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Overcoming the "valleys of death" in advanced therapies: The role of finance

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ABSTRACT

Advanced therapies are the frontier of medical research and have a relevant therapeutic potential and a profound social value. Despite this, their funding is hindered by many heterogeneous factors that obstruct their translation and survival on the market, even when approved and effective.

Using an extensive bibliometric and systematic review of 174 articles published between 2001 and 2023, this study aims to identify the factors hindering the financing of advanced therapies and suggest future research lines to overcome the biomedical and economic "valleys of death".

This study is the first review focused on advanced therapies from a financial perspective, and it contributes to advancing scientific knowledge in several ways. First, it highlights that finance academics paid little attention to the topic and most of their contributions are now outdated; therefore, there is the need to explore the new opportunities and solutions offered by financial innovation and the application of new technologies to financial activity. Second, it asks for an interdisciplinary approach to exploring advanced therapies' barriers from a holistic and process perspective and exploiting the social value generated by the development of innovative therapies. Finally, it analyzes the obstacles and value destroyed by the absence of an organic and coordinated process of public intervention, underscoring the imperative for further research to explore new public-private financial models and risk-sharing schemes and extend evaluation models by integrating financial and social value logic.

1. Introduction

Medical research is constantly evolving and incorporates technological innovations from different scientific fields. Financial resources are the lifeblood of medical innovation, from the generation of new ideas to their clinical testing and commercialization (Lo and Chaudhuri, 2022). Despite this, it is often difficult, or even impossible, to match demand (developers of drugs and therapies) and supply (investors) of financial resources, leading to financial rationing of medical research, which generates not only financial allocative inefficiencies but also, inequities and social costs. This is not surprising. Medical research is a complex, lengthy, and expensive process characterized by high uncertainty and a low probability of success (Lo and Thakor, 2022). These features are strongly unattractive to investors and obstruct access to funding.

This mainly occurs in advanced therapies comprising a set of gene, cell, and tissue engineering therapies intended to act on or regenerate organs, tissues, cells, genes, and metabolic processes in the body and permanently treat diseases (Restore, 2019). Often intended for rare and neglected life-threatening diseases, advanced therapies have the potential to satisfy the unmet healthcare needs of patients who are at greater risk of social exclusion insofar as the disease prevents a "full" social life (Pellegrini et al., 2018). Advanced therapies embody social value, mainly referable to patients' length and quality of life; economic value, referable to cost savings for national healthcare systems; and scientific value, related to biomedical innovation and therapeutic spillovers (Jönsson et al., 2019). At the same time, advanced therapies show higher complexities in the manufacturing and administration process and stricter regulatory and pharmacovigilance demand (Olesti et al., 2024; Goula et al., 2020; Abou-El-Enein et al., 2016), which usually

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results in longer timescale, higher development cost and more extensive financial needs than conventional drugs (de Labry-Lima et al., 2023; Hampson et al., 2017; Abou-El-Enein et al., 2016).

Due to severe scientific, operational, and financial intricacies, numerous innovative advanced therapies find themselves trapped in what is commonly referred to as the biomedical "valley of death," struggling to transition from the laboratory to the bedside (Adamo et al., 2023). A significant gap exists between the number of executed clinical trials worldwide and the number of advanced therapies that managed to be commercialized (Pimenta et al., 2021). Even after obtaining marketing authorization, advanced therapies face a second economic "valley of death", in which effective and valuable therapies are at high risk of being withdrawn due to pricing and reimbursement issues, leading to insufficient economic return for investors or producers (De Luca and Cossu, 2023; Craddock, 2015). In this uncertain context, developers and manufacturers must constantly search for limited, difficult-to-acquire funds.

The system of financial markets, institutions, contracts, and schemes, which we will call "Finance" from now on, may contribute to overcoming the biomedical and economic "valleys of death" of ATMPs. In particular, Finance can act by improving the continuity of financial resources at the disposal of developers, especially of SMEs (i.e., BioTechs) operating in this field, which play a significant role in translating novel advanced therapies and bringing them to the market (Tavridou et al., 2021; Lysaght et al., 2008).

The traditional functionalist approach (Merton and Bodie, 1995) attributes to Finance the role of enabling the satisfaction of the needs of economic and social systems through new combinations or reconfigurations of the role of its elements (intermediaries, markets, and contracts) capable of reducing and, possibly, overcoming the difficulties created by uncertainty, information asymmetry, unsustainability of transaction costs and incompleteness of assessment (Allen and Santomero, 1997) that characterize financial exchanges.

By adopting a functionalist approach, scientists and academics in finance could guide their research efforts in better understanding the causes of financial rationing and the difficulties of interactions between science and finance. This can contribute to the development of innovative funding solutions in the field of advanced therapies and the reduction of the existing funding gap. This is a crucial step in order to develop a theoretical framework that can then be used to understand and manage the specificities of the different economic contexts, national healthcare systems and authorities, and, last but not least, the role of the different universities and technology transfer systems, which today play a fundamental role in the development of advanced therapies (Lo and Chaudhuri, 2022).

In addition, compared to the past, nowadays, Finance might have more significant incentives and interest in investing in medical research, including that in the field of advanced therapies. Indeed, authorities are actively endorsing and promoting sustainable investment practices that take environmental, social, and governance (ESG) considerations into account when making investment decisions in the financial sector (Klinkowska and Zhao, 2023), driving the shift of financial resources toward more sustainable uses, including the healthcare sector (Kuzmina and Lindemane, 2017; Krech et al., 2018).

This study aims to identify the factors hindering the financing of advanced therapies and to outline research directions that could support the resolution of financing problems and the overcoming of the biomedical and economic 'valleys of death.' To achieve this, we have performed a bibliometric and systematic literature review of previous studies on advanced therapy development's economic and financial aspects to focus on the issues studied, aspects neglected, and possible future research directions. It summarises critical insights and identifies research gaps, trends, and directions. In particular, it allows us to answer the following research questions:

RQ1. How and to what extent have studies addressed financial issues related to supporting medical research in advanced therapies?

RQ2. Who are the most influential studies/contributors, and to which disciplinary areas do they belong?

RQ3. What peculiarities/challenges have the studies focused on?

RQ4. What are the possible research paths?

In addressing these RQs, we found a gap in attention paid by financial scholars whose contributions are often dated and thus out of step with the new opportunities created by financial innovations and technologies. We then draw the attention of academics and practitioners to different lines of future research that we believe can stimulate reflections and valuable studies, mainly if conducted interdisciplinary, to overcome the biomedical and economic 'valleys of death'.

To the best of our knowledge, this study presents the first bibliometric and systematic review of the theme of advanced therapies from a financial perspective, filling the gap left by previous reviews exclusively focused on scientific, operational, and regulatory research fronts (e.g., Hanna et al., 2018; Lloyd-Williams and Hughes, 2021; Pinho-Gomes and Cairns, 2022; Olesti et al., 2024).

The rest of the article is structured as follows: Section 2 describes and analyses the features of advanced therapies while discussing Finance's role in supporting their development. Section 3 describes data and methodology, Section 4 reports the results of the bibliometric analysis, and Section 5 maps the main contents and thematic areas. Section 6 is dedicated to a detailed review of the identified thematic areas. Section 7 discusses the results of the bibliometric and systematic literature review and suggests a possible research agenda. Section 8 concludes the review.

2. Background: advanced therapies and finance

2.1. Advanced therapies: biomedical and economic "valleys of death"

The terms "ATMP", "Advanced Therapy Medicinal Product", "regenerative medicine", or simply "advanced therapy" generally refer to the set of complex gene, cell, and tissue engineering therapies intended to act on or regenerate organs, tissues, cells, genes, and metabolic processes in the body and to permanently treat diseases (Pimenta et al., 2021; Restore, 2019; Gardner and Webster, 2016). In contrast to conventional drugs, advanced therapies are not based on chemicals or proteins as active substances but involve using and implantation of live modified human cells or tissues on the patient, who may or may not be the donor (Goula et al., 2020). More specifically, gene therapies are intended to treat diseases at the molecular level by modifying DNA sequences and compensating for genetic defects, thereby acting on the cause of the disease rather than the resulting complications. Instead, cell therapies and tissue engineering products consist of removing and reinjecting cells or tissues into patients after a substantial manipulation, altering the biological characteristics, physiological functions, and structural properties to replace or repair damaged tissues or organs (Hanna and Toumi, 2020).

