge.

2.8 Theoretical Frameworks

Several theoretical frameworks are compatible with this idea of a new role of the university:

- Mode 2 Knowledge Production framework (Gibbons; Limoges; Nowotny; Schwartzman; Scott & Trow, 1994)
- Triple Helix (Etzkowitz & Leydesdorff, 1997)
- Regional Innovation Systems (Uyarra, 2009; Benneworth; Coenen; Moodysson & Asheim, 2009)
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2.8.1 Mode 2 Knowledge Production

The concept was developed in 1994 by Gibbons. The main proposition of the study is the emergence of a new knowledge production system whose locations, practices and principles are much more heterogeneous than in the traditional one.

Table 2.3 Main characteristics of the two mode framework

Mode 1	Mode 2

Academic context	Context of application
Disciplinary	Transdisciplinary
Homogeneity	Heterogeneity
Autonomy	Reflexivity/social accountability
Traditional quality control (peer review)	Novel quality control

The main difference is the **context of application**: while mode 1 have always separated the theoretical knowledge from the actual knowledge production, mode 2 tries to fill that gap and avoid making the distinction between the two.

A second characteristic of Mode 2 is **transdisciplinarity**, a dynamic interaction between different disciplines, using either theoretical perspectives and practical methodologies to solve problems. Moreover, knowledge is not produced just in universities and laboratories, but in a diverse variety of organizations connected through networks - including government agencies and spin-off - resulting in a very **heterogeneous practice**.

In the end, researchers are becoming aware of the consequences of their work and they care more and more about making an impact. This characteristic is called **reflexivity**: knowledge is a process that comes from dialogues and debates rather than autonomous work, therefore it is able to incorporate different points of view. The quality control is changing as well, incorporating additional criteria of economic, political, social or cultural nature.

2.8.2 Triple Helix

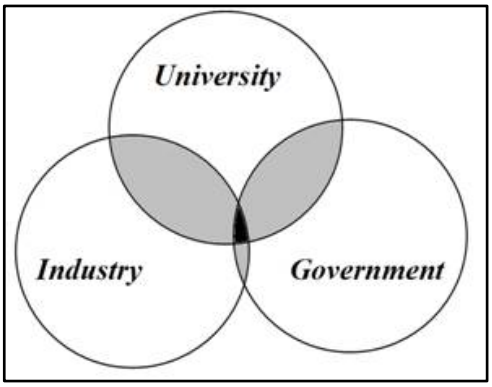

Figure 2.3 Triple Helix Model.

The framework was first theorized in 1990s (Etzkowitz & Leyedesdorff, 1995) and was applied by policy makers to foster the transformation to a knowledge-based society, giving a bigger role to universities. The **model analyses the interactions between universities, industries**

and governments, trying to explain the emergence of new hybrid organizations such as **technology transfer offices and science parks**.

In the model each actor is represented by a circle. With the development of the society the circles get closer together and the shared area of activities increased. Even if each entity keeps its main activity in its original field of expertise (knowledge production for university, commercialization for industry and regulation for the government), some entity might expand their operations. For instance, universities are becoming economic actor, increasingly taking part in commercial activity through patenting and licensing, moving beyond the production of basic research. The *"entrepreneurial university"* is defined by Etzkowitz with the following elements: the capitalization of knowledge, strong ties with industry and governments, a high degree of independence, and permanent evolution of the relationships between universities, industry and government.

In a developed country, the university, industry and government are more equal and none of them is necessarily the driving force of the triple helix model of innovation: **the cooperation between the three actors can boost the economic power**. (Etzkowitz & Leyedesdorff, 1995)

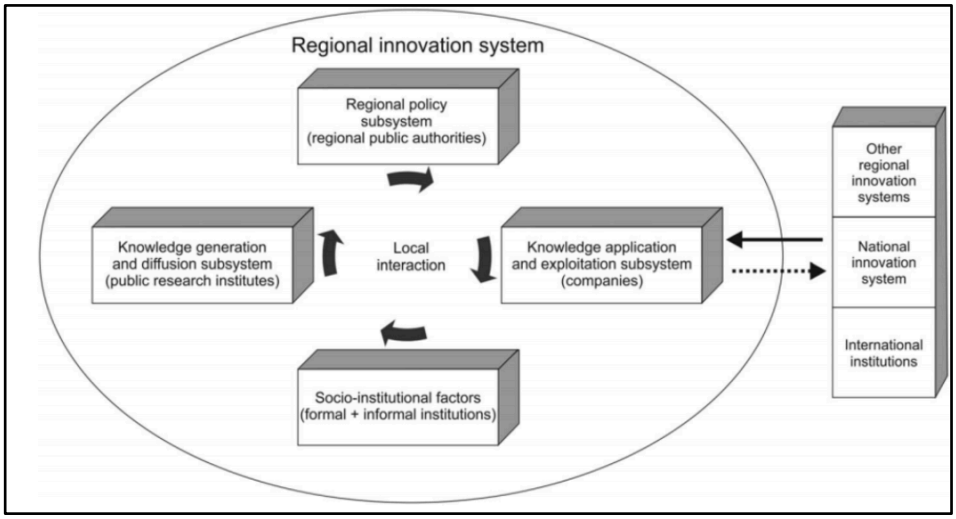

Figure 2.4: Regional Innovation Systems.

2.8.3 Innovation Systems

Innovation systems can be local, national or regional depending on their dimensions and the actors involved. A **regional innovation system** (**RIS**) encourages the rapid diffusion of collective knowledge, skills and best practice within a geographic area. It includes all the

activities that can help a start-up or a university spin-off to grow, such as networking platform, advising from business experts, coaching and investments (Cooke, et al., 2004).

Social and cultural cohesion, indeed, are enhanced by regional proximity, that helps to build the connectivity within the network, creating trust and sharing values. Open innovation models are also improving the relationships and interactions between the actors of innovation processes. Universities should make alliances with regions to better integrate economic and social development in education and research (Reichert, 2019).

An Ecosystems can be composed and influenced by different areas, it analyzes how required qualifications for human capital changed, how the university's learning methods and strategies adapted to different industrial needs, how the knowledge production and communication challenges evolved.

Europe governments are starting initiatives to enhance the local innovation system through funds and grants. So far, competitiveness has been the main goal of regional policy, but in the next years the innovation strategies of regional development will include a special attention to environmental and sustainability (Reichert, 2019).

2.9 Technology Transfer Offices

To support the activities of the main players in the transfer process chain, over time a series of subjects that we could define as "complementary" have been created, which act as a link between the world of research and the market. **Among the best known are the "Technology Transfer Offices",** also known as TTO. **The mission of these offices is to promote technology transfer through a series of activities**: first, to help researchers in positioning research programs on the market; but also by collecting and evaluating communications related to inventions; or even adopt the most suitable forms of protection, in addition to marketing intellectual property to existing companies or through the creation of new ones (spin-offs). In other words, **TTOs represent a transmission channel** between the world of research and the market. In some cases, they also contribute to provide research institutions with trends and indications coming from the market itself, playing the role of advisors in support of the top management of research bodies, as regards relations with businesses.

Furthermore, technology transfer helps companies to open innovation and startups to scale. In fact, once the technology to "bring on board" has been identified, a process consisting of several phases takes place for the company: first of all, the identification of a scalable business model, to which a "revenue model" can be associated; a patent sales (or licensing) model is another

relevant aspect of this process. After that is passed to the implementation of the technology, or the inclusion of the new product in the production we have the management of profits.
This is the classic modus operandi of startups. Indeed, even in small innovative companies, technology transfer can be functional to one's business. Specifically, it can speed up the "scaleup" process and facilitate the dynamics of internationalization.

2.9.1 Politecnico di Torino Technology Transfer Office

Politecnico di Torino is one of the most important technical university in Italy, with more than 35000 students and 50 different courses (bachelor and master) offered in engineering, architecture and design.
It has one of the most efficient Technology Transfer Office, with a very high number of patents and spinoffs created. It aims to foster an entrepreneurial culture inside the university and, thanks to the support and assistance given to inventors, the number of university's entrepreneurial outcomes is increasing.
Every year new patents for around 30 inventions are filed. The collaboration between research groups and companies is supported by the sharing of contents and licensing of patented technologies. The portfolio of inventions patented by Politecnico is fundamental in establishing technology-transfer processes to the benefits of companies (Politecnico di Torino, s.d.).

2.9.2 Specific project and laboratories of Politecnico di Torino to fulfill the third mission:

- LabTT: Inter-disciplinary laboratory for technology transfer;
- CLIK: Contamination Lab & Innovation Kitchen;
- EIC: Center for entrepreneurship and innovation;
- Knowledge Share project: a portal that contains over 1000 patents from 60 different universities, listed into categories and fields of applications. Each patent has a webpage in which the technology, the main features and the possible applications are clearly explained. Companies can access information and contact the universities that own the patents for possible partnerships and collaborations. The project involves Politecnico di Torino, Italian Patent and Trademark Office and Netval, an association whose mission is to give value to university research in the economic and entrepreneurial system.

2.10 **The role of incubators and accelerators**

Incubators and accelerators play a fundamental role in the growing of startup ecosystem in Italy. These organization support startups and spinoffs in the very initial stage, easing the access to specialistic competences and providing the resources that they may need in terms of technical evaluations but also business or legal consulting. Incubators are intermediators between young startups and the external environment, they guide the startup in its growth.

Two examples of Italian incubators and accelerators are Bio4Dreams and BioUpper.
Bio4Dreams is the first Italian incubator with private equity, founded in Milan in 2017 and focused on biotech and medtech. It was made to launch entrepreneurship projects and either researchers, universities, research centers and companies of biopharma and medical devices can propose their ideas, not only based Italy but also from other countries. Ideas can growth in personalized programs of 6 months, followed by an "incubation" of 2-3 years.
BioUpper is an accelerator that finances new business ideas in order to improve technological and competences transfer, to allow biotech and lifescience projects to be appealing on the market. It provides a funding of 150 thousand euros to share between the best three startups that apply to the project. Since the main part of researchers come from academy and lack business competences, they developed a custom empowerment program, offering access to structures, resources and networks.

2.11 Science and technology parks

Other common initiatives to enhance the collaboration between industries and universities are the science and technology parks (STPs). They can come either from the initiative of an industrial region to modernize itself with the support of a university or as a university strategy to engage with the industries of the territory. STPs have been established in the 1950s in the United States, with the initial aim to foster the commercialization of university research. In the next decades, many countries tried to imitate the Silicon Valley Model in order to integrate this mission in their regional development programs.

From the definition adopted by the *International Association of Science Parks and Areas of Innovation (IASP)* we can summarize five key elements that characterize STPs:

1. Specific economic development goal within a region;
2. Focus on fostering academy-industry relationships;
3. Priority on innovative and technology-based activities;

4. Provision of value-added services to companies;
5. Property-based initiative.

Therefore, STPs seem well placed to play a key role in innovation strategies for smart specialization. Indeed, they concentrate several research center and innovative companies and are likely to have high knowledge intensity. In the technical report of European Commission on the role of science parks in smart specialization strategies (Nauwelaers, et al., 2014) is defined the role of STPs, that should provide the right innovation ecosystem to encourage entrepreneurial discovery towards new competitive areas of activities. Moreover, three examples of STPs (in Finland, in England and in the Netherlands) are illustrated to show how they can be a stakeholder for innovation actors and shape smart specialization strategies.

2.11.1 H-Farm Campus

An Italian example of science park is H-Farm, founded in 2005 near Venice. H-Farm is a great innovation hub where entrepreneurs, professionals and students live together and contaminate each other with new ideas. It can welcome 3000 students and it's like an American campus with sporting center, space for events, classes, dormitories and restaurants. The goal is to promote and guide industries through the digital transformation, in order to produce culture and to develop new learning techniques and business models.

3 Intellectual Property

To fully understand the concept of technology transfer, it is necessary to start from the definition of intellectual property. Intellectual property is a set of rights that have been sanctioned to protect the creations of human intelligence and therefore give adequate incentives to those who engage in research or creation. In addition to representing a sort of guarantee for all those who create innovation within the universe of research, intellectual property essentially plays a role of connection with the productive world and with that of companies. For the latter, then, it represents one of the most effective tools to maintain positions of advantage over competitors, positions achieved through innovative efforts. Intellectual property makes technology transfer safer and more efficient, thus favoring the exploitation of innovation by existing or newly established companies (spin-offs and startups).

3.1 Legislation incentives & patents protection

A patent is a certificate that gives to the inventor the exclusive right to commercially use, for a fixed amount of time (usually 20 years), the results of his invention. The patent application contains, among the other things, a technical description of the invention and a set of claims. The claims are important since they represent the legal boundaries of what exactly will be covered by monopolistic rights, if the patent is eventually granted (Cantamessa & Montagna, 2016). It only covers the technical innovation, called "industrial invention", that can be presented as original solutions of a technical problem.

Requirements for patentability (Ministry of economic development, 2009):

- Industrial application (can be produced and utilized in industry);
- Novelty (not already included in state of technic);
- Originality (inventive activity, not-evidence of the invention for an expert of the sector);
- Lawfulness (inventions whose utilization is against the law cannot be patented).

3.1.1 Patenting procedure

The exclusive right to use the invention starts with the release of the patent. The procedure is long and complex: first, the patent application should be registered at the Italian Patent Office. Then, the office examines the admissibility requirements and the formality of the application.

Another office is in charge to examine the other characteristics and in the end decides to approve it or reject it (Ministry of economic development, 2009).
Many companies, universities and governmental organizations now have an Office of Technology Transfer (TTO) dedicated to identifying research which has potential commercial interest and strategies for how to exploit it. Through legislation, governments can encourage the private sector to use those technologies with commercial potential through technology transfer mechanisms such as Cooperative Research and Development Agreements, Patent License Agreements, Educational Partnership Agreements, and state/local government partnerships.

In the United States the legislation dealing with inventions arising from research funded by the government is the **Bayh-Dole Act** (Patent and Trademark law amendments act, 1980). This Act and equivalent legislation in other countries provided additional incentives for research exploitation and **it permits non-profit organizations and small business firm contractors to retain ownership of inventions made under contract** and which they have acquired, provided that each invention is timely disclosed and the contractor elects to retain ownership in that invention (Wisconsin-Madison University, 2018).
In 2005 in Italy was introduced The Italian Code of Industrial Property, a legislative decree to make an organic and structured discipline to defend and valorize the intellectual property, unifying more than 40 different texts ad laws to adequate to international agreements. The code refers to the contents of the Paris Agreement of 1883, the first international treaty on patents and industrial property. The agreement has been revised many times until the constitution of the World Intellectual Property Organization (WIPO) in 1967, based in Ginevra.

