

Moving drug discoveries beyond the valley of death: the role of innovation ecosystems

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Abstract

Purpose – The paper aims to explore the nature of initiatives and strategies of inter-organizational cooperation to cross the valley of death in the biopharma industry.

Design/methodology/approach – The authors conducted an exploratory case study analysis in the Biopharma Innovation Ecosystem in Greater Boston Area (USA), which is one of the oldest, and most successful IE in the US, specialized in the Biopharma domain, by conducting a round of expert interviews with key informants in the area, chosen as representatives of the different types of actors engaged in the drug development processes at different stages.

Findings – Main findings suggest that cooperation can contribute to surviving the valley of death by reducing the barriers within the drug development pipeline through the promotion of strategic relationships among actors of different nature, including the establishment of government-led thematic associations or consortia, agreements between university and business support structures, proximity to venture capitalist and the promotion of a general culture of academic entrepreneurship within universities.

Originality/value – The authors believe that this paper contributes to the literature by shedding light on the nature of the specific cooperative initiative the barriers in drug development and help to survive the valley of the death.

Keywords Drug development, Innovation ecosystems, Innovation management, Biopharma

Paper type Research paper

Introduction

It is widely accepted that the process of biotech-based drug development is among the most complex and riskiest industrial processes, due to the long duration and the high costs of the R&D process and most importantly, to its high level of vulnerability to any slight change in the environment, which can potentially alter the drug quality and nullify its efficacy. It has been estimated that the average cost for developing a biotech based drug (from its early discovery to its commercialization) may reach \$2.5 billion dollars (Milne and Malins, 2012) and that the whole process can take from 10 up to 15 years. Specifically, the process of biotech-based drug development, encompasses three main stages namely, (1) *Drug discovery* (i.e. target identification and validation; lead identification and optimization); (2) *Drug development* (including pre-clinical tests and clinical tests) and finally, (3) *Drug manufacturing* at commercial scale (Bianchi *et al.*, 2011; Reynolds and Uygun, 2018). Even then, dangerous side effects could manifest for some drugs after many years of commercialization. Consequently, regulatory approval guidelines became increasingly stringent, thus making an already slow system even slower. This, in turn, often makes financial resources difficult to obtain, especially for the early stages of translational research. Altogether, this makes particular challenging for companies and start-ups in the biopharma sector to overcome the phase between research and successful



innovation, which is known as the *valley of death*, i.e. the failure of research discoveries “from becoming new therapies or even making it to clinical trials” (Frank *et al.*, 1996). On the other hand, a growing body of literature has started to apply the concept of innovation ecosystem to biotech industry by describing the biopharmaceutical innovation process as a systemic interaction of different actors as large companies, startups, universities and research centers and so on (Owen-Smith and Powell, 2004; Gilding *et al.*, 2020; Stephens *et al.*, 2019; Hopkins *et al.*, 2019). However, despite the ecosystemic nature of the innovation process could be beneficial to cross the “valley of death” (e.g. Hudson and Khazragui, 2013), this general assumption has not been supported by empirical research. Indeed, scant attention has been devoted to the identification and discussion of specific initiatives and strategies of inter-organizational cooperation to achieve successful innovation in biopharma industry. In this light, our paper explores the nature of initiatives and strategies of inter-organizational cooperation to cross the valley of death in the biopharma industry, attempting to answer to the following research question: (RQ1) Which initiatives and strategies of inter-organizational cooperation can contribute to cross the valley of death in the biopharma industry?

To this purpose, we conduct an exploratory case study in the Biopharma Innovation Ecosystem in Greater Boston Area (USA), which is one of the oldest, and most successful IE in the US, specialized in the Biopharma domain. The area hosts many of the leaders in tech and life science (eighteen out of the top twenty drug companies have a major presence in GBA) as well as world-class academic and research institutions as Harvard and MIT. For the purposes of our study, we conduct a round of expert interviews with key informants in the area, chosen as representatives of the different categories of actors engaged in the drug development process at different stages. We identified the initiatives undertaken by the different types of actors (i.e. universities, governments and private industry) and the main cooperation mechanisms leading to the drug development process, including a variety of programs and partnerships to move promising discoveries beyond the valley of death. Our study contributes to extant literature on several fronts. First, we specifically analyze the role of IE in contributing to cross the valley of death by matching two different bodies of literature. In particular, while studies on IE are generally focused on the general role of ecosystem in biotech in facilitating knowledge transfer and funding opportunities (e.g. Owen-Smith and Powell, 2004; Gilding *et al.*, 2020), our study identifies specific network-driven strategies and initiatives to contribute to the survival of innovations through the valley of death, thus deriving more punctual implications for actors in the biopharma industry. Second, while extant literature tends to focus on one type of relationship of IE at a time (e.g. Hopkins *et al.*, 2019), our study considers the whole community of IE actors simultaneously and their leadership role along the different strategies, thus allowing for a more comprehensive view about the implications of being embedded in an ecosystem.

Theoretical background

With the aim of gaining insights on the main challenges characterizing the drug development pathway toward commercialization and how these can be overcome by the adoption of an innovation ecosystem perspective, next sections will first review studies identifying the main challenges characterizing the valley of death and then empirical research exploring the concept of innovation ecosystems and their role in moving innovation along the pipeline in biotech industry.

Valley of death in biopharma industry

The concept of *valley of death* grounds on the general idea of innovation as a multi-stage process. For the sake of simplicity, innovation sequence can be defined by three main stages (Auerswald and Branscomb, 2004), where the first phase consists of basic research, and the final stage develops into the commercialization and diffusion of an innovative product or

service. The path occurring between basic research to commercialization may often require a long time and may be characterized by significant bottlenecks and roadblocks. For these reasons, the phase in between the activities of research and new product development is often referred to as the *valley of death* (Branscomb and Auerswald, 2001; Markham, 2002; Merrifield, 1995). The concept of *valley of death* was first employed by Bruce Merrifield (1995) to define the issues of transferring agricultural technologies to Third-World nations (Markham *et al.*, 2010). Subsequently, the concept was employed with regard to the resource gap occurring between R&D labs or units and commercialization within companies and institutions to realizing the commercial viability of products (Branscomb and Auerswald, 2001; Markham, 2002). Nowadays, the concept of *valley of death* is used as a metaphor to define the lack of resources and expertise in the area of product development. The *valley of death* can happen during innovation processes across different types of industries. However, the pharmaceutical industry is the one in which the phenomenon has been observed more frequently and where the *valley of death* is defined as the failure of research discoveries “from becoming new therapies or even making it to clinical trials” (Frank *et al.*, 1996). The process of drug development can be summarized in three macro phases. First *drug discovery*, consists of the identification of a gene or a protein causing a certain disease and a validation process where the target is observed while interacting with human organisms (target validation); then, a new compound is developed to address the specific target and turned into an active principle for future drug development (lead identification and optimization). A second stage i.e. *drug development* includes a series of testing rounds namely, preclinical tests (on animals) and clinical tests on human patients (Phase I, Phase II and Phase III), which are necessary to achieve public authorities’ approval. Finally, the third stage refers to *drug manufacturing at commercial scale*, in which a master cell line containing the gene for a specific protein is developed for patient use. In the case of pharmaceutical development the *valley of death* (also termed as “translational gap”) encompasses stages from discovery to translation into effective proof-of-concept, including Phase II clinical development, which accumulates the highest attrition risk (Figure 1). Moreover, R&D expenditure for new therapeutic development has witnessed a significant increase which has not been corresponded by an equal growth in the number of new drugs. Indeed, quite the opposite has occurred. By way of illustration, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) tend to approve only about 200 novel drugs for human use (1,2) every three-year. In fact, even when drugs reach clinical trials, these still have only the 7–15% of possibilities to obtain market approval (Bunnage, 2011). In general, according to the Pharmaceutical Research and Manufacturers of America within the 5,000 to 10,000 compounds that enter the pipeline for drug development, only one receives approval (PhRMA, 2017). In addition to the difficulties in translating promising preclinical findings to efficacy in patients, one of the main issues leading biotechnological discoveries to the Valley of Death regards the entity of R&D expenditure needed throughout the entire innovation process. Indeed, it has been calculated that, on average, the cost to yield a single FDA-approved drug is approximately \$2.6 billion (including out-of-pocket costs of \$1.4 billion and time costs of \$1.2 billion, and the cost of development failures) (PhRMA, 2017), that is about the double compared to 10 years ago (Cummings *et al.*, 2014).