Often aiming to prevent or treat rare, ultra-rare, and neglected life-threatening diseases, most advanced therapies are personalized and definitive treatments (Hanna and Toumi, 2020), thus presenting scientific, operational, and financial aspects that obstruct their path from the laboratory to the marketing authorization, and stop them in the biomedical "valley of death" (Adamo et al., 2023). Indeed, the small target population and challenges in enrolling patients introduce limitations regarding the design of studies, which usually involve non-randomized, single-arm, and open-label trials, which may lead to biased and unreliable results (Lloyd-Williams and Hughes, 2021). The difficulties in assessing and providing robust statistics concerning the therapy's safety and effectiveness and the specific skill required in the regulatory process extend and complicate the path toward regulatory approval (Olesti et al., 2024). At the same time, the need for significant investments in equipment, facilities, and skilled personnel, as well as the

unavoidable replication of the manufacturing line for each patient, lead to long timescale and development costs, obstruct the scaling-up of production and profitability, and generate significant financial needs (Abou-El-Enein et al., 2016). Hence, developers and manufacturers have financial needs that are difficult to satisfy.

Even after securing marketing authorization, advanced therapies risk falling into a second economic "valley of death". Manufacturers of advanced therapies, aiming to recoup substantial investments and R&D costs, typically set considerably high prices, sometimes reaching a few million euros or dollars per patient. This leads to prolonged and challenging negotiations with National Health Systems, which may not always be willing or able to cover patient costs. Sometimes, even when a reimbursement agreement is reached, effective and valuable therapies are withdrawn due to insufficient economic viability since they are not profitable enough to cover manufacturers' costs of production and deployment while granting them adequate returns (De Luca and Cossu, 2023; Fontrier, 2022). This is frequent with advanced therapies targeting rare and orphan diseases, even though treating a small group of patients would not strain countries with a solid public health system. Instead, it would reduce overall long-term costs per patient (Palamenghi et al., 2022).

In light of the scientific, operational, and financial hurdles underlying the development of advanced therapies, and given their significant intrinsic value for patients and society, regulators have made several efforts to speed up their development and commercialization. For example, in the EU, several initiatives have been promoted to provide funding for research, offer regulatory guidance, streamline the approval process, and address pricing and reimbursement challenges. However, obstacles remain, particularly in ensuring affordable access and harmonized assessment and reimbursement strategies across jurisdictions (Pimenta et al., 2021).

2.2. Finance and advanced therapies

The literature on the financing of advanced therapies has mainly assumed an institutional perspective, focusing on the role of some types of financial intermediaries and the effects of their intervention on the funding of firms rather than on what is needed to reduce the funding gap in the development of advanced therapies.

Depending on the type of financial institutions involved, the role of Finance may be more or less stable and substantial (Ramos et al., 2022). However, it is still marginal compared to the potential volumes of resources that could flow into it.

Financial markets and institutions do not directly support individual projects or trials in advanced therapies. Instead, they indirectly support the development and commercialization of advanced therapies by financially backing SMEs (or BioTechs) carrying out early-stage clinical trials, typically more vulnerable to financial exclusion and rationing (Cosma et al., 2024). These SMEs play a pivotal role in translating novel advanced therapies and bringing them to the market (Tavridou et al., 2021; Lysaght et al., 2008).

Family offices are a long-lasting source of funding for early-stage SMEs, but they are still limited and driven by the causes near and dear to the family (Sambrano et al., 2019). Some exceptions include, for example, the intervention of Bezos Expeditions, the family office of Amazon founder Jeff Bezos, which invested $56 million in Juno Therapeutics. Following this investment, Juno Therapeutics secured additional funding from public and private venture capital funds and reached its Initial Public Offering (IPO) in the same year.

Similarly, the limited financial resources made available by incubators or investors/donors through crowdfunding portals are often inadequate to support the total cost (tens or hundreds of millions of euros) of the clinical trial process and approval of therapy, thereby making this alternative and innovative funding channel more suitable for financially supporting start-ups during their early stages (Grassi and Fantaccini, 2022; Heidari Feidt et al., 2019), when they usually carry out basic and preclinical research. For example, Capital Cell, one of the few equity crowdfunding platforms designed explicitly for early-stage BioTechs and life sciences companies, has successfully closed 119 funding rounds, raising over 100 million from angel networks, banks, VC and PE funds, non-profit foundations, and retail investors. The amount raised may not be enough to develop a single advanced therapy. However, the investor community fostered on the Capital Cell platform has been instrumental in the success of future fundraising for many biotechs.

Finally, capital infusions from private equity (PE), venture capitalists (VCs), and investment banks become crucial when SMEs need more significant financial resources to set up clinical trials, ensuring their years of business activity through multiple, large follow-on investment rounds. For example, in 2013, JP Morgan became an early supporter of Solid Biosciences, a BioTech company focused on developing gene therapies for Duchenne Muscular Dystrophy (DMD), by investing $5 million in its Series A funding round. This investment was atypical for an investment bank, which generally avoids early-stage ventures. JP Morgan's decision was likely influenced by its simultaneous preparation for the IPO of another BioTech company that also targeted DMD, allowing it to recognize both the business opportunity and the unmet medical need in this area (Kim and Lo, 2016). JP Morgan's early intervention allowed Solid Biosciences to start basic and pre-clinical research and attract funding from private and non-profit institutions in the following years.

From a functionalist perspective, the role of intermediaries goes beyond simple financing, generating positive effects on biotechs' subsequent ability to attract new financial sources and improve the credibility of their quality. Therefore, it is essential to investigate more deeply the development processes of advanced therapies from a financial point of view to understand better what determines barriers to financing and put Finance in a position to find new financial schemes capable of overcoming the risks generated by these factors. The role of Finance becomes even more relevant in light of the increasing risk aversion of large pharmaceutical companies (Franzoni et al., 2022) that, by acting as "network integrator" (Rafols et al., 2014), keep advanced therapies outside their research perimeter and strategically fund or acquire SMEs conducting late-stage clinical trials (Kim and Lo, 2016).

3. Data and methodology

In order to analyze the literature dealing with the financial issues of advanced therapies developed over the years, we use a bibliometric analysis accompanied by a systematic literature review (SLR) (Donthu et al., 2021; Tranfield et al., 2003; Smithers and Waitzkin, 2022). An SLR is guided by a review protocol that details the steps followed, ensuring the study's replicability (Lim and Weissmann, 2023). However, the qualitative nature of SLRs generates interpretation bias that the quantitative nature of bibliometric analysis allows to overcome (Boubaker et al., 2023). As stated by Zupic and Čater (2015), bibliometric techniques do not replace traditional systematic reviews but have the potential to complement them. In recent years, more and more researchers have used these two tools in a complementary way to analyze a large amount of bibliographic data and rigorously assess the state of the art, identifying research gaps, analyzing the evolution of the literature, and defining a set of future research directions (Marzi et al., 2024; Goodell et al., 2023).

The initial search for this study was conducted within Web of Science since this turns out to be one of the largest databases at the level of journal coverage, providing quality bibliographic data (Bouchard et al., 2015; Waltman, 2016; Boubaker et al., 2023). After conducting an initial cursory survey of studies that analyzed the topic of advanced therapies from a financial perspective, a comprehensive search string was finalized. Specifically, taking advantage of the logical AND/OR operators, we searched for all studies that contained the words "ATMP", "ATMPs", "regenerative medicine", or "advanced therap*" (as these keywords refer to and are inclusive of the set of gene, cell and tissue engineering therapies) combined with purely financial terms in the title, abstract in the

keywords or KeywordPlus (terms are described in Fig. 1). The initial search resulted in 449 studies. We then refined the result, keeping only articles and reviews published in English. We also excluded studies published in 2024 since these have not yet accumulated enough citations to certify their impact on the scientific community (Khan, 2022). This phase produced a sample of 353 documents. Finally, by reading the abstracts and full texts of the articles, we filtered the search and kept the studies relevant to the focus of this review. Using the criteria summarized in Figs. 1 and 174 published studies were selected from 117 sources.

The VoSViewer software (van Eck and Waltman, 2010) and the bibliometrix package of R (Aria and Cuccurullo, 2017) were used to analyze the bibliographic data of our sample. These tools were used to conduct performance analysis and network analysis. The performance analysis allowed us to identify the main contributors to the topic (sources, authors, countries), the most relevant studies, and publication and citation trends (Chiaramonte et al., 2022; Goodell et al., 2023). On the other hand, network analysis identified the relationships between the studies in the sample through the author's keywords (Callon et al., 1983; Donthu et al., 2021). Finally, to identify the development trends in the research field, a topic trend analysis was carried out using the author's keywords (Boubaker et al., 2023).

4. Performance analysis

Fig. 2 shows the publication pattern of research on the topic. The graph reveals that the first article that dealt with advanced therapies' financial issues and criticalities was published in 2001. After 2001, research on the topic began to develop only four years after no studies were published. Then, the annual production of studies has seen a growth that, although fluctuating, has been on a decidedly upward trend.

4.1. Most prolific contributors

In this section, we try to identify the main contributors to the topic. In particular, we examine the patterns in publications and citations. Publication indicates productivity, while citation gauges impact and influence (Donthu et al., 2021).

