Biopharmaceutical innovation ecosystems: a theoretical model and the case of Lombardy

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Abstract

Purpose – The purpose of this paper is to examine value creation pathways in biopharma innovation ecosystems (IEs) by establishing a theoretical model and providing insights into the Lombardy case.

Methodology – A two-step research strategy has been adopted. First, a panel study of the top IE stakeholder representatives was organized through semistructured interviews. Concurrently, a quantitative phase was carried out by collecting data to recognize the value creation pathways within the Lombardy biopharma IE.

Findings – The major paper findings lie in the developed theoretical IE model and its application to the Lombardy case, which provides a common basis of analysis for different biopharma IEs, e.g., Boston-Cambridge, San Francisco Bay area, Cambridge UK. The final thesis of the paper advocates the idea that although the Boston-Cambridge economic and technical figures show an IE that is extraordinarily different from the Lombardy IE, the latter has evolved based on its inherent limits and strengths and succeeded in deploying remarkable value creation pathways toward niche-biopharma markets and health and med-tech markets.

Value – This paper represents one of the first attempts to systematically and longitudinally analyze biopharma IE from a holistic perspective. The holistic and systemic framework developed in the paper can help to understand the potential of the IE approach for the biopharmaceutical industry. In this context, it is notable that multiplayer concurrent engagement through specific comparative advantages is an essential requirement for pursuing cutting-edge innovation within the biopharma industry.

1 Introduction

Over the past three decades, a breakthrough transformation has occurred in the world of pharmacology and drug development. By becoming the most prominent component of the life sciences, biotechnology has dramatically shifted the focus of the incumbent pharma industry from the traditional "small molecules", which have long been the basis for totally synthesized drugs, to new "large molecules" (or biologics), which are classified as proteins having a therapeutic effect. Biologics - e.g., biodrugs, advanced therapies, monoclonal antibodies, vaccines, and recombinant proteins - have triggered the advent of the new biopharma industry, which has disrupted pharmacology and drug development with the introduction of biological sources, especially those produced through biotechnology. Hence, the biopharma industry has grown with the view of "more for less", i.e., high prices for fewer patients, different from the traditional pharma concept of "less for more", i.e., low prices for the mass market (The European House – Ambrosetti, 2020). Today, the biopharma sector is projected to grow with a compound annual growth rate (CAGR) of 13.8% from 2018 to 2025 and a ultimate value target of $526,008 million (Allied market research, 2018).

Biopharma companies are innovation-driven, strongly science-based, nimble, and very accepting of risk, and thus the innovation processes within these firms are unique and far more radical than those in companies from other industries.

In broad terms, innovation is increasingly becoming a critical component of all companies. Striving to drive their innovation processes forward, corporations have shifted away from traditional, closed innovation models toward open innovation. However, the open innovation approach often delivers an overabundance of ideas that can be difficult for enterprises to navigate. To avoid having an overwhelming flow of ideas challenge the innovation system, corporations began to focus their innovative efforts on one - or a limited number of - particular location where several stakeholders are based or where the company is keen to locate its headquarters. This latter approach builds what is called an innovation ecosystem (IE), in which large companies become nodes in a larger network rather than a single player carrying breakthrough ideas to the market. These networks thrive by pushing fewer, but more focused, emerging ideas toward the technology frontier and exploiting the cross-fertilization of resources enabled by multistakeholder proximity within the IE.

Although IEs have existed for some time, their approaches must adapt to changes in the 21st century global context. The unique characteristics of the biopharma industry recommend it as an interesting research field for investigating this renewed IE approach. Functioning within a tacit knowledge-intensive industry, biopharma companies strive to leverage complex and intense science-based interactions to create useful synergies. Thus, partnerships with IE stakeholders - e.g., startups, university research centers, and venture capitalists - are increasingly required in this industry.

Due to this highly complex and dynamic context, the investigation of the innovation pathways within IEs is significant for both scholars and practitioners. Hence, this work aims to answer the following research questions: (RQ1) which comparative advantages are required for stakeholders to pursue cutting-edge innovations by engaging with the biopharma IE; and (RQ2) how does the IE value creation pathway toward biopharma markets evolve in conjunction with specific IE driving forces. For this purpose, this paper follows a three-section research framework. The first section traces the literature review based on a thorough analysis of the theoretical background of IEs, their different research perspectives, biopharma IE models, and the limits of the current literature. The second section reports the extensive methodology at the basis of this research. The last section aims to discuss the research outcomes by establishing a theoretical IE model and reviewing it through the Lombardy biopharma IE case study.

2 Literature Review
The IE literature review is extensive and articulated in different fields. Therefore, to develop a valuable literature review for this purpose of this work, this section has been divided into three parts: the IE concept, the biopharma framework, and the limits of the existing literature.

2.1  The IE concept

Everett Rogers (1962), a professor of communication studies, was the first to emphasize that innovation diffuses through a social system. The IE literature shows a greater appreciation of the connections among the many innovation actors. Enumerating the interactions among the IE's component organizations highlights the richness and diversity of players that can, in principle, give rise to emergent behavior.

In this respect, locations with a dense, interconnected set of innovators and stakeholders have existed since the 18th century. If we draw on the metaphor of a biological ecosystem, local IEs refer to the complex, dynamic systems within which innovators operate—systems characterized by an array of interacting actors, resources, relationships, and conditions working together to either enable or impede innovation (Hoffecker, 2018).

Jackson (2011) defines IEs as “the complex relationships that are formed between actors or entities whose functional goal is to enable technology development and innovation”. These actors are either geographically localized or strategically linked to focus on developing a specific technology. Autio and Thomas (2014) proposed another commonly accepted definition: “a network of interconnected organizations, organized around a focal firm or a platform, and incorporating both production and use side participants, and focusing on the development of new value through innovation”. According to these definitions, IE comprises two distinct but largely separated economies: the research economy, which is driven by fundamental research, and the commercial economy, which is driven by the marketplace (Oh, et al., 2016). Under the MIT definition of innovation as “taking ideas from inception to impact” (Murray and Budden, 2019), IE engagement is focused on the utilization of new opportunities and the collation of knowledge and resources to generate "new-to-the-world" ideas. By establishing relationships among key stakeholders - entrepreneurs, government, risk capital, universities, and corporations - in the innovation space, a corporation can deploy its comparative advantages and position itself as a competitor on an ever-changing and growing global scale of innovation. To sustain this engagement, all stakeholders need to evolve, adapt, and reimagine their approach (Murray and Budden 2019).

The aforementioned authors are just a few of many that have explored innovation dynamics through the IE approach. In fact, over time, the number of publications aiming to provide a contribution to the IE literature has increased at an exponential rate (Audretsch et al., 2019). Figure 1 shows the trend in the number of publications citing the term “innovation ecosystem” in their abstracts or titles since 1997. These papers feature different perspectives, ranging from context to relationships, and embrace different dimensions of analysis.