In summary, the problem with moving through the valley of death is two-fold: on the one hand the long timespan involved and, on the other, that failure tends to accumulate in later stages development, when the costs incurred become significantly higher. A growing research body has examined the causes of the valley of death in the biopharma industry (Paul *et al.*, 2010; Hudson and Khazragui, 2013; Wessner, 2005; Bennani, 2011; Guertin, 2016; Zurdo, 2013), by identifying a number of challenges and resource gaps along the process that may eventually lead to a translational gap, including financial and other economic and technical factors. In general, the most commonly reported cause concerns the *high-risk of failure* that characterizes drug development industry (Finkbeiner *et al.*, 2010). It has been estimated that for every

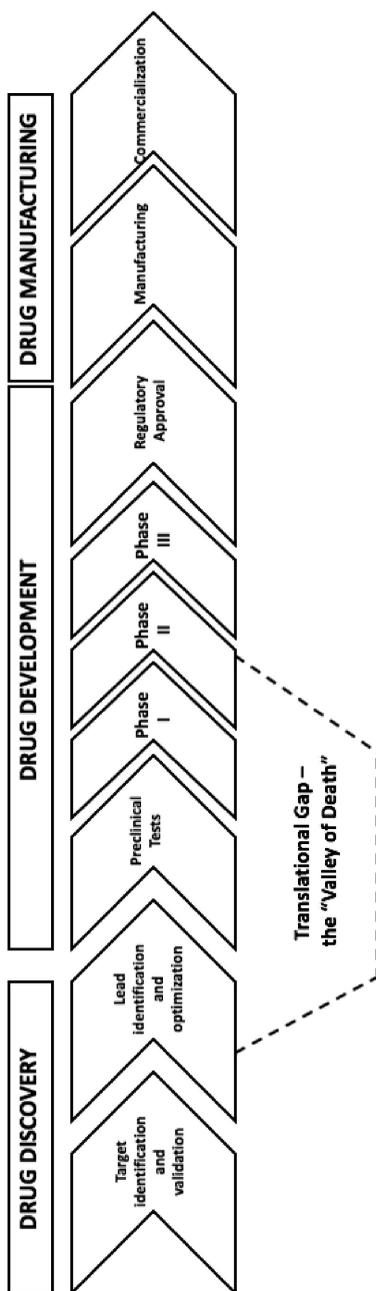


Figure 1. The valley of death in the drug development process

5,000–10,000 compounds that move in the drug discovery pipeline only 250 will eventually go to pre-clinical development (Zhang and Surapaneni, 2012). Only five will move forward to phase I, and only one will receive public authorities' approval for market purposes (Cummings *et al.*, 2014). This in turn, causes inevitable pressure on companies with regards to their priority areas of investment and lead to funding gaps toward less competitive therapies' areas characterized by higher levels of failure. As a way of illustration, empirical research has shown that in the specific case of anticancer drug development, the ability to translate new potential disease targets into therapies is poor, with a failure rate of approximately 90% (Adams, 2012). Secondly, many scholars agree that another major hurdle to translational research lies in the *lack of funding* during the phase between drug discovery and manufacturing. In this light, Heller and Peterson (2005) described the *valley of death* as the place "where good lab discoveries go to die because they lack the funding necessary to become a commercial product." Indeed, literature argues that seeking funds for translational research is becoming increasingly difficult, due to the high levels of uncertainty at this stage. Specifically, National Institutes of Health (NIH), venture capital and biopharmaceutical companies tend to be more conservative and risk-averse in their funding decisions, by investing primarily in clinical research. Also, since costs have grown, a tendency in investing at later phases along the research continuum has been observed. Approximately, 60% of NIH research project grants support basic research, while only 30% supports clinical research (Butler, 2008; Wehling, 2009). Another cause leading drug discoveries through the *valley of death*, according to extant studies, concerns the researchers' *lack of technical expertise*, which is necessary to move their discoveries through the pipeline. More specifically, scholars argue that principal investigators often do not have any expertise in intellectual property, regulatory and privacy issues, among others, that are required to carry their innovation forward and that are generally beyond the reach and experience of those conducting government-supported basic research. Hence, access to business support structures and to specialized technical infrastructure is key in translational and clinical research. Moreover, one of the main problems relates to the declining role of the so-called clinician–scientists (Roberts *et al.*, 2012). Differently from basic scientists, clinician–scientists are able to move their research from bench to bedside, thanks to their unique capacity of incorporating results of clinical studies in novel research and treatment approaches. More specifically, clinician–scientists use patient reactions and results of failed experiments to develop new hypotheses and alternative opportunities of treatment, overlooked by past experiments. Compared to basic scientists, clinician–scientists are generally more knowledgeable about clinical trials and consequently, they can more easily follow up on perceived failures. More importantly, they are often involved in collaborations with government, industry, and private organizations, which allows them to develop project management skills that in turn increase the probability of projects' success. As we mentioned earlier, academic institutions are significantly involved in the earliest stages of the process of drug development and one of the main challenges is to bring drug discoveries outside the boundaries of the university. This difficulty is often due to the *lack of support from technology transfer offices* and to the *lack of professional incentives to academics*, which represent two additional barriers to crossing the valley of death. Indeed, one of the main tasks of TTOs is to find a "home" for university inventions deriving from basic research and that are at their very early stage (Van Norman and Eisenkot, 2017). Ideally, a successful TTO should understand the fields in which the academic institution is productively innovating, and foster relationships with commercial entities whose unmet needs tend to lie in those fields, to ultimately match appropriate investors with products (Etzkowitz and Göktepe-Hultén, 2010). However, TTOs – whose mission is primarily to out-license promising inventions from their academic laboratories – cannot usually provide the type of support required to move an idea through the pipeline and turn them into a proof-of-concept (e.g. IP assets' management, licensing; an understanding of business management and practicalities, contract law; connections to outside

industrial and investment communities). Hence, innovations developed by academic spin-off risk to not survive the *valley of death* due to the lack of sufficient support from the institutions of origin. Another factor hindering drug discoveries from crossing the *valley of death*, from a university perspective, refers to the *lack of professional incentives to academics*. Even in the case when academic researchers had the knowledge required and the support available to move their discoveries through the pipeline, they may not have professional incentives to do so. Reward and promotion structures in academia rewards individual success and do not sufficiently encourage the kind of collaboration that translational research requires and there is a clear difficulty in assessing outcomes of translational research to reward effort (Adams, 2012). Indeed, translational research generally does not lead to publication in high-ranked journals, which is the standard metric of professional success in basic science fields (Butler, 2008). Other rewards for academics are generally traceable to tenure by their universities for obtaining public grants, and being assigned patents on their inventions. Also, if they are interested in collaborating with firms to turn their discoveries forward toward therapies and commercialize them, they may be subject to charges of conflict of interest. Altogether, these barriers discourage most academic scientists from bringing their research to the next level. The issues mentioned above (i.e. *high-risk of failure; lack of funding; lack of technical expertise; lack of professional incentives to academics; lack of support from technology transfer offices*) represent, according to reviewed studies, the most recurrent barriers that the actors operating in the drug development industry have to deal with to ultimately survive the *valley of death*. In this regard, most scholars in the field, suggest collaboration between companies from the pharmaceutical industry, academia, investors and government institutions as a viable solution to alleviate some of the most common causes of the *valley of death* and contribute to the commercialization of promising drug discoveries (Ekins *et al.*, 2011; Portilla *et al.*, 2010; Albats and Aleksander, 2017; Hudson and Khazragui, 2013; Jackson, 2011). It has been observed that the diverse community of actors participating in the drug development process (including research institutions, academic spinoffs, contract research organizations (CRO), biotech firms, big Pharmas, public institutions, venture capitalists and business angels) are increasingly resorting to collaborative networks for reducing the risks associated to the R&D process and increasing the chances of success for their discoveries to be brought to the market. Indeed, rather than creating new in-house infrastructure, there has been an increase in the level of cooperation between scientists at academic centers, biopharma and CRO/CMO sectors. By way of illustration, Ekins *et al.* (2013) argue that partnering with CRO/CMOs is becoming an integral part of R&D approach as these are fundamental in order to obtain key scientific evidence for drug development programs for clinical success and keeping intellectual property intact. Oftentimes CROs have infrastructure to carry out operations that used to be under the domain of basic science laboratories within big Pharmas. Also, by sharing precompetitive data and models, actors can significantly accelerate discovery across the board (Ekins *et al.*, 2013). Similarly, Hudson and Khazragui (2013) examine patterns of collaboration among the different actors across the biopharma innovation process in the UK, the EU and the USA. The study shows the role of governments in implementing newer models of innovation policy to encourage the collaboration between researchers from the pharmaceutical industry and academia to bring basic research to the market in a joint effort to cross the *valley of death*. In this vein, Portilla *et al.* (2010) argue that collaboration among all stakeholders in translational research is vital for its success, by supporting this argument with the case of the Clinical Innovation and Translational Science Awards (CTSA) Program Assets Portal, led by the University of California, with the purpose of matching investigators with pharmaceutical compounds that are not being actively developed and can be repurposed for other indications, such as rare diseases. The portal drew the attention of both academic researchers and pharmaceutical companies, showing the potential to identify, through cooperation, novel uses for compounds whose commercial development for the original indication was previously interrupted. From a different perspective, Albats and Aleksander

(2017) investigated the evolution of collaboration models between academia and business in drug development industry, by exploring in-depth the role of online platforms in crossing the “valley of death” between academia and business. The authors found that, despite the various functions being fulfilled by various platforms, these collaborative tools support practitioners, by providing solutions for their own needs in knowledge transfer and optimizing the resource efficiency in managing knowledge transfer.