The Code of Industrial Property includes two articles to the matter of **employees' inventions (art. 64) and universities and public sector's researchers (art. 65)** (Legislative Decree 10 february 2005, valid from 19 march 2005)

The inventors keep the moral right of the idea, but the property rights to file the patent and to use it is given to the employees, following the idea that the profit should mainly be of the promoter, organizer and sponsor of the research activities.
There are different possible scenarios and different solutions to share the industrial rights:

1. **Service invention**: research and inventions are the primary activity for which the person is paid. In this case is easy to tell that the employee has all the property rights, since the inventors is already receiving a salary for that service.
2. **Company invention**: the invention is realized during a job in which is not expected inventive activity. The property rights are still of the employee, but the inventor is entitled to a "fair reward".
3. **Incidental invention**: the invention doesn't have an objective connection with the employer's tasks. In this case the employee has the right to release the patent. However, the law establish that the employee has a "option right" to acquire or license the patent. The price has to be fixed taking into account the possible help that the inventor received during his work in order to realize that invention.
4. **Researcher's invention**: the inventor is employed by a university or public administration office having research as a mission. In this case, the research is exclusive entitled of the rights of the patent. If there are more researches the rights are equally shared. Universities and public administration have the right to license the patent and to establish the maximum price of the license to third parties, if they don't specify anything, they get 30%. In any case, the inventor has the right to get at least the 50% of the revenues.

3.2 Strategy for Intellectual Property

When an invention has been developed, a firm must define a **strategy** for managing the intellectual property and for sustaining the competitive advantage that might come out of it (Cantamessa & Montagna, 2016, pp. 100-103). The process to commercially exploit research varies widely. It can involve licensing agreements or setting up joint ventures and partnerships to share both the risks and rewards of bringing new technologies to market. Spin-off are used where the host organization does not have the necessary will, resources or skills to develop a new technology and are particularly common in universities, whenever a private funding in needed.

3.3 Patenting Decisions

The classic approach to manage intellectual property is to apply for a patent. If the patent is awarded, the patent-holder can use it in many ways, depending on the organizational and financial resources of the company/start-up:

1. **Exploit its monopolistic rights** by producing a product based on the patent.
2. **Transfer the monopolistic rights** to another party by either **selling the patent or by licensing it**. It's the best option when the firm lacks the key resources or the security to exploit the market potential. Common problems may be the slow development process and the range of products to cover different market segments.
3. Use the patent to **prevent** other firms from developing products based on the technology it has invented.

In the case of a sale, the firm completely ceases its involvement with the invention. In general, the uncertainty surrounding the commercial value of the invention implicate many risks, therefore the buying firm might offer a limited amount of money.

Instead of selling the patent, the firm may opt to **license the monopolistic rights in exchange for royalty payments.** Depending on the agreement reached, the license may be unlimited or bear limitations in time, geography, destination market, and sublicensing rights. The royalty fee is usually specified as a percentage on the revenues accruing from the sale of products based on the patent, so that **risks are split between the two firms**. The licensor may also cooperate with the licensee's product development activities to facilitate the technology transfer process, in which case additional payments may be required to cover the related effort.

3.4 Cost and time of patenting

From a financial perspective, the value of a patent can be accounted for by considering the costs incurred to develop the technology. A better evaluation can be made by estimating the net present value of future cash flows that might derive from its commercial exploitation.

Together with undeniable advantages, the choice of patenting an invention also has several **drawbacks** due to high costs and risks, which must be carefully considered before engaging in this process.

1. **Administrative and maintenance fees** for filing the patent application and for renewing the validity of the patent over time.
2. **Patent attorney** who will have to spend time and effort to write a strong patent application.
3. **Geographic coverage of the patent** to gain effective protection and maximize the economic value of the invention its necessary to obtain patent protection in a sufficient number of countries, starting from the ones in which the market for the invention might be larger.

4. **Enforcement of the patent** in case imitators are infringing the intellectual property. If infringement is suspected, the patent holder must then start a legal procedure that can have uncertain outcomes, requires considerable time and implies significant costs to pay lawyers and expert witnesses.

Aside from its costs, patenting exposes inventors to a few risks:

1. **Disclosure** allows competitors to gain know-how and use it to improve the invention or circumvent it.
2. **Blocking patents** from competitors may reduce the economic value of the invention.
3. **After expiration date** competitors can legally start commercializing the product themselves.

3.5 Patenting cost for academic spinoffs and profits' share in academic context.

Startups or spinoffs who would like to get an European patent will need to confirm it in specific states. The cost depends on the state and it is around 3 thousand euros per state (of which 50% are generally paid from the involved Department and 50% from the university).
Moreover, there are annual maintenance fee either in approval phase and concession phase. They grow in time, starting from 300-600 euros per country, and are paid directly from the involved Departments (they can have a dedicated fund to support patenting activities or ask the inventors to sustain the cost with their funds of research).
Once the patent is commercially exploited, the distribution of the profits must follow the regulation of the university regarding industrial and intellectual property.
At Politecnico di Torino the rules are the following:

1. Each part involved gets a refund for the expenses sustained to file the patent;
2. The remaining part is shared between inventor and university (50% each).
3. In case of more inventors involved, the 50% entitled to them is shared based on the contribution given by each member (declared in the Disclosure Form).
4. For the academic part, if the expenditures were shared between central administration and departments, the profits will be shared proportionally. If only one sustained the expenses, the division will be 10% - 40%. If a third party sustained the expenses, the profits will be shared equally (25% each).

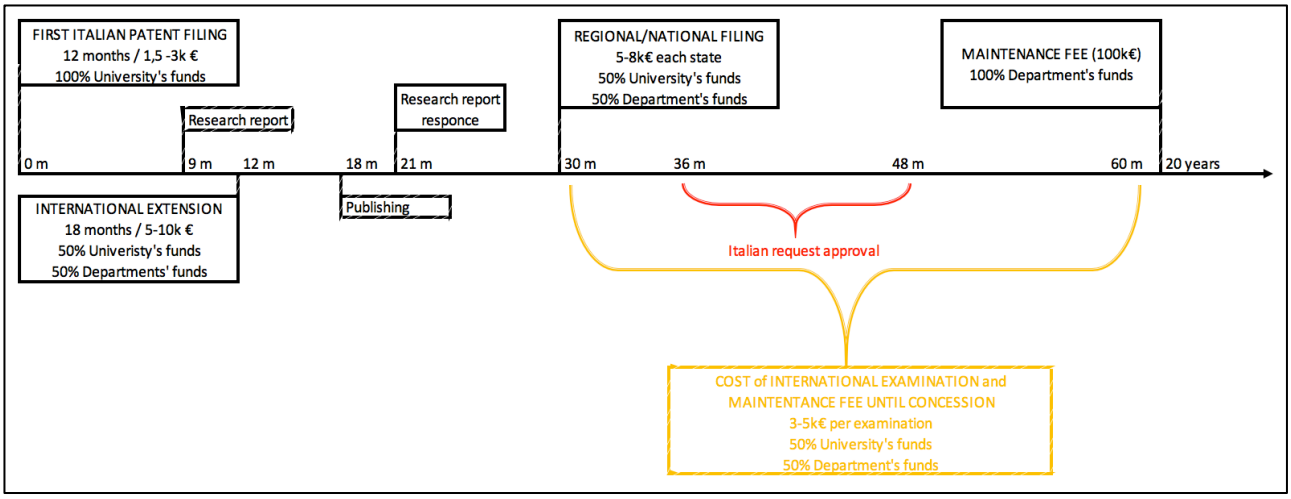

Figure 3.1: Costs of patenting, five years horizon.

4 Financial Schemes

Every new business needs some capital in order to start growing. It can be used for research, hiring professionals, buying equipment, renting an office, licensing or other overhead costs. The first thing to do is to define a budget based on your needs. Then, there are several options to obtain funding. In this work we are focusing on startups and spinoffs that are research-based inventions created inside the university, therefore some of the initial costs can be supported by the institution that can provide spaces, materials and personnel, beside eventually offering training or consulting either technical or in term of business. However, sooner or later we will have to deal with the funding problem: it's not enough to have an idea, you should also know how to effectively communicate it and sell it.

4.1 The business plan

In order to get financed, the idea should be properly described in a Business Plan. The business plan is a strategic document that illustrates your goals in three to five years and how you plan to get there. It forces the team to think through the value proposition, personnel, marketing assumptions, operations, and financial projections. It's particularly important for startups and companies wanting to progress to the next level of operations.

Nevertheless, a business plan is essential for raising capital. Most of the investors, indeed, require it to better understand the risks and feasibility of the project.

It usually starts with the executive summary, in which the reader gets an overview of the idea and goals and the main advantages and financial highlights are presented. After that a description of the technology is needed, along with details of strategic relationships, administrative issues, intellectual property owned, expenses, and the legal structure of the company. The document follows with market researches, strategies and a focus on management and personnel: presenting the team and explaining how their competences will help in the achieving of business goals is really important because a resolute management team with lots of experience may lower perceived risk for investors. In the end it should be provided a financial prospect with projection on profits and loss.

4.2 What investors want

The parameters that interest the most the investors are the following:

- Existence of a market need;
- Determined and harmonious team;
- Cost of developing and commercialization of the product related to the predicted revenues;
- Dimension of the market and growth opportunities;
- Competitors.

4.2.1 Pitching your idea

Every presentation is an opportunity to learn and gain experience, however if it is done properly it can also get investors' interest and may be a fundamental step for the success of a start-up. As we know, storytelling is fundamental. At the beginning it's important to grab the emotional attention of the audience and then guide them through a solid, logical path, explaining what problem are you solving and how. In his Ted Talk on how to pitch a venture capitalist, David Rose provoke the audience: *"If you can't do a presentation, how will you run a company?"* But then gives some interesting advice, affirming that the inventor is not just selling his idea, he's selling himself and his skills. A venture capitalist wants to see integrity, passion, leadership, commitment and vision.

4.3 Complications for Biotech start-ups

In biotech start-ups it's even harder to get a funding, and the main reasons are the following:

1. High technology risk: to validate a technology a big capital is needed, but also in the following phases the risk is still very high and the probability to find the right drug or molecule are 1 in 250.000.
2. High cost: clinical trials can cost up to 2-3 billion euros
3. Long developing time: 10-15 years before eventually get a payback.

To address the first issue, as we have seen, governments and universities can finance the basic research, solving a market failure and giving opportunities to go through the first pre-clinic

tests. The university can provide for personnel, laboratories and materials, while the government can issue calls for grants.

For the second concern, a possible solution may be the cooperation with hospitals in order to better handling clinical trials and reduce the cost as much as possible. Regular discussion with experts since the beginning can help to set-up all the tests properly and save time and money. Nevertheless, instead of aiming at reducing costs may be easier to find alternative models to finance biotech startups.

A similar talk can be argued for point 3, time of developing can be reduced by starting off with the right foot and programming with attention roadmaps, deadlines and milestones. Nevertheless, in many cases time is needed to see the long-term effects of some therapies, including survival rates and tumoral mass reduction, and cannot be shortened in any way.

Given these circumstances, what pushes an investor to risk his money in a so complicated project? What can compensate uncertainties, time and cost? In every investment project the investor chooses the level of risk he is willing to overtake in exchange of a specific economic return in case of success. As it is easy to imagine, the higher the risks, the higher the returns. In the next paragraphs we are going to see what kind of financing scheme better suits the early stage of development.

4.4 Financial Tools

When a project is just starting, it is hardly financed by debt capital. Return on investment are uncertain and far away in time and there are not the conditions to sustain the debt.
Therefore, most of the projects proposed by startups and spinoffs are usually funded with risk capital, that can be raised in several ways. Typically venture capital funds or business angels can decide to invest their money and overtake a risk in exchange for a substantial return if the project succeed, but for the biotech industry we have a slight difference. As we have seen in the previous paragraph, the high uncertainties on the technology, high costs and long development time, can scare away most of the investors. Therefore, for biotech startups, the most used financial instruments in the **early stage of the research** are **public funds, grants or prizes**.

4.4.1 Grants

Grants can be given by governments to graduate students and researchers to pay for equipment and salaries, but some of them can also be assigned to academic collaborations with industries to facilitate the commercialization of an invention. In the next chapter we will describe the work of European Research Council and explore the different existing grants and their main characteristics and goals.

Anyway, it is not enough to take part to these events in order to successfully enter in the market. ERC financing indeed are usually made for basic research and the researchers who apply to it mainly have academic intentions. That's why a new kind of grants has been created in order to explore market opportunities starting from university research.

4.4.2 Prizes

To have a good reputation is fundamental when trying to raise capital. It is therefore relevant to publish articles in the most appreciated journals of the field, to file patents for the discovered technologies and also to join conferences and contest either public or private. Competitions are obviously a good way to start challenging the team, learning from others and get some reputation, but the economic reward is usually too low to actually be helpful. Therefore, the inconsistency of the prizes has been pointed out to be a weak point for this financial instrument. Even if sometimes consulting services and business courses are offered, some researchers who took part in different competitions explained that those services are useless if they lack the personnel to actually follow through with the project.

We think that prizes of competitions for startups and entrepreneurs should be re-designed in order to sustain at least the salary of a small team that could work full time on the winning idea. Moreover, we argue that it's better to pay two or three researchers for a shorter time rather than one single person for a longer period of time: when building a business, timing is essential and a limited temporal horizon can encourage the team to work with more determination and passion. In the end, it goes without saying that a close-knit group can achieve greater results than a single-minded one.

4.4.3 Business Angels and Venture Capitalists

Once a few results are achieved **Business Angels** or **Venture Capitalists** may start getting interested in the project.

Angel investors are individuals with capital who privately invest in new businesses in exchange for a share of the company. They often take control of the startup, but they also give experience and advice. They can be found on specific platform and websites and even if getting an investment is hard, it is important to start creating a network and get some thoughtful advice.

Venture Capitalism is a form of equity financing and it is very common in the biotech industry since venture capitalists take big risks and invest million euros in seek of massive returns. They collect capitals from banks, corporations, insurance companies, retirement funds or individuals, in order to invest in unlisted companies. They are quite choosy and only one start-up in 200 gets to receive their trust: it is hard to capture their attention. They also demand control, but they will help with management, promotion and network opportunities in order to protect their investment. Recently a lot of angels' groups were created, in order to share investments opportunities.

Some famous Italian networks are "Italian Angels for Growth"[2], "Il club degli investitori" [3] and "Angels4impact"[4].

4.4.4 The Model of Founding Angels

Initially applied in north America, the founding angels' model is now growing also in Europe. The model focuses on the commercialization of pre-seed and seed stage technologies developed within universities and research centers.

Founding angels can fill the financial gap and build biotech industries together with scientist, way before the entrance of business angels and venture capitalists. Their role is to give experience and support in daily operations, fostering the go-to market, but they also have experience in biotech industry and a solid network. Like other private or business investors, they are paid in equity.

[2] Support young tech business in their growth path.

[3] 150 business angels looking for smart innovative entrepreneurs.

[4] 60 young business angels with a focus on impact investing on early-stage startup with high growth potential.

This model is important because start-ups and spinoffs, in order to succeed, do not only need capital, but also assistance and support to balance the typical academical mindset of researchers and inventors. Moreover, they are key to build the startups' reputation: when the founding angels are onboard, it is way easier to get more financial support in the next phases, when business angels and venture capitalists start to get involved (Festel, 2011).

Table 4.1: Investors' timing and strategy.

	Founding Angels	Business Angels	Venture Capitalists
Startup's stage	Very early	Early	Mature
Investment size	10.000€	100.000€	>500.000€
Money invested	Own money	Own money	Investors' money
Strategy	Flexible	Flexible	Shorter time possible to exit.

4.4.5 Why does this model work for the investors?

The uniqueness of the founding angels' investment strategy offers clear advantages. They engage with the startup at an early stage, when the investment volume needed is quite low, competition with other investors is less and there is a high value creation potential.