The most current literature has contributed to the scholarly discourse with the following research strands.

According to the regional ecosystem approach (Acs et al., 2014, 2017), spatial boundaries are an important variable for describing the ecosystem based on its economic activities. In pursuing these activities, each player leverages local resources – e.g., physical, human, and intellectual – complementing its core competencies. Scholars studying regional ecosystems argue that large firms, academic institutions and government bodies are key stakeholders for developing a functional system that focuses on breakthrough innovation (Fritsch and Slavtchev, 2011; Cooke and Leydesdorf, 2006; Asheim and Isaksen, 2002; Lau and Lo, 2015). Therefore, when these stakeholders share their comparative advantages, they create value beyond what any single firm focused on a closed innovation system could have created alone (Adner, 2006).

Headlines such as "Shanghai Scores as Top New Tech Hub in the World as Silicon Valley Gap Grows” (Fannin, 2014) and "Munich edges out London as Europe’s top tech city” (Ranger, 2014) offer comparisons of regional economies exploiting valuable resources within spatial boundaries. These geographical shifts in technology development activity support the idea that funds and talent do not suffice to keep a region at the technology frontier. Moreover, the regional ecosystem approach suggests that a broader support structure underpinning a well-connected innovation system is needed to spur a favorable pathway to value creation.

In this regard, Vendula and Kim (2019) identify the five general dimensions that most studies consider while exploring the influence of context on new venture performance: i) supportive entrepreneurial culture, ii) access to finance, iii) access to human capital, iv) innovation capacity, and v) formal support organizations for entrepreneurs. Acs et al. (2014) identify 14 elements for ranking countries and regions on the basis of their innovation and entrepreneurial capacities, e.g., ability to identify and develop entrepreneurial opportunities, startup skills, risk acceptance, cultural support, human capital/expertise, competitiveness of entrepreneurial products/services, and availability of risk capital.

A second strand of analysis refers to the entrepreneurial ecosystem approach (Audretsch and Belitski, 2017). This approach has been defined as “a set of interdependent actors and factors coordinated in such a way that they enable productive entrepreneurship” (Stam, 2015). In contrast to other
2.2 The biopharma framework

The advent of the biopharma industry has boosted some specific features of the incumbent pharma industry toward their limits. In fact, a stronger renewed biopharma need to address multidisciplinary competences, tacit knowledge, and environmental complexity exploration and exploitation has restored the requirement that a higher number of interconnected firms and institutions participate at different stages and with different roles in the biodrug development process.

Therefore, referring to the above IE classification, it appears in the literature that the most recognized model in the biopharma industry is the corporate model (Bianchi et al., 2011; Khilji et al., 2006; Chiaroni et al., 2009; Weiblen and Chesbrough, 2015). In fact, authors researching these topics tend to focus on how biopharma companies have implemented hierarchy-driven governance to exchange technologies and knowledge with external organizations in different classes - e.g., universities, competitors - in the different stages of the R&D and innovation development process - e.g., drug discovery and drug development (Bianchi et al., 2011).

To better describe this corporate model, different sequential stages are identified: basic research, innovation and invention, early-stage technology development, product development, and production and marketing (Haour, 2004). Two important features of the model are that i) it outlines various important activities in its life cycle - e.g., patenting, U.S. Federal Drug Administration (FDA) approval, clinical trials, product design, production, and marketing - and ii) it directly refers to at least two critical functions, R&D and funding and financing, indirectly indicating a third one, the use of collaboration to keep companies funded and active in research. This model also highlights the relevance of different corporate functions involved in...
the two sequential biodrug discovery phases, the prediscovery and the postdiscovery phases, in terms of pursuing patents and inventions and building a viable business (Khilji et al., 2006).

Moreover, in relation to this biopharma industry model, scholars and practitioners usually distinguish between (1) those firms known as product biotech that are willing to directly market their own drugs; (2) all other firms, usually referred to as platform biotech, which provide support technologies or carry out specific activities in the innovation process; and (3) universities and research centers, which support advances in basic technologies and biotech-related scientific disciplines (Bianchi et al., 2012).

In a further development of the aforementioned model, another dimension similar to the IE approach tries to add new stakeholders to the process. In this respect, Rose et al. (2015) depict a 'village' and emphasize the role of patient advocacy organizations (PAOs) in the system. ‘Village’ should be recognized as a pharma ecosystem where risk and innovation in biodrug discovery are shared and successfully managed by commercial entities, both large and small, and entrepreneurs in academia and biotech. Criteria other than clinical and scientific expertise may be considered in the choice of partners, specifically time and availability for face-to-face interaction, whenever possible.

Thus, geographic location emerges as a criterion that allows people to meet, engage and work collaboratively, but cooperation cannot ignore the definition of scientific objectives addressed by PAOs. In this respect, science and the ability to positively impact patients are important motivators that need to be shared by cooperating partners (Rose, 2015).

Finally, a more recent dimension of analysis explores how firms organize themselves and modify their management practices to facilitate the implementation of the new innovation management paradigm. From this perspective, Weiblen and Chesbrough (2015), Boni (2019), and Panetti et al. (2019), to name a few, focus on the types of engagement that large biopharma companies use to connect with startup companies and other organizations, e.g., board interlocks vs government bodies, agreements for the mobility of talent vs universities, licensing agreements vs startups, and co-participation in thematic associations vs PAOs.

### 2.3 The limits of the existing literature

The literature investigating the IE concept and biopharma framework is affected by some limits. First, in broad terms, the related literature tends to overuse the term IE without precisely explaining the conditions and the features under which the surveyed contexts embrace the IE notion.

Second, most of the contributions focus on either a specific edge within the IE network or a single connection between the nodes of the network. In fact, the literature mainly sheds light on how a single actor aims to leverage IE resources through, e.g., a big pharma-centric approach, a university-centric approach, or a university vs. industry link, rather than considering a single actor pursuing mutual value creation through a structured and balanced relationship within a system of actors.

Finally, the main models proposed in the literature appear outdated for addressing the current innovation dynamics. In fact, sequential and over-strictly bounded models are generally unable to address the increasing biopharma industry complexity in terms of the requirement to both engage a large range of innovation sources and stakeholders and aim toward a large array of custom biodrug solutions.

### 3 Methodology

This research was performed by generating different levels of an IE model and validating it through interviews with several stakeholders, with the aim of collecting information about the interrelationships among different actors in the Lombardy IE. A first draft of the model was drawn according to the IE stakeholder model (Murray and Budden, 2018), which includes five stakeholders: corporations, universities, government bodies, startups, and risk capital providers.