Innovation ecosystems and the valley of death

Some studies show that with particular regard to biotech industry, the innovation and manufacturing process involve a systemic interaction of actors of different nature as small biotech companies, start-ups, large biopharma companies, universities and research centers. The concept of innovation ecosystem has been originally used to reflect the economic dynamics between actors and entities whose functional goal is to enable technology and innovation. According to one of the early proponents of the concept i.e. D. J. Jackson, the actors of innovation ecosystem include institutional entities such as universities, research organizations, business firms and risk capital providers as venture capitalists and business angels (Jackson, 2011). These actors combine the material resources (funds, equipment, facilities) and human capital (researchers, entrepreneurs, skilled employees, etc.) that are necessary to combine two different, but inter-related economies: *research economy* (responsible for the generation of new knowledge and technologies) and *commercial economy* (responsible for knowledge and technologies' commercialization). According to the innovation ecosystem perspective, these two economies should be coupled i.e.: “resources available to the research economy are coupled to the resources generated by the commercial economy, usually as some fraction of the profits in the commercial economy” (Jackson, 2011). In this regard, Frenkel and Maital (2014) suggest that the quality of innovation ecosystems depends not only on the quality of its elements (i.e. actors, institutions, resources), but also in their ability to develop relationships and a certain culture of cooperation that would contribute to lead innovation from the research economy to the commercial economies, thus surviving the valley of death. Also, these linkages should emerge gradually and spontaneously, on the basis of self-organization and adjustment, which requires a different approach than the traditional institutional-regulatory approach (as in the case of National Innovation Systems). Conversely, an innovation ecosystem approach requires achieving a balance between the supply-side and demand-side interventions, public and private initiatives, long-term and short-term perspectives, quality of elements and their relationships, target policy interventions and smooth functioning of the market logics.

Much of the studies on innovation ecosystems has focused on the assessment of their quality by analyzing the drivers of IE performance, as the actors' heterogeneous composition (e.g. Etkowitz, 1993a, b and Etkowitz and Leydesdorff, 1995; Budden and Murray, 2015; Carayannis and Campbell, 2006, 2016); the spatial dimension (e.g. De la Mothe and Paquet, 1998; Cooke, 2001, 2004; Asheim and Coenen, 2005); the infrastructural endowment and policy incentives (e.g. R&D expenditure; Venture investments; incubators and acceleration programs) and finally, on the relational dimension (e.g. Saxenian, 1994; Ahuja, 2000, Owen-Smith and Powell, 2004; Russell *et al.*, 2015), with specific regard to the creation of collaborative/complementary and competitive/substitute relations (Granstrand and Holgersson, 2020). Another strand of studies have privileged the focus on the effects of IE creation in terms of production of new knowledge and contribution to the regional growth (e.g. Bajmócy, 2013; Campanella, 2014; Guan and Chen, 2010; Lerro and Schiuma, 2015). Finally, However, some authors have focused on the importance of not only collaborating but also competing actors in IE (e.g. Rohrbeck *et al.*, 2009; Gawer, 2014; Mantovani and Ruiz-Aliseda, 2016; Hannah and Eisenhardt, 2018). In addition, since that it is well-know that

the processes of innovation in biopharma industry involve a community of different actors, typical of an innovation ecosystem (Jackson, 2011), a growing body of literature has paid attention to the study of the innovation ecosystems dynamics in this specific industry. From a relational perspective, Owen-Smith and Powell (2004) studied the impact of network organizational heterogeneity in innovation networks on knowledge transfer dynamics, by analyzing contractual linkages among dedicated biotech firms, public research organizations, VC firms, government agencies and biopharma companies in the Boston biotechnology innovation system, suggesting that the nature (public or private) of the organizations alters the flow of information through a network. Similarly, Gilding *et al.* (2020) adopted a network perspective to investigate Australian biotech firms' networks ability to access new knowledge and intellectual property, raise early stage funding and bring products to market, suggesting that local collaborations with public research organizations positively affect new knowledge and early-stage funding but not the ability of bringing products to market, thus highlighting the failure of PROs in catalysing collaborations with distant partner organizations directed towards commercialization, as Big Pharmas. From a different perspective, Stephens *et al.* (2019) focused on the factors that drive the localization and the retention of entrepreneurs in biotech innovation ecosystems in Silicon Valley, Austin, Boston, and New York City, suggesting that the attractiveness of ecosystems is related to higher degrees of connectedness and frequency of funding opportunities. Finally, Hopkins *et al.* (2019) developed a framework for characterizing governance modes to spur investor to support biotech firms showing the challenges of maintaining synergistic relationships between state and non-state actors. The studies reviewed above, suggest the key role of cooperation among the actors along the innovation process to survive the valley of death. However, with the exception of Hopkins *et al.* (2019), scant attention has been devoted to the empirical study of which and how specific policies and initiatives, at the ecosystem level, can contribute to the survival of innovations through the valley of death.

Empirical study

Methods

This paper adopts an inductive approach (Gioia *et al.*, 2013) aimed at building theoretical propositions starting from the exploratory case study in the Biopharma Innovation Ecosystem (IE) in Greater Boston Area (USA), which is one of the oldest, and most successful IE in the US, specialized in the biopharma domain. Case study analysis is useful for deeply understanding a complex phenomenon because it is rich with empirical instance by focusing on the dynamics present in a single setting (Eisenhardt and Graebner, 2007; Streb, 2010; Gibbert and Ruigrok, 2010; Gehman *et al.*, 2018). Theory building from case study is appropriate (1) when there is either no theory or a problematic one; (2) for analyzing complex processes; (3) for identifying constructs that are "hard to measure" and finally, (4) for analyzing cases referring to "unique exemplars" (Gehman *et al.*, 2018). All of these circumstances apply to our study. More specifically, we conduct a critical case study which, compared to multiple or collective case studies, is more adequate when the case itself is either a representative or typical case, as in the current research. Also, in our case, a critical case study would allow for formulating propositions to be tested in future research, starting from the selection of a case study that meets all conditions that we are willing to explore. Despite the advantages above, a single case study analysis has as a main limitation the lack of generalizability of the research results. This limitation can be partially overcome by an appropriate selection of the case. As a method of case study selection, we used the paradigmatic case method (Flyvberg, 2006), which refers to the careful selection of a prototypical case that can reveal key elements of a phenomenon under consideration.

The selection of the case study: the Greater Boston Biopharma ecosystem

The case study has not been randomly selected. First, we select the *Greater Boston Biopharma ecosystem* since it is – along with the Silicon Valley – one of the oldest, best-known and most successful IE in the US, and at the international level. More specifically, the *Greater Boston Biopharma ecosystem*, together with San Francisco, is generally referred to as one of the key geographical clusters that nowadays dominate the biopharma landscape thanks to a unique blend of science, entrepreneurship skills, risk-taking culture, especially in the City of Cambridge. Indeed, Cambridge hosts one of the world largest concentrations of biotechnology-related companies, particularly within the area of Kendall Square, which hosts, among the others, the Massachusetts Institute of Technology (Saxenian, 1994; Breznitz and Anderson, 2005; Owen-Smith and Powell, 2004). Secondly, we selected the *Greater Boston Biopharma ecosystem* due to the fact that its development is, historically, due to the joint effort of different types of stakeholders, whose diverse nature is one of the most distinctive characteristic of innovation ecosystems compared to other forms of territorial agglomerations (e.g. clusters or districts). Indeed, the rise of biopharmaceutical industry in the Greater Boston Area (GBA) traces back to the 1970s, with the development of genetic engineering and the establishment of Biogen through the endorsement of the Cambridge City Council after having realized the potential of this new field during a time in which molecular biology was predominant. However, it was not until more recent years that the cluster reached its biggest growth. In 2008, the governor of Massachusetts promoted the *Massachusetts Life Sciences Act* that promised to invest 1 billion dollars for the development of the biotech industry. This led to a tremendous increase of jobs, capital flows and buildings that contributed to turn the area in one of the leading US Life Sciences clusters for the number of patent ownership per capita, venture capital funding and number of IPOs. The region is home to many of the leaders in tech and life science (eighteen out of the top twenty drug companies have a major presence in GBA) as well as world-class academic and research institutions as Harvard and MIT. The area hosts approximately 250,000 students across 52 higher education institutions and can rely on the largest concentration of life science researchers in the country, as well as world-class medical facilities, including the top three NIH-funded hospitals. As a result of direct access to top talent, the GBA ecosystem has attracted a dynamic community of investors. More precisely, VC funding is of 2,580 millions of dollars, which represents the 38% of the total funding of United States in GBA, which in turn, makes the area particularly attractive to innovative entrepreneurs.

