Precision Medicine and Engineering 3 (2026) 100063

Contents lists available at ScienceDirect

Precision Medicine and Engineering

journal homepage: www.sciencedirect.com/journal/precision-medicine-and-engineering

Review

Advanced therapy medicinal products: Emerging therapeutic frontiers and evolving regulatory landscapes

Alessio Bucciarelli [a,*], Antonella Motta [a,b]

[a] BIOtech Research Center and European Institute of Excellence on Tissue Engineering and Regenerative Medicine, Department of Industrial Engineering, University of Trento, Trento, Italy
[b] Department of Biochemistry and Microbiology, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, 10330, Thailand

ARTICLE INFO

Keywords:
Advanced therapy medicinal products
Gene therapy medicinal products
Somatic cell therapy medicinal products
Tissue engineered products
Combined advanced therapy medicinal products

ABSTRACT

Advanced Therapy Medicinal Products (ATMPs) are reshaping therapeutic paradigms by enabling disease-modifying and regenerative interventions that address the root causes of pathology. This review explores the scientific, clinical, and regulatory dimensions of ATMPs, focusing on their classification into gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (sCTMPs), tissue-engineered products (TEPs), and combined ATMPs (cATMPs). While GTMPs and sCTMPs have demonstrated increasing clinical maturity and market penetration, TEPs and cATMPs remain underrepresented despite a substantial scientific foundation in tissue engineering. This discrepancy highlights a critical translational gap likely driven by manufacturing complexity, challenges in mechanism-of-action validation, and regulatory ambiguity. We provide a comparative analysis of the regulatory frameworks in the European Union and the United States, emphasizing how differing classification schemes, definitions of substantial manipulation, and market authorization pathways impact product development. By examining commercial products, scientific principles, and evolving regulatory strategies, this review aims to clarify current trends, identify persistent barriers, and propose directions for harmonizing innovation with clinical and regulatory readiness across all ATMP categories.

1. Introduction

The perception of advanced therapy medicinal products (ATMPs) has changed dramatically in recent years, transitioning from experimental research to a key element of clinical practice. No longer limited to specialized laboratories, ATMPs are now gaining attention from a broad range of stakeholders, encompassing academic researchers, biotech startups, major pharmaceutical companies, regulatory agencies, and healthcare providers. While traditional small-molecule drugs and biologics have long underpinned modern medicine, ATMPs represent a new frontier in which living cells or genetic sequences themselves may be crafted to fight disease at its source. The rise of this field shows that traditional boundaries between research areas are blurring, creating a collaborative space for molecular biology, materials science, immunology, bioengineering, and clinical practice.

This domain comprises several innovative modalities. Gene therapies, for instance, aim to correct disease-causing mutations by adding, removing, or editing genetic sequences in a patient's cells. The introduction of advanced gene-editing methods, including

This article is part of a special issue entitled: New Avenues in PM&E published in Precision Medicine and Engineering.

* Corresponding author.
E-mail address: alessio.bucciarelli@unitn.it (A. Bucciarelli).

https://doi.org/10.1016/j.preme.2026.100063
Received 23 September 2025; Received in revised form 5 January 2026; Accepted 27 February 2026
Available online 28 February 2026

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9, base editors, and prime editing, has profoundly influenced this sphere, enabling more targeted interventions than ever before [1,2]. Already, certain gene therapies have produced life-altering outcomes in patients with inherited retinal disorders, immune deficiencies, or neuromuscular diseases, reducing complex pathologies to something that can potentially be corrected at a fundamental genetic level. A notable illustration is the treatment of spinal muscular atrophy (SMA), where a one-time intravenous infusion of a gene therapy vector has altered the clinical course for young patients who previously faced severely limited treatment options [3]. Alongside gene therapies, cell-based products have captured increasing attention. Chimeric antigen receptor T cells (CAR-T), for example, are now recognized as revolutionary agents in certain forms of leukemia and lymphoma. By reprogramming a patient's own immune cells to identify and destroy malignant targets, this strategy offers new hope where conventional chemotherapies have failed [4]. Beyond hematological cancers, cellular immunotherapies are being investigated for solid tumors, infectious diseases, and even autoimmune disorders, illustrating just how adaptable these approaches can be. Furthermore, regenerative medicine applications harness adult stem cells (such as mesenchymal stromal cells (MSCs)) or induced pluripotent stem cells (iPSCs) to repair damaged tissues. This might soon offer relief for individuals with chronic heart disease, osteoarthritis, or non-healing wounds. The third major category, tissue-engineered products, pushes the boundary even further by aspiring to produce functional tissues and possibly entire organs in the lab. Researchers are working to develop living implants that closely resemble natural tissues by carefully combining specially selected cells with biocompatible scaffolds, frequently produced using advanced methods such as 3D bioprinting, in an effort to develop functional replacements for damaged or diseased tissues [5]. This approach may ultimately mitigate organ donor shortages and reduce the risks associated with traditional transplantation. Although still in relatively early stages compared to gene or cell therapies, tissue engineering is progressing steadily, propelled by rapid advances in materials science, imaging technologies and a deeper understanding of cellular differentiation and tissue organization.

From a regulatory perspective, ATMPs have compelled a reevaluation of existing oversight frameworks. In the European Union (EU), the Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA) now plays a central role in reviewing these products, assessing their quality, safety, and efficacy profiles before they reach patients [6]. In the United States (US), the Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) guides the approval process for cell and gene therapies [7]. Both entities have begun crafting specialized approval pathways and issuing evolving guidance documents that reflect the need for flexibility in an area defined by rapid scientific and technological growth. The development of regulatory pathways for these complex living products is a substantial challenge due to their intricate, patient-specific manufacturing and quality control processes, which are vastly different from those used in traditional pharmaceuticals.

The manufacturing and supply chain requirements for ATMPs present some of the most formidable hurdles. Unlike pills or even standard biologics, ATMPs may rely on cells extracted directly from a patient, modified in a centralized facility under strictly controlled conditions, and then transported back to the clinic as a personalized therapy. Ensuring the chain of custody, maintaining sterile conditions, and verifying the product's quality and potency at every step is both time-consuming and resource intensive. Gene therapies, on the other hand, depend on substantial quantities of viral vectors or similar complex delivery methods, all requiring rigorous purity and concentration standards. Addressing these issues demands not only improvements in bioprocessing technologies but also the development of new analytical tools and standardized protocols. A collaborative ecosystem involving industry, academia, and regulatory bodies is crucial for building robust manufacturing platforms [8].

Cost and availability are also major factors in ATMP discussions. The very attributes that make these therapies powerful (their complexity, personalization, and targeted mechanisms) also contribute to high development and production costs. Some gene and cell therapies carry price tags exceeding several hundred thousand dollars per treatment, which poses serious questions for healthcare systems already under stress. In response, new financing models and value-based reimbursement schemes are being explored. Pay-for-performance agreements, annuity-style payments, and risk-sharing contracts might help distribute financial burdens more equitably, ensuring that patients can receive potentially curative therapies without bankrupting payers or restricting access to only the wealthiest populations (in this context, it is worth acknowledging the Alliance for Regenerative Medicine [9]). Success in this sector depends on transparent dialogues among industry stakeholders, insurers, patients, and policymakers, who must work collaboratively to design frameworks that acknowledge the transformative value of ATMPs while maintaining sustainability. Ethical concerns arise because manipulating genes and creating tissues has implications beyond the individual. Issues related to genetic privacy, heritable genome editing, and potential off-target effects have prompted widespread debate. Public opinion on these matters varies, and consensus can be difficult to achieve. Nonetheless, establishing ethical guidelines that guide responsible research, and clinical application is imperative. These discussions must incorporate a diverse range of voices, including ethicists, clinicians, patient advocates, and policymakers [10]. Equally essential is the long-term monitoring of treated patients, both to ensure safety and to understand the durability of therapeutic benefits. Because ATMPs can produce lasting biological changes, vigilance in post-marketing surveillance and the maintenance of patient registries are critical strategies to detect any unforeseen consequences that may emerge over time [11].

Despite persistent challenges for scientists, clinicians, and regulators, the future of ATMPs remains undeniably promising. These methods have the potential to fundamentally alter the treatment of previously incurable diseases, providing durable or even permanent relief by addressing the underlying pathology. This paradigm shift has the potential to revolutionize patient outcomes and redirect research efforts towards the creation of more precise, mechanistically driven therapies. In the following sections, we will conduct a more in-depth examination of ATMPs, covering their classification, regulatory landscape, historical and scientific basis, current market products, and future pipeline products, thereby providing a comprehensive overview of this dynamic field. By doing so, we aim to lay the groundwork for future developments and informed decision-making in both research and regulatory contexts.