The interviews followed two stages. First, the interviews were directed at stakeholders identified by the aforementioned stakeholder model. These interviews were planned and executed with international big pharma based in the Lombardy district, Italian biopharma, universities and research institutions, and biopharma startups. The interviews were semi-structured: after explaining the aim and scope of the research, contributions and examples were requested, a free-wheeling discussion then followed. The discussion was organized around the extent to which the stakeholder representatives recognized the roles and dynamics of the IE model and whether they would address some changes to fit the model onto the Lombardy district context.

Based on the outcome of this initial stage, new stakeholder categories were identified, and a wider model was elaborated by including these new players and outlining their dynamics and roles within IE. To validate this wider IE model for the biopharma industry, the second stage of interviews was addressed to the new players and those within the stakeholder model. This second stage of interviews aimed to refine and finalize the entire IE model by recording opinions, integrations, and suggestions based on real cases.
The list of interviews is shown in Tab. 1.
| Stakeholder type                                      | Company Institution | Role (s)                                                      |
|------------------------------------------------------|---------------------|--------------------------------------------------------------|
| Large Biopharma                                      | Amgen               | Product Specialist, Cardiovascular                            |
| Large Biopharma                                      | Dompè               | Research and Innovation Manager                               |
| Large Biopharma                                      | Dompè               | Research Funding Manager                                      |
| Large Biopharma                                      | Dompè               | CSO (Research Director)                                       |
| Large Biopharma                                      | Italfarmaco         | R&D Portfolio Development and Management                      |
| Large Biopharma                                      | Italfarmaco         | Head of Pharma Technology                                     |
| Large Biopharma                                      | Janssen-Cilag       | Local Trial Manager                                            |
| Large Biopharma                                      | Novartis            | Chief Scientific Officer                                       |
| Large Biopharma                                      | Zambon              | Open innovation, Head                                         |
| Biopharma startups and firms                         | Genenta             | CEO                                                          |
| Biopharma startups and firms                         | Blast-Research      | Quality Manager                                               |
| Biopharma startups and firms                         | Blast-Research      | CEO                                                          |
| Cluster Organizations                                | Assobiotec          | Member of the Steering Committee                               |
| Cluster Organizations                                | Assobiotec          | General Manager                                               |
| Foundations                                          | Cariplo             | Assistant Director Scientific and Technologic Area           |
| Foundations                                          | Telethon            | Chief Scientific Officer                                       |
| Government Body                                      | AIFA                | Scientific administrator and Quality assessor                 |
| Innovation Centers                                  | NeuroZone           | President and Chief Scientific Officer (CSO)                  |
| Patient Advocacy Organizations                       | AIRC                | Chief Scientific Officer                                       |
| Patient Advocacy Organizations                       | AISM                | Chief Scientific Officer                                       |
| Patient Advocacy Organizations                       | AISM                | Pharma and Healthcare Corporate Relations Coordinator          |
| Outsourcing biotech provider                         | CVBF                | Clinical Research Associate & Trial Operations Coordinator, SOPs & Training |
| Outsourcing biotech provider                         | Pharma&Biotech      | CEO                                                          |
| Outsourcing biotech provider                         | (Freelance)         | Consultant                                                    |
| Outsourcing biotech provider                         | IQVIA               | Commercial Compliance & Quality Solutions EMEA               |
| Outsourcing biotech provider                         | Recipharm           | Technology & Process Transfer Manager                          |
| Specialized Venture Capitalists                     | Aurora science      | Co-founder and board member                                    |
| Universities, University Hospitals and Research Organizations | CNR               | Technology Transfer Manager                                    |
| Universities, University Hospitals and Research Organizations | CNR               | Researcher, IBIOM                                              |
| Universities, University Hospitals and Research Organizations | San Raffaele Hospital | Head of Research Business Development at San Raffaele Hospital |
| Universities, University Hospitals and Research Organizations | UniMi              | Researcher                                                    |
| Universities, University Hospitals and Research Organizations | UniMi              | Intellectual Property Office                                  |
| Universities, University Hospitals and Research Organizations | UniMi              | Entrepreneurship and Spin-Offs Office                         |
| Universities, University Hospitals and Research Organizations | UniPO              | Full Professor                                                |
| Universities, University Hospitals and Research Organizations | UniPR              | Head of TTO                                                   |
Concurrently, a quantitative phase was carried out by collecting data to recognize the value creation pathways within the Lombardy biopharma district.

In recent years, Lombardy biotechnology seems to have found a new dynamism, and some crucial developments are taking place. The interest in the Lombardy IE case was propelled by some distinctive features, e.g., Italy is first among Top 10 EU countries by production value of pharma SMEs, Lombardy pharma district is 4th in Europe in the same ranking (The European House Ambrosetti, 2020), over a period of 22 years - 1996-2018 - Italy was the first country in the world for research productivity both in terms of publications per researcher and number of citations per researcher and among the top 10 countries in the world for number of publications (The European House Ambrosetti, 2020).

Thanks to the significant contributions of interviewees and all the collected data, the model evolved through the survey into the final version, presented in this paper. Ultimately, the final draft of the model was then sent to the most significant interviewees for their confirmation and further suggestions.

4 Results And Discussion

4.1 The biopharma IE theoretical model

A basic premise to be considered when drawing the theoretical IE model is IE terminology. As displayed in Fig. 1, the term ‘innovation ecosystem’ has been popularized over the last twenty years at the risk of a loose and inconsistent meaning. Furthermore, as discussed in the literature review, this term tends to be applied to a wide range of contexts at the risk of misleading and idiosyncratic use. For these reasons, clarification of the meaning and prospect of the ‘innovation ecosystem’ terminology and its use in place of more traditional terminology - e.g., district, hub, technopole - appears to be relevant to any research-based review. On this ground, Granstranda and Holgerssonb (2020) define an IE as an “evolving set of actors, activities, and artifacts, and the institutions and relations, including complementary (collaborative) and substitute (competitive) relations.”

Accordingly, within this research topic, the ‘eco-system’ terminology refers to a system continuously evolving through specific driving forces rather than a system operating at a static maturity level. In addition, this system is not ex ante designed to thrive anywhere but rather within specific bounded territories characterized by inherent and favorable conditions - e.g., a concentration of innovation and entrepreneurial capacities - and the implementation of sustaining designed initiatives - e.g., support structures and long-term policies.

4.1.1 The biopharma IE stakeholders

Because the biopharma innovation process differs from any other technology-intensive industry, the biopharma theoretical IE model needs to embrace many stakeholders. This is due to the inherent difficulties, nonlinear configuration, and complexity of the biopharma innovation process.