Expert interviews

For the purposes of our study we conduct a round of *expert interviews* with key informants in the area, chosen as representatives of the different categories of IE's actors and that are engaged in the drug development processes at different stages. Interviews aim at exploring how being embedded in an innovation ecosystem helps the actors to overcome the barriers typical of the *valley of death*. The interviewed organizations were selected in order to ensure that the variety of the ecosystem's population was fairly represented. The sample selection was executed in accordance with four guidelines:

- (1) Ensure an adequate representation of the diverse types of stakeholders involved in the drug development process (large firms, startups research organizations; government institutions);
- (2) Aim for territorial representation capable of identifying the dynamics of actors in drug development processes in the metropolitan area of Greater Boston;

- (3) Focus attention on organizations with a sufficiently long history and experience that can offer insights into the issues related to the *valley of death* in the biopharma industry;
- (4) Maximize the heterogeneity of the drug development stages covered by the sampled organizations.

Expert interviews have been organized and carried out with 18 key informants that occupied leading positions in different organizations located in Greater Boston Area (GBA) having a central role in the drug development innovation process. Specifically, our sample of key informants includes (1) 6 academic institutions with a propulsive role in the biopharma cluster development; (2) 1 regional government agency with a focus on biotech industry; (3) 1 not-for-profit organization with a focus on biotech industry; (4) 3 large biopharmaceutical companies (two that de-localized part of its core R&D activities in the area and one that originated in the area); (5) 1 medium biotech firm; (6) 6 small biotech firms in pre-incubation, incubation, start-up and growth phases respectively (De Cleyn and Braet, 2006). The interviewed experts were selected considering their role and in particular, their ability to answer to questions regarding cooperation practices within their organizations. More specifically, we conducted in-depth interviews with at least one individual in charge of managing R&D cooperation processes within his organization. The list of participants who took part in each interview is reported in Table 1, while the profiles of the represented organizations are illustrated in Table 2. The interviews have been conducted following a narrative approach (Polkinghorne, 1988; Czarniawska, 2004) with the aim of investigating how cooperation practices contribute to surviving the *valley of death* in the biopharmaceutical industry and more specifically, which specific types of public and private initiatives can be useful in this regard (RQ1). The interviews had a duration ranging from 60 to 90 min each, and have been conducted directly by the authors at the organization's facilities and through online meetings following a predefined protocol. Indeed, each interviewee has been preliminary trained to follow the protocol, presenting a sequence of subjects, including:

- (1) Organizations' activities within the process of drug development pipeline;
- (2) The discussion of the most significant barriers preventing research discoveries from becoming new therapies in the industry of drug development, with specific reference to: *lack of funding; lack of technical expertise; lack of support from technology transfer offices; lack of professional incentives to academics; high-risk of failure;*
- (3) Discussion about useful cooperation strategies and initiatives (within their experience in the context of their innovation ecosystem) to overcome the barriers to moving new discoveries forward in drug development pipeline.

By adopting a story-telling technique the respondents were asked to freely share their opinions with a minimum number of interruptions by the interviewer, which allowed us to learn more about actual events and prevent personal views and theoretical perspectives from interfering with data collection efforts. The interviews were recorded and transcribed as part of the data analysis process. In addition, relevant written documents were collected from both the interviewees and other sources, including sampled organizations' annual reports and press releases relating to their participations to specific initiatives and programs under analysis. By combining the above sources of information, we have been able to reconstruct the cooperation practices more commonly used to avoid the valley of death within biopharma industry.

Position	Organization	Stakeholder
Full Professor	MIT Dept. of Chemical Engineering	Academic institution
Associate Dean, Clinical and Translational Research	Harvard University's Clinical and Translational Science Center	Academic institution
Chief Science Officer	Tufts University – Medical Center	Academic institution
Managing Director	Boston Biomedical Innovation Center (B-BIC)	Academic institution
Research Associate	Broad Institute	Academic institution
Co-Director, Community and Team Science	UMass Center for Clinical and Translational Research	Academic institution
General Counsel and Vice-President for Academic and Workforce Program	Massachusetts Life Science Center	Government
Director of Member Engagement	Massachusetts Biotechnology Council (MassBio)	Not-for-Profit Organization
Research Associate	Novartis	Large biopharmaceutical companies (foreign)
Head of R&D Center (Cambridge)	Bristol Myers Squibb	Large biopharmaceutical companies (national)
Senior Vice President, R&D Strategy and External Innovation	Ironwood Pharmaceuticals, Inc.	Large biopharmaceutical companies (local)
Alliance Manager	Alnylam	Medium biotech firm
Chief Executive Officer	Revive-med	Small biotech firm
Chief Executive Officer	Angiex	Pre-incubation stage
Chief Executive Officer	Kymera Therapeutics	Small biotech firm
Chief Executive Officer	QuenchBio	Start-up stage
Chief Executive Officer	Obsidian	Small biotech firm
Chief Executive Officer	Blue Therapeutics	Small biotech firm
		Growth stage

Table 1.
Expert interviews – list of participants

Source(s): Authors' own elaboration

Findings

In general, most of our interviewees reported that their operations fall in the drug discovery stage (MIT, Harvard Catalyst; Tufts; UMass; Broad Institute; MLSC, Revive-Med, Angiex; Kymera; QuenchBio; Blue Therapeutics; MassBio), three in the drug development (Ironwood; Alnylam and Obsidian), while two Big Pharmas were also involved in the process of drug manufacturing (Novartis; Bristol Myers Squibb), which allows for a fair and balanced representation of the actors involved in the drug development process in terms of operations.

As for the most significant barriers preventing research discoveries from becoming new therapies in the industry of drug development, all of our respondents mentioned the lack of funding (18) and the high-risk of failure (18); followed by the lack of technical expertise (9); the lack of support from technology transfer offices (7) and finally, the lack of professional incentives to academics (6) (Table 3).

The core part of the interview aimed at exploring in more detail how the implementation of the initiatives and strategies identified by our expert respondents in the context of their