The risk is easily mitigated with a diversification strategy: founding angels choose different projects and expect higher returns as a result of a lower total risk. According to Gunter Festel, founding angels can help to close the technology transfer gap, acting as a link between academia and the business world (Festel, 2011).

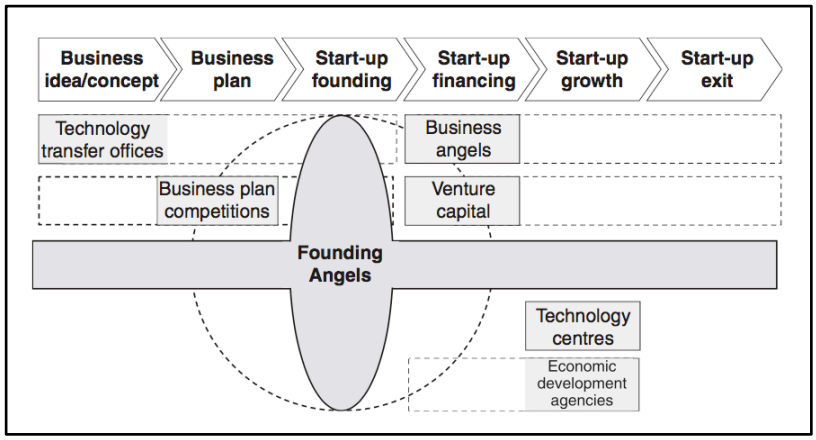

Figure 4.1: Founding angels support in the start-up process chain

4.4.6 Crowdfunding

Crowdfunding is the process of raising money from a large number of people in order to fund a project, a company, or a cause. Different kind of crowdfunding platform exist nowadays, and people can support a project with a donation or, in other cases, invest their money to get rewards, equity and more. The concept of crowdfunding is not new, but it exploded in the web a few years ago. Since then, many platforms have been developed and today it is a reliable financial tool that offers the opportunity to private and industrial investors to invest in a diverse range of activities with high yield, and to entrepreneurs to get in touch with more business partner than before.

In most crowdfunding campaigns a goal amount is set and it is showed how much money has been raised so far, how many people backed the crowdfunding campaign and how much time is left for the campaign. The difference from institutional funds is that crowdfunding bring access to funds at the moment in the life of the startups they need it the most. Moreover, crowdfunding is the fastest way to raise money and it is way more flexible than venture capitalists that usually ask for 50-70% of the equity against the average 25% of the crowdfunding platforms.

Also in Italy, in the last few years, some crowdfunding companies were funded and got the Consob's authorization to collect capital for innovative startups and PMI (small and medium sized businesses) through equity crowdfunding. **Next Equity Crowdfunding**, for instance, works in collaboration with incubators, universities and research bodies to find, improve and select projects with great potential, so that startups and entrepreneurs can raise the funding to launch their businesses.

But what about biotech companies? Can this model still be applied for startups whose development process can last for over a decade? Biotech experts were skeptical about equity crowdfunding and believed that venture capitalist highly specialized in the field were still the best option. The case of **Ecrins Therapeutics**, nevertheless, proved the contrary. In 2015 they raised 660 thousand euros for a project on cancer drugs. The CEO Andrei Popov explained that institutional investors (venture capitalist) get usually involved during clinical stage with several million euros of investments, while their project was still at an early stage. The crowdfunding,

on the other hand, collected the contribution of many business angels and small investors and helped get through the animal studies (Fernandez, 2019).

Crowdfunding Investors are not usually life science experts, but commit to stay with the company in the long run: by investing in the preclinical phase, the exit is not expected to be very soon. It's actually a very risky and long-term investment, made to really participate in the development of the company. As crowdfunding is still relatively new for the biotech industry, most companies that have successfully raised money through crowdfunding haven't had an exit yet. In other markets, equity crowdfunding has a failure rate of 10-15% and it has been assumed to be the same for biotech.

Crowdfunding has become a way of giving visibility to and validating the potential of a company and VCs are looking at crowdfunding as a proof that the entrepreneur is able to communicate and sell his project properly.

4.4.7 Partnership and licensing

Another possibility is to cooperate with existing companies. Sometimes, small biotech startups can stipulate partnerships with bigger realities, because they would not have the strength to do market discovery and market research alone. The existing companies can support high cost due to prototyping or testing and they are more experienced in handling the mandatory procedures and selling agreements.

Licensing agreements are also quite common for their simplicity and the form of payments in tranche: at the beginning, a payment up-front is given to cover the expenses already sustained by the startup for research and development. Moreover, whenever a pre-established goal is reached, another payment is made. Once the product is commercialized, the company can pay to the researchers a percentage of the earnings (commonly called royalties).
Usually, companies that license products also take care of the cost associated to clinical trials. The researchers can also be given shares of the company as a remuneration.

4.4.7.1 Clinical Trials – an overview of cost and duration at each stage

In the biotech industry inevitable and expensive steps are clinical trials. At each phase of the trial the project can be rejected because it does not meet a specific need (it may be toxic for the human body or not effective as planned…). At each phase the number of patients involved is higher and the cost grows exponentially. For these reasons, each venture capitalists fund focuses on a specific stage that corresponds to a defined target-risk and target-gain.

The developing process of a new drug is critical and companies spend in this activity the majority of their human and economic resources. In order to commercialize a new drug, ten to fifteen years of researches are needed. Each study phase is regulated by specific international guidelines that guarantee the consistency of data, safety and well-being of subjects taking part in the trials.

During trials, only one on ten thousand molecules tested reach the end of the process, with costs that rapidly increase over time and can easily overcome one billion euros.

At the beginning of the trial, the drug should pass a series of laboratory's tests (either in vitro and in vivo) required by law and fundamental to have the adequate knowledge on the chemical compound. The following phase of the clinical experimentation is run on an increasing number of patients and it is conducted within universities, hospitals, public or private research centers.

The four phases are the following:

- ***Phase 1*** – Clinical pharmacology and toxicology;
- ***Phase 2*** – Clinical investigation on efficacy;
- ***Phase 3*** – Global drug evaluation;
- ***Phase 4*** – Post-marketing evaluation to reveal collateral or rare side effects.

The distribution of investments on each phase shows that clinical studies counts for the 43,1% of the total budget of Research and Development and they can lasts from six to sixteen years based on therapeutic area and social context.

Usually, planned funding amount at two million for phase 2 and 3 of in vivo test, 13 million for phase 1 of trial and 25 million for phase 2. The costs that a biotech startup will sustain are

mainly due to test and trials. It is therefore essential to rely on a constant and wealthy funding to move forward in the process without unnecessary breaks.
Of course, to work on different projects at the same time will stress more the financial resources and the team, but it will also guarantee higher probability of success.

4.4.7.2 Timing to get the funding

The procedures to finance a project are still quite long and complex, in particular for public financing and grants. After a specific grant is assigned to a project, 6 to 24 months may pass before the startup actually gets the payment.

Table 4.2: Average time to get the money for each financial scheme described.

Financial scheme	Average time
Crowdfunding	1 month
Business angels	3 months
Venture capitalist	Quick in UK or US, 6 months in EU
Partnerships	Depends on the agreement
National grants	6-12 months
International grants	12-24 months

4.5 Biotech industry in Italy

After the description of the most utilized funding scheme, a short presentation of the Italian startup ecosystem is due. In the last few years, indeed, biotech started to flourish in Italy.
In order to keep the positive trend, companies should keep investing on researchers and their companies, while governments should lighten the bureaucracy through tax exemption and simplification. It is also important for universities to give the proper incentives to push researchers through patenting and founding new businesses. Only through these initiatives Italy will become competitive in biotech at an international basis, finally exploiting the scientific excellence of our research center and contributing to PIL growth and occupation rate.

Biotech represents, therefore, a group of enabling technologies that found application in several industrial and economic sectors. The number of traditional companies that integrate biotech products in their processes to reduce their environmental impact is increasing.

In the last years, Italy finally started supporting innovation, recognizing its fundamental role for the future economic development. Alongside with other measures, it was essential to establish the status of "innovative startup" and the adoption of tax reduction on intellectual property. Financial initiatives started to sustain life sciences startups and Individual Savings Plan were established.

4.5.1 Number of industries and turnover

At the end of 2019 the turnover in biotech was over 12 billion euros, with an average annual increase of 5% between 2014 and 2018. 13 thousand people work in the biotech field in Italy, of whom 34% in R&D. The report of 2018 of Assobiotec and Enea, affirms that there are 571 biotech companies in Italy.
Investments in R&D reach 760 millions, with a growth of 25% compared to 2014.
In the last two years biotech companies got the main part of the total investments.
Between 2017 and 2019 more than 50 new biotech startups were registered. Among the others, Nouscom closed an operation of 42 million euros in 2017 and Erydel closed a financing round of 26,5 million euros in 2018. (Balena, 2019)
80% of biotech industries is made of micro and small businesses, that had a propulsive role in the growth dynamic of the entire industry. Almost half of the biotech companies operates in Milano's School of Management prove that digital health (clinical foder, database, big data) costs were 1,3 million euros in 2017 with a growth rate of 2% (Impactscool magazine, 2020).

4.5.2 Geographic distribution of biotech industries

Biotech activities are concentrated in Lombardia, first Italian region for number of industries (195, 28% of all), investment in R&D (30%) and turnover (45%). Anyway, a slow development in North East has been registered and an increasing diffusion in the Center (Lazio) and South. It's also worth mentioning Campania, where the 20% of biotech industries are located.

5 European Research Council's Grants

The European research council (ERC) is the most prestigious European agency that finance all kinds of innovative researches, with the mission to keep the best researchers in Europe and create new research standards. It is an independent agency founded in 2007, through a cooperation of entities in the European Union. ERC is made of two bodies: scientific council and executive committee. The scientific council directs the ERC and defines strategy, financing instruments and methodology of evaluations for the projects. The executive committee implements and applies the chosen strategies.

The only success criterion is excellence and no discriminations of country and genre are made. The funded projects are frontier, disruptive and high-risk researches. The approach is generally bottom-up: it is the researcher that proposes a topic of investigation and decides how to conduct his studies. The proposal can be curiosity driven but you should be invited. Then, all the requested documentations on idea, plan and budget should be filled before the deadlines. After that, a committee of international peer reviewers evaluates the projects based on excellence and unicity. All the funding is eventually given to the principal investigators that can manage it independently inside of the selected Host Institution (HI), public or private.

Since it was born, the ERC sustained European Research through 5 main type of funding schemes:

- Starting Grant (StG);
- Consolidator Grant (CoG);
- Advanced Grant (AdG);
- Synergy Grant (SyG);
- Proof of Concept (PoC).

5.1 Starting Grant (StG)

Starting grant is a solid investment that usually amounts from 1 to 2,5 million euros and is intended for young researchers with 2 to 7 years of experience. The private investigators' job is to procure a substantial progress in its research field. The money can cover the entirely of the research and can be used in a quite flexible way: to pay for travel expenses of researchers

moving to different countries, to buy lab equipment or to pay for renting a structure and all the experimental cost that the team may encounter.

5.2 Consolidator Grant (CoG)

Ideated to support expert researchers with 7 to 12 years experience with a great record of achievements, several important publications in scientific journals and an interesting research proposal. The grant is given mainly to consolidate the team or independent research project. The amount granted is 2 million euros for a five years project, but in some cases an additional 1 million euros can be made available to cover eligible exceptional costs.

5.3 Advanced Grant (AdG)

Advanced Grants are for established, international leaders with a proven track record in the previous 10 years. It is made to fulfill high-risk innovative projects that can open new directions of investigation in a specific field. The maximum amount granted is 3,5 million euros for a 5 years project.

5.4 Synergy Grant (SyG)

It promotes substantial steps forward in the research and encourages new productive fields of study. It is intended for groups of researchers (from 2 to 4 people), who should prove that their different skills and academic trainings are necessary to properly address a complex problem, that could not be carried on by individual researchers.
Proposals are therefore evaluated by taking into consideration also the synergetic effects. The fund can be up to 10 million euros for a period of 6 years. 4 extra million euros can be requested to cover travel costs, purchase of major equipment and access to large facilities.

5.5 Proof of concept (PoC)

The Proof of Concept (PoC) is a particular grant made to help university researchers validating their new discoveries, both technically and in terms of commercial exploitation. **The proof of concept increases the TRL of an RBI up to a level where it can be successfully marketed**. Through proof of concept it's easier to identify technologies that can be applied to develop new products or to integrate existing technologies in order to increase the benefits for the customers.

The validation of technical characteristics and commercial feasibility of the RBI is made with the combination of three elements: money, expertise (external stakeholders and entrepreneurs) and entrepreneurship trainings (for scientists and researchers in general).

The PoC does generally not involve the creation of new organizational structures, as with the accelerators, and the researchers can continue to conduct their own research within the university.
Therefore, PoC represents an effective tool for the transfer of RBIs between academia and industry, and they have indeed led to an increased number of spin-off based on the on RBI developed inside the university, as well as the number of technologies granted in licensing from universities to companies.
This instrument is particularly useful for three reasons:

- It provides an assessment of the potential commercial value, encouraging scientists to commit to make the RBIs evolve in a direction that allows them to meet the requirements of the market;
- The adaptation of the technology to the market is increased, as it requires scientists to prepare both a strategic plan for the development of the technology (which identifies the value proposition of their RBI) and a business plan.
- It mitigates the inhibitory factors that typically undermine technology transfer, by allowing the reduction of any relational inhibitors as the disconnection between the industry and the external environment or the frictions that can occur with external actors.

For as much, proof of concept is essential to realize something completely new. A large-scale project would require much time and money and it is fundamental to know in advantage if it is going to work or not. Moreover, PoC stimulate the marketing of RBIs through the creation of enabling institutional, cultural and relational factors.

5.6 Principal Investigator's Role

After getting a ERC grant, the role of the researcher change and she/he has to become a project manager. The PI indeed will acquire a series of responsibilities as choosing the team, monitor the start of the project research activities and monitor the costs and time of them to assure that they are on time and in the budget. The PI has also the authority to publish articles and papers

about the project as a senior author. On a bureaucratic point of view, she/he is responsible to access the facilities of the host institution, transfer funding to a new host institution, and also request changes in research activities due to new circumstances, unexpected discoveries or results.
Moreover, the Grant Agreement establish that the PI should spend a reasonable amount of time on the research project:

- At least 50% for Starting Grant (StG);
- At least 40% for Consolidator Grant (CoG);
- At least 30% for Advanced Grant (AdG).

The PI must also implement all the activities described in the Grant Agreement according to ethical principles (integrity inside the research), international right, EU rights and national right and at last she/he has to respect the schedule for project implementation and guarantee the visibility of the European funding in communications, websites and publications.

5.7 History and Details of Proof of Concept Funding Scheme

The idea of Proof of Concept was initially developed in United States in 1967, when the council for American research defined a proof of concept as a phase of developing in which the hardware is build and tested in order to prove the feasibility of a new idea. PoC was therefore used in IT field with software and hardware, in order to test emerging technologies. In the following years, the instrument was extended to different fields from cinema to cybersecurity. Companies in all industries need proofs for their new concepts. In healthcare when a new drug is developed the proof of concept is used to test the side effects. The results of these tests lay down the basis for future financing and development.