The biopharma innovation process is characterized by specific inherent difficulties associated with the making of safe and efficacious solutions, i.e., biodrugs, health-tech and med-tech products and services. In fact, the uncertainty as to whether major investments will ultimately pay off handsomely is especially high since the success rates in the biodrug innovation process remain steadily low. This high uncertainty is amplified by the presence of stringent regulations and intense scrutiny over the entire development process. For all these reasons, along with the amount of time needed for the solution to wind its way through the discovery and development process, the opportunity cost of capital in the biopharma industry appears high, creating its own challenges. In fact, the timeline between establishing a new venture - i.e., initial investment – and receiving any return - i.e., product availability in the market - can take over 10 years. Furthermore, the biopharma innovation process is mostly based on tacit knowledge that requires intense science-based interactions.

Regarding the nonlinear configuration, the biopharma innovation process tends to evolve toward a nonlinear, circular, and nonordered-stage model made up of long-term research, short-term research, and development, production, and commercialization, as shown in Fig. 2. These stages can be viewed as the elements of a cyclical model, where long-term research might not be the only source of innovation, and innovation might also emerge from any other stage. As an example, thanks to new digital technologies, e.g., the Internet of Medical Things (IoMT), new drugs may be conceived based on the analysis of data collected on patients. In considering the development of a biodrug, the three recursive stages aim to i) identify a biological target by increasing the body of knowledge underlying a disease; ii) define a promising drug candidate by focusing the research efforts; and iii) develop the new biodrug by involving production and marketing. This same process configuration can also be applied to innovative platform technologies, i.e., health-tech and med-tech products and services.
Regarding complexity, some drivers must be considered. First, the biopharma industry increasingly aims to personalize and customize therapies. In this context, the output of the innovation process ceases to be a standardized biodrug for a large range of patients but instead is a solution dedicated to a smaller-to-individual pool of patients. Second, biopharma solutions show high complexity due to both a multidisciplinary combination of technologies and a wide variety of integrated solutions ranging from biopharma drugs to beyond-the-pill products and services. Finally, another driver of complexity is the relation between product and process. In fact, a commonly used expression within the biopharma industry observes that “the product is the process”, suggesting the difficulty in handling the product-focused phase and the process-focused phase separately.

In light of the aforementioned features, the biopharma innovation process requires concurrent multiplayer engagement. Therefore, the following stakeholders take part in the biopharma innovation process by providing distinctive contributions:

- **Large biopharma**: attract innovation capacities and provide entrepreneurial capacities;
- **Government bodies**: set policies and rules sustaining innovation and entrepreneurial capacities and provide a source of funds through government programs;
- **Specialized venture capitalists**: fuel the growth of IE entrepreneurial capacities;
- **Biopharma startups and firms**: develop short-term innovation capacity and scale-up the solution;
- **University, university hospital and research organizations**: develop long-term innovation capacity and translate results toward impact;
- **Innovation centers**: support the development of innovation projects, their execution and their sustainability;
- **Foundations**: stimulate ecosystem innovation capacity by supporting long-term and short-term research;
- **Cluster organizations**: promote the innovation and entrepreneurial capacities of the region;
- **Outsourcing biotech providers**: provide supporting services for research, development, and manufacturing;
- **Support ecosystem partners**: shape innovation spaces by creating strong and connected communities;
- **Patient Advocacy Organizations**: shape and lead research agendas by lobbying players of different concerns;
- **Financial institutions and law firms**: provide financial resources and legal services.

### 4.1.2 Stakeholders’ comparative advantages engaging biopharma IEs

By starting with the aforementioned stakeholders’ contributions, the value creation process was analyzed in depth through the interviews reported in the methodology section. These interviews highlighted a set of comparative advantages that spur the engagement of different players within the IE. The collaboration between IE stakeholders at the technological frontier relies on coordination mechanisms that range from market-oriented governance, where many stakeholders commit to specific research streams, to hierarchy-based governance, where one or more stakeholders lead specific research projects. In this view, comparative advantages are not to be interpreted as a company resource per se but rather as required drivers of IE engagement. Fig. 3 illustrates the complete theoretical model, showing on the left side the support stakeholders, in the center, the five primary stakeholders positioned at the pentagon vertices, and on the right side, the exit markets. The outlined comparative advantages associated with each stakeholder in the model allow us to better analyze the evolution of IE on the grounds of both its polarization toward the different exit markets and its performance in value creation. These comparative advantages are discussed here below for each stakeholder.

**Large Biopharma** - Despite the increasing tendency to focus on the preferred drug list (PDL) and to license new opportunities, large biopharma acts as a magnet because it provides several comparative advantages: i) substantial financing capacity ready to be used in different ways, e.g., research contracts with universities, corporate venture capitalist (CVC) transactions, or mergers and acquisitions (M&A); ii) specialized infrastructure for drug discovery and drug development; iii) drug discovery skills to better connect with other actors and robust competences in product development; iv) a relevant entrepreneurial capacity that is deployed through different engagement mechanisms, e.g., calls to action, hackathons, incubators, and accelerators - in this respect, see Kohler (2016); v) distinctive market dynamics and knowledge supported by marketed drugs datasets. Thanks to these comparative advantages, large biopharma generates sophisticated demand fostering active collaboration with start-ups, universities and other stakeholders.

**Government bodies** - Government bodies represent a key stakeholder in IE by i) supporting innovation projects through public funds, mainly in the long-term research phase; ii) offering attractive policies for IE, such as favorable tax credits, industrial law codes, and intellectual property rules; iii) contributing to the development of an entrepreneurial culture; and iv) approving, inspecting, and defining biopharma standards through independent
regulatory agencies (AIFA, EMA and FDA) that oversee new drugs, labs, and manufacturing compliance and provide support services – e.g., regulatory sciences training, scientific and qualification advice, innovation meetings.

*Specialized venture capitalists* - Specialized venture capitalists provide financial resources and expertise to the IE. They screen valuable new opportunities and fund startup projects through a range of seed rounds from the very early stages of research to the later stages closer to the market. Specialized venture capitalists and IE are sorted according to which innovation loop they aim to finance. If they are willing to invest in a 'seed' round, 'Series A' funding, they provide small amounts of capital to startups pursuing their first innovation loops, their first sets of experiments, and their first assumptions tests. Other investors prefer to invest in series B, C, or D, which effectively map onto subsequent innovation loops.

These specialized venture capitalists can also act as business angels offering technical skills and expert support to new business ventures.

*Biopharma startups and firms* - The mission of these companies is to work on the technological frontier, both as temporary enterprises - startups - and as permanent innovation-driven firms. They provide two types of comparative advantages: i) distinctive innovative capabilities, both core - development of biodrugs, advanced therapies, monoclonal antibodies, vaccines, recombinant proteins - and complementary - development of breakthrough platform technologies such as health-tech and med-tech products and services; ii) they are highly oriented toward developing and pursuing a single idea/project and put all their resources in this endeavor (result-driven approach). Because of their unique inclination to take risks, they are crucial to IE value creation.