MIT Department of Chemical Engineering	Formally established as a separate department in 1920, MIT's Chemical Engineering department (ChemE) has not only set the standard for instruction and research in the field, it continues to redefine the discipline's frontiers. With one of three undergraduate programs focusing on chemical-biological engineering for students interested in the emerging biotech and life sciences industries, and two of three graduate programs providing an experiential course of study in chemical engineering practice in collaboration with MIT's Sloan School of management, ChemE at MIT is quite unlike chemical engineering anywhere else. In 2017, for the 29th consecutive year, <i>US News and World Report</i> gave its top rankings to both ChemE's graduate and undergraduate programs among US chemical engineering departments. In 2017, for the seventh straight year, MIT Chemical Engineering has been ranked first in the world by QS World University rankings. More than 10% of the alumni are senior executives of industrial companies. Nearly 25% of the recipients of major awards presented by the American Institute of Chemical Engineers and the American Chemical Society's Murphree Award have been alumni or faculty of MIT. Source: https://cheme.mit.edu
Harvard Catalyst (Harvard University's Clinical and Translational Science Center)	Founded in May 2008, Harvard Catalyst is a shared enterprise of Harvard University, its ten schools and its seventeen Academic Healthcare Centers (AHC), and the Boston College School of Nursing, MIT, Harvard Pilgrim Health Care, and other community partners. Its mission is that of improving human health by establishing collaboration and offering tools, training and technologies to clinical and translational investigators. Harvard Catalyst is a member of the NIH-funded Clinical and Translational Science Award (CTSA) Consortium, and shares tools, technologies, and best practices with other consortium members locally (i.e. Boston University, Tufts University, University of Massachusetts Medical School) and nationally. Source: https://catalyst.harvard.edu/
Tufts University – Medical Center	Tufts Medical Center is a world-leading academic medical center, focused on providing excellent patient care and teaching future doctors. Located in downtown Boston in Chinatown and the Theatre District, Tufts Medical Center is a center for biomedical research and is the principal teaching hospital for Tufts University School of Medicine. Source: https://www.tuftsmedicalcenter.org/
Broad Institute	Broad Institute of MIT and Harvard was founded in 2004 to improve human health by using genomics to advance knowledge in the field of the biology and treatment of human disease, and to contribute to the development for a new generation of therapies. Source: https://www.broadinstitute.org/
Boston Biomedical Innovation Center (B-BIC)	Boston Biomedical Innovation Center (B-BIC) is a life sciences academic institute funded by the National Institutes of Health to increase the return on investment in research. Its mission is that of speeding the translation of research technologies into commercial products accessible for doctors and their patients, for the good of society B-BIC members consists of a consortium of academic medical centers in Boston including Brigham and Women's Hospital, Harvard Medical School, Massachusetts General Hospital, and the Massachusetts Institute of Technology. Source: https://b-bic.org/
UMass Center for Clinical and Translational Research	The University of Massachusetts Center for Clinical and Translational Science (UMCCTS) is based at the UMass Medical School in Worcester and is part of the NIH Clinical and Translational Science Award (CTSA) consortium. As Massachusetts' only public university system (UMass) the center partners with two of the state's safety net clinical systems (UMass Memorial Health Care, UMMHC; Baystate Health), sharing an enduring focus on public engagement and societal benefit. The UMCCTS engages a broad range of collaborators (community agencies, patient groups, foundations, industry, the national NIH/NCATS-sponsored CTSA network). Source: https://www.umassmed.edu/cts/

(continued)

Table 2.
Expert interviews –
represented
organizations

Massachusetts Life Science Center (MLSC)	The Massachusetts Life Sciences Center (MLSC) is an investment agency that supports life sciences innovation, education, research and development, and commercialization. The MLSC is charged with implementing a \$1-billion, state-funded investment initiative to create jobs and support advances that improve health and well-being. The MLSC offers the nation's most comprehensive set of incentives and collaborative programs targeted to the life sciences ecosystem. These programs propel the growth that has made Massachusetts the global leader in life sciences. The MLSC creates new models for collaboration and partners with organizations, both public and private, around the world to promote innovation in the life sciences. Source: www.masslifesciences.com
Massachusetts Biotechnology Council (MassBio)	MassBio is a not-for-profit organization founded in 1985 which represents and offers services and support to organizations and individuals in the life sciences industry located in Massachusetts. MassBio's mission is to advance Massachusetts' leadership in the life sciences to grow the industry, add value to the healthcare system, and improve patient lives. MassBio represents one of the premier global life sciences and healthcare hubs, including 1,300+ affiliated members dedicated to preventing, and treating diseases through transformative science and technology. Source: https://www.massbio.org/
Novartis	Novartis is a Swiss multinational pharmaceutical company based in Basel, Switzerland. It is one of the largest pharmaceutical companies by both market capital and sales. Novartis manufactures the drugs clozapine (Clozaril), diclofenac (Voltaren), carbamazepine (Tegretol), valsartan (Diovan) and imatinib mesylate (Gleevec/Glivec). Additional agents include ciclosporin (Neoral/Sandimmune), letrozole (Femara), methylphenidate (Ritalin), terbinafine (Lamisil), and others. Source: www.novartis.com
Bristol Myers Squibb	Bristol Myers Squibb Company is an American pharmaceutical company, headquartered in New York City, which has located its R&D facilities in Cambridge (USA) Bristol Myers Squibb manufactures prescription pharmaceuticals and biologics in MANY therapeutic areas, including cancer, HIV/AIDS, cardiovascular disease, diabetes, hepatitis, rheumatoid arthritis and psychiatric disorders. Source: https://www.bms.com/
Ironwood Pharmaceuticals, Inc.	Ironwood Pharmaceuticals, Inc. is a biotechnology company. The Company is advancing product opportunities in areas of unmet needs, including irritable bowel syndrome with constipation (IBS C), and chronic idiopathic constipation (CIC), hyperuricemia associated with uncontrolled gout, uncontrolled gastroesophageal reflux disease (uncontrolled GERD), and vascular and fibrotic diseases. It operates in human therapeutics business segment. Its product, linaclotide, is available to adult men and women suffering from IBS C or CIC in the United States under the trademarked name Linzess, and is available to adult men and women suffering from IBS C in certain European countries under the trademarked name Constella. It is also advancing IW-3718, a gastric retentive formulation of a bile acid sequestrant with the potential to provide symptomatic relief in patients with uncontrolled GERD. Its vascular/fibrotic programs include IW-1973 and IW-1701, which targets soluble guanylate cyclase (sGC). Source: www.ironwoodpharma.com
Alnylam	Alnylam is leading the translation of RNA interference (RNAi) into a whole new class of innovative medicines with the potential to transform the lives of patients who have limited or inadequate treatment options. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of a wide range of debilitating diseases with high unmet medical need. Alnylam was founded in 2002 on a bold vision to turn scientific possibility into reality, which is now marked by its robust discovery platform and deep pipeline of investigational medicines, including 4 programs in late-stage clinical development. Source: www.alnylam.com
Obsidian Therapeutics	Obsidian Therapeutics, founded by Atlas Venture in 2016, is a biotech firm based in Cambridge, which develops next-generation cell and gene therapeutics that employ precise exogenous control of transgenes for improved safety and efficacy. Source: https://obsidiantx.com/

Table 2.

(continued)

Angiex	Angiex was founded is a start-up biotech firm that develops vascular-targeted biotherapeutics. Angiex targets fundamental aspects of endothelial biology with a focus on angiogenesis; its lead product is an antibody-drug conjugate therapy for cancer. Angiex was launched with IP from Beth Israel Deaconess Medical Center, is resident at LabCentral in Cambridge, and recently closed a \$3 million Series A round. Angiex founders discovered VEGF-A, have been recognized as the world's leading experts in tumor blood vessel biology, developed new methods for per cell mRNA quantification, founded four companies, and wrote a best-selling diet book. Source: https://angiex.com/
Kymera Therapeutics	Kymera Therapeutics is a seed-stage therapeutics company focused on targeting the traditionally undruggable proteome within key pathways involved in inflammation, immunity, and oncology. Its approach combines the power of effective genetic silencing with the flexibility and drug-like properties of small molecules to harness the body's innate protein regulation machinery. Source: https://labcentral.org/resident-companies/kymera/
ReviveMed	ReviveMed is a precision-medicine platform that leverages the data from small molecules or metabolites. Metabolomics (which is the study of small molecules such as glucose or cholesterol) is essential for developing the right therapeutics for the right patients. However, because identifying a large set of metabolites for each patient is costly and slow, metabolomic data has been under-utilized – and the firm aim at filling this gap. ReviveMed technology, which was developed at MIT and published in Nature Methods, uniquely overcomes the difficulty of using a large set of metabolomic data, and transform these data into actionable insight. Currently, they are working with a few strategic partners from leading pharma/biotech companies, while developing their own metabolomics based therapeutics. Source: www.revive-med.com
Blue Therapeutics	Blue Therapeutics is an early-stage biotechnology company focused on developing potent, non-narcotic painkillers. By using their novel GPCR heterodimer targeting approach, the company has been able to achieve up to 50x the painkilling potency of morphine, but without addictive side effects. Their lead clinical candidate, BLUE-181, is currently advancing through IND-enabling studies in support of first-in-human clinical trials. Source: https://www.bluetherapeutics.com/
QuenchBio	Quench Bio is a biotechnology company leveraging new insights into gasdermin biology and innate immunity to develop medicines for severe inflammatory diseases. The company targets the pore-forming protein Gasdermin D, a central player in both pyroptosis and NETosis pathways that mediates the release of inflammatory cytokines, alarmins, DNA and NETs. Source: https://quenchbio.com/

Table 2.

innovation ecosystem, could contribute to reducing the barriers in drug development industry leading to the *valley of death*. The following sub-sections illustrate main findings relative to specific initiatives and programs – at the ecosystem level – to cope with each of the barriers to moving new discoveries forward in drug development pipeline, as reported by experts. In some cases, the experts made explicit reference to specific and existing initiatives, in other cases the discussion was in more general terms about potential strategies, without making explicit reference to existing programs.