The European Research Council (ERC) launched the first Proof of Concept grant in 2011.
The aim of this new financing scheme was to encourage researchers in exploring and exploiting the potential commercial value of their inventions, and to foster the continuous influence between research, innovation and society.
In 2019 the budget for PoC was 30 million of euros, utilized to support 200 projects (**150 thousand euros each for eighteen months**).

5.8 Strengths and weaknesses of PoC

PoC are quite easy to achieve and often lead to a real advancement of the project towards next financing phases. At the same time, it happens that they are accomplished without a real strategic perspective in the long term, since they only allow to cover up some small parts of the whole project but not to go much further.

Some industries dictate the development steps of a technology. In many cases a market analysis and feedback collection has not yet been carried out and the market risks are high.

Many startups, in order to obtain a small financing, take part to events not fully relevant to reach their goals, and they begin to invest money in many different activities, away from their core business. A good alternative to prevent this to happen is the Venture Factory method: it is a type of financing that gives a first tranche of financing as a PoC and, after the success of the first part, provides a second round with a biggest perspective.

PoC is for sure a good concept, however in the biotech field high volumes of investments are needed to prove the success of the project, and a PoC is too small to pay for all the testing.

As a matter of fact, in the biotech field years may pass before actually seeing a result.

A PoC of 18 months (against 6-12 months of the others existing ones) and a budget of 150k€ (instead of 50k€) could be already considered a good step forward for the success of PoC.

5.8.1 Proof of Concept at Politecnico di Torino

In 2016, Politecnico di Torino has launched the first **"Call for funding of the proof of concept"**, open to all scholars university (grouped in teams) and was aimed at helping academics to advance their Research-Based Invention (RBI) on TRL scale, from an average initial level of 3-5 up to a final level of about 6. The purpose was to encourage young researchers (doctoral students in particular) to participate in the activities of technology transfer, that's why one of the requirements was to have at least one team member younger than 35 years. Another condition was that the RBI should be backed by a patent owned by the university. Finally, a professor or researcher had to present the details on how to advance the RBI on the scale TRL within six to nine months from the start of the project.

For the program it was provided **funds of up to € 50,000 per project**, to cover the expenses incurred in the advancement of the RBI on the scale TRL.

Moreover, before starting the project, a two-months training is given by the Politecnico di Torino's incubator I3P in order to do market research, so that before beginning to develop the

prototypes in the laboratory the teams already have an idea of the market condition. During the market research the researchers must talk with the stakeholders of their projects and with the potential users and customers in order to get all the possible feedbacks and know how address the PoC to make it as effective as possible.

5.8.2 Other Proof of Concept Programs

Recently, "**Proof of Concept - PoC Program 2020**", the new call of the investment fund **Vertis Venture 3 Tech Transfer (VV3TT) was presented at HIT - Hub Innovazione Trentino**, which addresses technology projects for Industry 4.0 developed in universities or research institutes. VV3TT PoC Program 2020 provides professors and researchers with the **financial resources and entrepreneurial training** necessary to carry out experiments that demonstrate the feasibility of a technology or a potential technological product/service, simulating a real market situation. The degree of maturity of the eligible projects must fall within a Technology Readiness Level between 3 and 5 but have not yet become real prototypes.

The selected projects will receive an investment of **up to 70 thousand euros**, to be allocated to the prototyping or marketing of their product/service over a period of approximately one year. If the objectives of the PoC project are successfully achieved, the VV3TT fund will be able to invest up to 4 million euros in the new company co-founded together with the researchers.

5.8.3 Other Initiatives to promote start-up creation within university research

The **Italian Master Startup Award** promoted by **PNI Cube**, the **Italian Association of University Incubators and Academic Business Plan Competitions** (also known as Start Cup), is a national recognition that rewards the results achieved on the market by startups born in the academic field in their first years of life. This is above all a way to obtain visibility and also represents an example to follow for all those who, precisely in the university field, begin to develop research and hence business projects.

Among these many start-up born as a spinoff of the universities that link on biotechnology and the best ideas can give birth to companies, thanks to incubators, hubs and partnerships and to dedicated events, such as BioInItaly Investment Forum, organized by Assobiotech (national association for the development of biotechnologies, which is part of Federchimica), according to which the value of biotech in Italy is approximately 7.7 billion euros.

6 Case Study

This section in divided in two parts: first we introduce the case study design and methods, explaining how data were collected and presenting three propositions on the topic.
The second part focuses on proving the above-mentioned propositions with the results of our analysis and also referring to the final report on Proof of Concept prepared for the ERC Executive Agency under the auspices of the ERC Scientific Council by Charles Wessner and Federico Munari. Finally, to prove proposition number three, we will present our research on team dynamics based on Valentina Cauda's team of Politecnico di Torino and work, also referring to the article of Daniele Battaglia, Emilio Paolucci and Elisa Ughetto: "Opening the black box of university proof-of-concept programs: project and team-based determinants of research commercialization outcomes".

6.1 Part I – Design and Methods

The case study is a particular methodology used to analyze a specific problem through a practical example. The goal is to generalize a theory starting from different hypothesis. Since often case studies are focused on a single case, the purpose is just to understand the reason why a certain decision was made and with what results, without any presumption to speak about statistics.
Therefore, Case Studies are the preferred strategy to answer to "how" and "why" questions and are the best option when the investigator has small control on the events or when the phenomenon is contemporary. Besides that, case studies are appropriate to analyze organizational and managerial processes, growth of industries and real contexts with many variables that a statistic and rigorous study couldn't afford to take into consideration. However, in order to be reliable, the case study must be structured properly: the goals should be clearly presented, along with the used data and how they have been collected and examined. The power of case study is its ability to handle a huge number of documents and information gathered with direct experience, interviews and data, overcoming the limits of classic methods of analysis.
The case study conducted in this thesis can be described as "explanatory". A single case, indeed, will be used to analyze a few concepts presented before and to see the problems through a practical example.

We started this work by examining in depth the problem of the valley of death, the gap between academic research and industrial applications on the market. As described in Paragraph 2.5, despite all the incentives to move research into production, the problem of bridging TRL-4 to TRL-6 has proven to be difficult to solve.
The reasons of this phenomena can be the lack of communication and cooperation between academia and industry and the lack of solid and proper financing.
Therefore, the first question that we asked ourselves was about the role of the involved actors and how universities, industries and governments could intervene in order to fill this gap.

Starting with the role of the government and focusing on the funding schemes previously presented, in this Master Thesis we are going to take into consideration the decision of European Research Council to finance university research through different forms of grants. In particular, we are going to compare Starting Grant, Consolidator Grant, Advanced Grant and the Proof of Concept Grant, previously described in chapter five and summed up in the table below.

Table 6.1: Recap of the main characteristics of ERC Starting Grant and Proof of Concept.

Type of grant	Size	Duration	Main objective
Starting	1 to 2,5 M€	5 years	Disruptive research. To procure a substantial progress in a specific research field.
Consolidator	2,75 M€	5 years	For expert researchers to continue their progresses.
Advanced	3,5 M€	5 years	For established leader to fulfill high-risk projects and to open new directions of study.
Proof of concept	150 k€	18 months	To increase the TRL of an RBI up to a level where it can be successfully marketed.

Our goal is to confirm what emerged from previous literature, that is the successful outcomes of a project does not only depend on the extent of the financing but is strictly related with the structure of the project and the team's personal characteristics. Moreover, we would like to understand why a particular funding scheme works better than another one (in the context of technology transfer). Based on these insights, we advance the following propositions:

Proposition 1: “In initial TRL stages (2-3) PoC are necessary to address the technology’s development”.

Proposition 2: “Even if ERC Proof of Concept programs are smaller than ERC Starting Grants, they are more efficient because they force researchers (1) to focus on a specific industrial application of their studies; (2) to define a clear strategy and goals; (3) to evaluate timings and cost of the project. Therefore, it is easier for the researchers to attract investors and industrial partners”.

In the first part of the case study, we will collect and analyze data on all the Italian Principal Investigators (PI) who won ERC Grant in the last 10 years. In particular, we will focus on the PI’s personal results: we will compare not only the number of publications, awards and patents, but also the industrial experience of the researcher.

Moving forward with the university, their mission should be to promote a more entrepreneurial spirit among researchers, who still have a work style, culture and mentality that is often not appropriate to cope with industrial challenges. As we argued in chapter 5, in order to succeed the research team should be heterogeneous and each member should have a specific and unique competence; the ambitions of the researchers should be high and clear from the start and finally the structure of the project should be properly defined in its goals and strategies, timelines and milestones. Based on these insights, we advance the following proposition:

Proposition 3: “The learning process of the PI and her/his team on entrepreneurship, industrial challenges and mentality is fundamental in order for the project to advance in the development and finally succeed”.

Throughout all the case study we will present different projects carried by the same team in the last years and we will show their strategies and achievements under different circumstances. The personal experiences of the team members and responsible of each project will be extensively presented.

In the end, we will also analyze the possible cooperation with the English company Therakos from the point of view of the future startup. In doing so, we will present a practical example of collaboration with industry and we will have a chance to analyze the pro and cons, showing the

importance of reputation and intellectual property rights and we will finally evaluate possible exit strategies.

6.1.1 Data collection and analysis

Data were collected through the ERC website in the page related to fact and figures of the funded projects of the last years (ERC European Commission, s.d.). Then, in order to reduce the variables, the data were filtered through the domain "life sciences". We decided to examine only the projects concluded in 2019, so that we could see the progresses made after the conclusion of the projects. Additionally, only projects held in Italian host institutions (HI) were selected. In conclusion, we have 32 Starting Grants, 21 Consolidator Grants, 38 Advanced Grants and 43 Proof of Concept, lasting from 2010 to 2017, for a total number of 134 projects. No data were available for the selected categories for ERC CoG from 2010 to 2012 and PoC of 2010.

Table 6.2: Number of projects analyzed for each Italian ERC Grant

Years	Starting	Consolidator	Advanced	Proof of concept	Total
2010	6	-	7	-	13
2011	8	-	6	1	15
2012	4	-	5	3	12
2013	2	8	7	2	19
2014	2	5	4	7	18
2015	3	2	5	8	18
2016	4	5	3	11	23
2017	3	1	1	11	16
Total	32	21	38	43	134

Of the 134 projects analyzed, 45 (33,6%) were conducted by female PI while 89 (66,4%) by male PI. The age (considered at the moment of the conferral) of PoC awardees slightly increased during the years, while younger researchers are applying to – and winning – StG in the last years. Other grants StG, CoG and AdG are assigned based on the researcher experience, so the age is obviously increasing in a range from 34 to 65 years. Nevertheless, a consideration on this result should be made: when ERC was born, CoG did not exist (indeed, we do not have data on

the CoG projects before 2013). This is why all the researchers below 45-50 years old were applying to StG, causing a disadvantage for the younger ones, who could not compete in terms of experiences and CV. Therefore, the introduction of an intermediate grant (the CoG precisely) caused a decrease in the average age of researchers applying to Starting Grant, which shifted from 41 to 34, as it is shown in the graph below.

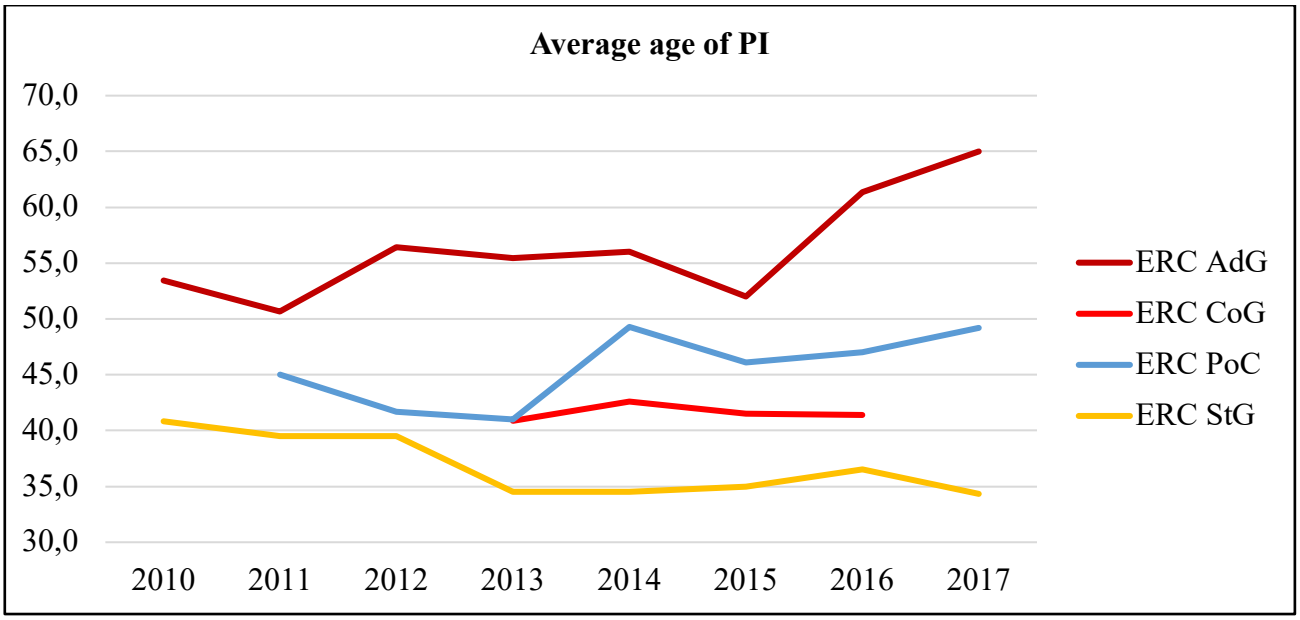

Figure 6.1 Trend of PI's age for different grants assigned between 2010 and 2017.

Additional information on the PI and her/his team's experiences have been found through linkedIN or through their personal curriculum. Moreover, in order to measure the industrial results, the number of patents filed by each PI have been collected through the WIPO website (Database WIPO, s.d.). The data will be analyzed by comparing the results of the four groups of researchers in terms of average number of publications, patents and industrial experiences (measured in terms of collaboration, licensing, start-ups or additional private investments gained). To prove our propositions, as explained above, we decided to do a case study. Therefore, in addition to the data collection of ERC Grants and analysis of the previous literature, we decided to examine three projects of the TNH Lab of Politecnico di Torino, guided by Prof. Valentina Cauda. First, we worked with Prof. Valentina Cauda and Prof. Emilio Paolucci to develop a business plan for the project Nanopils and later we evaluated the risks and the strategy for the project XtraUS. Hereafter, we interviewed Dr. Andrea Ancona about the project U-Care, also born from the collaboration with Valentina Cauda. In the end, we

distributed a questionnaire to the team members to gain insights on their learning experiences during their career as researchers.

6.1.2 Context and limits of the case study

Technology transfer is an extremely extended context and therefore case study is the most suited method to present and fully explore the situation. Nevertheless, in order to reduce as much as possible the number of considered variables, we decided to confine the analysis to a specific industrial and geographic context. In particular, in this Thesis we will analyze only biotech projects conducted by Italian researchers or in Italian universities.

We selected biotech industry for the following reasons:

- To validate a technology in the health and biotech sector huge and reliable financing is essential;
- Biotech is a highly innovative sector;
- Biotech is a case of market failure: the risk is too high for investors in the early stages, so governments must intervene.