Table 1 shows the most cited and most prolific authors. Among the most cited are Lysaght M. J., Farid S.S., and Reyes J. Among the most prolific, we find Farid S.S., with four publications on the topic and who mainly focused on bioprocess economics and manufacturing optimization, Mason C., Mittra J., and Rao M., with three publications on the topic and who mainly focused on business model evolution, commercialization and regulatory prospects of advanced therapies.

Following Hasan et al. (2023), we also performed the analysis of the authors' characteristics (Fig. 3). It reveals that the main contribution to the literature has been from academics that operate in the United States (188) and in the UK (121), followed then by Germany, Spain, Iran, and Canada. Furthermore, Fig. 3 shows that the most productive countries in finance and advanced therapies research have worked collaboratively. This probably stems from cross-country collaborations of academics, scientists, and clinicians in developing new and innovative therapies and understanding the underlying challenges and success factors.

Table 2 shows the most prolific and impactful sources hosting research that has analyzed the financial aspects of advanced therapies. In particular, we find that neither the most cited nor most prolific

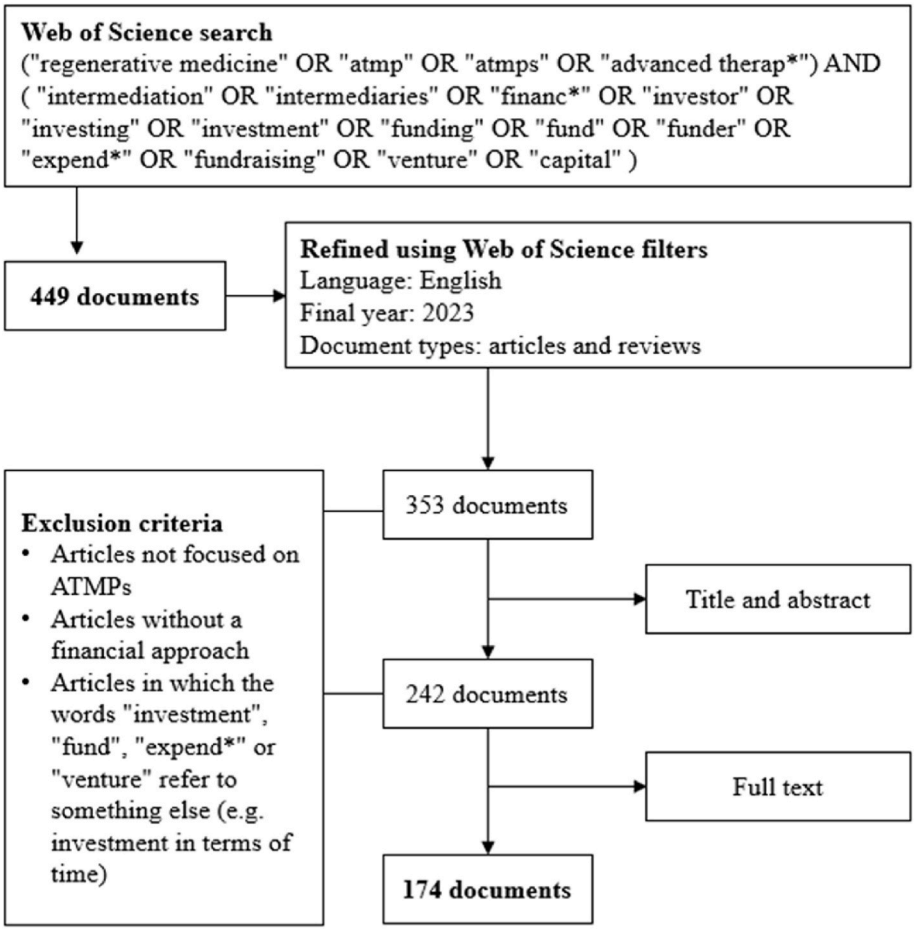

Fig. 1. Search and filtration strategy for bibliometric review.

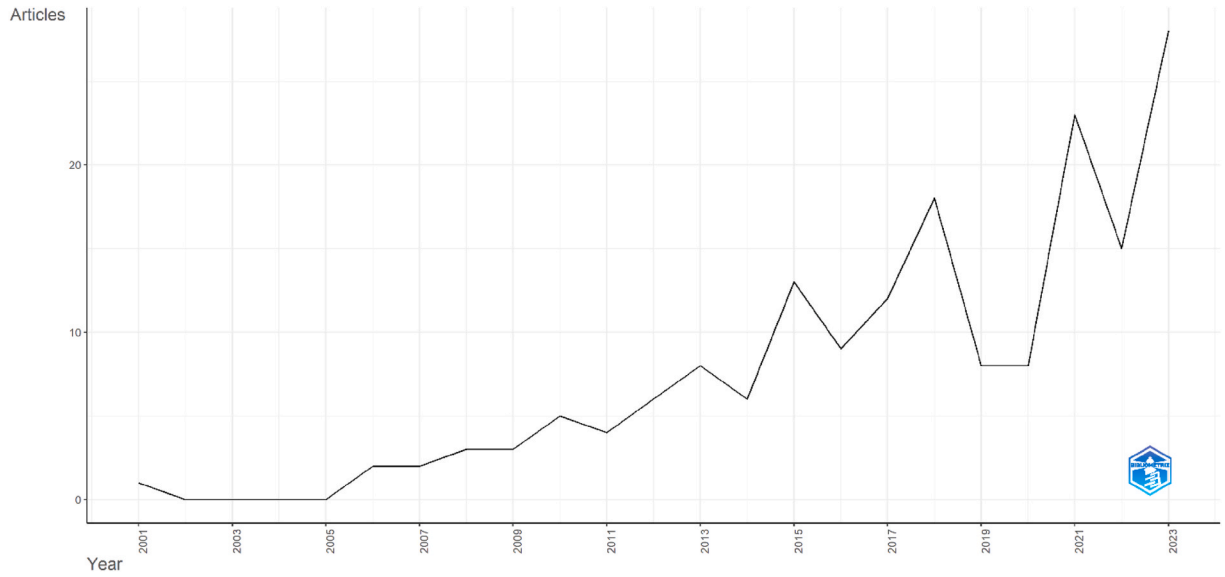

Fig. 2. Annual scientific production (2001–2023).

Table 1
Most cited and prolific authors.

Most cited authors		Most prolific authors	
Author	TC	Author	NP
Lysaght M. J.	287	Farid S. S.	4
Farid S.S.	240	Mason C.	3
Reyes J.	151	Mittra J.	3
Hassan S.	141	Rao M.	3
Rowley J.	141	Lysaght M. J.	2
Simaria A. S.	141	Daar A. S.	2
Vanek P.	141	Hoekman J.	2
Varadaraju H.	141	Leufkens H. GM	2
Warren K.	141	Hildebrandt M.	2
Deweerd E.	136	Bubela T.	2
Jaklenec A.	136	Koehl U.	2
Daar A. S.	113	Bayon Y.	2
Greenwood H. L.	102	Ronfard V.	2

Note: TC: Total citations; NP: number of publications.

journals belong to the areas of finance or business economics. In particular, *Regenerative Medicine* appears to be the most cited journal (230) and also the most prolific, with 18 publications on the topic. We also find that the only journals with an economic-financial approach present in the sample are the *European Journal of Health Economics*, *Applied Health Economics and Health Policy* and *Pharmacoeconomics-Open*, all of which present only one publication.

Finally, Table 3 reveals the most cited studies in the sample. The article that has accumulated the highest number of citations is that of Lysaght and Reyes (2001), biomedical engineers who analyzed the expansive phenomenon of start-ups specializing in tissue engineering and highlighted the emergence of a robust commercial activity in the engineering sector involving not only the United States but also Europe and Australia. The second article, with several citations, is that of Simaria et al. (2014), biochemical engineers who address the challenges of achieving scalable and robust manufacturing processes for allogeneic cell therapies. The third study by number of citations is that of Lysaght et al. (2008), which represents a logical continuation of the study published in 2001 by Lysaght and Reyes. With a global perspective, this study provided a detailed estimate of the extent of private sector development and commercial activity in the aggregate field, including tissue engineering, regenerative medicine, and stem cell therapies. The study highlighted a fivefold increase in economic activity compared to five years earlier and, above all, shed light on the resilience of a sector that seemed to bode well for the future of regenerative medicine.

5. Conceptual structure

The investigation in the previous sections reveals how scholars and journals have addressed financial issues and criticalities of advanced therapies with little or no purely financial background. This preliminary result confirms the need to perform a bibliometric and systematic analysis to investigate the research structure on the topic thoroughly. Therefore, we integrate bibliometric analysis with thematic analysis and co-occurrence analysis, which represent methodological approaches widely adopted by management scholars to shed light on the conceptual structure of a research field (Zupic and Čater, 2015).