*Universities, university hospitals and research organizations* - These are the science, technology, engineering, and math (STEM) talent tank of the IE, often outsourcing research projects to large biopharma companies. Hence, as a long-term innovation engine of the IE, research institutes provide advanced knowledge in the form of publications, patents, and citations.

In addition to their long-term innovation capacity, research institutes are called upon to implement further comparative advantages to work with the other IE players. In this respect, their translational capacity aims to turn early-stage academic research into potential market applications – proof of concept (PoC) – through technology transfer offices and liaison staff and support researchers in advancing the technology readiness level (TRL), e.g., pitch days, seminars, spin-off ventures, patient pools, and key opinion leaders. Finally, these research institutes provide IE with specialized infrastructure in terms of unilabs, cell factories, and data networks.

*Innovation centers* - Innovation centers act as a bridge between startups/university spinoffs and large pharma. The former have projects with high innovative content but low TRL, while the latter have excellent knowledge of the market and management skills but greater aversion to risk. To propel this connection, innovation centers provide IE with various comparative advantages: i) support structures, such as specialized laboratories, coworking spaces, and incubator programs; ii) fixed-term, cohort-based, mentor-driven programs, i.e., accelerators; and iii) other business services such as technology transfer programs for academic projects, consultancies and scientific support.

*Foundations* - These stakeholders mainly play their role in the long-term research phase. Thanks to recognized expertise in project evaluation and a well-defined mission, these organizations shape long-term research agendas by networking different players around their life science objectives and by addressing philanthropic approaches, soft money, and endowments. Their funding programs, usually accessible through calls for tender, are oriented towards positive effects on society rather than economic returns on investment.

*Cluster organizations* - Cluster organizations offer activities of interest to all IE actors, such as training and workshops, to promote ongoing activities and services monitoring funding opportunities. Moreover, they offer activities specifically designed for certain groups of players, such as the creation of aggregations to participate in European and regional calls for funding. Cluster organizations can directly participate in initiatives, such as fairs and trades shows, or funding programs to attract financial resources and to launch successful joint projects among companies, universities and R&D centers and institutions (Giusti et al., 2019). Furthermore, cluster organizations increasingly promote global networks and multinational relationships to avoid the cognitive implosion of territorial clusters and remain innovative and competitive (Matricano and Sorrentino, 2015). Ultimately, cluster organizations lobby institutions and investors to strengthen research opportunities and innovative initiatives within the IE.
Outsourcing biotech providers - These organizations encompass outsourcing services from research—i.e., contract research organizations (CROs)—development, and manufacturing—i.e., contract development and manufacturing organizations (CDMO).

Support ecosystem partners - These players’ comparative advantages make a twofold contribution to IE. First, they design and develop innovative urban spaces capable of facilitating the sharing of tacit knowledge through both serendipitous encounters and inspirational work environments. Second, they offer innovative services supporting the life needs of IE talent, entrepreneurs, patients, and caregivers, e.g., smart mobility and smart logistics solutions. Regions that embrace innovation must also establish regular places for networks to form and people to interact.

In this regard, Morrison (2013) says, “a region that embraces innovation must also establish regular places for networks to form and people to interact. Oddly though, many regions still do not have the “civic spaces” — regular forums, meet-ups, and gatherings — where actors in the market and civic economies interact regularly that is essential for ecosystems to flourish.”

Patient advocacy organizations (PAOs) - PAOs play an important and strategic role in bringing together different stakeholders –, e.g., regulatory agencies, industry, academia, national research institutes and patients - to create an environment that can efficiently and effectively assist in research and drug development (Rose, 2015). Their contribution to IE is threefold. First, they provide direct counseling and education for patients for clinical trials. In addition, PAOs oversee the ongoing disease and collect critical follow-up data to address research. Ultimately, they shape research agendas by lobbying the concerned partners for research funding and operational progress.

Financial institutions and law firms - These players support the IE in two ways. First, financial institutions - e.g., banks, family offices - fuel the system, primarily start-ups and new ventures, by offering loans and equity funds. Second, law firms support IEs by providing professional services to address complex negotiations, e.g., licensing, IPOs, and patents.

Biopharma, health and med-tech, and financial markets - The demand side of biopharma IEs can be broken down into three markets: biopharma, health and med-tech, and financial markets. The main market is the biopharma market, which is the source of demand for biologics drugs, e.g., biodrugs, advanced therapies, monoclonal antibodies, vaccines, and recombinant proteins, addressing target patients. The complementary market is the health and med-tech market, which sustains demand for beyond-the-pill platform technologies, e.g., biomedical solutions, medical devices, diagnostics, medicine 4.0, and digital technologies. Finally, financial markets are marketplaces that sustain demand for resource allocation and create liquidity for corporations and startups.

4.2 How the biopharma Lombardy IE creates value

The agglomeration of innovative activities in Lombardy—and more specifically in the area around Milan—derives from this region's position as one of the major centers of academic research in medicine and biology and its high concentration of research laboratories, both academic and industrial. In addition, Milan is the primary financial center of Italy (Orsenigo, 2001).

In Europe, considering the health per capita added value, health-care excellence, the scientific density of medicine-related publications, and research quality, Lombardy emerges as one of the most vibrant pharma regions along with Cataluña, Baden-Württemberg, and Île de France (Assolombarda, 2018).

Therefore, the theoretical model shown in Fig. 4 and above has been applied to the Lombardy biopharma cluster on the basis of both qualitative and quantitative analyses. The qualitative analysis was carried out through the interviews illustrated in the methodology section. Concurrently, a quantitative investigation was conducted within a timeframe ranging from 2016 to 2019. It is expected that the 2020 COVID-19 pandemic will accelerate all the dynamics studied and reported here.

The research aimed to investigate the cause-effect relationship between the driving forces and the value creation pathways directed toward the related markets, i.e., biopharma, health and med-tech, and financial markets. The driving forces of IE encompass specialized infrastructure, funding, sophisticated demand, human capital, and culture and incentives. Hereafter, a thorough review of Lombardy IE is unfolded using these driving forces as interpretative lenses.
**Specialized Infrastructure**

The specialized infrastructure consists of all tech equipment and facilities that are available within the IE, e.g., coworking spaces, UNI labs, research hospital institutes, cell factories, technology platforms, and IoMT.

Despite showing a quite significant density level, e.g., more than 200 hospitals and 19 state-of-art hospitals, within the Lombardy region (YesMilano, 2019), these types of specialized infrastructures seem to have a limited impact on overall Lombardy IE performance due to the collaborative capacity and their own productivity. In fact, peculiarities of the Italian public system peculiarities - e.g., public lifetime employment, cumbersome labor regulations, specialized competence lagging - some critical infrastructure that stems from public-private partnerships (PPPs) might experience jeopardized productivity and suboptimal performance. Furthermore, these infrastructures tend to mostly rely on stand-alone, small, and under-specialized units. For the above reasons, the Lombardy case study, through the infrastructure lens, appears to be quite fragmented for pursuing a fruitful collaboration within IE.