2. Classification of ATMPs in Europe and the United States and regulatory framework

In Europe (EU), the classification of ATMPs is clearly defined by Regulation (EC) No 1394/2007 [12], which divides these products into four principal categories: gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (sCTMPs), tissue engineered products (TEPs), and combined ATMPs (cATMPs). This regulatory framework was established to address the unique complexities associated with biological and cell-based therapies, ensuring that products intended for clinical use are held to rigorous standards of quality, safety and efficacy. The EU regulatory system's granularity in classifying ATMPs reflects an intent to tailor the development and evaluation processes to the specific characteristics of each product type. A clarification of the distinction between these categories has been provided by the CAT in a reflection paper [13]. The main distinction among the different GTMPs relies on the Mode of Action (MoA), which might be defined as the way in which the product achieves its intended therapeutic effect (whether through gene expression, cellular activity, or tissue restoration). Key aspects that define the MoA include the origin and type of cells or substances used (for instance, whether they are genetically modified), the function these components perform in the recipient (and whether it differs from their function in the donor) and the nature of the therapeutic effect, whether it is biochemical (as in gene or somatic cell therapy) or structural or mechanical (as in tissue engineering). Additionally, the role of any non-cellular components, such as scaffolds or matrices, is also critical: if they are integral to the therapeutic action and qualify as medical devices, the product may be classified as a cATMP. In Table 1 and Fig. 1 we summarized the main differences among the ATMP categories, and in Fig. 2, we provide a general workflow to determine the ATMP category based on the type and manipulation of cells or biological tissues.

GTMPs are biological medicinal products that contain or consist of recombinant nucleic acid sequences used with the intent to regulate, repair, replace, add, or delete a genetic sequence in order to treat, prevent, or diagnose a disease. Importantly, the therapeutic effect must directly relate to the recombinant nucleic acid sequence or its expression product. sCTMPs, on the other hand, are composed of cells or tissues containing viable cells that have either undergone substantial manipulation or are used for a function in the recipient that is different from the essential function they perform in the donor. These products exert their effects through pharmacological, immunological, or metabolic action. TEPs are products that contain or consist of engineered cells or tissues containing cells, whether viable or non-viable, used with the aim of regenerating, repairing, or replacing human tissue. Under Regulation (EC) No 1394/2007, cells, or tissues containing cells, are considered “engineered” if the cells have been substantially manipulated or are intended for non-homologous use (i.e., a function different from the essential function they originally performed). The distinction between sCTMPs and TEPs lies mainly in their intended clinical use: sCTMPs treat diseases primarily through biological activity, whereas TEPs aim to restore or replace tissue structure and function.

It is worth noting that both sCTMPs and TEPs rely on the regulatory definition of “substantial manipulation”, which refers to

Table 1
Description of the ATMP categories as defined by the EU regulation (Regulation (EC) No 1394/2007) [12].

ATMPs	MoA	Description
GTMPs	The therapeutic effect is directly linked to the recombinant nucleic acid sequence or the product of its expression. A gene that codes for a missing enzyme is inserted, and its expression corrects a metabolic disorder.	These products contain an active substance that is a gene (delivered by viral or non-viral vectors) or a genetically modified cell. The therapeutic effect is achieved primarily through the modification of genetic material. As a result, GTMPs undergo additional safety assessments, especially regarding potential risks like insertional mutagenesis or off-target effects. CAR-T therapies are included in this category because without genetic modifications the therapy wouldn't be effective.
sCTMPs	The cells act pharmacologically, immunologically, or metabolically.	These involve the use of cells that are often manipulated or expanded ex vivo. Their therapeutic effect is derived from the cellular functions (secrete cytokines, stimulate immune responses, or regulate metabolism). Even if cells are modified to enhance their function, if the primary mode of action is based on the cells' natural properties rather than on a direct genetic change, they are regulated as sCTMPs
TEPs	The cells or tissues are primarily used to regenerate, repair, or replace human tissues, often through structural or mechanical support, not active biochemical signaling.	TEPs are products that contain or consist of engineered cells or tissues containing cells and are specifically designed to regenerate, repair, or replace human tissue. Their therapeutic effect derives primarily from the biological activity of the cells, which enables the reconstruction or restoration of tissue structure and function. TEPs frequently involve a combination of cells with biomaterial scaffolds or matrices; in such cases, the additional material is not considered a medical device, as it serves solely as a supporting matrix for the active cellular component and does not exert an independent therapeutic effect. Fully decellularized tissues, in the absence of viable cells, do not meet the definition of TEPs, irrespective of their intended application, and are therefore regulated outside the ATMP framework unless they are combined with cells to form a tissue-engineered construct.
cATMPs	A combination of biological and mechanical actions where a medical device component (e.g., a scaffold or matrix) is integral to the function of the product.	These are ATMPs that include, as an integral part of the product, one or more medical devices. The device isn't just a container or an accessory; it plays an active role in the therapeutic effect. In many cases, TEPs become cATMPs when they incorporate a scaffold or matrix that is considered a medical device.

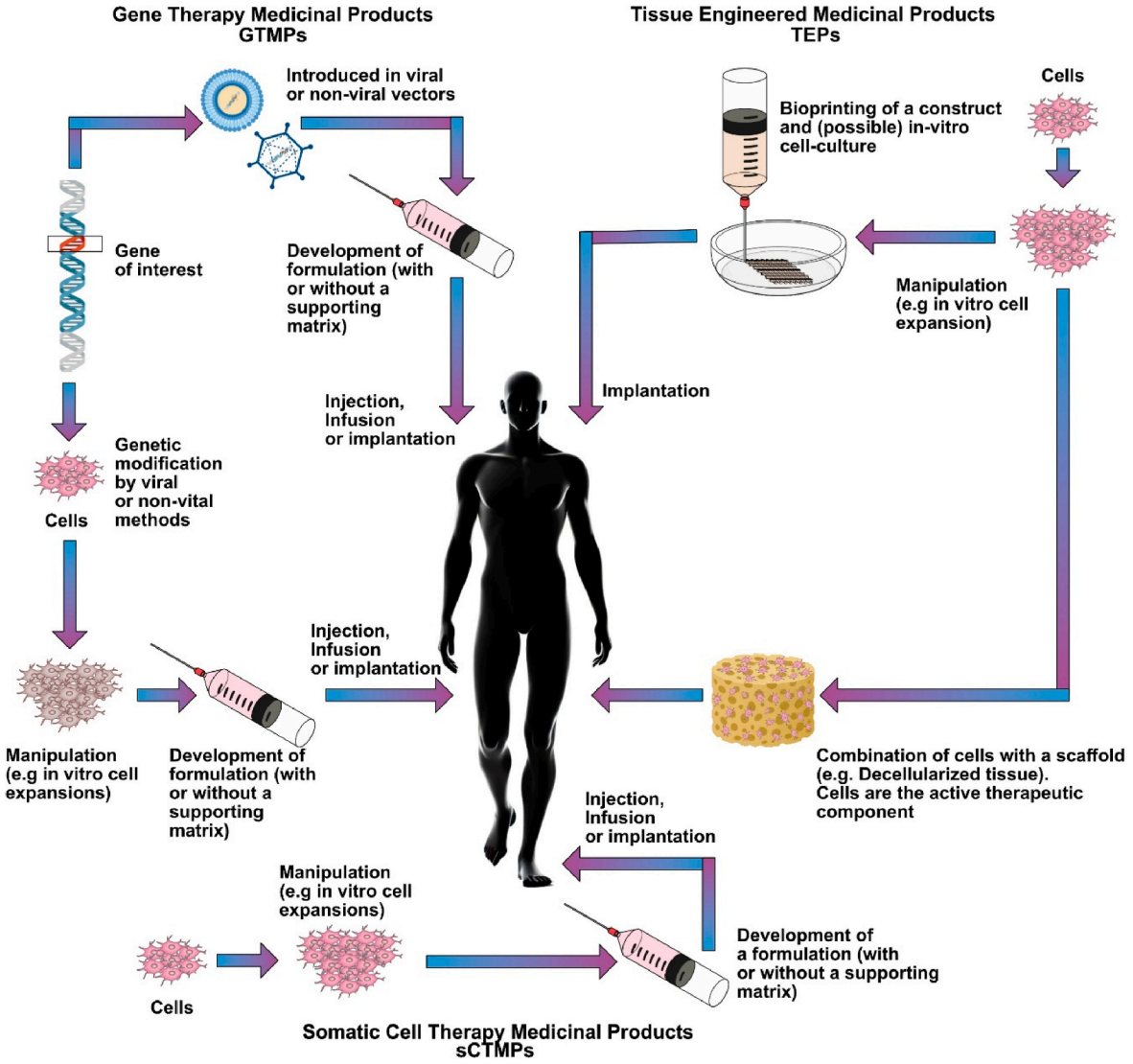


Fig. 1. Schematic summary of ATMPs as defined by the EU Community. ATMP includes four categories: GTMPs, sCTMPs, and TEPs. It should be noted that the scheme does not capture the complexity of the classification based on the MoA. Therefore, for instance, if a genetic modification is minor, non-recombinant, or does not result in therapeutic gene expression, and the cell itself is doing the therapeutic work, not the inserted gene, then a case could be made for sCTMP classification. We also excluded from the scheme the cATMPs, which is the combination of one of the three main categories (GTMPs, sCTMPs and TEPs) with medical devices.

processing that alters the biological characteristics, physiological functions, or structural properties of cells or tissues in a way that is relevant to their intended clinical use. EU legislation explicitly specifies which manipulations are not considered substantial; all other procedures are regarded as substantial. A summary of the most common substantial modification (to develop a sCTMP or a TEP) and the sole modification to be considered non-substantial (according to the EU regulation [12]) is reported in Table 2. Finally, cATMPs incorporate one or more medical devices as an integral part of the product (for example, cells embedded in a scaffold or matrix). The device component must comply with relevant medical device regulations and play a supportive or structural role in therapy.