5.1. Thematic analysis

In order to explore the structure of research on advanced therapies dealing with financial issues, we carried out a thematic analysis on the co-occurrence of keywords (Cosma et al., 2023). The positioning of these themes determines their classification: those in the upper right quadrant are deemed “motor themes,” pivotal and well-developed; themes in the upper left quadrant are labeled as “niche themes,” developed yet isolated; while those in the lower left quadrant are termed “emerging themes,” indicating they are underdeveloped. Lastly, the lower right quadrant comprises “basic themes,” denoting their relevance despite being less explored in the literature (Cosma et al., 2023).

The thematic map (Fig. 4) reveals that the topics linked to innovation, funding of advanced therapies, and, in general, financial issues of research on advanced therapies appear to be niche, i.e., topics particularly isolated throughout the literature. Furthermore, despite belonging to the upper left quadrant, these topics present a lower level of development than other niche topics, such as those linked to bioprocess economics or cell factories.

5.2. Science mapping

Mapping scientific knowledge is crucial for pinpointing the thematic domains forming the theoretical groundwork or foundational pillars within the studied field (Manesh et al., 2020). The investigation of keyword co-occurrence is depicted through a network diagram illustrating the interconnections among these keywords. (Fig. 5). This analysis reveals the existence of three distinct research clusters dealing

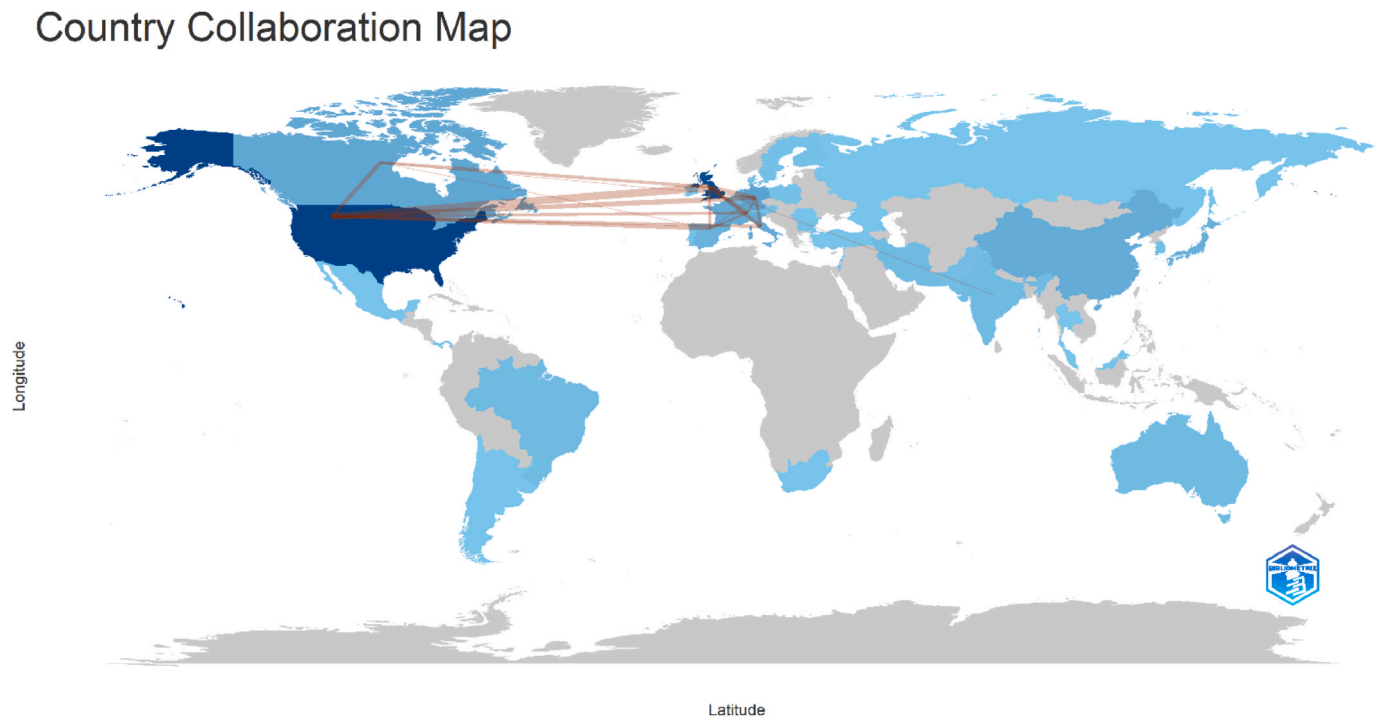

Fig. 3. Country scientific production and collaboration.

Table 2
Most cited and prolific sources.

Most cited sources		Most prolific sources	
Source	TC	Source	NP
Regenerative Medicine	230	Regenerative Medicine	18
Tissue Engineering Part A	221	Cytotherapy	7
Journal of Tissue Engineering and Regenerative Medicine.	168	Frontiers in Bioengineering and Biotechnology	6
Tissue Engineering	151	Tissue Engineering Part B-Reviews	5
Biotechnology and Bioengineering	141	Regenerative Therapy	5
Cytotherapy	133	Stem Cells and Development	4
Frontiers in Bioengineering and Biotechnology	127	Tissue Engineering Part A	3
Advanced Drug Delivery Reviews	114	Journal of Tissue Engineering and Regenerative Medicine	3
Frontiers in Medicine	104	Frontiers in Medicine	3
Current Medical Research and Opinion	95	Stem Cells Translational Medicine	3
Biochemical and Biophysical Research Communications	95	Clinical Therapeutics	3
Tissue Engineering Part B-Review	88	Advanced Drug Delivery Reviews	2
Social Science & Medicine	82	BMC Medicine	2
Biotechnology Journal	76	Health Policy	2
Stem Cells Translational Medicine	72	Transfusion Medicine and Hemotherapy	2
BMC Medicine	72	Journal of Technology Transfer	2
Stem Cells International	65	New Genetics and Society	2
Regenerative Therapy	64	Frontiers in Pharmacology	

with financial issues of advanced therapies from different perspectives, according to which we assigned the labels of Fig. 5 (Kim et al., 2023):

- The first thematic area (blue cluster) includes studies that, from a financial and managerial perspective, address challenges and best practices for entrepreneurs engaged in the development of advanced therapies and explore the funding sources (both private and public) available to them;
- The second thematic area (green cluster) includes studies that, from an operational and regulatory perspective, address the challenges in terms of economic evaluation, pricing and reimbursement, and compliance with regulations underlying the manufacturing and commercialization of advanced therapies;
- The third thematic area (red cluster) includes studies that, from a scientific and industrial perspective, highlight the barriers and challenges clinicians face while developing advanced therapies while also enclosing practical evidence and guidelines for a successful translation.

Keyword *overlay analysis* also allows us to analyze the temporal distribution of the keywords contained in each cluster. In Fig. 6, the blue keywords are chronologically more remote and thus describe topics that have not played a central role in the recent literature. In contrast, the green and, even more so, the yellow keywords represent current topics and, thus, recently covered in the literature. This analysis reveals that words related to the financial and managerial aspects of advanced therapies have been addressed more in the past than in the present, highlighting the lack of attention that academia has been devoting to these topics in recent years despite recent evidence shedding light on the presence of several barriers to funding in medical research and, more specifically, in research on advanced therapies (Restore, 2019).

6. Thematic clusters: results

The network analysis (Fig. 5) revealed the existence of three thematic clusters dealing with financial issues of advanced therapies from different perspectives: a blue cluster with a financial and managerial perspective, a red cluster with an operational and regulatory perspective, and a green cluster with a scientific and industrial perspective. This Section explains the individual clusters by reviewing the articles that best fit the three knowledge clusters.

6.1. First cluster (blue): financial and managerial perspective

The first thematic area concerns studies that, from a financial and

Table 3
Most cited studies.

TC	Title	Authors	Source	Year
151	The Growth of Tissue Engineering	Lysaght, M. J., & Reyes, J.	Tissue Engineering	2001
141	Allogeneic Cell Therapy Bioprocess Economics and Optimization: Single-Use Cell Expansion Technologies	Simaria, A. S., Hassan, S., Varadaraju, H., Rowley, J., Warren, K., Vanek, P., & Farid, S. S.	Biotechnology and Bioengineering	2014
136	Great expectations: Private sector activity in tissue engineering, regenerative medicine, and stem cell therapeutics	Lysaght, M. J., Jaklenec, A., & Deweerd, E.	Tissue Engineering Part A	2008
102	A proposed definition of regenerative medicine	Daar, A. S., & Greenwood, H. L.	Journal of tissue engineering and regenerative medicine	2007
93	Nanomedicine: Past, present and future - A global perspective	Chang, E.H., Harford, J.B., Eaton, M.A., Boisseau, P.M., Dube, A., Hayeshi, R., Swai, H. & Lee, D.S.	Biochemical and biophysical research communications	2015
86	Cell Therapy: Types, Regulation, and Clinical Benefits	El-Kadiry, A. E. H., Rafei, M., & Shammaa, R.	Frontiers in Medicine	2021
82	From bench to bedside? Biomedical scientists' expectations of stem cell science as a future therapy for diabetes	Wainwright, S. P., Williams, C., Michael, M., Farsides, B., & Cribb, A.	Social science & medicine	2006
76	Human pluripotent stem cell-derived products: Advances towards robust, scalable and cost-effective manufacturing strategies	Jenkins, M. J., & Farid, S. S.	Biotechnology journal	2015
73	From bench to FDA to bedside: US regulatory trends for new stem cell therapies	Knoepfler, P. S.	Advanced drug delivery reviews	2015
65	Perspectives for Clinical Translation of Adipose Stromal/Stem Cells	Patrikoski, M., Mannerström, B., & Miettinen, S.	Stem cells international	2019
58	Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe	Ten Ham, R. M., Hoekman, J., Hövels, A. M., Broekmans, A. W., Leufkens, H. G., & Klungel, O. H.	Molecular Therapy-Methods & Clinical Development	2018

managerial perspective, address challenges and best practices for entrepreneurs engaged in developing advanced therapies and explore the funding sources (both private and public) available to them.