Strategic initiatives to compensate the lack of funding

With regard to the lack of funding, it is noteworthy that there are some specific therapeutics areas, as neurodegenerative diseases, that experience a significant funding gap due to their high level of uncertainty. These types of diseases, in fact, are usually difficult to treat through drug therapies, which makes them less attractive to the eyes of investors. In order to reduce this specific barrier, the Massachusetts Life Science Center (MLSC) i.e. the Government arm that supports life sciences in innovation has promoted the establishment of thematic associations, as in the case of the Neuroscience Consortium, which was created with the aim of filling the gaps in research funds through the organization of periodical operative meetings

	A. Lack of fundings	B. Lack of technical expertise	C. Lack of support from technology transfer offices	D. Lack of professional incentives to academics	E. High risk of failure
MIT Department of Chemical Engineering	✓	✓	✓	✓	✓
Harvard Catalyst	✓	✓	✓		✓
Tufts University – Medical Center	✓				✓
Broad Institute	✓				✓
B-BIC	✓			✓	✓
UMass Center for Clinical and Translational Research	✓		✓		✓
Massachusetts Life Science Center (MLSC)	✓	✓	✓	✓	✓
MassBio	✓		✓		✓
Novartis	✓	✓	✓	✓	✓
Bristol Myers Squibb	✓	✓			✓
Ironwood Pharmaceuticals, Inc.	✓	✓	✓	✓	✓
Alnylam	✓	✓		✓	✓
Obsidian Therapeutics	✓	✓			✓
Angix	✓				✓
Kymera Therapeutics	✓				✓
ReviveMed	✓				✓
Blue Therapeutics	✓				✓
QuenchBio	✓	✓			✓

Table 3.
Expert
interviews-results

between different stakeholders in the field of neurodegenerative diseases, including venture capital and business angels. In so doing, the government even without providing direct funding to research, it is still able to manage the direction of private capitals towards less attracting research areas by promoting a continuous dialogue among investors and researchers. As reported by MLSC General Counsel: “Only by bringing periodically around the same table investors, researchers and companies it is possible to shed light on the reasons for a mismatch between market and research expectations and try to address it.” Similarly, the Broad Institute has taken initiative in order to shed light on less appealing therapeutic areas by launching the Rare Disease Days is an international event held every year in Cambridge with the aim of raising awareness within the ecosystem about the need for research on rare diseases having a significant impact on entire populations. As our Broad Institute respondent remarked “each year the Broad Institute organizes a focus on Rare Disease event showcasing rare disease research in our ecosystem community (. . .) which is in

line with Broad Institute commitment to investigating the genetic roots of rare diseases and to implementing those discoveries to ultimately develop new and effective therapies.” From a different perspective, in order to contribute to the lack of funding affecting the innovation process in drug development industry, the Chief Science Officer (CSO) at Tufts Medical Center launched the Office of Business Development and Industry Translation (ORBIT) with the aim of accelerating innovations’ commercialization in the marketplace by providing funding opportunities for both early and later stage innovations. Indeed, ORBIT exposes Tufts Medical Center’s investigators to new business opportunities by establishing partnerships with both industry and investment communities with the aim of launching new startups. Thanks to a dedicated industry business development team, who is in charge of identifying strategic matching opportunities between academia and industry’s pipelines to be translated into profitable innovations whether these are at early or late stages of development. Indeed, as Tufts Medical Center CSO reported “Our research portfolio provides a wealth of high value prospects for partnerships, ranging from late stage inventions that can be quickly turned into valid products, to promising innovations in earlier stages of development which are ready to partner for focused, 12-to-18-months proof of concept studies.” Furthermore, a board of external venture capitalists, private investors and entrepreneurs i.e. the Innovation and Venture Capital and Entrepreneurism Steering Committee (INVEST) was established as part of ORBIT in 2012, with the aim of bridging Tufts Medical Center’s most commercially valuable innovations into market appealing investment opportunities. Finally, the UMass Co-Director, Community and Team Science mentioned their Small Pilot and Research Knowledge Program (SPARK), which provides pilot funding for clinical and translational research and access to the Clinical Research Center and other UMCCTS cores. The ultimate goal is that of “supporting studies with an impact in terms of clinical care and research methodologies, supporting students and trainees, and providing access to funds for pilot and preliminary data for external grant submissions.”

Strategic initiatives to compensate the lack of technical expertise

As for the lack of technical expertise characterizing most of basic researchers while moving their discoveries through the pipeline, our results showed different types of strategies for researchers and scientists to find complementary skills within the ecosystem. On the one hand, the establishment of agreements for the access and use of external infrastructures, as in the case of incubators and accelerators, would provide significant advantages in terms of knowledge transfer resulting from the spillover effect of the environment provided by hosting organizations. Apart from the well-known advantages in terms of visibility and costs efficiencies deriving from renting a space within an innovation center, it is also the opportunity of casual encounters with industry operators that enhances the chance of knowledge exchange. Also, incubators and accelerators generally offer services of business consultancy to scientists and engineers that lack capabilities in this field. A few respondents mentioned LabCentral in Kendall Square (Angiex) or the Martin Trust Center at the MIT (ReviveMed) as beneficial to compensate their lack of expertise in specific areas as these structures contribute to “enhance connectivity among different disciplines and sectors and ultimately to smoothen knowledge disabilities and promote know-how trading,” quoting Angiex CEO and co-founder. The importance of this micro-proximity was also confirmed by the CEO of the newly formed Quench Bio who, with reference to his decision to establish in Cambridge, said “Biotech companies in Boston Area are continuously getting launched, overturned, or absorbed, but the ecosystem persists since the people tend to stick around. This facilitates to recruit for the next startup idea, and it generates a multigenerational brain trust, available for free consulting in the queue for coffee.” More in general, as reported by the Head of the newly established Cambridge R&D Center of Bristol Myers Squibb it is important to establish partnerships with heterogeneous partners where micro-proximity is a value

added, which explains the company's decision to establish an R&D center in Cambridge: "Bristol Myers Squibb Cambridge is different since locating at the heart of this life sciences ecosystem permits us to foster alliances and cooperation within academia, research institutions, hospitals and biotech firms (...) each of these potential partners has niche scientific or technological competencies that can support us in continuing to move research along the pipeline to find answers for critical and unmet patients' needs." Interestingly, it also emerged that Venture Capital and Seed Investments relationships *per se* turn out to be ground for the transfer of new knowledge due to the complementarity of the skills between scientists' scientific know-how and investors' support for business operations. As reported by one of the interviewed experts (Kymera's CEO) especially in the case of funding VC, the start-up or the academic spinoff is usually provided with support on every aspect of the business management, including assistance for hiring the right people and for seeking potential partnerships to exploit the developed innovation at its best. As affirmed by Kymera's CEO "close ties with investors play a key role in fostering relationships with investors and living in the same space makes a huge difference. Proximity allows to have more frequent interactions with a network of operators in the area that may eventually function as a talent validation device, which turns out to be particularly useful for risky operations as in the case of VC and seed fund." As a side note, while exploring the relationship between Kymera and Atlas Venture – a VC company headquartered in Kendall Square – it emerged that it is not uncommon for VCs to host their portfolio companies in their office spaces. Also, especially in the case of VC founders, relationships tend to be long-term, thus implying an investment not only in money but also in time, which – as reported by Alnylam's CEO – "allows for a more efficient corporate resource management." As a consequence, the proximity to VC would enhance learning opportunities for scientists about how surviving the valley of death. Finally, while interviewing the Associate Dean of the Harvard Catalyst, i.e. the Harvard University's Clinical and Translational Science Center, it emerged that initiatives and programs in cooperation with local business schools are particularly useful in order to overcome the lack of technical expertise in the drug development process. By way of illustration, the Translational Innovator, a program launched by Harvard Catalyst in partnership with Harvard Business School, provides investigators with support during the early stages of a project in terms of project management, grant writing programs and pilot funding to improve the conduct of their research thanks to a dedicated team. Indeed, to quote our expert: "our team actively studies the research process and conduct of the innovation process, including potential collaborative partnerships. Investigators are provided with new technologies and facilities, to advance their research and create successful new companies."