Since classification is primarily based on the mode of action (MoA), there are specific cases in which a therapy may be classified differently than might be expected at first glance. Fully decellularized tissues do not qualify as TEPs per se, as the ATMP regulatory framework applies only to products containing cells. Decellularized tissues, regardless of whether they are used in autologous or non-autologous applications, are therefore generally regulated as medical devices, provided that no viable cells are present and that the primary mode of action is structural. When a decellularized, scaffold is combined with cells, either through recellularization prior to implantation or when cellular repopulation is an integral part of the intended therapeutic effect, the resulting product may fall within the definition of a TEP, depending on the origin, manipulation, and intended function of the cells. CAR-T cell–based therapies are most commonly classified as GTMPs. In cases where T cells are modified without the introduction of recombinant deoxyribonucleic acid

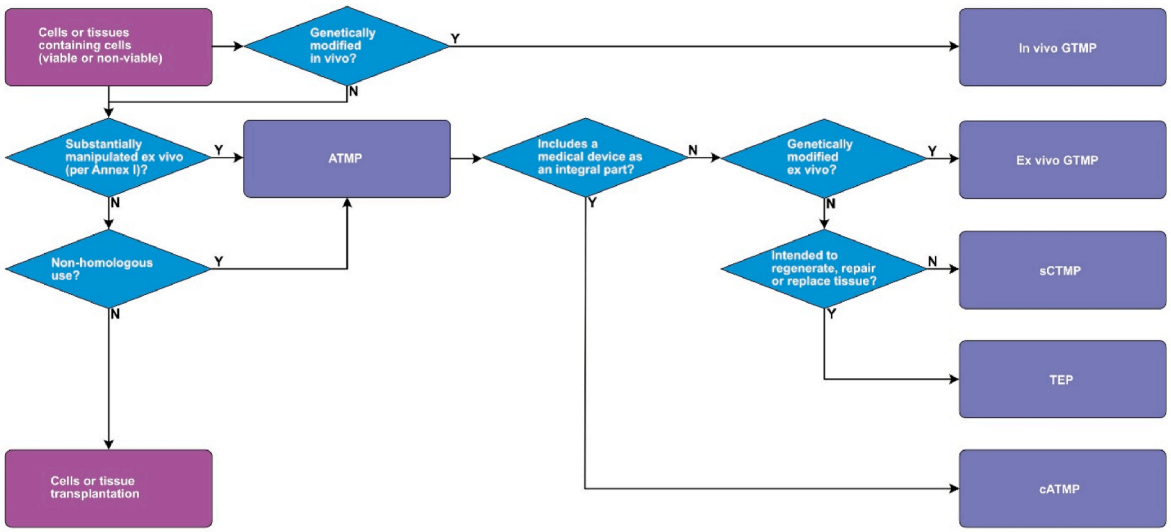


Fig. 2. Decision tree for the classification of Advanced Therapy Medicinal Products (ATMPs). This workflow illustrates a regulatory decision pathway for the classification of ATMPs based on the nature of the starting material and the type of manipulation applied to cells or tissues containing cells. The decision process begins by assessing whether the cells or tissues are genetically modified in vivo or ex vivo, leading to classification as in vivo or ex vivo gene therapy medicinal products (GTMPs). For non–genetically modified products, classification proceeds through the assessment of substantial manipulation (as defined in Annex I of Regulation (EC) No 1394/2007) [12] or non-homologous use, which determines entry into the ATMP framework. Products that incorporate a medical device as an integral part are classified as combined ATMPs (cATMPs). In the absence of a medical device, further classification is based on the intended therapeutic purpose: products intended to regenerate, repair, or replace human tissue are classified as tissue-engineered products (TEPs), whereas products exerting their effect primarily through pharmacological, immunological, or metabolic activity are classified as somatic cell therapy medicinal products (sCTMPs). Products that do not meet the criteria for substantial manipulation or non-homologous use fall outside the ATMP framework and are regulated as cells or tissue transplantation. While this decision tree provides a structured classification approach, the final regulatory classification is determined by the primary mode of action (MoA) of the product.

Table 2
Distinction among substantial and non-substantial manipulation. Both sCTMPs and TEPs must contain "substantially modified" cells or tissues. The regulation (Regulation (EC) No 1394/2007) [12] only specifies the Non-Substation Manipulation, so any other procedure should be considered substantial. Substantial manipulation includes but is not limited to the provided list, which summarizes the most common procedures in developing an sCTMP or a TEP.

Substantial Manipulation	Non-Substantial Manipulation
Enzymatic digestion (e.g., to isolate stromal vascular fraction)	Shaping
	Centrifugation
Cell expansion or culture (e.g., proliferation in vitro)	Soaking in antibiotic or antimicrobial solutions
	Sterilization
Genetic modification (e.g., transfection, viral transduction)	Irradiation
	Cell separation, concentration, or purification
Differentiation or activation in vitro	Filtering
Decellularization (if the tissue is then used for a different essential function)	Lyophilization
	Freezing, cryopreservation, or vitrification
Combination with a scaffold if it affects behavior or integration	Grinding
	Cutting
Bioprinting, where structural or functional properties are controlled or altered	

(rDNA) (for example, through targeted gene disruption to remove a surface receptor to prevent immune rejection) and where the therapeutic effect is mediated primarily by cellular activity rather than transgene expression, such products may be classified as sCTMPs [13]. A noteworthy detail is that, because the regulation omits any specification of the source of cells and tissues, xenogenic ATMPs are included in the regulatory framework, even though such products are not typically addressed within the scientific literature.

In contrast to Europe's detailed classification, the US employs a more risk-based approach to the regulation of advanced therapies. While the term "ATMP" is not formally used by the US FDA, products that fall within this category in Europe are generally regulated as biological products under the Public Health Service Act [14] and the Federal Food, Drug, and Cosmetic Act [15]. In the US, cell and gene therapies are primarily classified based on the extent of manipulation and the intended use of the cells. For example, minimally

manipulated cells that are used for homologous purposes are regulated under the Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) framework [16]. In contrast, products that are more than minimally manipulated or used in a non-homologous manner are subject to the more rigorous premarket approval process as biologics [17]. This means that while the US does recognize distinct categories such as gene therapy products and cell therapy products, it does so within a broader biologics framework that emphasizes a risk-based evaluation of manufacturing processes, potency, and clinical safety [18]. Moreover, in the US, combination products (which are analogous to cATMPs in Europe) are regulated through a unique process that involves the Office of Combination Products [19]. For instance, a product that combines a cell-based therapy with a medical device component would require an integrated review to ensure that both elements meet the requisite standards. An example in the US context is the use of CAR-T cell therapies, where the genetic modification of T cells (a gene therapy aspect) is performed ex vivo and the cells are subsequently administered as part of a product that may include supportive devices for cell delivery. Although the regulatory language differs from EU, the underlying principle of ensuring that each component of a complex therapy is safe and effective remains consistent across both jurisdictions.

The differing regulatory approaches in Europe and the US have significant implications for global development strategies. EU developers benefit from a more prescriptive classification that clearly outlines the requirements for each ATMP subtype. This clarity can facilitate a smoother pathway through clinical development, as the classification directly informs the design of preclinical studies, clinical trials, and manufacturing controls. In the US, however, the emphasis on risk-based evaluation allows for a certain degree of flexibility; developers may leverage designations such as the Regenerative Medicine Advanced Therapy (RMAT) designation, which provides expedited review processes and more frequent interactions with the FDA [20]. Both regulatory frameworks underscore the importance of understanding the product's mode of action and the level of manipulation involved. In Europe, for instance, the distinction between minimal and substantial manipulation is central to determining whether a product qualifies as an ATMP. Minimal manipulation (such as simple cell separation or washing) typically does not trigger the ATMP classification, whereas substantial manipulation (e.g., extensive cell expansion, genetic modification, or the incorporation of a scaffold in a tissue engineering product) does. Similarly, in the US, the FDA's guidance emphasizes that products undergoing more-than minimal manipulation or those used for non-homologous purposes fall under a higher risk category that necessitates a full Biologics License Application (BLA) review (US Code of Federal Regulations, Title 21, Part 1271 [21]). It is also worth noting that while the regulatory criteria in both regions aim to ensure that only safe and efficacious products reach the market, the pathways for obtaining marketing authorization differ. In Europe, ATMPs are evaluated through a centralized procedure via the EMA, which provides a single marketing authorization valid across all member states. This centralized review is complemented by the role of CAT, which offers scientific recommendations on product classification and development strategies. In the US, the approval process is handled by the FDA's Center for Biologics Evaluation and Research (CBER), and the review process may vary depending on whether a product qualifies for expedited pathways such as RMAT or falls under standard review timelines.