Lysaght and Reyes (2001). Lysaght et al. (2008) and Kim et al. (2019) analyze the quantitative dimension of regenerative medicine, highlighting positive trends in size, clinical trials, R&D investments, employment, and the economic-commercial scope of the phenomenon. Despite this, clinical trials in regenerative medicine are limited compared to the overall number of traditional drugs' clinical trials and are characterized by frequent discontinuation. Results show that SMEs play an essential and predominant role in clinical research in regenerative medicine.

SMEs operating in regenerative medicine deal with a high-risk, high-cost, and relatively low investment space characterized by an ever-evolving regulatory framework. In this context, Ginty et al. (2011) affirm that one of the critical elements for the successful commercialization of regenerative medicine products is detailed early-stage assessment and the demonstration of a solid value proposition able to satisfy and meet the requirements of all stakeholders (patients, regulators, investors, payers and clinicians). In induced Pluripotent Stem (iPS) cells research, Prescott (2011) identifies three key elements underlying a successful business strategy, i.e., the pipeline of high-quality products, credible third-party endorsement, and an effective sales and marketing strategy. For this purpose, collaboration and strategic alliances with academic institutions and large biopharmaceutical companies are paramount.

Johnson and Bock (2017) explore how regulatory, scientific, and financial uncertainty around regenerative medicine affects entrepreneurial behavior in the UK, suggesting the need for coping strategies adoption and partnership development. Valuable partners encompass universities, government entities, large biopharmaceutical companies, national healthcare providers, and national-level funders, including private and public funding.

Among funding sources, Banda et al. (2018) show that public investments in innovation infrastructures and facilities, clinical centers, advisory services, and grants are currently bridging the gaps characterizing the value chain of SMEs engaged in developing regenerative medicine products. The importance of public funding initiatives in supporting the development and commercialization of regenerative therapies is also emphasized by Thompson and Foster (2013), Chang et al. (2015), and Kenney and Patton (2018). Other studies also highlight the increasing role of foundations and charities, which started applying venture capital-like investment approaches within the non-profit context and bringing additional financial and relational resources (Reeve, 2012). Capital infusions from venture capital and private equity investors are essential, but there is a misalignment between their investment horizon and the typical timescale of the development of regenerative medicine products (McAllister et al., 2008; Prescott, 2010).

From an investors' standpoint, Bertram et al. (2012) surveyed to understand better the governmental and financial industry's funding rationale in regenerative medicine. Interestingly, all investor types consider regenerative medicine more difficult to evaluate than other biotechnologies. The key factors affecting investment decisions are the uncertainty around clinical validation and the clarity of the regulatory pathway. However, private financial investors (which include venture capitalists, investment funds and banks) pay more attention to time to market than governmental investors and are more willing to fund companies that are already in clinical-stage development, reducing the extent of risk and increasing the probability of a positive financial return, usually pursued through M&A and IPO exit strategies. Early-stage start-up companies attract limited interest, explaining why new ventures indicate access to capital as the primary barrier to success.

6.2. *Second cluster (green): operational and regulatory perspective*

The second thematic area includes studies that, from an operational and regulatory perspective, address the challenges in economic evaluation, effectiveness, pricing and reimbursement, and compliance with regulations underlying the manufacturing and commercialization of advanced therapies.

Within this thematic area, Pinho-Gomes and Cairns (2022) discuss the challenges faced by health authorities during the assessment of Advanced Therapy Medicinal Products (ATMPs). This stems from the difficulty in assessing the clinical effectiveness of ATMPs due to the limitations of the studies available (single-arm and open-label studies with small sample sizes and short follow-ups). The lack of valid and

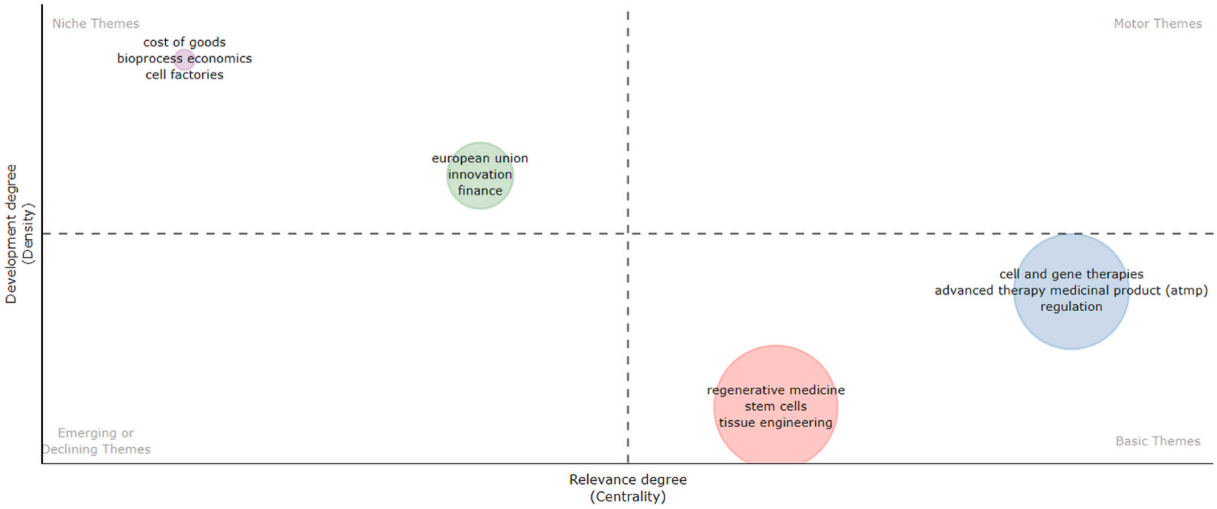

Fig. 4. Thematic map.

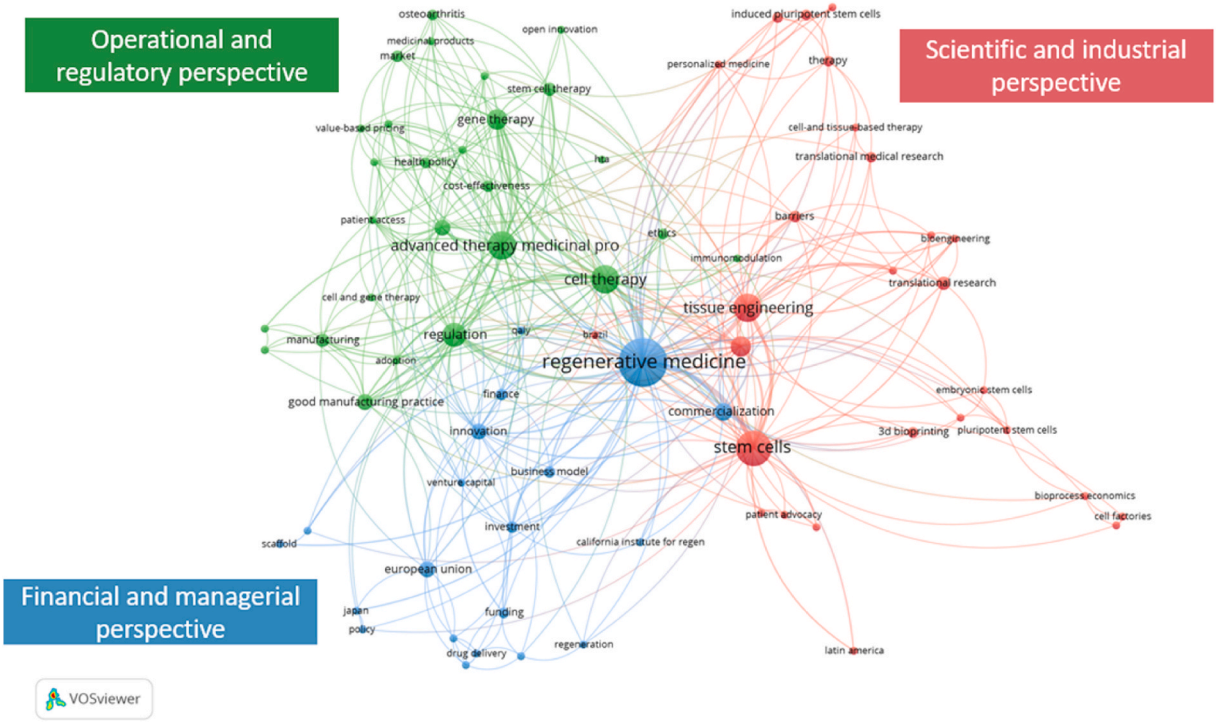

Fig. 5. Co-occurrence analysis.