However, the Italian cluster exhibits a compelling number of excellent cases among cell factories, research hospital institutes, innovation centers, and production facilities, that are mainly committed to synthesized drugs and off-patent drugs. Regarding cell factories and research hospital institutes, there are indeed a few centers qualified for advanced therapy medicinal products (ATMPs) - more than 5 research hospital institutes and more than 5 cell factories accredited by AIFA for chimeric antigen receptor T-cell (CAR-T) production and administration - within the Lombardy area (Osservatorio Terapie Avanzate, 2019). Regarding the innovation centers, Lombardy IE has exhibited active accelerators since 2015, with many projects evaluated and funded (The European House – Ambrosetti 2020). Finally, Italian contract development manufacturing organizations (CDMOs) are ranked first in Europe, showing consistent excellence in production facilities (The European House – Ambrosetti, 2020).

Data-network specialized infrastructure is increasingly gaining importance in expanding innovation capacity by sharing insights into biologics, diseases, and annexed requirements. The Lombardy IE shows some initiatives currently under-development in the field of regulatory sciences and genomics - e.g., the Big Data Steering Group of the European Medicines Agency (Heads of medicines agencies, 2021).

**Funding**

Compared to widely known biopharma IEs - e.g., Boston-Cambridge, San Francisco Bay area, Cambridge UK - the Lombardy IE is clearly underfunded. The amount of money annually raised by the Lombardy IE is approximately one order of magnitude lower than that raised by the cited IEs.

Large biopharma companies, government bodies, and venture capitalists are the main financing sources of an IE. From the large biopharma company standpoint, Lombardy IE has a population of private companies that are medium-sized enterprises and usually unlisted on the stock market. These two features explain the weak influence of Italian biopharma companies in funding the IE. In addition, Italian family capitalism, where shareholders and management overlap, is unlikely to succeed in unlocking the needed resources for IE. Regarding the incumbent Italian branches of global biopharma companies, it is worth noting that although these global biopharma companies view the Italian market as appealing, they focus their investments mainly on the commercialization process due to drug prices, on clinical trials due to associated costs and Italian medical experts, and on outsourced production due to the recognized Italian capacity. Hence, their investments in new drug R&D are very limited within the Italian region; however, these large companies carry out specific investment initiatives directed toward developing new health and med platform technologies.

From the government standpoint, the Italian Lombardy IE struggles to raise adequate funding within a context where low percentages of GDP are addressed to R&D and a very small number of R&D projects are financed by European Community – a 3.2% success rate for all submitted projects within the 2014/2020 period (The European House - Ambrosetti, 2020). This latter point illuminates an Italian structural weakness in the conversion of European planned resources into addressed initiatives and ultimately into financed project implementation.

Finally, from the venture capital standpoint, the numbers show a great gap between the amount of venture capital (VC) investments raised by widely known biopharma IE and by the Lombardy IE. Taking 2018 as a reference, Massachusetts biopharma companies raised $4.8 billion in VC investment (MassBio, 2019) versus 0.16 billion euros of VC funding in life sciences raised by the entire Italian region (Assobiotec, 2019).

Despite this underfunded financial framework, Lombardy IE has been identified as worthy of contributions from foundations and PAOs. These stakeholders exercise great influence by effectively targeting Lombardy IE efforts toward a shared mission. Therefore, even with low amounts of capital, Lombardy biopharma possess unique capacities for fulfilling narrow objectives by leveraging their comparative advantages in terms of project evaluation, research agenda accomplishment, and partnership maturity level.

In conclusion, the Lombardy IE has recently received new and robust strands of investment from the main funding sources discussed here that focus on the biotech innovation district recently born in the Expo 2015 ex-area in Milan.

**Sophisticated demand**
In this study, sophisticated demand refers to biopharma IE demand that can spur innovation and entrepreneurial capacities. Sophisticated demand is mainly created by large organizations focusing on cutting-edge biotech projects and propelling networks of university labs, startups, specialist technology providers, and innovation centers. Government bodies can also support sophisticated demand by setting research policies, objectives, and funding. In particular, government programs can pool financial resources to achieve strategic goals by aggregating a collective commitment among research institutes, foundations, and biotech firms, i.e., research consortium organizations.

The biopharma IE does respond to this internal demand by accordingly providing a critical mass of expert stakeholders who can fulfill these challenging needs. Under these conditions, the IE usually upgrades its expert stakeholder intensity, e.g., startups on the supply side of advanced biopharma solutions, research institutes providing a state-of-the-art body of knowledge, TTOs supporting long-term research translational capacity, and innovation centers sustaining early-stage innovation projects through accelerator programs. Hence, more sophisticated demand is generally seen as a precursor to scientific advances at the technology frontier.

In this respect, Lombardy shows a limited vibrant IE compared to widely known biopharma IEs, e.g., Boston-Cambridge, San Francisco Bay area, or Cambridge UK. This is evident from the number and turnover rate of Lombardy startups, the systemic lack of senior liaison staff within Lombardy university TTOs, and the small number of patents filed by Lombardy research institutions; in 2018, Italy ranked ninth in Europe for patents filed (Assobiotec, 2020b). Despite its limited vibrant environment, the Lombardy IE shows an intensity of biotech initiatives directed toward orphan drugs, e.g., 3 of 12 authorized orphan drugs stem from Italian research (The European House - Ambrosetti, 2019), rare diseases, AMPTs, e.g., 20 Italian equity biotech firms with ATMP projects in 2019 (Assobiotec, 2020a), and health and med-tech markets, e.g., 54 firms (27% of the total) in Lombardy that develop diagnostic products and services for human health (Assobiotec, 2020a).

Human capital

In the biotech industry, the conversion from basic and applied knowledge to economic exploitation generally requires intense multidisciplinary science-based interactions. In this context, where most of the knowledge is tacit, the human capital necessary for biotech IE calls for wide-ranging competences, from technical-scientific inception to go-to-market impact.

Regarding technical-scientific competences, the level of Italian talent indeed serves as a worldwide reference. In fact, the updated available data representing a 22-year time span (1996-2018) show that Italy is top-ranked worldwide for research productivity in terms of both the number of publications and citations per researcher (The European House – Ambrosetti, 2020). These figures are remarkable considering that the number of Italian researchers remains underdeveloped due to the poor ability to attract STEM talent from abroad and retain domestic talent. In fact, Italy lags other major European countries - Germany, the United Kingdom, France and Spain - with only approximately 200,000 researchers at the end of 2018, nearly one-third of the research staff in Germany and half of that in France (The European House – Ambrosetti, 2020). The Global Talent Competitiveness Index (GTCI) measures how countries’ policies and practices enable them to attract, develop and retain human capital that contributes to productivity. In the context of GTCI, Italy is in the bottom of the rankings in both the attract and the retain scorecards (World Economic Forum, 2017).