2.1. Expedited pathways for ATMPs in the EU and US

In practical terms, these divergent schemes translate into distinct development logics for ATMPs in the EU and the US, even when the underlying products are similar. Taking as example a GTMPs, in the EU, all ATMPs, must follow the centralized EMA route and undergo early formal classification with the involvement of specialized committees such as the CAT, so that the regulatory status, expectations for quality, non-clinical and clinical data and the likely post-marketing obligations are framed from the beginning of development. Within this structure, sponsors can access tools such as the priority medicines (PRIME) scheme [22], which is intended for products addressing an unmet medical need and offering promising early evidence; PRIME provides early and frequent scientific advice, early appointment of rapporteurs and coordinated input across EMA committees, effectively allowing the development plan to be optimized prospectively for a future centralized marketing authorization application that may plausibly seek conditional marketing authorization if the data package is still incomplete at the time of initial submission but the benefit–risk balance is considered positive [22]. Conditional marketing authorization, in turn, is a legally defined EU instrument that enables time-limited approval based on less mature clinical data in serious or life-threatening conditions, with the explicit imposition of post-authorization measures such as confirmatory trials, disease registries and extended safety follow-up [23]; as a result, many first-in-class gene therapies and certain CAR-T products have been brought to market on the basis of single pivotal studies coupled to stringent long-term commitments, and developers often design their pivotal programmes and pharmacovigilance strategies with this conditional pathway in mind from very early phases [23–25]. In contrast, in the United States, comparable products are regulated as biologics within the BLA framework [17] at the CBER, without a distinct ATMP legal category or a dedicated ATMP committee, and sponsors typically rely on expedited designations such as breakthrough therapy designation and RMAT status to accelerate development and review.

Both programmes are layered on top of the standard BLA route and do not change the fundamental approval standard, but they offer intensive, iterative interaction with the agency, support for innovative or adaptive trial designs, and the possibility of leveraging intermediate endpoints, small or single-arm studies and real-world or historical controls when scientifically justified. This offers considerable flexibility in the process, but it means that the specific evidence needed is decided on a case-by-case basis, instead of using a pre-established template with conditions. In practice, this means that in the EU early classification as a GTMPs, enrolment in PRIME and the prospect of conditional marketing authorization “anchor” the overall development strategy around a centrally coordinated, ATMP-specific pathway with clearly articulated post-authorization obligations, whereas in the US breakthrough and RMAT designations shape development by intensifying regulator–sponsor dialogue within a broader biologics framework, influencing trial design and review timelines without imposing an additional ATMP-specific structural layer, and thus generating different patterns of evidence generation, lifecycle planning and risk-management for similar advanced therapies [24,25].

A practical example is the approval of Kymriah, a CD19-directed CAR-T therapy from Novartis for pediatric/young adult relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) and adult relapsed/refractory diffuse large B-cell lymphoma (DLBCL), which received accelerated FDA approval on August 30, 2017 via the BLA pathway. It leveraged Breakthrough Therapy Designation (granted earlier based on preliminary ELIANA trial data showing high response rates in unmet-needs ALL) and Priority Review, enabling review in ~6 months rather than the standard 10 for BLAs; approval relied on a single-arm pivotal study (n = 63 for ALL) with overall remission rate as the primary endpoint, coupled to confirmatory post-marketing commitments for durability [25–27]. In the EU, the EMA granted Marketing Authorization on August 23, 2018 (nearly a year later) following the centralized procedure under ATMP Regulation (EC) 1394/2007, with classification as a GTMP confirmed by the CAT. It benefited from PRIME designation (June 2016, the first ATMP to do so), providing early scientific advice and a dedicated rapporteur to optimize the development plan; approval was based on the same ELIANA data but under a conditional Marketing Authorization (CMA) framework, requiring specific post-authorization efficacy/safety studies, patient registries, and periodic safety update reports through 2038 [25–27].

3. Scientific foundations of ATMPs

While regulatory frameworks define how ATMPs are developed, evaluated, and authorized, they are ultimately built upon distinct scientific and technological principles that determine their therapeutic potential, manufacturing complexity, and risk profile. A clear understanding of these scientific foundations is therefore essential to contextualize both the regulatory strategies discussed above and the evidence requirements imposed throughout the ATMP lifecycle. The following section shifts the focus from regulatory pathways to the underlying biological and engineering concepts that characterize GTMPs, sCTMPs and TEPs. The discussion of cATMPs was excluded because, as a combination of one of the three main categories and a medical device, its scientific foundation is inherent in the existing ATMP discussion.

3.1. Gene therapy medicinal products (GTMPs)

Gene Therapy Medicinal Products (GTMPs) represent a paradigm shift in biomedical science, offering the possibility to treat or cure diseases by targeting the root molecular and genetic mechanisms rather than addressing downstream symptoms. These products are defined as biological medicinal interventions containing recombinant nucleic acid sequences intended to regulate, repair, replace, add, or delete specific genetic sequences in human cells, with their therapeutic effect deriving directly from the introduced nucleic acid or its expression product [28]. The conceptual foundation of GTMPs can be traced back to the discovery of Deoxyribonucleic acid (DNA) as the hereditary material by Avery, MacLeod, and McCarty in 1944 [29], followed by Watson and Crick's elucidation of the double-helix structure in 1953 [30]. These milestones set the stage for genetic engineering, which emerged in the 1970s with the advent of recombinant DNA technology, allowing scientists to insert, delete, or modify genes within organisms. The first successful gene therapy trial in 1990, which treated a four-year-old girl with adenosine deaminase (ADA) deficiency, marked the beginning of GTMPs as a clinical reality [31].

Unlike conventional therapeutics that act on proteins or metabolic pathways, GTMPs intervene at the genomic level, employing molecular biology tools to alter gene expression or function in a targeted and sustained fashion. At the cellular level, gene therapy operates by introducing exogenous genetic material (most commonly DNA or Ribonucleic acid (RNA)) into a patient's cells, where it is transcribed and translated to produce a therapeutic protein, interfere with pathological gene expression, or induce specific genome modifications [32–35]. This is typically achieved using vectors that carry the therapeutic sequence into cells, which may either integrate into the host genome or remain episomal. Viral vectors, particularly those derived from adeno-associated viruses (AAVs), lentiviruses, retroviruses, or AAVs, are engineered to efficiently deliver genetic payloads while minimizing pathogenicity and immunogenicity [32]. These vectors are favored for their high transduction efficiency, tissue specificity, and ability to sustain gene expression, either transiently or permanently depending on the vector design and cell type targeted [32]. Non-viral vectors, including lipid nanoparticles, cationic polymers, and physical methods such as electroporation, offer safer alternatives that avoid the risk of insertional mutagenesis but typically yield lower gene transfer efficiency and transient expression profiles [32]. Once inside the target cell, the delivered nucleic acid must bypass cytosolic degradation pathways, enter the nucleus if DNA-based, and engage the host transcriptional machinery. Depending on the vector system used, the introduced gene may integrate into the host genome (as in retroviral or lentiviral systems) or remain episomal (as with AAVs or plasmids), with each modality influencing the durability and safety of gene expression. Integration can provide long-term correction in dividing cells, which is desirable for certain hematological or inherited disorders, but it also carries a risk of disrupting endogenous gene function and possibly contributing to oncogenesis, as observed in early trials for X-linked severe combined immunodeficiency [36]. In contrast, episomal vectors typically offer safer profiles and are particularly suited to non-dividing tissues such as muscle or neurons, where vector dilution does not occur rapidly [32].