We decided to analyze Italian projects because the gap is more marked due to:

- Less cooperation between university and industry compared to other countries;
- Less entrepreneurship spirit compared to other countries' researchers.

Nevertheless, it is important to be aware of the limits that case studies bear and this case study in particular has the limits of being one single team that is carrying on projects that are still incomplete. Moreover, there are no scientific methods to conduct complex analysis through case studies, therefore the validation of the proposed hypothesis is based on qualitative observations and the definition of "success" has been established considering the startups ecosystem and technology transfer context.
On the other hand, to work on an open case allows to improve the awareness of the team's own strengths and weaknesses in order for them to learn from their past mistakes and hopefully succeed in their future challenges.

Final conclusions can be deduced only after the projects are commercialized or sold. Following studies can be conducted in the future to further analyze the topic, maybe comparing the work and experience of different teams and confirming or confuting what sustained in this thesis.

6.2 Part II - Results of the analysis

In the following section we are going to discuss the above-mentioned propositions one by one, using the data collected for all the different grants promoted by ERC (StG, CoG, AdG and PoC). As mentioned above, in order to restrict the analysis, we have considered only the grants of the Life Science Category hosted in Italian Institutions between 2010 and 2017.
We will argue that the introduction of PoC have been a stimulus for researchers to look at their scientific work with an entrepreneurial approach and to focus on improving the TRL of their discoveries in order to commercialize some of them. Moreover, the structure of the application to PoC itself is an incentive to set clear goals that are also time and cost bounded. In the end, we will see how the learning process of the PI and his/her team are the key to success.

6.2.1 PoC results in advancing the TRL of an invention

Before PoC were created, researchers were mainly focused on their basic research, looking for disruptive innovation and concentrating their energy on publications of their results, while TRL level advance was not really taken into consideration. The PoC, launched in 2011 from the ERC, started to revolutionize the research field, inspiring a change of mentality in researchers. Researchers were therefore stimulated to look at their technologies with entrepreneurs' eyes: if something had a commercialization potential, they could ask a specific grant to properly study and evaluate it.

The funding could be used to cover the activities in the initial phase of transformation from research to a commercial proposal, that is to say pre-competitive phase of development, helping with:

- Feasibility study and technical problems;
- Intellectual property issues and protection;
- Budgeting and commercial strategy;
- Networking for subsequent financing round;

- Expenses for founding a new company.

As we said in Chapter 3, a fundamental step towards market exploitation is the patenting of a technology. To prove the impact of PoC in initial TRL stages we present the data collected from ERC website and in Figure 6.2 we show that PoC grantee have a bigger number of patents than their colleagues. Therefore, while **PoC might encourage the researchers to have a more practical approach**, also the opposite could be argued: researchers that are more likely to apply for ERC PoC funding are also the ones that already have **an attitude to entrepreneurship**, and find in PoC a way to valorise their previous research in patents and protecting their intellectual property.

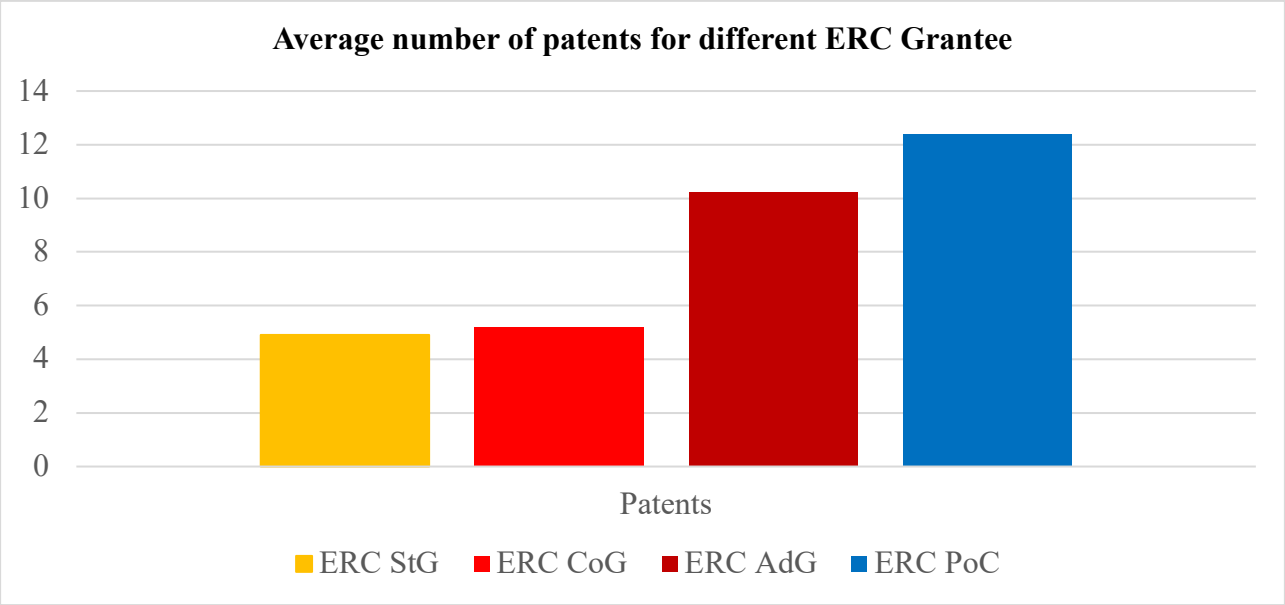

Figure 6.2 Average number of patents for different ERC Grantee in Life Sciences field between 2010 and 2017 (Italian HI only).

Our findings regarding Italian biotech grantees seems coherent with the complete analysis guided by Wessner and Munari. Analysing all the projects between 2011 and 2017, they found out that more than 42% of the ERC PoC grant holders made at least one patent application as a result of their PoC project. The likelihood of generating one or more new patent applications is significantly higher in the group of ERC PoC respondents than in the other ERC grants (only 17% of projects of StG, CoG and AdG generated at least one patent application). (Wessner & Munari, 2017). These numbers on patents applications confirm what we stated in the first hypothesis: PoC are a useful financing instrument to address the technology's development in the beginning.

6.2.2 PoC effectiveness in attracting investors and partners

Moving on with Proposition 2, we will discuss the efficiency of PoC. Once again, we recall the final report on the ERC Proof-of-Concept Programme written by Charles Wessner and Federico Munari. They studied the success of PoC grantees, with the goal to better understand how well the PoC scheme contributes to maximize the value of ERC-funded research by facilitating the development of its commercial and social potential. From their analysis it comes out that over a quarter of the awardees fully achieved their PoC objectives and more than half have partly achieved the established goals. The success was measured including number of applications for patents, patents, licensing agreements, R&D collaborations and contracts, consulting agreements, new company formation and public engagement (Wessner & Munari, 2017).

Even though it was hard to properly measure the efficacy of PoC grants in terms of startups created or licensed technologies (since the name of the initial project is not always mentioned in the resulting start up or licensed technology), we tried to evaluate the PoC effectiveness in attracting investors and partners by analyzing the industrial experiences of PIs.

Starting from the data collected on the ERC website, we collected information on research experiences by the numerous private and university websites, linkedIN profile and curricula. As it is shown in the Figure 6.3 below, a level between 0, 1 and 3 of "industrial experience" was assigned to each according to the following criteria:

- 0 if PI has only worked in university context.
- 1 if PI had brief industrial experiences (less than 1 year as an external consultant or collaborator).
- 3 if PI worked in a tech company (R&D for instance), leaded teams on industrial project development, been president/founder/CEO of activities/startups.

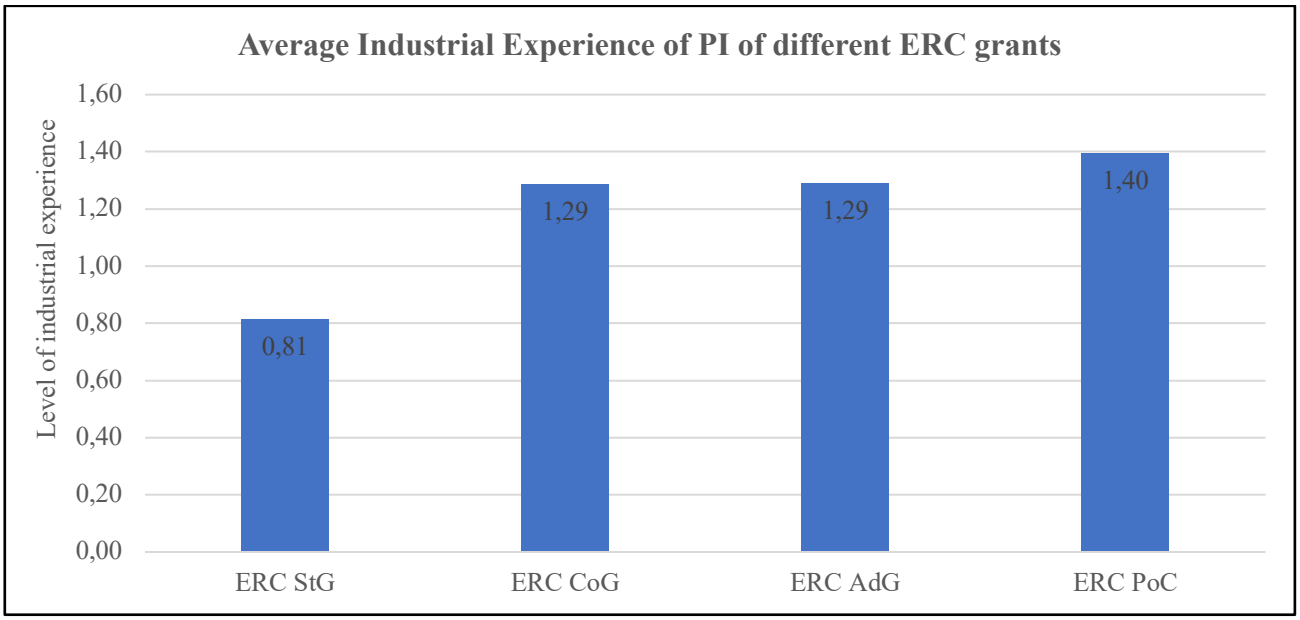

Figure 6.3 Industrial Experience of PI (qualitative scale chosen by the candidates, data based on linkedIN, CVs, private and university websites)

As we already know, researchers can apply to ERC PoC only if they already had another grant. This limitation was made in order to select really innovative projects with a strong research background and a team that was already working together. From our interviews with Prof. Valentina Cauda, it emerged that having a robust project is indeed an important condition in order to understand what technology could really make an impact. Therefore, since PoC awardee group is composed by some of the same researchers that are considered in StG, CoG and AdG, the fact that PoC awardee have more industrial experience is revealing: the researcher that have more industrial experience are more likely to apply also for a PoC. Nevertheless, we point out that the variance is small (particularly with Consolidator and Advanced awardee, which have a more comparable level of experience) and that the experience we considered is up to date: PoC itself might have procured an industrial experience after its conclusion.

The tendency to cooperate more with the industrial world could happen for two reasons: on one side the change of mindset for PoC awardee, which will be further analyzed in the next paragraphs, while on the other hand there is a theme of reputation.

Large companies working in the same field are always looking for innovation and cutting-edge technologies but, as we said before, they are not willing to undertake the high risks in the first phases of development. However, when a project is backed by an institution like ERC, the situation may change: if the project is been reviewed and approved by expert researchers worldwide, it means that there is a high potential and the perceived risks are lower.

Therefore, after getting a PoC, it is easier for the researchers to attract investors and industrial partners.

6.2.3 The fundamental team's learning process

Previous literature has emphasized the existence of obstacles and inefficiencies that can hinder the successful commercialization of RBI, in particular the lack of **resources** available to support technology transfer and **the lack of managerial and communication skills** between academics and their industrial counterparts. We have already treated the first issue and we have extensively presented the solutions that governments and institutions as ERC have proposed in the last few years. Now we are going to focus on the second problem: the competences and skills of the research teams and PIs and their change of mindset while working on an industrial project. Indeed, we argue that the role played by the team is essential in order for the project to succeed.

We will start by talking about the preparation of the application itself. Indeed, this is the moment in which the first change of approach needs to occur. The focus is not anymore on which project could be more disruptive, challenging or world-changer. The question is what technologies the market really need right now, what technologies can improve a product or a service in a simple manner and could be developed in a limited amount of time. The researcher is asked to stop theorizing: the PoC wants a precise goal and a well-defined plan to reach it. According to the ERC website, the application will indeed be evaluated on the basis of three criteria:

1. **Innovation potential**: how the planned activities will help to move the output of research towards the initial steps of pre-commercialization (that is how TRL will be improved).
2. **Impact**: how the technology will generate benefits to the economy, society, culture, public policy or services.
3. **Technical and commercial feasibility of the project**: which are the risks? Are they proportional to the required investment? Every project has its own, but it is fundamental to recognize them and to have a plan to minimize them.

This is how, in the first place, the PoC grant pushes PI into a new entrepreneurs' mindset. The application clearly demands what we stated in the second hypothesis: to evaluate, to choose, to plan.

6.2.4 Data collection

In order to present a practical example of team dynamics and prove our third argument, we will start with a brief introduction of the team members of the TNH Lab (TrojaNanoHorse Laboratory), led by Prof. Valentina Cauda. We will proceed by analyzing their answers to the questionnaire and then we will present three projects on which the team is currently working.
The information about these projects were mainly provided by Valentina Cauda during our numerous meetings, moreover two of the three projects presented were deeply analyzed (by our colleagues and us) as group projects for Emilio Paolucci's exam on entrepreneurship and business planning.

Information about the learning process and evolution of the team were gathered by interviews with two of the team members (the ones most involved in the analyzed projects: Dr. Andrea Ancona and Dr. Silvia Appendino) and an anonymous questionnaire distributed to the whole team.
The questionnaire included both open and closed questions, covering age and sex information, education, international and industrial experiences and finally personal opinions on the most important skills to have, the ones that have improved more while working together and the ones that they recognize in their PI. In the last question it was asked which obstacles were harder to overcome. A total of 6 responses were collected. In the Table 6.3 below are presented the TNH Lab members and their tasks.

Table 6.3 TNH Lab members and main responsibilities.

Name	Role	Main Tasks
Valentina Cauda	Associate Professor, Director of TNH Lab	Leads the research activities. PI of ERC Starting Grant and ERC PoC.
Tania Limongi	Senior Biologist	Specialized in pathophysiology, studies different localization techniques of single molecules, micro devices, nano-constructed and techniques of fluorescence microscopy and advanced flow cytometry.
Francesca Susa	PhD student	Studies new drug release system and extracellular vesicles.
Marta Canta	Junior Post Doc	Studies molecular mechanisms, drug combination effects against cancer cells, focusing on the toxicity of zinc oxide nanoparticles in cancer cells lines and evaluating ZnO NP security in terms of biocompatibility and biodegradation.
Luisa Racca	Junior Post Doc	Studies the combined effects of nanoparticles and ultrasound on cancer cells. Currently focused on the physical and biological characterization of ZnO nanoparticles, in order to use the system for the treatment of human carcinomas.
Bianca Dumontel	PhD student	Works on developing hybrid zinc oxide nanoparticles (ZnO) for cancer therapy, focusing on the optimization of the synthetic parameters to improve the biocompatibility and the stability of the ZnO nanoparticles in biologic tools.
Veronica Vighetto	PhD student	Evaluates the radical species generation from zinc oxide nanocrystals and their internalization in cells.
Marco Carofiglio	PhD student	Synthesis and characterization of zinc oxide nanoparticles (ZnO) and substrates for biomedical application.
Silvia Appendino	Admin & Projects	Manages administrative matters and all financial aspects, writes project proposals for H2020 and for other regional and national competitions.
Andrea Ancona	Junior Post Doc	Study on the interactions of nanoparticles and ultrasounds. Most recently he worked in technology transfer office and he is learning how to build a startup.
Sugata Barui	Senior Post Doc	Marie Sklodowska Curie Individual Fellow, focuses on multifunctional nanotheranostics against pancreatic cancer within the MINT project.