In addition to the STEM talent point of contention, the Lombardy IE’s human capital stands out for its unique competences in i) custom therapies - addressing, e.g., rare diseases, ATMPs, oncology; ii) clinical operations; and iii) a wide range of biopharma technical roles, e.g., pharma chemists and technologists, biotechnologists, bioengineers, biologists, and genomic technologists.

However, these skills are not sufficiently valued due to a widespread lack of managerial skills, e.g., communication, business development, go-to-market, and negotiation competences. Regarding management, it is not surprising that the commercial phase—sales, distribution, and marketing—is the most difficult for Italian spin-off companies. The background of the founders is typically technical, which explains why commercialization is often “hostile” for them (Chiesa and Piccaluga, 2000).

While a standard TTO in Italy is made up of 5.8 employees on average, the Stanford tech transfer office staff, for example, is made up of 9 teams: directors, licensing associates, intellectual property management, intake and sponsor compliance, agreements, business development and strategic marketing, industrial contracts office, business operations and accounting and information systems (The European House – Ambrosetti, 2020).

Culture and incentives

Multiple factors can jeopardize the value creation effort of Lombardy biopharma IE. These affecting factors can be grouped into four macro strands: translational incentives, risk-taking culture, red-tape constraints, and public commitment.

The first refers to all the translational incentives to exploit the quality of life sciences academia. In this regard, the Italian model of IPR appropriability in the public sector - university, university hospital and research organization - is based on the so-called “professor's privilege”. This privilege states that any inventions developed belong to the professors or researchers who conceived them. This mechanism binds technology transfer, as the
Italian biopharma companies - while avoiding the issues of an underfunded region, risk aversion, and red-tape constraints.

In the biopharma market, as depicted in Fig. 5, the Lombardy IE tends to address market niches, e.g., orphan drugs, niche busters, or ATMPs. In these market niches, the IE can leverage talented human capital, specialized research centers, and targeted investments - e.g., foundations, PAOs, unlisted Italian biopharma companies - while avoiding the issues of an underfunded region, risk aversion, and red-tape constraints.

IE pathways for value creation

In accordance with the cross-stakeholder review on the ground of the aforementioned driving forces, Fig. 5 outlines the influence level of each stakeholder with respect to the maturity of their comparative advantages; these are highlighted in bold when effectively deployed. The concept of influence level refers not to the stakeholders' inherent capacity to pursue their mission but rather to the impact that each stakeholder has on the whole biopharma IE. Hence, as depicted in Fig. 5, the influence level of each player is evaluated based on a two-level ranking scale, weak or strong influence, and shown by the vertical arrows beside each stakeholder.

The Lombardy IE driving forces shape value creation pathways directed toward the biopharma, health and med-tech, and financial markets.

On the public commitment side, the Lombardy IE is affected by multiple factors. Above all, low government stability tends to discourage the entry of new investors. Indeed, the political stability index - a composite measure based on several metrics from multiple sources including the Economist Intelligence Unit, the World Economic Forum, and the Political Risk Services - gives Italy a score of -2.0 within a range of -2.5 (weak) to +2.5 (strong) (SEBOIO Public Affairs & Reputation on Management, 2019). In addition, the government lacks a long-term public strategy, oftentimes facing discontinuous rules and policies in the frequent transitions between administrations. In addition to its low government stability, Italy shows a fragmented and often dysfunctional public system. In fact, public administration generally fails to address IE needs through centralized, one-stop-shop organizations, i.e., it lacks a reference point providing clear, updated, and structured information to Italian and foreign IE stakeholders willing to invest in biopharma innovation.

Regarding the risk-taking culture, the Italian context shows a low risk-taking appetite. This cultural characteristic impacts the whole Lombardy IE, starting from family Italian biopharma enterprises, which, due to their abovementioned intrinsic nature, are less prone to systematically undertake high-risk investments, and extending to the low capitalization of the Italian stock exchange and financial market, which scarcely enables access to financial resources and liquidity. This risk aversion also shows itself in the low number of biopharma specialized VCs, low startup intensity in terms of number and turnover rate, and a low number of startup IPOs, e.g., in 2019, only 2 IPOs on the Milan Alternative Investment Market (AIM) (IR Top Consulting, 2019) vs. 10 Massachusetts biotech IPOs on the U.S. main financial market (MassBio, 2020). Finally, it is worth emphasizing that the almost nonexistent adherence to postmortems affects Italian risk-taking culture. In fact, the Italian context and Italian entrepreneurs seem to be less willing or ready to accept failures, whereas in the US, failures are seen as less traumatic, and it is common for entrepreneurs to fail more than once before starting a truly successful business (Chiesa and Piccaluga, 2000). This aspect inevitably jeopardizes the exploitation of the lessons learned from failure, which is an essential component of innovation and invention.

Coming to the third point, bureaucracy and excessive regulation, commonly known as red tape, are burdens limiting overall IE performance and incentives. Red tape has a strong negative influence on the Lombardy IE economy. As red tape includes all sorts of rules, paperwork, permits, taxes, procedures or requirements for doing business, it tends to highly jeopardize the appeal of the Lombardy IE, e.g., it takes an excessively long time to start a clinical trial, 17 weeks in Italy vs. 5 weeks in the UK and 9 weeks in Germany. As a last negative note, it was calculated that in Italy, more than 50% of the elapsed time between the investigation and go-to-market authorization is spent completing bureaucratic steps that create no value for either the patient or the National Health System (Assobiotec, 2020b).

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Regarding the health and med-tech market, as shown in Fig. 5, the value creation pathways tend to thrive by drawing on platform technology providers, beyond-the-pill innovation capacity, and sophisticated demand triggered by large global pharma companies. They also rely on an innovation process featuring lower costs, shorter payback times, lower risks, and less regulation compared to new biodrug development.

Finally, as outlined by the dotted line in Fig. 5, the value creation pathways toward the financial markets are affected by a few factors. From a broad perspective, Italian family-based capitalism seems to prevent biopharma companies from being listed on the stock exchange and biopharma startups from pursuing IPO exit strategies. Other more specific factors - such as a low maturity level for translational, scale-up, and entrepreneurial capacities - affect the Lombardy IE's capability to convert from long-term research to short-term market opportunities, so it is missing a consistent flow of value creation pathways toward financial markets.

The cause-effect relationship between the IE driving forces and the value creation pathways shapes the Lombardy IE and explains its evolution in conjunction with its innovation and entrepreneurial capacities.