The scientific classification of GTMPs is typically based on their mechanism of action: gene addition, gene silencing, or gene editing. In addition, a functional copy of a gene is introduced to complement or replace a defective endogenous gene, an approach validated in several monogenic disorders, such as hemophilia and spinal muscular atrophy [32]. In gene silencing, therapeutic sequences such as small interfering RNAs (siRNAs), short hairpin RNAs (shRNAs), or antisense oligonucleotides are delivered to suppress the expression of disease-causing genes, especially in the context of gain-of-function mutations or dominant-negative effects [32]. Gene editing made possible by targeted nucleases such as CRISPR-Cas9, zinc finger nucleases (ZFNs), and Transcription Activator-Like Effector Nucleases (TALENs), enables precise modification of endogenous DNA sequences to correct mutations or ablate disease-associated genes. CRISPR-based systems in particular have emerged as the most versatile tools for therapeutic genome engineering, with the ability to introduce specific nucleotide changes or create double-strand breaks that are repaired by the host cell's

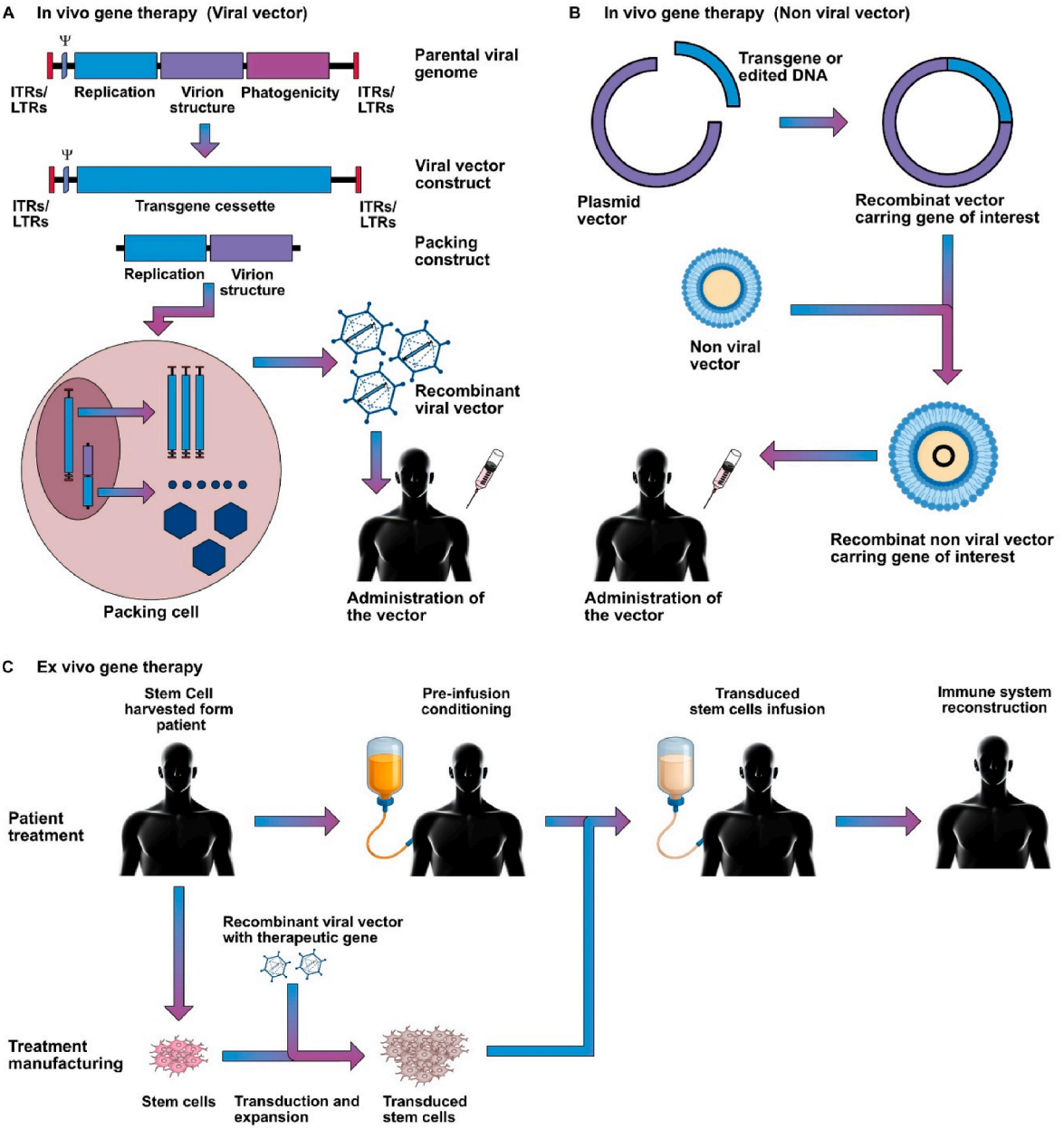


Fig. 3. Overview of Gene Therapy Modalities Using Viral and Non-Viral Vectors. **(A)** In vivo gene therapy with viral vectors: This approach involves the direct administration of a viral vector carrying the therapeutic gene into the patient. A viral vector is engineered by replacing the pathogenic and replication elements of the parental viral genome with a therapeutic transgene cassette, flanked by essential sequences such as ITRs (inverted terminal repeats), LTRs (long terminal repeats), and Ψ (packing signal). Packaging constructs provide the necessary viral proteins for vector assembly in packaging cells. The recombinant viral vector is then purified and administered systemically or locally to the patient to mediate gene delivery in situ. **(B)** In vivo gene therapy with non-viral vectors: Here, the therapeutic gene is incorporated into a plasmid or synthetic DNA molecule, which can be complexed with delivery systems to form a recombinant non-viral vector. This vector is then administered directly to the patient. **(C)** Ex vivo gene therapy: This method involves harvesting patient-derived cells, followed by gene modification outside the body. The cells are transduced with a recombinant viral vector encoding the therapeutic gene during the manufacturing process. After transduction and expansion, the genetically modified cells are re-infused into the patient following a conditioning regimen to enhance engraftment. The modified cells can then restore or augment the patient's immune or hematopoietic system function.

endogenous machinery [32]. Recent advancements in base editing and prime editing have further enhanced the precision of these techniques by enabling single-nucleotide modifications without introducing double-strand breaks, reducing the potential for off-target effects and chromosomal rearrangements [37]. A further distinction is made based on delivery route and context: in vivo (Fig. 3A and

B) versus ex vivo (Fig. 3C). In vivo gene therapy involves the direct administration of vectors into the body to target affected tissues, whereas ex vivo approaches involve the isolation of patient cells, their genetic modification outside the body, and subsequent reintroduction (a method particularly useful for hematopoietic stem cell disorders and T-cell-based immunotherapies such as CAR-T cells) [32].

The disease context also influences GTMP design. Monogenic disorders are prime candidates for gene addition or editing because their pathology is rooted in a single genetic defect, while complex polygenic diseases may benefit from the introduction of protective genes or modulation of specific signaling pathways [32]. Cancer gene therapy strategies, which often blur the lines between immunotherapy and gene therapy, may involve the delivery of immune-activating genes, suicide genes, or tumor-targeted oncolytic viruses to directly attack malignant cells or enhance immune surveillance [38]. Despite the growing clinical success of GTMPs, their widespread application remains constrained by challenges in delivery efficiency, immune responses, and precise expression control. Pre-existing immunity against viral vectors, particularly AAVs, may neutralize vector particles before they reach their target, while