Strategic initiatives to compensate the lack of support from technology transfer offices

To counterbalance the lack of support from technology transfer offices – our results highlight the key role of business support infrastructure as accelerators and incubators which, besides providing office desks and lab equipment, have also dedicated staff for business consultancy in terms of IP regulations and commercialization channels. Indeed, incubators and accelerators generally offer services of business consultancy to scientists and engineers that lack capabilities in this field by establishing ad hoc partnerships with the scientists' home institutions. In addition to strategic partnerships with business support structures, our results emphasized the importance of mentorship networks to compensate the lack of support from TTOs in providing continuous support to move the idea from the university to the marketplace. In this vein, an interesting initiative is the one that emerged from the conversation with the Associate Dean of the Harvard Catalyst, who mentioned the Clinical and Translational Mentor Database, a program dedicated to Harvard medical students and researchers who can skim mentorship opportunities by looking at research projects conducted at Harvard Medical School in more than 30 areas, and contact the principal

investigators of their areas of concern. As the Dean reported “The Clinical and Translational Mentor Database program allows investigators to be provided with a continuous support by experts in their fields, to learn from previous experience in research commercialization and enlarge their business network” thus replacing TTOs in moving drug discoveries outside the boundaries of the university. Similarly, the Director of Member Engagement from MassBio referred to MassConnect as a useful initiative to compensate the lack of support from TTOs dedicated to their affiliated academic members. More specifically, the program provides the possibility for investigators to be involved in a two-month mentorship by industry experts who provide feedback about the commercial feasibility of their research-based business ideas. As reported by our interviewee “Researchers receive invaluable advice and coaching on defining their value proposition, writing pitches, and establishing business networks.” In addition, the program provides expertise from selected MBA students with life science knowledge to serve as project managers for those applying to MassConnect. The validity of the program was also confirmed by one of our interviewees, whose startup (BlueTherapeutics) took part to MassConnect, as he reported “We have formed an heterogeneous and solid team thanks to MassConnect. We took part in many accelerator and incubator programs, and we particularly appreciated the possibility to have ‘focus group’ sessions on specific issues which worked very well for both us and our mentors.”

Strategic initiatives to compensate the lack of professional incentives to academics

As for the lack of professional incentives to academics, most experts referred to MIT as a case of best practice in terms of stimulating not only students, but also academic staff to start their own businesses. MIT has a longstanding tradition in stimulating academic entrepreneurship. One of our experts, the MIT Dean of Chemical Department is himself a serial entrepreneur, while the CEO of Revive-med reported that her business is a MIT spinoff. MIT supports academic entrepreneurship in different ways. In particular, it emerged that academic staff can devote one working day to their professional activities, without being subject to additional taxes on their salaries. Also, for those researchers willing to patent an innovation deriving from research activities, MIT covers all initial costs associated to the patent application and registration, as reported by Revive-Med CEO. Furthermore, the Managing Director at the Boston Biomedical Innovation Center referred to the DRIVE program as one of their most successful initiatives in terms of providing academic staff with the required incentives to move their research discoveries along the pipeline. Indeed, the program provide faculty from the B-BIC academic member institutions with investments up to \$350,000 for and translational research “including regulatory, reimbursement, and business development aspects that are part of an overall commercialization strategy” as the interviewee reported.

Strategic initiatives to compensate the high-risk of failure

Finally, as for the high-risk of failure characterizing the drug development process, main results showed the importance of initiatives aimed at sharing results across the different ecosystem’s actors during the pre-competitive phase. One of the main issues is that failures in the biopharma industry are not generally published and therefore, bringing around the table different stakeholders allows avoiding the duplication of efforts, including mistakes. As a way of illustration, the Alliance Manager from Ironwood, reported his experience in arranging periodical target specific symposia for sharing pre-competitive knowledge with competitors and major research actors in the area (e.g. Novartis, MIT, Harvard and Tufts) for the development of a specific molecule. These meetings, which have a grassroots origin (from company scientists’ initiative), take place in an informal way. Typically these meetings can be part of “a small poster session, with five to seven participants and a couple of speakers. One interesting point is that, despite the high confidentiality of the information exchanged, there

is no need of non-disclosure formal agreements due to the level of trust and mutual understanding that naturally emerges among the participants.” With regards to Co-participation in Public Thematic Consortia, as in the case of the abovementioned “Neuroscience Consortium” - it emerged that this practice was particularly important even for reducing this type of barrier as it allows the “sharing of experiences in the pre-commercial phase,” i.e. target identification and validation. Table 4 summarizes main results from the emerging from the experts interviews.

In summary, while discussing possible initiatives and strategies that actors can implement to overcome the barriers to moving new discoveries forward in drug development pipeline, the respondents reported a variety of strategies and initiatives reflecting, in each

A. Lack of fundings	<ol style="list-style-type: none"> (1) Promoting thematic events and permanent thematic associations to shed light on less appealing diseases within the ecosystem community, including academic, financial, industry and institutional players (e.g. <i>Rare Disease Days; Neuroscience Consortium</i>) (2) Providing funding opportunities by identifying strategic matching opportunities between academic and industry’s pipelines both at early or late stages of development (e.g. <i>ORBIT; SPARK</i>)
B. Lack of technical expertise	<ol style="list-style-type: none"> (1) Provision of business support structures offering workspace and business consultancy services to enhance the chance of knowledge trading and smoothen the knowledge disabilities (e.g. <i>LabCentral; Martin Trust Center at the MIT</i>) (2) Engaging investors in activities of management support to their portfolio companies; (3) Promoting the participation of researchers to programs in cooperation with Business Schools to receive support during the early stages of a project in terms of project management, grant writing programs and pilot funding to improve the conduct of their research (e.g. <i>Translational Innovator; MassConnect</i>)
C. Lack of support from technology transfer offices	<ol style="list-style-type: none"> (1) Promoting the location of academic spinoffs in business support structures with dedicated staff for business consultancy in terms of IP regulations and commercialization channels (e.g. <i>LabCentral; Martin Trust Center at the MIT</i>) (2) Participation to mentorship networks to move an academic idea outside from the universities’ boundaries to the marketplace by learning from previous and valuable experience in research commercialization and enlarge their business network (e.g. <i>Clinical and Translational Mentor Database; MassConnect</i>) (3) Promoting the participation of investigators to programs in cooperation with Business Schools to receive support from MBA students with life science knowledge to serve as project managers (e.g. <i>MassConnect</i>)
D. Lack of professional incentives to academics	<ol style="list-style-type: none"> (1) University regulations allowing the use of one working days for academics to be dedicated to entrepreneurial activities, without being subject to additional taxes on their salaries (e.g. <i>MIT policies</i>) (2) University support in covering all initial costs associated to the patent application and registration related to their affiliated academic staff discoveries and innovations (e.g. <i>MIT policies</i>) (3) Dedicated funds for academic faculty to be invested in translational research (e.g. <i>DRIVE</i>)
E. High risk of failure	<ol style="list-style-type: none"> (1) Promoting periodical target specific symposia and informal meetings for sharing pre-competitive knowledge among competitors and major research actors in the area (e.g. <i>Ironwood poster session; Neuroscience Consortium</i>)

Table 4.
Main initiatives and strategies, according to the main barriers

case, a leadership role exerted by one of the innovation ecosystems' stakeholders. These include: (a) Industry-driven strategy i.e. (1) *thematic symposia among competitors*; (2) *strategic location of R&D centers within the ecosystem* (b) Government-driven strategy i.e. (3) *public thematic consortia*, (4) *incubators and accelerators*; (c) Investors-driven strategy i.e. (5) *provision of management support from investors*; (d) University-driven strategy i.e. (6) *programs in cooperation with business schools*; (7) *provision of funds dedicated to academic staff for translational research* (8) *establishment of mentorship networks*, (9) *academic policies supporting patenting activities* and finally, (10) *the promotion of an entrepreneurial culture within universities* (MIT academic staff and patenting regulations) (Table 5).