6.2.5 Data analysis

The data collected show that the research group is very young: two third of the researchers are aged between 20 and 30 while the others are between 30 and 40. As we already know, indeed, in order to apply to ERC Grants at least one member of the team should be less than 35 years old. In fact, is very important to have young members into the team, so innovative ideas can also come out thanks to the opinions exchange and ideas and different cultures comparison.

The team is composed for the biggest part by women, which is not unexpected since the enrollment statistics at Politecnico di Torino show that among the students of Biomedical Engineering there is a bigger prevalence of girls.
Carrying on with our analysis, all of the team members did their Master or PhD at the Politecnico di Torino and only one of them had done an international experience during his/her academic career.
Regarding the level of experiences 4 members of the team (36%) worked in the research field for more than 5 years.
The group did not have great industrial experiences nor connections with companies, in fact only one person had this type of experience while writing his/her master thesis.

The interviewees were then asked to choose the three most important personal skills from a list of 9 fundamental soft skills, listed in the Figure 6.4. After, they were asked which skills were improved the most during their research careers.

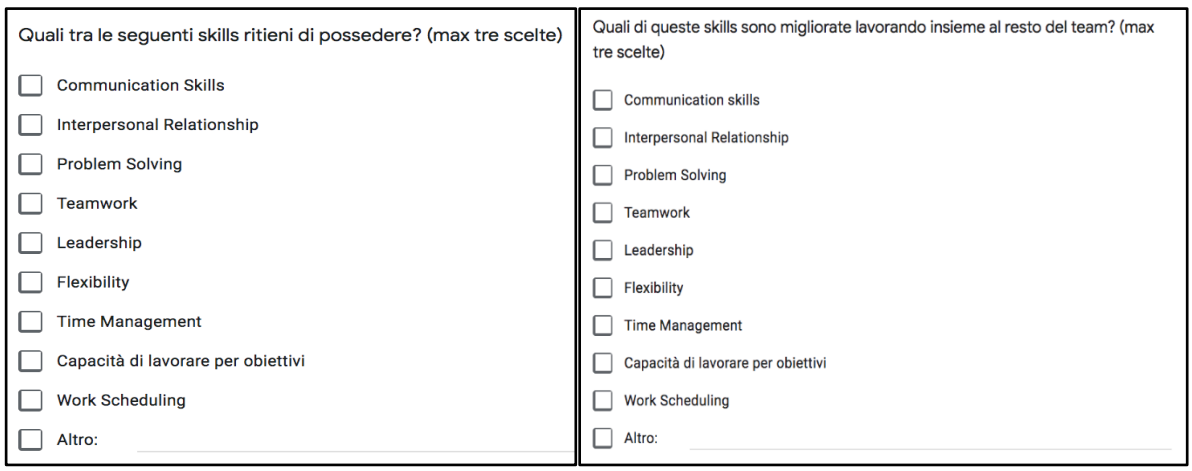

Figure 6.4 Extract from the questionnaire (1. which skills do you have? 2. Which skills have improved the most during your work with the team?).

The three most common personal skills were Teamwork, Flexibility and Problem Solving, while the ones that were enhanced through the learning experience were Personal Relationships, Goal Orientation and Teamwork, as shown in Figure 6.5 below. In both cases, nobody chose "leadership", which may seem odd, since leadership qualities can contribute to a productive and enthusiastic work atmosphere. This topic was later discussed with Dr. Valentina Cauda, who explained that in her team the respect for each other is fundamental and all the decisions are made together as a group, so that leadership is not really a skill that is exposed or enhanced in this context. Nevertheless, apart from the agreed activities of the group, each PhD student has its own topic to work on: initiative and independence arise the most in this case. Moreover, heterogeneous groups made by people with different backgrounds, personality, and levels of seniority have a positive impact on the discovery experience and can be really helpful to generate that debate and contrast that is needed to learn and grow as a unite group.

A **greater heterogeneity** of the background, in fact, is associated with a higher level of human capital that can help to address complex issues and facilitate problem solving. Indeed, when team components have different backgrounds, there is a broader set of knowledge and skills, which can increase the ability to recognize opportunities and to cope better with unforeseen situations.

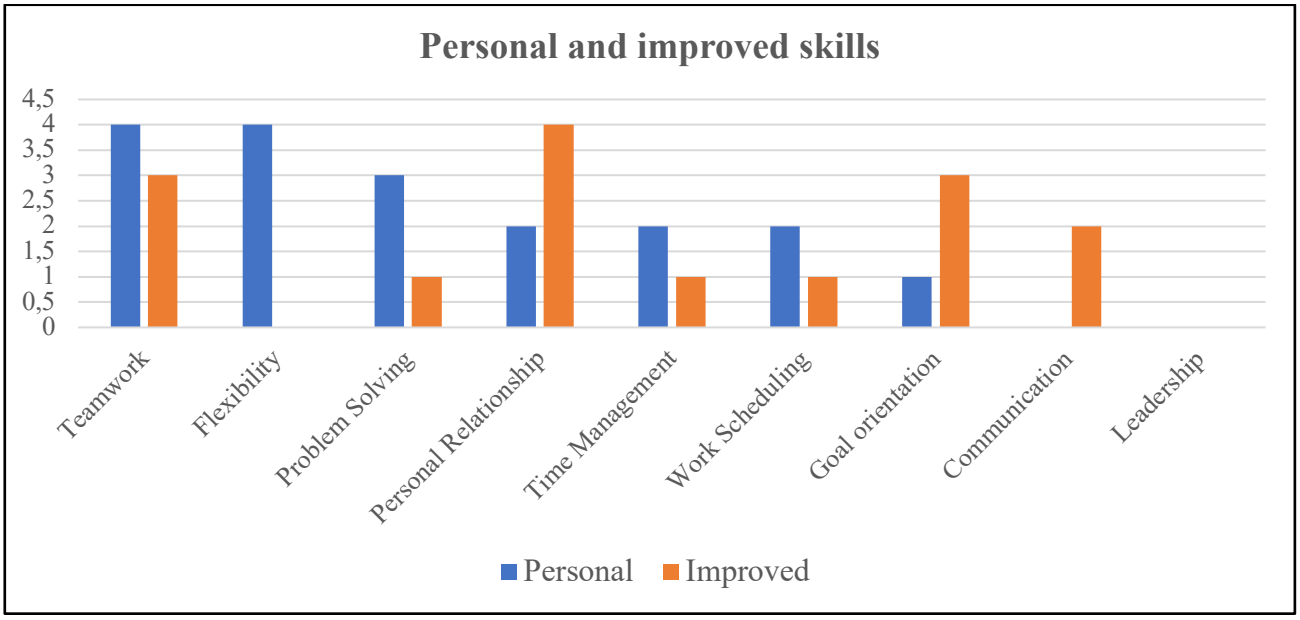

Figure 6.5 Personal versus improved skills in Prof. Valentina Cauda's team.

After that, team members were asked to choose the three personal characteristics that best represented their PI. The most common answers were “initiative”, “determination” and “creativity”.

As we said above, to have an entrepreneurial mindset and being resolute is essential for the PI: during the application for a PoC – as it happens when presenting to investors - not only the project itself will be evaluated, but also the PI and her/his ambitions and personal characteristics. The PI should be a pragmatic leader, able to keep high motivation in the team, to schedule tasks and milestones, to properly report the results and find opportunities to engage with companies. In order to reach such ambitious goals, it is important that the leadership is held by a single person: if everyone should follow stubbornly its own ideas there will not be harmony in the group. Activities are all related between each other and everyone should do its part, everyone is responsible for the outcomes.

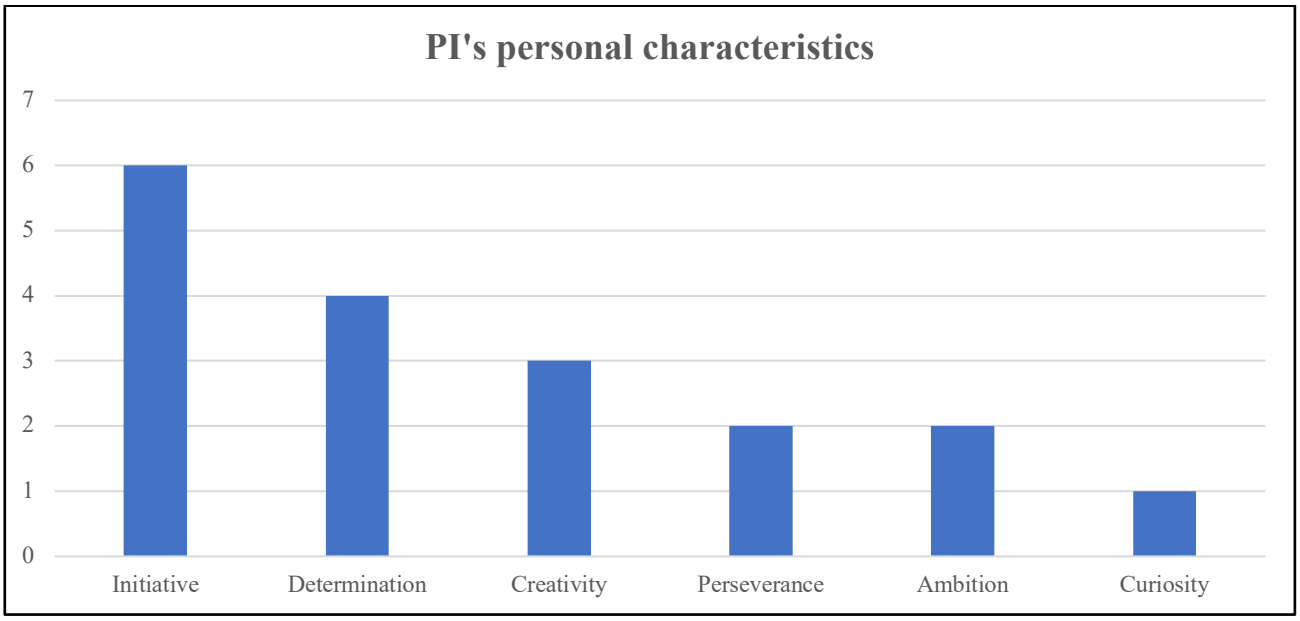

Figure 6.6 PI's personal characteristics according to her team's answers.

Finally, team members were asked about the biggest difficulties and problems that they encountered and how they managed to overcome those obstacles. The most common answers can be summarized in two macro-topics:

- **Technical problems:** limited access to materials and tools that slow down the process and the scheduled experimental activities.

- **Communication problems**: lack or difficulty in communication among some group members.

On the one hand, technical problems as missed arrivals of materials, delivery errors and long times to repair tools may cause delays and frustration among the team and can be only partially avoided with a better internal organization, since one of the biggest issue is the bureaucracy and the procurement system of public administration. On the other hand, communication issues are due to the numerosity of the people involved, the different personalities and ideas: even if these contrasts might bring out conflicts, and disagreements, they are actually part of the learning process and are a good stimulus to growth.

Therefore, the tensions are absolutely normal inside the group at the beginning, especially while working on innovative, disruptive ideas.

To mitigate the arising tensions different approaches may be followed: the group leader (the PI in our case) should manage these internal conflicts in order to avoid team failures.

Daniele Battaglia, Emilio Paolucci and Elisa Ughetto, in the article "Opening the black box of university proof-of-concept programs: project and team-based determinants of research commercialization outcomes" suggested that the size of the team should also be factored in alongside with heterogeneity. The group dimension, indeed, influences **internal communication**, **mutual monitoring** between team members and **individual motivations** in participating in efforts.

When teams are small, they generally face less problems of social integration: they can leverage on a greater number of interactions among the members participating, which enable the mutual understanding of different knowledge domains, relieving cognitive problems that may arise in larger teams.

A larger team instead reduces the ability and incentive of team members to monitor each other, thus increasing the likelihood of opportunistic behavior. This problem is particularly relevant in the context of academic spin-offs, where academic members have different motivations and expectations, consequently certain opportunistic behaviors are likely to emerge.

In the team considered in this study there are 11 people. It could be considered a group of medium dimensions if compared to other research group (that could generally vary between 2 and 20 people). As in all circumstances, it could happen that someone expansive or a little aggressive overcomes someone who is shy or introverted, so that the biggest issues have been about poor communication.

6.3 Projects of TNH Lab and Team Dynamics

To conclude our considerations on the team's learning process, we are going to present the projects carried on in the last few years. In Table 6.4 below are listed the three projects of the TNH lab that we are going to analyze.

Table 6.4 Comparison of the three chosen projects carried on by TNH Lab in the last years.

	Nanopils	U-Care	XtraUS
Founder	Valentina Cauda + Roberto Piva	Andrea Ancona + Valentina Cauda	Valentina Cauda
First Ideated In	2017	2017	2020
First Economic Funding	2020	2020	2021
Fundings	Started as part of the research financed by the European Research Council as an ERC Starting Grant 2015 - PoC Instrument, Fondazione Compagnia di San Paolo and Fondazione Links.	VV3TT 2018 POC Program, European Investment Fund (EIF) and Cassa Depositi e Prestiti (CDP) within the ITAtech platform.	Grant Preparation under the ERC-2020-PoC call, with GA 957563, title: "Fighting cancer relapse with remote activation of smart and targeted nanoconstructs"
Problem	Multiple Myeloma is a mortal disease with a 90% relapse rate and serious side effects. 60k people are currently treated in Europe, with high health cost due to the use of a mix of drugs.	490k patients yearly recovered in Italy with Acute Kidney Injury (AKI), health cost of 3B€/year, currently the urine level is read manually and is therefore inaccurate.	Circulating tumor cells (CTCs) in the blood stream have a key role in cancer progression, recurrence and metastasis spreading. High recurrence rate of primary tumor disease, requiring further treatments.
Solution	Nanoconstruct for cancer therapy able to target and treat cancer cells. The drug is transported and released directly inside the tumor. High specificity can reduce the doses and the side effects.	Diagnostic device to monitor accurately and continuously the urine production, a software based on AI to promptly detect acute kidney injury (AKI) through machine learning.	**Prevention of cancer relapse** and achievement of an early cure of recurrence. It applies an extracorporeal blood circulation set-up exploiting a novel stimuli-responsive, targeted and non-immunogenic nanoconstruct, remotely activated against CTCs.