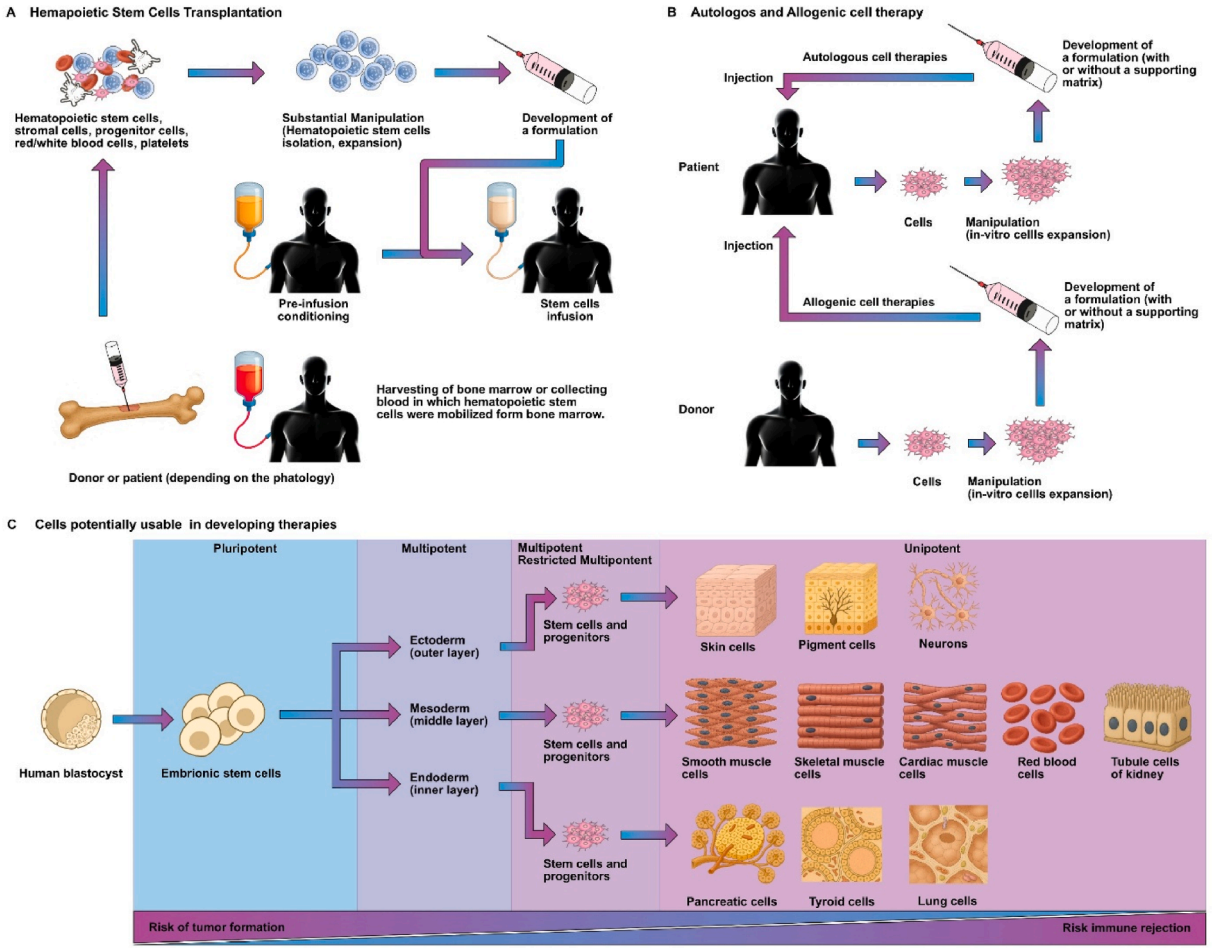


Fig. 4. Overview of Cell Sources and Strategies for Cell-Based Therapies and Stem Cell Transplantation. **(A)** Clinical workflow for HSCT. HSCs, along with other stromal and progenitor cells, are collected either from the donor's or the patient's bone marrow or mobilized peripheral blood. These cells undergo substantial manipulation, including isolation and expansion. The patient undergoes pre-infusion conditioning (e.g., chemotherapy or radiotherapy) to prepare the body for receiving the new cells. The expanded and formulated stem cells are then infused into the patient. This approach is used for treating various hematological malignancies and disorders and can involve either autologous or allogeneic sources depending on the disease context. **(B)** Autologous and Allogeneic Cell Therapy. Autologous cell therapy involves harvesting cells directly from the patient, followed by in vitro manipulation such as cell expansion. The manipulated cells are then formulated (with or without a supporting matrix) and re-injected into the same patient. Allogeneic cell therapy uses cells derived from a donor. These cells undergo similar in-vitro manipulation and formulation before being administered to a recipient. While autologous therapies reduce immune rejection risks, allogeneic therapies offer scalability but may pose a higher risk of immune response. **(C)** Hierarchical view of stem cell differentiation. Human embryonic stem cells (hESCs), derived from the blastocyst, are pluripotent and capable of differentiating into cells from all three germ layers: ectoderm, mesoderm, and endoderm. Each germ layer gives rise to multipotent progenitor cells, which can further differentiate into more restricted multipotent or unipotent cells. The diagram reports only a limited typology of differentiated cells. The diagram also visually highlights a risk spectrum, with pluripotent cells carrying a higher risk of tumor formation (e.g., teratomas), while more differentiated cells pose greater risks of immune rejection.

vector-encoded proteins can elicit immune responses that limit therapeutic efficacy or pose safety risks [39]. To address these issues, researchers are exploring capsid engineering, transient immunosuppression, and immune cloaking strategies [32]. Furthermore, the use of regulatable promoters, synthetic gene circuits, and tissue-specific enhancers is under investigation to improve the spatial and temporal control of therapeutic gene expression. In parallel, emerging platforms such as messenger RNA (mRNA) based GTMPs, which deliver transient protein expression without altering the genome, and hybrid systems that combine genome editing with RNA delivery, are expanding the therapeutic landscape, offering new possibilities for diseases previously considered untreatable [40].

3.2. Somatic cell therapy medicinal products (sCTMPs)

Somatic cell therapies are defined by their capacity to exert therapeutic effects through the biological activity of viable human somatic cells that have been subjected to substantial manipulation or employed in a functionally non-homologous context. From a scientific standpoint, the rationale underpinning these therapies is grounded in fundamental principles of cell biology, regenerative signaling, and host-cell interactions. Unlike traditional pharmacological agents, which act through defined receptor-ligand interactions or enzymatic pathways, somatic cells operate as complex, context-responsive entities capable of dynamically engaging with host tissues and orchestrating multifaceted biological responses [41,42]. Treatment of blood cancers using adult stem cells as part of bone marrow transplants has been a known application since the 1950s [43]. This procedure involves whole-body irradiation or the killing of malignant cells in multiple myelomas and leukemia. Following this, the patient undergoes a bone marrow transplant, which contains a small number of hematopoietic stem cells (HSCs) that subsequently migrate to the bone marrow stem cell niches, where they begin the process of replenishing the patient's blood supply. This therapy was the basis of the development of HSC transplantation (HSCT) (Fig. 4A), which is currently used to cure different pathologies, including but not limited to the list in Table 3 [44,45].

The primary mechanisms by which sCTMPs exert therapeutic benefit can be broadly categorized into three interrelated modalities: cell replacement, paracrine signaling, and immunomodulation. Cell replacement is based on the fact that the implanted cells can replace or supplement cell populations within the recipient that are either dysfunctional or missing entirely. This paradigm is particularly relevant in tissues with low regenerative capacity, where exogenous cells can engraft, differentiate and contribute directly to tissue architecture and function. Autologous chondrocyte transplantation for cartilage defects [49] and limbal stem cell transplantation for corneal repair exemplify this principle [50,51]. These therapies are based on the premise that cells expanded ex vivo can restore their physiological function upon implantation, contributing structural and functional elements to the target tissue. However, an increasing amount of evidence suggests that the therapeutic benefit of many somatic cell products does not strictly rely on permanent engraftment or differentiation. Instead, a large proportion of their efficacy appears to derive from their secretome, which can be defined as the overall secretion of bioactive molecules by the cell (cytokines, chemokines, growth factors, and extracellular vesicles). These molecules act in a paracrine manner to modulate the local environment. This so-called “paracrine hypothesis” has been particularly well studied in MSCs, whose regenerative influence extends to angiogenesis, anti-apoptosis, and modulation of fibrotic processes [41,52]. Notably, these cells can exert therapeutic effects even when they are transiently present or rapidly cleared from the recipient, indicating that the duration of engraftment is not always proportional to efficacy. Such findings have led to a conceptual shift in regenerative medicine, wherein transplanted cells are viewed not merely as building blocks for tissue regeneration but also as bioactive agents capable of mobilizing endogenous repair mechanisms through trophic signaling [42]. Immunological modulation constitutes another critical aspect of somatic cell therapies. Several therapeutic cell types, including MSCs, dendritic cells (DCs), and T lymphocytes, have demonstrated the capacity to interact with the immune system in a regulatory or stimulatory fashion. MSCs, in particular, have been shown to suppress T-cell proliferation, inhibit dendritic cell maturation, and shift macrophage polarization, largely through the release of molecules such as prostaglandin E2, indoleamine 2,3-dioxygenase (IDO), and interleukin-10 [52,53]. These immunomodulatory effects have been harnessed in the treatment of inflammatory and autoimmune conditions and are an intrinsic part of the therapeutic profile of MSC-based products. On the opposite end of the spectrum, DCs manipulated ex vivo to present defined antigens can elicit targeted cytotoxic immune responses when reintroduced into the body. This antigen-presenting capacity transforms them into a living vaccine platform capable of instructing the adaptive immune system to recognize and attack pathogenic targets [54].

Table 3
Major Disease Categories Treated with Hematopoietic Stem Cells. This table summarizes the primary categories of diseases for which HSCT is used as a treatment or life-extending therapy [46–48]. It includes both malignant and non-malignant conditions, with examples listed by their full names and the typical type of transplant (autologous or allogeneic) employed for each condition.

Disease Category	Examples	Type of HSCT
Blood cancers	Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), Non-Hodgkin Lymphoma (NHL), Multiple Myeloma (MM), Hodgkin Lymphoma (HL)	Autologous or Allogeneic
Bone marrow failure	Aplastic Anemia, Myelodysplastic Syndromes (MDS)	Allogeneic
Inherited blood disorders	Sickle Cell Disease (SCD), Beta Thalassemia Major	Allogeneic
Immune deficiencies	Severe Combined Immunodeficiency (SCID), Wiskott–Aldrich Syndrome	Allogeneic
Autoimmune diseases	Multiple Sclerosis (MS), Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (Scleroderma)	Autologous (in clinical trials)
Metabolic/genetic disorders	Hurler Syndrome (Mucopolysaccharidosis I), Adrenoleukodystrophy (ALD), Krabbe Disease	Allogeneic

Homing behavior further distinguishes somatic cells as therapeutic agents. Many therapeutic cell types exhibit an innate capacity to migrate toward sites of injury or inflammation, guided by chemotactic gradients and adhesion molecules. The Stromal cell-derived factor 1 (SDF-1)/C-X-C chemokine receptor type 4 (CXCR4) axis, for instance, is critical in directing cell migration to ischemic or damaged tissues. This property facilitates targeted delivery without requiring invasive localization and is particularly advantageous in systemic administration strategies [42]. Upon arrival at the target site, cells can sense microenvironmental cues and adjust their behavior accordingly, a phenomenon linked to their intrinsic plasticity. The secretome of MSCs, for example, has been shown to vary depending on culture conditions, preconditioning stimuli, and the inflammatory profile of the host tissue [55].