Discussions

In general, from the results of our analysis it emerged a significant high perception of the “high risk of failure” drug development innovation process as a major cause of the *valley of death*, coherently with the arguments made by Zhang and Surapaneni (2012), Cummings et al. (2014), and Adams (2012), about the high pressure on companies that lead them to carefully select therapeutics areas based on their market competitiveness. Another highly perceived cause to the *valley of the death*, refers to the researchers’ “lack of technical expertise” that are necessary to move their research from bench to bedside, including the ability of repurposing failed experiments into new opportunities of treatment (Roberts et al., 2012). Secondly, the in-depth discussion of strategies to overcome main barriers within the drug development process, confirm the importance of conducting cooperative practices to survive the *valley of death* (Ekins et al. 2011; Portilla et al., 2010; Albats and Aleksander, 2017; Hudson and Khazragui. 2013; Jackson, 2011) with specific regard to those practices that emphasize the cooperation between actors of different nature, in the context of an innovation ecosystem (Jackson, 2011; Frenkel and Maital, 2014) for the purposes of knowledge transfer (Owen Smith and Powell, 2004); funding opportunities (Gilding et al., 2020). In contrast with Hopkins et al. (2019), our study suggests the effectiveness synergistic relationships between state and non-state actors. However, differently from previous studies, our paper contributes to extant literature by shedding light on the nature of the specific cooperative initiatives that reduce the barriers in drug development and help to survive the *valley of the death*. More specifically, we suggest that while *thematic symposia among competitors* and *public thematic consortia* would contribute to reduce the *lack of funding* and the *high risk of failure* in drug development by, on the hand, shedding light on rare diseases or less market appealing therapeutic areas in need of

Industry-driven	Government-driven	Investors-driven	University-driven
(1) Thematic symposia among competitors; (2) Strategic location of R&D centers within the ecosystem	(3) Public thematic consortia and; (4) Incubators and accelerators;	(5) Provision of management support from investors	(6) Programs in cooperation with business schools; (7) Provision of funds dedicated to academic staff for translational research; (8) Establishment of mentorship networks, (9) Academic policies supporting patenting activities and finally, (10) The promotion of an entrepreneurial culture within universities (MIT academic staff and patenting regulations)

Table 5. Main initiatives and strategies, according to the IE’s actor leadership role

support, by gathering diverse actors that can contribute from different angles to move discoveries along the pipeline. On the other hand, such initiatives contribute to reduce the rates of failures by allowing to share key knowledge in the precommercial phase among competitors working the same area, which can ultimately avoid significant losses of money and time. Also, initiatives identifying *strategic matching opportunities (programs of business demand – research supply matching)* between academic and industry’s pipelines – whether these are at early or late stages of development – were suggested as reducing issues related to the lack of funding. Secondly, the provision of business support structures offering workspace and business consultancy services could compensate for the *lack of support from technology transfer offices* and the *lack of technical expertise* by enhancing the chance of knowledge trading ad *casual encounters* for those actors found in micro-proximity, smoothening the knowledge disabilities by providing assistance in terms of IP regulations and commercialization channels. Similarly, the participation of academic researchers to programs in cooperation with local business schools to receive support during the early stages can also help reducing these two barriers as these programs allow to receive support in terms of project management. With specific regard to the *lack of support from technology transfer offices*, our results also suggest the establishment of mentorship networks as a valuable support to move an academic idea outside from the universities’ boundaries to the marketplace as it allows learning from previous and valuable experience in research commercialization and enlarge researchers’ business network for future market opportunities. Finally, *academic policies supporting patenting activities*, the provision of dedicated funds for academic faculty to be invested in pilot translational research, and the adjustment of university regulations in order to allow academic staff to dedicate working time to their entrepreneurial activities (i.e. promotion of an entrepreneurial culture within universities), be useful to reduce the *lack of professional incentives to academics*. More specifically, we derive the following propositions (Figure 2):

- (1) The lack of funding can be reduced by the promotion of multi-stakeholder periodical meetings through the establishment of permanent thematic associations or consortia, orchestrated by a government institutions and by university-led programs matching research offer and business demand.

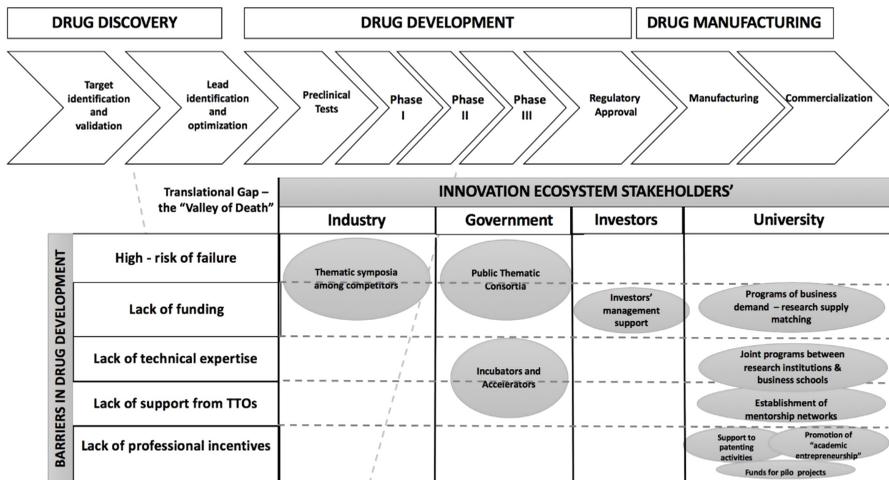


Figure 2. Surviving the valley of death within an innovation ecosystem

- (2) The lack of technical expertise can be compensated by the establishment of agreements between academia and business support structures (as incubators and accelerators) for the access and use of external infrastructures and provision of business consultancy services, as well as by the proximity to VC for the provision of business assistance, besides capital and the establishment of joint programs between research centers and local business schools.
- (3) The lack of support from technology transfer offices can be smoothened through the establishment of mentorship networks accessible to researchers, and agreements between research centers and local business schools and/or business support structures (as incubators and accelerators) that can provide consultancy in terms of IP regulations and networking opportunities.
- (4) The lack of professional incentives to academics, can be addressed by promoting a “culture of academic entrepreneurship” within universities by designing accurate academic policies to stimulate commercialization of research results and by providing dedicated funds for academic faculty to be invested in pilot translational research.
- (5) The high-risk of failure characterizing the drug development process can be reduced through the establishment of *thematic symposia among competitors* or *public thematic consortia* to share pre-competitive knowledge.

Conclusions

The process of biotech-based drug development is among the most complex and riskiest industrial processes due to a significant number of barriers preventing research discoveries from becoming new therapies namely, the lack of funding, the lack of technical expertise, the lack of support from technology transfer offices, lack of professional incentives to academics and the high risk of failure. This paper aims to explore the nature of initiatives and strategies of inter-organizational cooperation to cross the *valley of death* in the biopharma industry. To this aim, we conducted an exploratory case study in the Biopharma Innovation Ecosystem in Greater Boston Area (USA), which is one of the oldest, and most successful IE in the US, specialized in the Biopharma domain, by conducting a round of expert interviews with key informants in the area, chosen as representatives of the different types of actors engaged in the drug development processes at different stages. Main findings suggest that cooperation can contribute to surviving the valley of death by reducing the barriers within the drug development pipeline through the promotion of strategic relationships among actors of different nature, including the establishment of government-led thematic associations or consortia, agreements between university and business support structures, joint programs between research institutions and local business schools, dedicated funds for academic pilot projects and proximity to venture capitalist, and the promotion of a general culture of academic entrepreneurship within universities. We believe that this paper contributes to the literature by shedding light on the nature of the specific cooperative initiatives to reduce the barriers in drug development and help concerned actors to survive the *valley of the death*.

In particular, our study is the first attempt to analyze the role of IE to overcome the valley of death. Indeed, most studies examine the IE in biotech industry, the general exploration of the role of IE (Owen-Smith and Powell, 2004; Gilding *et al.*, 2020) without considering the specific initiatives that ecosystems actors can implement to cross the valley of death. Moreover, while extant literature tends to focus on one type of relationship of IE at a time (Hopkins *et al.*, 2019), our study identifies specific network-driven strategies and initiatives by considering the whole community of IE actors simultaneously and their leadership role along the different strategies, thus allowing for a more comprehensive view about the implications of being embedded in an ecosystem. This work carries also some significant implications for

managers, by informing about which cooperation practices could help their companies achieving better results for the commercialization of their innovation avoiding the valley, including co-opetition practices to avoid the replication of failures. The study has also implications for policy making, by illustrating the programs and strategies that local institutions can implement to help their community of actors working in biopharma industry to achieve efficiencies in their innovation processes, with specific regard to those programs that promote dialogues among stakeholders of different nature and contribute to fill funding gaps in less competitive therapeutics areas. Finally, Technology Transfer Offices should adopt a more strategic approach in promoting partnerships with public and private partners within the ecosystem and, more in general, having a facilitator role in incentivizing relationships and promoting the academic policy tools to move drug discoveries beyond the valley of death, including the establishment of more progressive IP policies to encourage early stage uptake and commercialization of university IP. However, this work is not free from limitations. First, the panel of expert interviews could be expanded to include new categories of stakeholders participating in the process. Secondly, findings are not generalizable as these refer to the specific case of biopharmaceutical industry. Future research is invited to overcome the above limitations.

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