reliable data also raises uncertainty in estimating the cost-effectiveness of ATMPs, with the risk of over- and under-estimation of utility gains of treatments. The authors suggest the need for adaptations of the traditional Health Technology Assessment (HTA) framework that provides an organizational structure and methodological approach to evaluate clinical, economic, and social effectiveness and impact on the organization of health services. However, traditional HTA needs to be adapted by delving into the new criteria introduced in underlying Cost-Utility Analysis (CUA), such as the life-extending criteria, the severity of the disease, the innovation and additional costs of the technology, the impact on inequalities, and the benefits for patients and society. Also, Coyle et al. (2020) make recommendations on possible adaptations of the HTA framework for a fairer evaluation of ATMPs, including the incorporation of additional elements of value, such as those related to societal benefits (e.g., savings in long-term social care costs, financial positive effects for patients' family, etc.), and Multi-Criteria Decision Analysis (MCDA).

The uncertainty around determining ATMPs' value also has implications for identifying the "right" pricing and reimbursement method that can reconcile the economic sustainability of the healthcare system with the profitability of ATMPs' manufacturers. In this regard, Goodman et al. (2022) identify two main categories of Alternative Payment Models (APMs) that give added incentive payments or forms of risk mitigation to provide high-quality and cost-efficient care. The selection of the "right" APM model depends on several factors, including the indications of the therapy, its relevant health-related outcomes, its cost compared to standard therapies, and the probability of achieving the set targets.

Michelsen et al. (2020) state that outcome-based APMs may be a feasible solution to access high-cost, one-shot curative therapies.

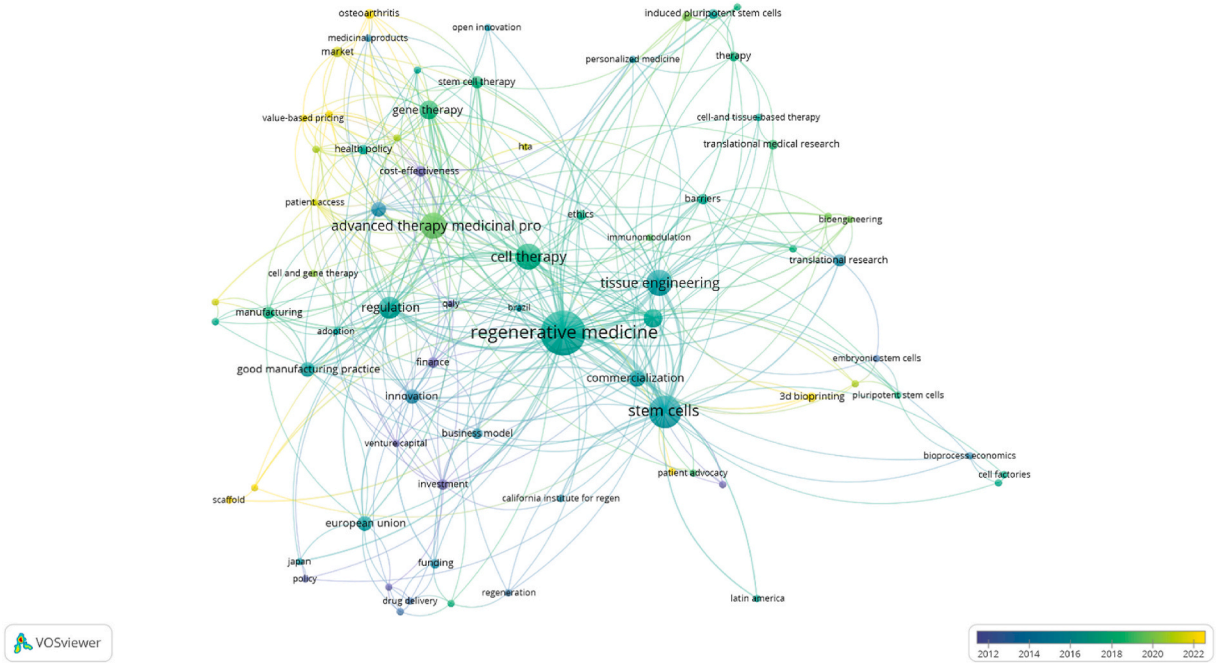

Fig. 6. Overlay analysis.

However, its implementation faces numerous difficulties in reaching agreement among the various stakeholders due to the absence of a governance structure that controls the roles and responsibilities of all stakeholders.

Pearce et al. (2014) focus on ATMPs' mandatory compliance with Good Manufacturing Practice (GMP) to ensure quality, safety, and efficacy regulatory requirements. The authors conclude that the heterogeneous implementation of regulations is a considerable barrier to the development of ATMPs because of the high cost and unrealistic expectations of product qualification requested for their approval.

Knoepfler (2015) studied the trend toward accelerating the study of stem cell products in human patients by examining the mechanisms the Food and Drug Administration (FDA) considered to accelerate their introduction for serious and unresolved diseases. A recent contribution by Pimenta et al. (2021) highlights that special mechanisms to accelerate the assessment of advanced therapies are common in countries other than the US, including the European Union, Brazil, Japan, South Korea, and China. Despite these efforts, the authors emphasize a large gap between the number of executed clinical trials worldwide, the number of advanced therapies that managed to be commercialized, and the uncertainty around reimbursement strategies. In this vein, Iglesias-López et al. (2023) highlight that non-harmonized assessment of ATMPs and heterogenous pricing and reimbursement schemes across different jurisdictions pose severe challenges to ATMP developers, make data-sharing inefficient and increase regulatory costs and time-to-market. Nevertheless, an increasingly common interest is aligning guidelines and technical aspects for developing advanced therapies to accelerate patients' access to developed treatments and generate significant long-term benefits for manufacturers and patients.

6.3. *Third cluster (red): scientific and industrial perspective*

The third thematic area includes studies that, from a scientific perspective, highlight the barriers and challenges clinicians face while developing advanced therapies while also enclosing practical evidence and guidelines for a successful translation.

Among the most cited papers in the sample, Wainwright et al. (2006) contribute to this thematic area by exploring the factors influencing stem cell therapies' translation "from bench to bedside" in the area of diabetes ("from bench to bedside" is an expression used to describe the process by which the results of research done in the laboratory are directly used to develop new ways to treat patients). External expectations, such as those of governmental and funding bodies and large pharmaceutical companies, and the quantitative/qualitative distance between (basic) scientists and (applied) clinicians, strongly influence translation's success in addition to the scientific barriers yet to be overcome. Similarly, Chehelgerdi et al. (2023), focusing on using induced pluripotent stem cells (iPSC) for cancer treatment, state that one of the significant challenges is the generation of high-quality iPSC. The reprogramming process underlying iPSC generation often shows genomic abnormalities, limiting the therapeutic potential and increasing the safety risks of iPSC, including tumorigenicity.

Ten Ham et al. (2018) surveyed European companies on ATMP development challenges. Regulatory issues, technical difficulties, scientific challenges, and financial concerns were identified. Companies declared difficulties in testing the efficacy and safety of therapies addressing rare and previously untreated diseases due to the small number of patients and little disease progression knowledge. Even in the final clinical phases, companies state that there are severe challenges in executing trials, enrolling a sufficient number of participants, and recruiting skilled personnel with ATMP-specific knowledge.

Spencer et al. (2015) provide a strategic insight into their experience translating their basic research into a clinical-grade product to treat angina, focusing mainly on operational and scientific difficulties given that public and non-profit funders supported the therapy.

From an industrial standpoint, other studies provide an in-depth overview of the scalability, robustness, and cost-effectiveness challenges of ATMPs' manufacturing process, such as Simaria et al. (2014) that propose an integrated decisional tool combining bioprocess economics and optimization for allogeneic different cell therapy products. In a similar vein, Jenkins and Farid (2015) review the factors influencing the two main cost metrics in the manufacturing of human pluripotent stem cells (hPSCs), i.e., capital investments and cost of goods, while paying attention to progress made on improving the economic and operational feasibility of hPSC bioprocessing.