The selection of cell types for somatic cell therapy is driven by a combination of functional relevance, expandability, and immunological compatibility. The two possible strategies are the use of the patient's own cells and the use of donor cells (Fig. 4B). Autologous cell therapies (e.g., using a patient's own bone marrow or skin cells) have the benefit of being immunologically compatible, avoiding rejection by the immune system. However, they require harvesting cells from each patient and manufacturing a personalized product, which can be time-consuming and costly. Allogeneic therapies use cells from a donor or a universal cell line, enabling "off-the-shelf" treatments that are immediately available and can be produced in bulk. The challenge with allogeneic cells is the risk of immune rejection, as the recipient's immune system may recognize the cells as foreign. Traditionally, any foreign tissue is expected to elicit an immune reaction requiring immunosuppression (as is the case in organ transplantation) [56]. In Table 4, we reported the main typology of cells used in sCTMPs, each selected for their ability to perform a specific biological role in the target tissue [53,57]. However, potentially all cells are useable to develop sCTMPs (Fig. 4C), from stem, multipotent, cells to differentiated, unipotent, cells. It should be noted that the higher the cell potency is, the higher the possibility of developing teratomas and the lower the possibility of rejection from the recipient.

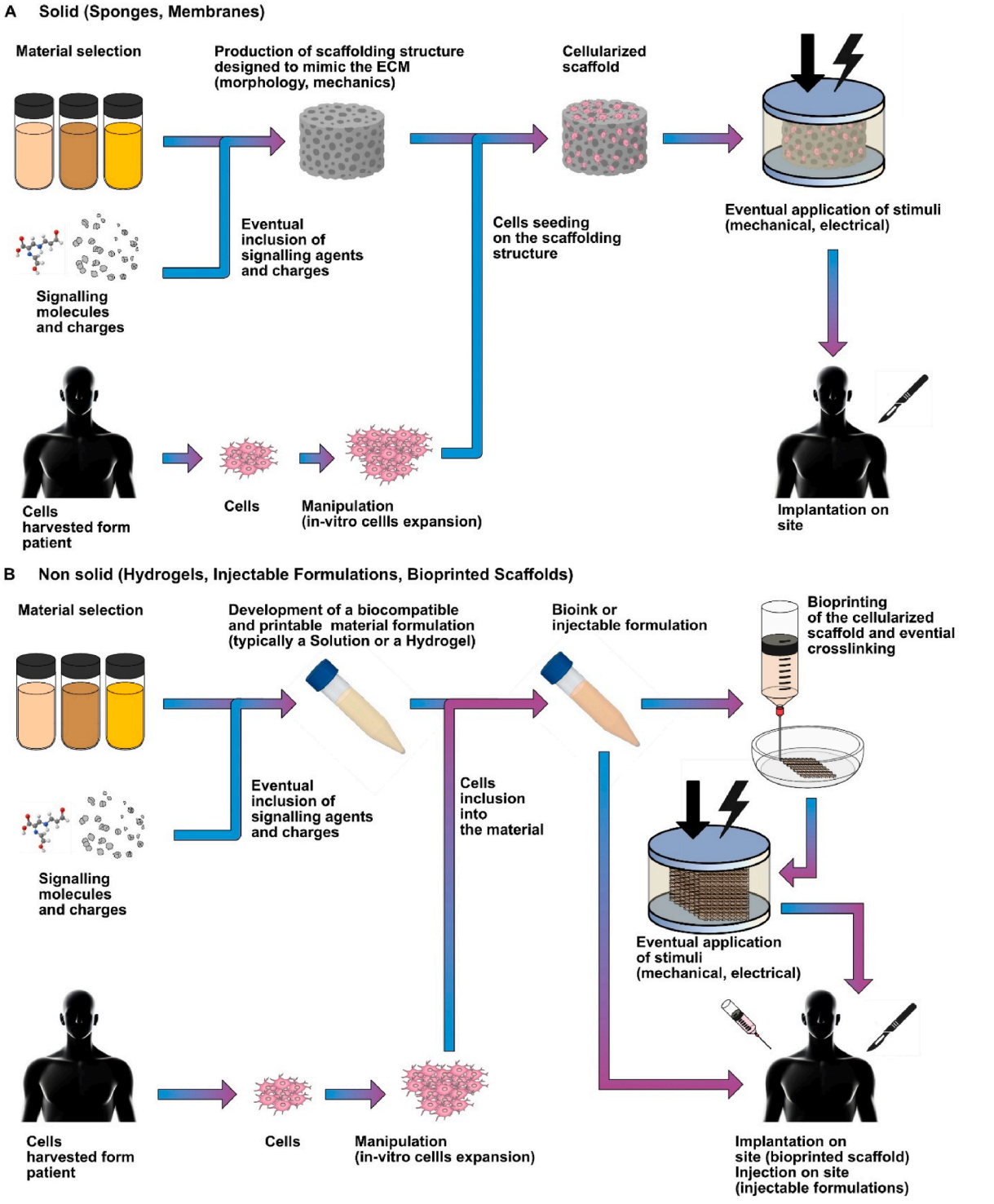
3.3. Tissue engineered products (TEPs)

TEPs represent a convergence of biology, materials science, and medicine, aiming to restore or replace damaged tissues through biologically active scaffolds. The scientific foundation of these therapies is based on understanding how cellular behavior, tissue architecture, and the microenvironment regulate regeneration. At its core, TEPs are based on the principle that living cells, when provided with the right structural and biochemical context, can recreate the functions of lost or damaged tissues. This principle mirrors developmental biology, where cells differentiate and organize into functional structures during embryogenesis, and tissue repair processes, where cells migrate, proliferate, and restore homeostasis after injury. Leveraging this biological potential, TEPs are designed to replicate or assist natural healing by delivering cells, structural frameworks, and instructive signals in a coordinated manner. The foundation of TEPs is Tissue Engineering (TE) which is the convergence of three components (often described as the tissue engineering triad): cells, scaffolds, and regulatory signals [60].

In the scheme of Fig. 5 we reported the strategies used to integrate these three components in two cases: solid scaffolds (Fig. 5A) and non-solid scaffolds (Fig. 5B). The primary distinction lies in the way cells are incorporated into the scaffold; in the former scenario, they are seeded onto it, while in the latter case, they are typically blended into the scaffolding material. This depends on the characteristic of the material and on the technique used to fabricate the scaffold. Several techniques, including but not limited to foaming, compression

Table 4
Summary of Cell Types used in sCTMPs. This table provides an overview of the principal cell types employed in sCTMPs, categorized by biological source, functional characteristics, and representative clinical applications [53,58,59]. The Description column clarifies each cell type's identity and therapeutic role.

Cell Type	Description	Source	Key Features	Examples
Hematopoietic Stem Cells (HSCs)	Blood-forming stem cells that regenerate hematopoietic lineages	Bone marrow, peripheral blood, cord blood	Multipotent; engraft and regenerate blood and immune systems	Standard in treating blood cancers, SCID; both autologous and allogeneic use.
Mesenchymal Stromal Cells (MSCs)	Multipotent stromal cells with regenerative and immunomodulatory capabilities	Bone marrow, adipose tissue, umbilical cord, placenta	Secrete trophic and immunomodulatory factors; immunoprivileged; used widely	Applied in osteoarthritis, Graft-versus-Host Disease (GvHD), Crohn's, systemic lupus
Induced Pluripotent Stem Cells (iPSCs)	Somatic cells reprogrammed to an embryonic-like pluripotent state, capable of generating therapeutic lineage-specific cells	Reprogrammed adult somatic cells	Pluripotent; can differentiate into virtually any cell type; scalable and renewable	Used to generate neural, cardiac, or pancreatic cells; applications in neurodegenerative and metabolic disorders
Dendritic Cells (DCs)	Immune cells specialized in antigen presentation to T lymphocytes	Peripheral blood monocytes (patient-derived)	Antigen-presenting; activate adaptive immune responses; used in vaccines	Sipuleucel-T in prostate cancer; also used in infectious disease trials
Lymphocytes/Immune Effector Cells (T, natural killer (NK) cells)	Cytotoxic or helper immune cells involved in adaptive and innate immunity	Patient or donor-derived	Direct cytotoxic or immune function; can be expanded or selected ex vivo	TIL therapy in melanoma; virus-specific T cells; NK cell infusions
Tissue-Specific Cells/ Progenitors	Specialized or progenitor cells (PCs) from tissues, used for targeted regeneration	Specific tissues (e.g., cartilage, pancreas, muscle, Central Nervous System)	Tailored to specific tissue functions; used in regenerative therapies	Includes chondrocytes, myoblasts, islets, neural progenitors, fibroblasts