5 Conclusion

As explained above, the advent of the biopharma industry has disrupted the pharmacology and drug development world by introducing biological sources, especially those produced by biotechnology. Over the years, this drug therapy paradigm shift has led to powerful new innovation engines that incessantly push toward the creation of new biologics, e.g., biodrugs, advanced therapies, monoclonal antibodies, vaccines, and recombinant proteins. Compared to other industries, in many respects, the biopharma innovation process appears to be particularly challenging. In fact, today, along with their inherent challenges - e.g., high uncertainty, major investment requirements, long-term returns, stringent regulations, and a tacit knowledge-intensive industry - biopharma companies are striving to re-configure their innovation processes using a nonlinear approach to capture all innovation sources along the inception-to-impact path - i.e., long-term research, short-term research, and development, production and commercialization. A further challenging dimension is the high renewed complexity coming from personalized custom solutions, a multidisciplinary combination of technologies, and a strong interconnection between product and process.

In light of all this, the generation and economic exploitation of knowledge in the biopharma industry requires intense science-based interactions. The IE approach, leveraging geographical proximity and local interactions, facilitates and accelerates biopharma innovation processes by creating useful synergies among different stakeholders, e.g., startups, university research centers, and venture capitalists.

Considering the aforementioned limits of the existing literature, this paper represents one of the first attempts to systematically and longitudinally analyze biopharma IE from a holistic perspective. The introduced theoretical IE model (Fig. 3) responds to RQ1 by drawing a theoretical model that encompasses all the key stakeholders involved within the biopharma innovation process and the comparative advantages required to engage with IE.

To overcome the potential misleading use of the IE term in the literature, for research purposes, this paper has defined the 'eco-system' not as designed ex ante to thrive anywhere but rather as designed for operate within specific bounded territories under both inherent and favorable conditions and the implementation of sustaining designed initiatives.

By applying the theoretical IE model to the case of Lombardy (Fig. 4), the paper also answered RQ2 by investigating the cause-effect relationship between the Lombardy IE's driving forces and its value creation pathways. Relying on expert interviews as a central part of the methodology, the investigation highlighted the value creation pathways of the Lombardy IE for the main and complementary biopharma markets.

From this perspective, the research outcomes support the concept of the IE as a system continuously evolving through specific driving forces rather than one operating at a static maturity level. More specifically, the thesis of the paper argues that although the Boston-Cambridge IE snapshot shows economic and technical figures - e.g., employment, lab inventory, investments, biodrug development pipeline - that offer extraordinarily little basis for comparison with those of the Lombardy IE, the latter has evolved based on its inherent limits and strengths, as discussed through the IE driving forces in the "How the Lombardy biopharma IE creates value" section, and succeeded in deploying remarkable value creation pathways toward niche-biopharma markets and health and med-tech markets.

As far as the limitations are concerned, this paper focused its qualitative analysis - i.e., semi-structured interviews - on just the Lombardy case and addressed a comparative quantitative analysis with other IEs, and mainly with Boston-Cambridge IE. The same in-depth analyses of other IEs in other regions and countries may better illuminate our findings by validating stakeholder and comparative advantages within the theoretical IE model.

Implications for research and practice

The developed theoretical IE model and its application to the Lombardy case provide a common basis of analysis for different biopharma IEs, e.g., Boston-Cambridge, San Francisco Bay area, Cambridge, UK.

Both scholars and practitioners will hopefully find the holistic and systemic framework developed in the paper useful for understanding the potential of the IE approach for the biopharma industry. More specifically, scholars can adopt and develop this theoretical IE model for future studies.
addressing research either to other biopharma IEs or to different perspectives. For example, the authors are committed to studying the IE engagement underpinning specific success projects and the governance mechanisms driving IE value creation. Practitioners, such as managers, entrepreneurs, and policymakers, can spur the arguments developed in the article for addressing broad initiatives and exploiting all IE resources in a more effective and efficient manner.

Declarations

>> The authors declare that they have no conflict of interest.

>> Competing interests: The authors declare no competing interests.

>> Participant consent: the participants consented to participate at the interviews.

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**Figures**

![Figure 1](image)

Trend of the number of publications with innovation ecosystems in the abstract and in the title since 1997 - source: Scopus
Figure 2

The biopharma circular innovation process: long-term research, short-term research, and development, production, and commercialization

Innovation centers
- Support structures (co-working, incubator)
- Business accelerator (accelerator programs, entrepreneurial coaching)
- Tech-Transfer (advisory, scientific support, business services, Catalyst programs)

Foundations
- Research agenda (networking, research programs, project evaluation)
- Funding (grants, endowments, philanthropic approach, soft money)

Patient advocacy organizations (PAO)
- Demand (front-end dataset providers)
- Funding
- Research influence and reputation (partnership maturity level)

Cluster organizations
- Promotion (networking, cross-cluster cooperation)
- Lobbying (communication and investor relations)

Outsourcing biotech providers
- Research services (contract research organizations - CRO)
- Contract development and manufacturing services (subcontractors, CDMO)

Support ecosystem partners
- Urban spaces design (open spaces, meeting places, streets, plazas)
- Life-nets services (smart mobility, retail, logistics, …)

Financial institutions and law firms
- Lending, equity funding (banks, family offices)
- Professional services (IPR, Patent, IPO, licensing)

Universities, university hospitals and research organizations
- STEM talent
- Specialized infrastructures (laboratories, cell factories, data network)
- Long-term research capacity
- Translational capacity (FD, PhD, grants, spin-off, liaison staff, key opinion leaders)

Biopharma startups and firms
- Core (innovation capacity, bio drugs talent)
- Complementary innovation capacity (health tech, med tech talent)
- Scale-up capacity (shark-tanking, result-driven approach)

Specialized venture capitalist
- Venture funds (De-risking, smart-money, seed capital)
- Specialized business and technical skills (business accelerators, Business Angels)

Government bodies
- Public funds
- Public development policies and rules (tax credits, intellectual property, industrial policy, data network)
- Culture (risk-taking, incentives)
- Regulatory compliance and services (new drug, labs, and manufacturing approval, inspections, standard setting, regulatory science training, scientific advice)

Biopharma market
- Demand (blockchain, bio drugs, advanced therapies, monoclonal antibodies, vaccines, recombinant proteins, …)
- Complementary technologies

Health & med-tech market
- Demand (beyond the Wall, technologies, services)

Financial market
- Demand (stock exchange, IPO, share prices, trading)

Figure 3

The biopharma IE theoretical model: stakeholders’ comparative advantages and value creation pathways toward biopharma markets
The Lombardy Biopharma IE: stakeholders' influence level, stakeholders' effectively deployed comparative advantages, and the value creation pathways toward biopharma markets.