7. Discussion

Financial resources are the lifeblood of medical research and the development of drugs and therapies for all patients, which are prerequisites for improving public health and social and economic inclusion. In the specific field of advanced therapies, characterized by a higher risk of research discontinuity or interruption, longer timescale, higher development cost, and more significant financial needs than conventional drugs, Finance may contribute to improving the continuity of financial resources at the disposal of SMEs (or BioTechs) developing advanced therapies and avoiding their loss in biomedical and economic "valleys of death".

In this work, we tried to identify financial issues and criticalities of developing advanced therapies, summarise the main insights, and show strands, trends, and future research avenues through a bibliometric and systematic literature review.

Regarding our first research question, **RQ1** (How and to what extent have studies addressed financial issues related to supporting medical research in advanced therapies?), the bibliometric review reveals that despite the increasing number of contributions dealing with the financial issues and criticalities of advanced therapies (Fig. 2), the most cited and prolific journals do not belong to the areas of finance or business economics (Table 2), confirming that finance studies paid little attention on the role that financial institutions and markets may play in progressing advanced therapies from bench to patients' bedside. Life science experts have mainly addressed this topic. Moreover, the thematic analysis on the co-occurrence of keywords shows that the topics linked explicitly to financial aspects of medical research in advanced therapies appear to be niche and isolated, thus less developed and relevant compared to other themes (Fig. 4). Finally, the overlay analysis highlights the lack of attention that academics belonging to financial disciplines have been devoting to these topics in recent years. Overall, the review highlights the urgency of innovative and numerous contributions by financial researchers who can better address the funding gaps of medical research in advanced therapies, enhancing financial innovation and applying rigorous and systematic models, methods, and schemes to contribute to the success of SMEs involved.

Regarding the second research question**, RQ2 (**Who are the most influential studies/contributors, and to which disciplinary areas do they belong?), the study by Lysaght and Reyes (2001) is the most influential work (Table 3). The authors analyzed the expansive phenomenon of start-ups specializing in tissue engineering. They highlighted the emergence of robust commercial activity in the engineering sector involving the United States, Europe, and Australia. The other two most influential studies were published by Lysaght et al. (2008) and Simaria et al. (2014) and are the logical continuation of the previous study, analyzing the financial issues of advanced therapies. These three contributions and their authors belong to the medical, biotechnology, and bioengineering disciplines. Interestingly, the most productive countries have worked collaboratively, highlighting the presence of cross-country collaborations between academics, scientists, and clinicians in developing new and innovative therapies and understanding the underlying challenges and success factors (Fig. 3).

Regarding the third research question**, RQ3** (What peculiarities/challenges have the studies focused on?), the common link underlying the 174 contributions considered in this review is the evidence that medical research in advanced therapies shows peculiarities contributing to increased timescale, costs, risk, financial needs, and operational and regulatory uncertainty. These features are unattractive to investors and obstruct access to financial resources. The systematic review enabled us to identify three thematic areas, each addressing the financial issues of advanced therapies from different perspectives:

1) Studies with a financial and managerial perspective, exploring the potential benefits of strategic alliances and adequate disclosure on the ability of entrepreneurs to overcome scientific and technical hurdles and to attract public and private investors, thus addressing companies' financial needs;
2) Studies with an operational and regulatory perspective, analyzing how the limitations of clinical trials in the field of advanced therapies (non-randomized, single-arm, and open-label studies) generate uncertainty around the economic assessment, approval patterns, pricing and reimbursement of the therapies while highlighting regulatory challenges;
3) Studies with a scientific and industrial perspective, exploring the challenges clinicians usually face in the lab, including scientific barriers in testing the safety and effectiveness of therapies, problems and costs of the supply chain, and difficulties in optimization, cost-effectiveness, and scaling-up of production.

The above-mentioned thematic areas confirm the lack of attention paid by finance academics in supporting the development of advanced therapies. Financial markets and institutions are among the possible private investors of SMEs that manufacture such valuable therapies. However, none of the studies considered in this review provides a detailed picture of their funding activity, rationale, and the assessment and allocation mechanisms implemented or available.

7.1. Research agenda

The last research question we answer is "What are the possible research paths?" **(RQ4)**.

We conclude the study by pointing out the future research directions identified in the extant literature and proposing research streams to stimulate further qualitative and quantitative studies from finance academics.

7.1.1. Future research directions: suggestions from extant literature

Some future research directions identified by the analyzed contributions are summarized in Table 4. Financing the development of advanced therapies is challenging, and the extant literature recognizes this well. Studies adopting a financial and managerial perspective suggest that a careful analysis of the financial needs of innovative therapies is of utmost importance in identifying the most suitable allocation of public and private funds along the entire research pipeline. Funding models based on risk pooling and sharing, such as dedicated public funds and more muscular insurance systems, begin to be considered by academics but necessitate further investigation.

Furthermore, extant studies focused on SMEs' developing advanced therapies suggest that strategic partnerships, in particular with large pharmaceutical companies and academia, and open innovation practices could be beneficial, even if further research should stress and quantify the benefits of such coping strategies in terms of manufacturing optimization, organizational flexibility, resource and knowledge sharing, innovation and survival/failure of companies.

From an operational and regulatory standpoint, extant studies suggest that further research exploring and proposing adaptations of traditional valuation methods (HTA) is needed to analyze the different practices adopted by health authorities in different countries and identify harmonization strategies. Also, new approaches in generating evidence and evaluating advanced therapies, eventually extracting, collecting, and analyzing data worldwide by implementing machine learning and artificial intelligence technologies, could lead to pricing and reimbursement mechanisms, maximizing affordability and accessibility for patients. Overall, further research should develop recommendations for implementing novel reimbursement schemes, analyzing how they can work in practice and overcome the existing barriers.

From a scientific and industrial perspective, the extant literature also underlines the need for additional research exploring the root causes of scientific and technical uncertainties faced by basic, preclinical, and clinical researchers in advanced therapies. Such uncertainties are mainly linked to scientific barriers to testing the safety and effectiveness

Table 4
Research agenda.

Cluster	Theme	Research agenda	Source
Cluster 1 (blue)	Financial and managerial perspective	• More systemic analyses of the need for potentially disruptive innovations in regenerative medicine • Need to explore optimal public and private funding strategies to move regenerative medicine from concept to therapy • Need to investigate "ATMP-specific fund" as likely sustainable models for ATMPs • Future studies should address the need for more muscular insurance systems for regenerative medicine, essential for internationally aligning and harmonizing the progress of regenerative medicine worldwide • Further research could stress the benefits of collaborations and open innovation consortia in terms of innovation, decentralized manufacturing, organizational flexibility, and combination of stakeholder resources, knowledge, and objectives • Further studies can illuminate strategies and management and organizational infrastructure able to balance organizational flexibility with greater coordination within the diverse nexus of players and networks of innovation platforms and ecosystems • Further studies could explore the drivers and outcomes of coping strategies, including survival/failure of regenerative medicine ventures	Nguyen et al. (2022), Banda et al. (2018). Hanna et al. (2018), Hossain and Milne (2018), Papadaki (2017), Johnson and Bock (2017), Teng et al. (2014), Okada et al. (2017).
Cluster 2 (green)	Operational and regulatory perspective	• Real-world evidence will be the most effective way to separate hype from hope and to establish the most sustainable mechanisms to fund such products • Machine learning and artificial intelligence technologies can be implemented for extracting, collecting, and analyzing clinical data and stratifying patients with rare diseases • Adaptations of the conventional decision-making process rather than entirely new methods may improve appraisals of ATMPs • Further analytical and comparative studies among countries focused on the HTA concerns of ATMPs should be performed • Need for new approaches to generate evidence and develop payment and reimbursement models to ensure affordable life-saving therapies • Solid scientific and ethical standards must be explicitly developed and adapted to the clinical translation of regenerative medicine.	Pinho-Gomes and Cairns (2022), Kamusheva et al. (2021), Pani and Becker (2021), Pimenta et al. (2021), Michelsen et al. (2020), Blasimme and Rial-Sebbag (2013).
Cluster 3 (red)	Scientific and industrial perspective	• Further research should include the exploration of the root causes of challenges linked to the novelty of the field, new and orphan indications, and scientific and technical uncertainties • To understand the challenges, overall costs, and supply chain robustness of these life-saving cell therapies more comprehensively, the entire process from tissue procurement to post-administration should be considered • Case studies could help create decision-making tools to design scalable and financially feasible ATMPs	da Silva et al. (2021), Lam et al. (2018), Ten Ham et al. (2018).

of therapies, problems and costs of the supply chain, and difficulties in optimization, cost-effectiveness, and scaling-up of production, usually leading to financial unsustainability. Future research based on case studies could help create decision-making tools to design scalable and financially feasible production of advanced therapies. In this sense, further studies are needed to develop comprehensive decisional tools, considering the entire process from supplies procurement to post-administration of therapies.