The characteristics and commitment of the research groups can indeed affect the success of RBIs commercialization, but another important factor to take into account are the technological characteristics of the product object of the study. We will show which factors shaped the strategies and working methods of the group and how the external variables influenced the outcomes. In their article, Daniele Battaglia, Emilio Paolucci and Elisa Ughetto argument that a major source of heterogeneity among RBIs that are funded through PoC is in their **technological characteristics**. The technological attributes specific to each RBI will refer to the type of technology at the base of RBI (closer to basic research or applied research) and to its maturity (the TRL reached).
As we explained at the beginning of this work, low levels of TRLs (below three) indicate that the RBI is in a basic research phase, where new technologies and concepts have only been theorized. Intermediate levels (four to five) indicate that the technology underlying the RBI was tested and validated (either in a laboratory or in an industrial environment). High levels of TRL (between six and seven) indicate instead that the RBI is ready for commercialization.
Clearly, the higher the technological maturity of an RBI, the greater the likelihood that it will be brought to market. Within the range of RBI funded under proof of concept schemes, some research projects experience significant improvements in the TRL scale and leap up to three levels while others experience only small progresses of one level.

As introduced in Chapter 4, startups of biotech industry have bigger difficulties to get the proper funds compared to other sectors. In particular the projects that we analyzed can be put into different risk categories depending on the technology objective of the study: each project will need a different strategy to overcome those risks and convince the investors.

On a scale of increasing risk level, projects may focus on:

1. New biomedical devices for diagnosis.
2. New drugs to develop a better treatment.
3. Combination of new biomedical device and new drug to develop a better treatment.

The project **U-Care** fits in the first category: the major risk is connected to the technology working principles, but in this specific project the device developed has very limited interactions with human body, the regulations are easier and the trials are shorter: it should not be hard to prove the correct function of the technology and the market risk is limited since the

problem is clear. As a consequence, the investments needed are smaller and the payback is good enough for the investors.

The project **Nanopils** has a higher level of risk: the drug delivery system and the molecules object of the research have a probability of 1 on 250.000 to pass all the trials and finally being approved. The time and cost of trials grow exponentially: between 2 and 3 billion euros and from 12 to 15 years to appear on the market. In the first phases investors do not have any proof that the project will work and have a great impact, which makes it almost impossible to get a private investment at the beginning. In the end, the project **XtraUS** is in the third category and the risks are even higher: it associates the technical risks of a new device with all the restriction of a new treatment.

6.3.1 Nanopils

Nanopils was the first project undertaken by the research team in parallel to the ERC Starting Grant, from which it shares some ideas and novelties. The ambitious goal was to develop a drug delivery system (dds) to fight cancer, able to recognize and deceive cancer cells. The device could carry one or two drugs through the blood and release the active principles directly inside the tumoral cells.

Working either as a carrier and as a distributor, the dds allows to use smaller doses and decrease the side effects on patients. Since it is more efficient, the treatment could help to decrease the relapses number, entailing a saving on drugs cost and great benefits for patients.

The value of the idea resides in its great flexibility, that makes the technology perfect to be adapted to fight different kinds of solid tumors.

Nevertheless, on a business point of view, the device could help recover the value of drugs that were firstly rejected for being toxic or not well bio-distributed. Thanks to the dds, the needed dose can be reduced and therefore be less toxic, and the distribution function would not be a problem anymore. Moreover, patenting the combo of drug and dds, tratments would be improved and the appropriability of the value would be longer.

Even if the dds could potentially be used to fight different types of cancer, it was fundamental to choose a specific one in order to test and validate the technology. The multiple myeloma was chosen because it is a mortal disease with no definitive therapy and relapses occur in the 90% of the cases, but also because of the study of Prof. Roberto Piva from the University of Turin, also working on the project, on the synergic effects of AGI-6780 and Carfilzomib to treat this particular cancer.

From an economic point of view, multiple myeloma is the second most common blood cancer and even if it occurs in older patients (on average at 70 years old), there are currently 60.000 sick people in Europe that are bearing the heavy side effects of the available treatments.
Hospitalization is long and cost of drugs is high due to the synergic mix of 3 and more drugs for at least five years (about 100.000 euros for patient yearly in USA – 4 billion drug market per year in Europe).
In the next three years test in vivo will be carried on and from those results it would be easier to define the real potential of the technology. To complete this first phase 2 million euros are needed in order to cover technical and legal consultation, human resources, laboratory cost and consumable goods. The parameters used will be the test animals' survival rate and percentage decrease of tumor mass. The data would be compared with the therapies that are currently used.

The technological risk of the startup is evident: two millions are required just to pass the first phases of the development (in vivo test) and the path is still long before getting reliable results. The positive aspect is that the technology is modular: if the test for multiple myeloma will not be good enough, it would be possible to address the efforts into a different project or focus on a new cancer.
Through promotion and reputation, Nanopils could try to become a producer of dds and cooperate with pharmaceutical industries, helping them in improving the efficacy of their drugs and patenting new ones that may have been discarded during the previous procedures.

After several years without grant, thus based only on the scientific collaboration of the two partners, prof. Cauda and Prof Piva, Nanopils received funding from a PoC Instrument of LifTT funding, with a budget of 50'000 Euro (Duration: 12 months, Jul 2020 – July 2021).

6.3.2 U-Care

The project U-Care started in 2017 and at the moment is pre-incubated at the Startup Incubator I3P of Politecnico di Torino. The project was firstly ideated by Andrea Ancona during his PhD for a course of telemedicine and it is supervised by professor Valentina Cauda in the role of Co-founder and Chief Scientific Officer. The goal is to develop a new diagnostic system based on Artificial Intelligence in order to foresee and monitor in short times the acute kidney injury (AKI). U-Care solution allows to automatize the measurement of urine and analyzes the data with an algorithm developed through machine learning. With this new clinical procedure, the

quality of patients' lives will improve: the percentage of late diagnosis will decrease accordingly with the number of treatments needed, leading to smaller costs for hospitals.

The market analysis brought good results: four players are currently working on similar projects (competition is not always bad, since it is a manifestation that the idea could be good and the market needs it) and the potential sells in Italy amount to 36,5 million euros yearly, so that the potential return on investment is 10 times bigger than the initial one.

U-Care received fundings for a PoC from the grant offered by VV3TT in 2018, it was than funded by European Investment Fund (EIF) and from Cassa Depositi e Prestiti (CDP) within the platform ITAtech. In the table below we listed the award received during the last year.

Table 6.5 List of prizes won by U-Care in the last year.

Date	Prize
Gennaio 2020	Pre-seed funding of 50.000 € from Proof of Concept di Venture Factory (Vertis sgr).
Maggio 2020	Selected for a three-months acceleration program from Bioupper. 120.000 € to use on IBM Cloud platform for 12 months. The initiative brought a collaboration with Novartis.
Maggio 2020	Selected by Intesa San Paolo Innovation Center to present in Initiative/BioInItaly Investment Forum;
Luglio 2020	Selected for the second phase of the programme Jumpstarter organized by EIT HEALTH;
Luglio 2020	Selected for StartUP Bootcamp 2020 from Meet in Italy for Life Sciences: 35.000€ prize.
Ottobre 2020	Winner of Start CUP Piemonte Valle d'Aosta: 35.000€ prize.
Ottobre 2020	Winner of Digital Marathon Digithon 2020.
Novembre 2020	Winner of National Prize "Innovazione PNI".

All these events are a great way to give visibility to the project and the team and it is frequent to get in contact with investors during these competitions. The events are also useful to settle

deadlines and goals. Despite the apparent success, during the years Andrea Ancona could never focus full time on the project. During the PhD he was dedicating around 20% of his time and now it is still around 30%. This situation is a huge limit for the fast growth of projects: if the funding or the prizes were able to sustain 1-2 people full time even for a short period it could be easier to develop the technology and bring it on the market. Nevertheless, now that the project is finally well-defined the team is looking for a bigger investment (minimum 300.000 up to 2.5 M€) so that Andrea could spend all his energies on U-Care once the startup would be properly founded.

As we said in the previous chapters, reputation is fundamental to get noticed and obtain a funding. Prizes and competition are not the only way to get your business idea validated and in biotech is also important to obtain certifications or clinical validation. Startup in the biotech/medical field will usually need a big player to commercialize their devices and the companies that help in the first phases are usually buying the technology or licensing the patent if the project is successful. In the long run, this kind of cooperation is a good deal for the startups. In the last years, U-Care cooperated with the Italian Society of Nephrology (SIN) and with Novartis Italia in order to study cardiac-renal diseases. Other cooperations were signed with doctor Dario Roccatello (Head of Nephorlogy division of Ospedale San Giovanni Bosco, Torino), doctor Riccardo Faguglia (Head of Nephorlogy division Ospedale Santa Maria, Terni), Doctor Vincenzo Cantaluppi (Head of Nephorlogy division, AUO Novara) and doctor Massimo Manes, (AUSL, Aosta). As a technological partner we acknowledge Politecnico di Torino, IBM and Novasis Innovation.

6.3.3 XtraUS

XtraUS (Extra corporeal Ultrasound) is the most recent project started by TNH Lab with the ERC Proof of Concept Grant and born from one of the most innovative ideas of the former ERC Starting Grant of Prof. Valentina Cauda. The goal is to prevent cancer relapses, since many patients get into a recurrence of their primary tumor disease and need further treatments after the first diagnosis. The relapses seem to be connected to the circulating tumor cells (CTCs), that have a key role in cancer progression, recurrence and metastasis spreading. However, they are present in a small amount and are difficult to detect by conventional laboratory tests.

XtraUS goal is to make the first treatment permanent, so that patients can completely avoid relapses and all the connected side effects. This project will help to complete the state-of-the-art in cancer relapses prevention and metastasis reduction by eliminating the Minimal Residual Disease (MRD).

The technology developed by the TNH Lab consist in a novel stimuli-responsive, targeted and non-immunogenic nanoconstruct, remotely activated against CTCs. The device will enter the blood circulation and will be activated through ultrasound irradiation: in order to avoid the barrier made by the human tissues, the treatment will be integrated with extracorporeal circulation machine that are already used for other therapies, so that the therapy would be applied on the blood while it is outside the human body. The treatment is safe for the patients since it does not endanger the healthy tissues.

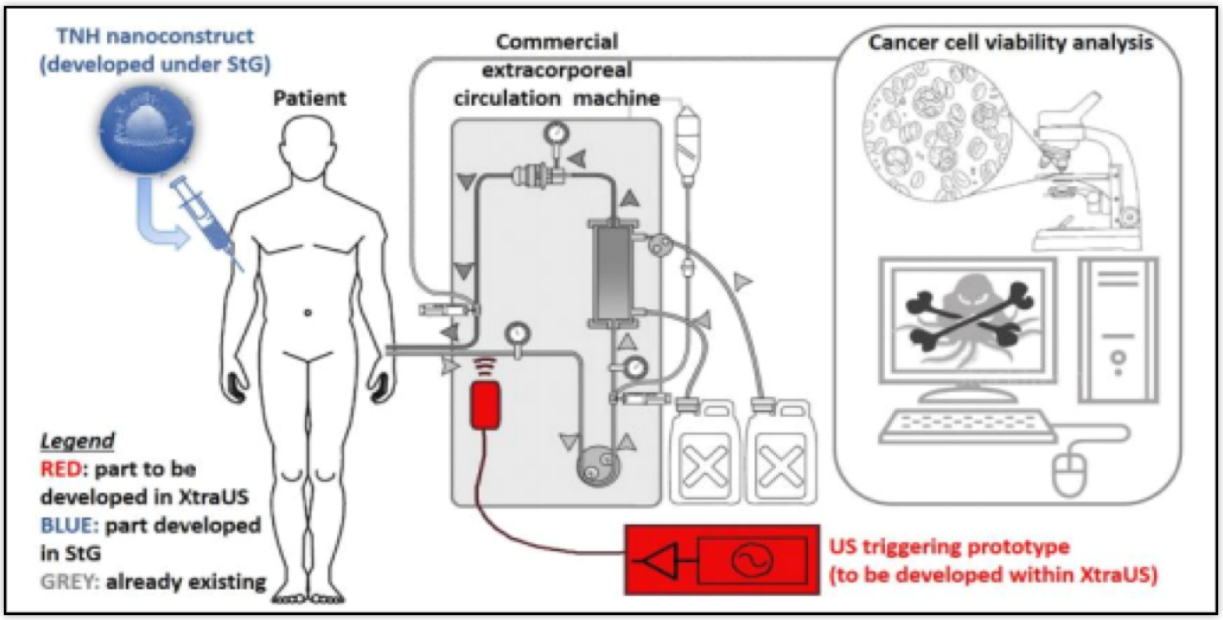

Figure 6.7 Diagram of XtraUS device joined to commercial extracorporeal circulation machine.

The main characteristic of this technology is its adaptability and the potentiality to cure different kind of tumors (since CTCs are not related to only one cancer). Nevertheless, also with XtraUS it will be important to focus on a specific area at first to test the product and see the market response. In this case the chosen beach-head market was the colo-rectal cancer, which present a high mortality rate and relapses in the 95% of the cases in the first 5 years. The disease is most common in people aged between 60 and 75 years old. After the first chemotherapy the tumor typically relapses with higher aggressivity and drug resistance, as well as establishing

metastasis. The treatment proposed by the TNH Lab is safe and less invasive than chemotherapy, but also cheaper (half of chemotherapy, one-third of Extracorporeal Photopheresis from the first extimation). It may also be used as pre-emptive therapy in synergy with other treatments as blood oxygenation and traditional haemodialysis. The benefits would be tremendous in terms of life expectations and quality of life for patients, but also for the sanitary system, reducing the long hospitalization and highly specialized visits, on the way to make cancer a curable disease. After the validation, indeed, the treatment could be effective with other blood and solid cancers as prostate, pulmonary or triple negative breast cancer. Other condition as transplant rejection, type one diabetes, multiple sclerosis could be treated as well.

The ERC PoC is focused on the creation of a theranostic nanoconstruct made of zinc oxide's crystals, which are mainly toxic for cancer cells and less on healthy cells. While with Nanopils the technology was a drug delivery system, in this project the used nanoparticels already have intrinsic toxic effects and no chemotherapeutical drugs are needed. In order to avoid the toxicity to affect also the healthy tissues, the nanocrystals are integrated into a biomimetic lipidic bilayer, of artificial orign (liposome) or natural origin (extracellular vesicles). This coating fulfils two functions: it keeps the nanocrystals stable in the blood and makes them less recognizable by the immune system. Furthermore, the nanocrystals can be activated with ultrasound irradiation to exploit a highly cytotoxic anticancer activity. Thus the best parameters (intensity and frequency) for ultrasound irradiation are being studied, so that the zinc oxide's crystals could be activated and kill the cancer cells.

With the ERC PoC the new technology could evolve from a basic treatment on in-vitro cancer cells to a treatment of CTC in-vivo and explores the synergy between ultrasounds and nanoparticles. The team is now dealing with the technical problem of irradiation: it is important to develop a system of extracorporeal blood circulation on which perform the ultrasounds. Thin channels and cartridges are currently used in the existing system, but that could not be enough to properly irradiate and activate all the cells. The researchers are working on different solutions to increase the area of blood treated at the same time.

The steps needed to validate the technology are the following:

- **Test in vitro:** the cells circulating in thin channels will be treated with ultrasound to show the proper active and cancer cell killing.

- **Test in vivo:** The cancer will be treated locally in test animals in order to identify a valid solution.
- **Clinical trials:** it requires a huge investment but it leads to a lower level of risk.

In the following Table the main characteristics of XtraUS are compared with the existing technologies.

Table 6.6 Comparison between XtraUS and existing technologies.

Technology	Xtraus	Ecp	Chemo	Nanobubble Assisted Us	Assisted Sonodynamic
Targeted	x			x	
Personalized	x	x			
Whole Blood Treatment	x		x	x	x
Reduced Collateral Effect	x	x		x	
Versatile To Other Therapies	x	x	x	x	x
Extracorporeal	x	x			

6.4 Learning Process

After a brief description of the three projects, we would like to analyze the learning process of the team and present how the experiences made in the very beginning influenced the decisions taken on the following projects. Some differences may be due to the technologies' characteristics, which as we said previously can have a great influence on the TRL's improvements. In the Table 6.7 we sum up the main differences between the presented projects.

Table 6.7 Comparison between the three projects analyzed.

	Nanopils	U-Care	XtraUS
Product/Service	Drug Delivery System	Biomedical device for diagnosis	Combination of device + drug
Risk Level	2	1	3
Research-based	Frontier, innovative	Well known technology	Frontier, innovative
Type of Technology	PUSH	PULL	PUSH
Temporal Horizon	Long-term	Short-term	Long-term
Partnership	Agios (WIP)	IBM, Novasis Innovazione, Novartis, Società Italiana di Nefrologia	Therakos (WIP)
TRL improvements	1→4	1→6	1→4

6.4.1 Technology-ideation process: market pull versus technology push

When a real customer need is first identified and then a solution is searched it is called "pull method". Under this method, **commercial applications are known before** the technology is developed. As it's easy to guess, investors love this method because uncertainties are reduced. If the technology works, the only variables left out are how to promote and distribute the product, but the success is almost guaranteed. On the other hand, if an organization develops new technological capabilities first, and then search for problems they can solve with them, it is "push method". Under this method, **commercial applications are known after** the technology is developed (Naganathan, 2019).

U-Care fits in the first category: a very specific and well-known problem (AKI) was analyzed and a solution was ideated for that specific issue, while Nanopils and XtraUS were technology-pushed innovations. A specific cancer was chosen but their uncertainty and flexibility make it harder to analyze the economic impacts on the market. Pharmaceutical industry is indeed a market where innovation is typically organized around R&D and animated by teams of scientists and engineers and a complete procedure for technological development is in place, perfectly punctuated by critical phases *(in vitro* tests, clinical trials...).

6.4.2 Temporal horizon

U-Care has a short-term horizon, with goals that are realistically reachable within 3 years. Since it is a medical device of class I which does not interfere with human body directly, the test and trials are quicker. The payback time is good and investors are willing to bet on the project. On the other hand, there is no way for Nanopils or XtraUS to shorten the times: the technologies are classified as class III of biomedical devices and the trials are long and expensive. As mentioned above, the cost of trials is several million euros and the process will take at least 10 years to be completed.

Even if some differences are strictly connected to the essence of the technologies, we can still underline few changes in the mindset and work approach of the researchers.
At the beginning, Nanopils was mainly focusing on discovery and research purposes, without an entrepreneurial mindset or a specific goal (indeed the research started within the ERC Starting Grant and not for a Proof of Concept). This is the reason why the project lacked a punctual market analysis and a customer discovery, which were made only later on. The interviews with doctors and the contacts with the market were not enough to fully cover the subject and also the participation to prizes and competitions was scarce. Obviously, Nanopils is really different from U-Care and the two projects are hardly comparable, but a change of mentality in the approach of the team to the problem is evident. First conceived as a PhD project, U-Care soon became a prototype with great potential to be commercialized. Compared to Nanopils, U-Care step up in terms of customer discovery and validation. With U-Care the contacts with stakeholders, interviews and questionnaires helped to choose the right direction, moreover the participation to many events helped creating a network of opportunities that lead to collaborations with either private and public investors as VV3TT in 2018, European Investment Fund (EIF) and Cassa Depositi e Prestiti (CDP).

6.5 Cooperation with industries

In the end we are going to see the cooperation dynamics with an industry and we will explore the strategies that can be adopted in order to better exploit the growth opportunities, get high funding and make a good reputation to lean on.

As a matter of fact a corporate collaboration is a necessary prerequisite to achieve strong and lasting goals: synergy allows to have quick processes, new, creative and effective insights and common projects. However, the small companies have to particularly face with their ability boundaries, that prevent them from effectively addressing certain market opportunities.

By comparing Nanopils and XtraUS, we did not see a big change in the cooperation with companies. Therefore, we discussed the topic with Prof. Valentina Cauda, who better explained the relationship that she had with the industries for both projects, acknowledging, at the same time, the importance of signing strong partnership to continue to test and prove the technology and finally to bring it to market. When she firstly won the ERC Starting Grant, mediatic attention was high and many companies contacted her to know more (i.e Johnson&Johnson, Thermo Fisher Scientific…). Lot of time was invested in presentation and networking, but unfortunately no concrete collaboration was established, since they were all asking for more reliable results than she could provide at the time.

After this negative experience with companies, Prof. Valentina Cauda realized that it was pointless to lose time in industrial relationships, at least before the results of the test in vivo, and it was better to focus on the scientific research and testing instead.

6.5.1 Therakos Company

Despite this previous experience, an English company, Therakos, got in contact with the technology of XtraUS, the team tried again to cooperate. Therakos Inc., bought by Mallinckrodt Group in 2015, is leader into the science progress of a lot of immune cells therapies exploiting a perfect experience match of medical devices, pharmaceuticals products and specialized treatments.

They have followed and improved the science of immunotherapy provided by the Extra Corporeal Photopheresis (ECP) for more than 30 years. ECP is a particular treatment that works with the immune system and it is activated by light and executed on blood cells, temporarily isolated outside the body. ECP is particularly used for the treatment of many different immune origin diseases and since the introduction of this innovative technology, about 25 years ago, Therakos has made possible the administration of over 700.000 ECP treatments worldwide. As

a matter of fact the main goal of this company is to use this therapy in order to find a resolutive care against cutaneous T-cell lymphoma (CTCL), a particular cancer type with a slow progression and a high incidence, in fact the latter has grown a lot, especially in men in the last years. Therefore, Therakos is a producer of extracorporeal blood machines, after all it is the only company who holds a clinical-approved, patented technology to treat cells with a therapeutic approach extracorporeally and they are interested in extending the area of applications of their devices. Therefore, if XtraUS should use their technologies, a new therapeutic function could be introduced to cure cancer, opening the profits to a whole new huge market. As we explained in Chapter 2, indeed, companies can be the financiers of research projects and this is a typical case of open innovation path: Therakos is searching for technological innovation outside the company itself. Moreover, the two technologies proposed by TNH Lab and Therakos have some similar points but also some different ones.

Among the similarities we can find: the specific goal regarding the extracorporeal blood treatment; the fact of offering themselves as secondary treatments (even if the photopheresis is used as primary treatment against CTCL); the exploitation of a combination of an agent and a radiation; both treatments use a cartridge/area where the irradiation happens.

Instead the main differences are the following: agent used (Therakos uses a particular photosentitizing agent called 8-MOP; XtraUS uses a inorganic ZnO nanoparticle); external activation (UV-A for Therakos and Ultrasounds for XtraUS); targeting (the chemical agent 8-MOP used by Therakos does not allow to preferentially treat a specific type of cell, i.e. the diseased one; in contrat the nanoparticles developed for XtraUS project allow to do a selective targeting of the diseased cells thanks to a monoclonal antibody and enable to treat them without a separation of the blood components); treatment duration (ECP lasts about 3 hours, divided into separation and irradiation; instead there are not precise definition about the timing of the XtraUS technology); costs (ECP has an average cost of €36’700 for patient; instead the treatment cost for patient proposed by this PoC is less than €15’000).

6.6 Technology test and possible changes suggestion

After these initial considerations, we focused on the testing of the provided technology in order to prove and verify its effective working principles. So, the company sent some materials, in particular cartridges, to the team for testing, in accordance to a specific “Materials Transfer Agreement”. The tests carried out were focused on ascertaining the presence or not of relevant

physical/chemical aspects inside these cartridges, where water enriched with a luminol solution has been flown to see if ultraspounf mediated inertial cavitation is taking place and if such cavitation gives rise to free radicals, enabling the luminol molecule to start emitting luminescence in the blue visible range.

During these initial experiments the following parameters were tested:

- Solution volume, thus height in the tested sample well;
- Presence or not of a lid on the well container;
- Frequency;
- Distance from the transducer.

Instead, for the experimental setup were used a Trasducer, LipoZero type (100% DC, f = 1 MHz, Power = 100%) and four type of containers: a single cockpit; a plate (with lid and no); a cartridge and a plastic square container.

Unfortunately, the cartridge was not perfectly compatible with XtraUS needs, so few modifications were asked in order to test the idea in the right conditions. In general, we can say that the different size and materials used and volume of the solution can enormously affect the ultrasonic field distribution and behaviour inside the liquid, in term of many phenomena: constructive/destructive interference, standing/traveling wave, resonance, absorption, transmission and reflection.
So, as possible solution, the team tried to use not the cartridge but its silicone tubes, usually used to transfer the patient's blood, since they are extremely thin. Using these tubes and irradiating the interested section, more liquid may be involved than the cartridge allowed to do; moreover, these tubes can be arranged in a spiral shape in order to treat more volume into the time unit. Therefore, it is a geometry matter, because the Therakos cartridge is too large and thin and it has two plastic flat faces that make disruptive interference with the sound wave. Another important aspect is the air interface, alternatively to air they could use an acoustic insulating material with an acoustic impedance similar to that of air. For example, they could cover the cartridge with a layer of this insulating material in order to simulate the behavior of the air near the lid. In fact, these soft materials should reflect back and recreate a lot of free radicals, exactly like air allows to do. Finally, they will have to find an appropriate material to solve the biocompatibility problem. Anyway, the cartridge will have to be reengineered based on a series of constraints, agreed between the company and XtraUS team, knowing either of the

scientific field or the application one, in order to make the technology compatible with the business device.

At this time the problem was again the disproportion between the investment required to the company and the reliability of the technology. Therakos was not willing to invest time and money to change the prototypes because the project was at an early stage and could not give certainties on the returns.

Even if the confrontation with a structured industry could be useful in shaping the project since the beginning, once again a problem of investment and reliability came up. Nevertheless, in this case, a fruitful cooperation could have reduced the developing times or lead to a co-development or even to a future acquisition in case of positive outcomes - and it still can: we hope that this first contact will open the road to a future cooperation.

6.7 Next step of this collaboration

Certainly, XtraUS proposed a new and innovative technology able to increase the value of their current asset but so that Therakos can take it into consideration they need more evidences.

Actually, the team led by the Professor Valentina Cauda is at an early stage where the money is not enough to carry on all the phases and to validate them in autonomy. So, they could use money getting by the ERC's funding to make the first steps, since, if everything should work out, money for the next phases would be directly provided by Therakos. In these terms all the test phases should be economically sized in order to see as far as possible with the grants received.

A Stage and Gate approach will be used to argued this specific step, here Therakos can be seen as an investor for giving money to cover the initial committed tests; if these tests lead to some positive results, the budget will be reviewed and then they will approached to the next step with the tests that will follow and again, if these worked, they will approach those after and so on, in order to align the scientific research conducted by Valentina Cauda's team with Therakos' market needs.

A perfect strategy to follow could be having a more detailed interaction specially with the Therakos technical/engineering side, because, from these previous studies done, the cartridge geometry is not appropriate with the ultrasound irradiation setup. So we are going to define non only an exit strategy but properly a development and co-development strategy, since the next steps require a careful evaluation about the way to follow, as a matter of fact together they could try to change and improve the technology geometry. XtraUS should adopt a proactive strategy

not only presenting a problem to the company and its possible solution proposal, but saying which geometries are tested and which are recommended to improve the general technology working and functions. So, they must convince the company to be their best alternative, with which they may update their product.

Finally, XtraUS have to understand if it might be more convenient for them to approach Therakos as a potential customer and sale or license them the patent about the sonosensitizer agent or, alternatively, to increase the project value building an independent startup and later to aim for a subsequent acquisition by Therakos or another one biotech company. In this way they could continue their R&D activities inside the company/startup and, at the same time, Therakos could also take an advantage buying not only the patent but also the whole company with their necessary competencies. However, the latter possibility is the least likely for many different reasons: first of all long time, high costs and extremely uncertain returns from the investments but also for lack of reputation, relationship skills, availability of investments, industry competencies missing and so on.

In conclusion, we can assert that collaboration with industries represent an indispensable subject for completing the technology transfer process, but it should happen at the right time: disruptive projects at their earliest phases of development will still need public funding to begin and grow.

An interesting cause for reflection is on the role of universities in making more collaborations with industries happening. Except for the entrepreneurial trainings and networks opportunities, a concrete way to help is to use Technology Transfer Offices as a proper resource of the team. In particular TTO employees should have the competencies to find and contact the proper industries for each project, helping the researchers to find investors. This kind of support could really be a game-changer for the PIs, who could focus more on the scientific parts and less on the fund-raising campaign. This opportunity has been offered from TTO of Politecnico di Torino and Università di Torino to Prof. Valentina Cauda and Prof. Roberto Piva, in order to find investors or cooperation with industries for Nanopils. A similar road could be taken for XtraUS, so that while the team will work on the scientific aspects, someone else could do market analysis and test the waters with companies.

7 Conclusions

After presenting the state of the art on technological transfer and relationships between governments, universities and industries, we collected data from ERC and studied a practical example, learning from the experiences of TNH Lab Research Team.

We can now draw the following conclusions.

Disruptive projects which are high-risk and high-gain should be supported by public institutions in the first phases of development. Grants offered by ERC have proven to be efficient: they allow researchers to work on frontier research and to lead a team of promising young doctors. Nevertheless, at least in the biotech field, an extension in the value and the duration of Proof of Concept (which now is 50.000 euros for a six-months period) could really improve the success-rate of the funded projects. After studying the practical example with Prof. Valentina Cauda, the suggestion that we propose is to double it, making it 100.000 euros for a twelve-months period for the projects that require lots of technical and expensive tests. Moreover, it would be useful to take off some weight from the PIs shoulders, who is now juggling between teaching, researching and learning business acumen while concerning about budget and funding issues. This could be made with two improvements: on one hand, budget should include human resources that could focus 100% on a specific project (they would be more responsible and productive), on the other hand, TTO of the universities should engage with industries and propose collaborations based on the companies' interests and recent works. This role of TTO would optimize the available resources: they have more knowledge on market trends and should have the competencies to propose the right match between an industry and a project.

Reputation generated by ERC Grant, together with the active participation at local and international competitions and events, allow to get more trust – investors perceived a lower risk than the initial one. Let us recall that investors do not only judge the project but also the whole team capabilities to overcome obstacles and properly present ideas. Either investors and companies are hard subjects to convince, but even harder to deal with and trust. It is therefore important to evaluate all the proposals and conditions and always choose the best strategies (also relying on advisors' suggestions) taking into account shares divisions, intellectual property and patents.

Companies attack new markets through Open Innovation, so it is important for them to engage with teams that do research in their same field. When the right collaboration occurs, the company gets a new product or service to wide its offer, while the PIs licenses its idea and maybe keeps working on it as an external consultant.

In terms of social utilities, TRL of the RBI is improved during the process and the GAP caused by the Valley of Death could finally be filled.

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