7.1.2. Future research directions: our proposed research agenda

The review of the literature and the lines of research that emerge reflect the atomistic approach to the topic, often fragmented into individual aspects or phases necessary for the development of innovative therapies. The literature replicates how individual phases are managed by researchers, clinicians, regulatory authorities, and public and private funders. There is still a lack of overview of the entire process and the interdisciplinarity necessary to study operational and financial needs adequately. This gap makes it impossible to identify and study operational and financial solutions and, therefore, to manage the entire development process and commercialization of advanced therapies.

Scientific, operational, and regulatory risks underlying medical research in advanced therapies make clinical and cost-effectiveness assessment challenging, dissuade capital infusions from potential funders and generate funding gaps. Overall, the biomedical and economic "valleys of death" raise the risk that advanced therapies will not reach the patients, even when they receive regulatory approval from health authorities. All this contributes to increased social and inequality costs. For this reason, future research should urgently contribute theoretically and empirically to the subject and organically focus on the internal and exogenous factors that influence costs, timing, uncertainty, and possible future revenues from advanced therapies, which may affect the ability to create value and attract financial resources. Finance could provide tools, evaluation models, and new operational, regulatory, and financial schemes that measure and demonstrate advanced therapies' social and economic sustainability.

A first field/line of research should address the high incidence of fixed costs characterizing the development process of advanced therapies, mainly originating from strict regulatory requirements (GMP), the need for special equipment and expertise, and the complexity of therapies. Beyond the participation in the open innovation ecosystem mentioned in the extant studies, future studies should introduce and test consortium structures to cut the huge fixed costs determined by GMP requirements. Consortium models might help to overcome the sterile atomistic view of the monetization of intellectual property, generating virtuous mechanisms in which innovation processes are strengthened, new sustainable industrial models germinate, and innovative start-ups in the bio-medical field emerge. This contributes to a participative and sustainable community development process, enhancing excellence in research, hospital centers of clinical experimentation, investments, existing facilities, and the biomedical entrepreneurial network.

A second field/line of studies should focus on the self-financing capacity of individual advanced therapies. In particular, by observing the process underlying the development of individual advanced therapies, future studies should identify and propose possible economic models based on endogenous flows originating from the valorization of intermediate outputs (organoids, data, intermediate platforms, technological know-how, etc.) and the related reduction of financial needs up to the marketing authorization, with a concrete direct impact on the funding of research and its ability to attract funders. By increasing self-financing capacity and the attractiveness to external funders, these new economic and operating models could help prevent advanced therapies from getting lost in the biomedical and economic "valleys of death".

A third line of research should analyze the new possibilities offered by financial innovation and engineering. Moreover, it should analyze the different forms of supporting SMEs operating in advanced therapies that significantly bring such therapies to the market. These could bring to the identification of new and effective vehicles and financial public-private intervention schemes that, based on dedicated portfolio

selection criteria and methods for risk pooling and sharing, can expand and encourage the participation of private retail and institutional investors (including National Insurance Systems) and, consequently, better address the funding gaps of the development of advanced therapies and their translation and survival on the market.

A fourth new line of research could study how funders, including financial institutions, could incorporate additional elements of value, especially social value, in their decision-making process and assessment models. Despite developing sustainable investment practices that consider environmental, social, and governance (ESG) considerations when making investment decisions in the financial sector, the social considerations are not very in-depth due to a regulatory delay in identifying the taxonomies to be used. Beyond the alibis, it is clear that Finance is more inclined to enhance the elements (environmental and governance) that immediately translate into lower risks or higher returns for investments. In contrast, the social components translate into benefits that only partially or indirectly concern private investors. Social value is community wealth, and this is precisely the area where future research can contribute, studying mechanisms and schemes to consider social value and achieve its fairer distribution between communities, different healthcare systems, and investors. Financing advanced therapies could also contribute to reducing health inequalities (Bouchard et al., 2015) between patients with widespread diseases (more profitable) and rare diseases (less profitable) and, given their definitive nature, reduce inequalities in access to long-term medical care. Joint research by economists and financial and actuarial academics could also identify better ways of distributing social benefits for public and private health insurance. In this vein, to enlarge the participation of investment funds and other private funders (even not financial or industrial players), further research should also contemplate some form of social premium or public incentive to compensate for the more patient and less speculative capital and perhaps the possibility of introducing ESG bonuses (or ESG credits) linked to investments in biomedical research (especially when supporting the phases of translational research, with is the most exposed to financial rationing).

Finally, a relevant line of research should concern the health regulatory approach and policies. There are two relevant issues to be addressed, which would complete, from a financial point of view, what was proposed by Olesti et al. (2024). The first issue concerns the current case-by-case regulatory approach adopted in the approval process. It generates operational uncertainty and organizational complexity, extends the time-to-market of advanced therapies, and ultimately negatively influences funding. To avoid financial hurdles and better guide regulators and health authorities in their decision-making process, future studies could explore and develop regulatory assessment models designed for advanced therapies without transposing or adapting models already implemented to assess other conventional drugs, devices, and therapies. The second issue concerns reimbursement and pricing models. Research should investigate how to include social benefits and an appropriate risk premium for funders and developers of advanced therapies to compensate for the small number of patients (rare diseases) and the high uncertainty involved in development processes. This is particularly pursuable if the opportunity cost savings arising from the definitiveness nature of advanced therapies are considered, including the ability to transform a patient under prolonged care and without a whole social and working life into an individual no longer in need of care and able to work and create social value. Also, in this context, interdisciplinary research between life scientists, economists, financial and actuarial experts can help identify how to reconcile these benefits with the needs of different national health systems. It would help to limit cases of withdrawal of effective therapies from the market due to inadequate reimbursement agreements negotiated with National Health Systems (i.e., the so-called economic "valley of death").

8. Conclusions, implications, and limitations

This work aims to review the challenges hindering financing advanced therapies and outline research directions that could support their development and problem-solving.

The findings highlight that finance academics paid little attention to the topic; most of their contributions are now outdated and, therefore, do not consider the new opportunities and solutions offered by financial innovation and the application of new technologies to financial activity. This is a significant weakness in reducing the funding gap and in the operational and organizational optimization of the innovative therapy development process. The second conclusion concerns the need for interdisciplinary studies exploring advanced therapies' barriers from a holistic and process perspective. A third conclusion concerns the need to exploit the social value generated by the development of innovative therapies, also from a fundraising perspective. Finance is pivotal and enables the allocation of resources towards more sustainable initiatives. In this context, a future line of research could contribute to reducing the distance between Finance and social considerations (the component "S" of ESG-oriented decisions).

Following our functionalist theoretical approach, the study of the elements and obstacles that characterize the processes of biomedical research can contribute to identifying the activities that Finance must carry out to enable the development of advanced therapies.

In addition to highlighting the role that Finance can play in developing advanced therapies, the results highlight the obstacles and value destroyed by the absence of an organic and coordinated process of public intervention. The role of public resources is fundamental in making fundable therapies with uncertain profiles, development times, and financial needs incompatible with private investors' intervention. To this end, public resources should be allocated not only by looking at the scientific merit of the individual project but also at the whole process of therapy development. This would help reduce the inequalities that exist between patients with common (and well-treated) diseases versus those with rare or neglected diseases and overcome the biomedical and economic 'valleys of death' that characterize the translation and commercialization of advanced therapies.

The results pose a challenge to regulatory and pharmaceutical authorities. There is a need for a better balance between safety and quality requirements in the testing and approval processes of advanced therapies, particularly for rare and neglected diseases, along with reducing uncertainty in the authorization/registration process. The development of tailored regulatory assessment models specific to advanced therapies could overcome the challenges posed by the current case-by-case regulatory approach, which generates operational uncertainty, extends time-to-market, and hinders funding. Moreover, pricing and reimbursement models that account for social benefits and appropriate risk premiums are crucial to align the interests of ATMPs developers, healthcare systems, and patients, thereby reducing the withdrawal of effective therapies due to inadequate reimbursement agreements.

This work has some limitations, mainly related to the exclusive use of the Web of Science database. Although it is one of the largest databases at the level of journal coverage (Waltman, 2016; Boubaker et al., 2023), future research may address the topic by enlarging the sample of studies through multiple databases, such as Scopus or PubMed. Furthermore, the advent of big data and machine learning techniques could help future researchers perform a bibliometric review that includes the grey literature on the topic. Finally, it would be interesting to expand the bibliometric and systematic literature review to medical research financing in general, trying to pinpoint similarities and dissimilarities between advanced therapies and conventional drugs.

CRediT authorship contribution statement

Simona Cosma: Writing – original draft, Validation, Supervision, Formal analysis, Conceptualization. **Stefano Cosma:** Writing – original

draft, Validation, Supervision, Formal analysis, Conceptualization. **Daniela Pennetta:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giuseppe Rimo:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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