(caption on next page)

Fig. 5. Schematic representation of tissue engineering workflows based on scaffold types: Solid scaffolds and non-solid scaffolds. In both approaches, patient-derived cells are harvested and expanded in vitro. **(A)** Solid scaffolds (e.g., sponges, membranes): The process begins with material selection, followed by the fabrication of a 3D scaffold that mimics the ECM in morphology and mechanical properties. Signaling molecules and bioactive agents may be integrated into the scaffold. Expanded cells are seeded onto the solid scaffold, resulting in a cellularized construct. Optional mechanical or electrical stimulation can be applied to enhance tissue maturation. The final construct is then implanted at the target site. **(B)** Non-solid scaffolds (e.g., hydrogels, injectable formulations, bioprinted constructs): Similarly, the workflow starts with material selection and the development of a biocompatible and printable formulation, usually in the form of a hydrogel or solution. Signaling agents may also be incorporated. Expanded cells are mixed directly into the formulation, which is then either used for bioprinting of structured scaffolds (followed by potential crosslinking and stimulation) or administered via injection. These constructs may also receive mechanical or electrical cues before implantation or injection at the treatment site.

molding, salt-leaching, electrospinning, and electrowriting, can create solid, porous, or non-porous scaffolding structures suitable for cell seeding and colonization. In contrast, biofabrication approaches such as bioprinting involve the direct incorporation of living cells into the material matrix to create a bioink. In these cases, the supporting material is typically a hydrogel, which provides a hydrated, biocompatible environment to support cell viability and tissue formation [61].

The cellular component is central to the regenerative potential of TEPs. Depending on the target tissue and therapeutic strategy, cells used in TEPs can be autologous or allogeneic, and may include terminally differentiated somatic cells, tissue-specific progenitor cells, or stem cell populations such as MSCs, embryonic stem cells (ESCs), or iPSCs [62,63]. Autologous primary cells, such as chondrocytes or keratinocytes, offer immunological compatibility and are often employed in constructs where integration and longevity of the cell population are desired. However, limitations in cell availability, patient health, and the proliferative capacity of certain cell types have stimulated the use of stem cells and allogeneic sources [62]. MSCs, in particular, have attracted attention for their dual role as regenerative agents and modulators of the immune response. Their capacity to differentiate along multiple mesenchymal lineages and to secrete a range of trophic factors that promote angiogenesis, suppress inflammation, and stimulate resident tissue repair mechanisms makes them suitable candidates for various TEPs [63]. In the context of allogeneic use, their relatively low immunogenicity has enabled the development of off-the-shelf tissue constructs that exert their effect through transient engraftment and paracrine activity, rather than long-term tissue integration [63]. Furthermore, pluripotent stem cells, especially iPSCs, offer the potential to generate autologous-like cells from patient-specific sources, although challenges related to differentiation fidelity, tumorigenicity, and manufacturing consistency remain significant hurdles [63]. A key scientific consideration is the phenotypic stability of the implanted cells. Many cell types, particularly those expanded ex vivo, are prone to dedifferentiation or senescence, which can impair function and integration after implantation. Strategies to preserve or reinduce the desired phenotype often involve biochemical stimulation (e.g., growth factors, cytokines), co-culture with niche-supporting cells, or the use of biomimetic materials that deliver mechanical or topographical cues [63,64]. Moreover, the temporal dynamics of cell behavior (ranging from transient secretion of signaling molecules to long-term matrix synthesis and integration) must be aligned with the scaffold's degradation profile and the tissue's endogenous repair timeline.

The scaffold component of a TEP functions as a temporary or permanent surrogate for the native extracellular matrix (ECM), providing structural support while regulating cell behavior through mechanical and biochemical interactions [65–67]. Scaffold design encompasses a variety of material types, including naturally derived polymers (e.g., collagen, gelatin, fibrin, hyaluronic acid, fibroin, chitosan), synthetic polymers (e.g., polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL)), and decellularized extracellular matrices harvested from allogeneic or xenogeneic tissues [68–70]. Each material system offers distinct advantages: natural polymers are often inherently bioactive and support cell adhesion and migration, while synthetic polymers provide tunable mechanical properties and controlled degradation profiles [65,70]. A fundamental requirement for any scaffold is biocompatibility, which includes not only the absence of toxicity or adverse immune responses, but also the capacity to support appropriate host-tissue interactions. For biodegradable scaffolds, the rate and mechanism of degradation must match the rate of new tissue formation, with degradation by-products being non-toxic and easily cleared by the body [70,71]. Scaffold porosity and interconnectivity are likewise critical for facilitating cell infiltration, nutrient diffusion, and neovascularization (a process essential for sustaining implanted cells, especially in thick or metabolically active constructs) [72]. From a structural standpoint, scaffold architecture and mechanical properties are carefully engineered to reflect the target tissue's native biomechanics. Features such as fiber orientation, pore size, stiffness, and surface roughness can influence cell alignment, migration, and lineage commitment, especially for stem cells [72,73]. For instance, aligned fibers can guide anisotropic tissue formation in musculoskeletal applications, while stiffness gradients can direct stem cell fate toward osteogenic or adipogenic lineages [66,73]. Beyond passive support, next-generation scaffolds increasingly incorporate biofunctional motifs, such as cell-adhesion peptides (e.g., Arg-Gly-Asp (RGD) sequence), immobilized growth factors, or degradable cross-links that mimic dynamic tissue remodeling [66,74].The scaffold-cell interface is also a site of active biochemical signaling. Cells engage integrins and other receptors that sense substrate stiffness and topology, activating intracellular pathways that regulate proliferation, differentiation, and matrix production [73,74]. These cell-matrix interactions, also known as mechanotransduction, are essential for directing the development of functional tissue architecture and are a key design parameter in scaffold engineering [73,74].

The therapeutic efficacy of a TEP depends on its ability to functionally integrate with host tissue through a combination of structural, biochemical, and cellular mechanisms. Upon implantation, the scaffold may immediately restore physical continuity and mechanical function, while the embedded cells initiate the process of tissue remodeling by secreting ECM proteins, cytokines, and growth factors [66]. One of the primary biological processes underpinning TEP function is angiogenesis, which ensures oxygen and nutrient delivery to the construct. Rapid vascularization is essential, particularly for thick tissues, and may be supported by scaffold

design features, inclusion of angiogenic factors, or pre-vascularization strategies [5,75]. In parallel, host immune responses must be carefully modulated to avoid chronic inflammation or fibrosis. The phenotype of infiltrating immune cells (particularly macrophages (which can dictate whether the implanted construct is remodeled into functional tissue or encapsulated by a fibrotic scar)) [76]. Over time, a well-designed TEP undergoes constructive remodeling, wherein the scaffold is gradually resorbed and replaced by host-derived tissue. The success of this process depends on synchronized degradation of the scaffold, persistent functionality of the seeded cells, and favorable interactions at the interface between engineered and native tissue [65,66]. Mechanical integration is also vital, particularly in load-bearing tissues, where mismatch in mechanical properties or poor interfacial bonding can lead to graft failure. The biological activity of TEPs may derive from multiple overlapping mechanisms: (i) direct tissue replacement by long-term engraftment of implanted cells; (ii) paracrine stimulation of endogenous regeneration by short-lived cells; and (iii) immunomodulatory effects that create a permissive environment for host repair [64,66]. The relative contribution of each mechanism varies by tissue type, construct design, and patient context, but the overarching goal is the restoration of structure and function through a regenerative, not merely reparative, process.

4. Commercial ATMPs

This section discusses the principles of action, clinical applications, and regulatory significance of the commercial ATMPs available in Europe and in the US. It should be noted that the US does not use the umbrella term "ATMP" the way Europe does. In Europe, ATMPs specifically include gene therapies, somatic cell therapies, and tissue-engineered products under a single regulatory framework. In contrast, the US FDA regulates similar products under different frameworks. In Table 5, Tables 6 and 7, we included all the products that, to our knowledge, may be considered ATMPs following the EU classification.

4.1. Commercial gene therapy medicinal products (GTMP)

The spectrum of indications now covered by approved GTMPs is diverse, ranging from monogenic rare diseases (such as spinal muscular atrophy, inherited retinal dystrophies, and various primary immunodeficiencies) to complex acquired disorders, including hematological malignancies such as leukemia and lymphoma, hemoglobinopathies, and neuromuscular conditions. GTMPs are generally classified into two major mechanistic categories: in vivo and ex vivo gene therapies. In *in vivo* gene therapy, the therapeutic genetic construct (typically carried by a viral vector such as an AAV is delivered directly into the patient's body, targeting cells in situ to achieve a sustained physiological effect. This approach is most often used in conditions where direct access to the affected tissue is feasible, such as the retina, central nervous system, liver, or muscle, and has the advantage of being a one-time, minimally invasive treatment. Conversely, ex vivo gene therapy involves harvesting cells (most commonly autologous HSCs or T lymphocytes) from the patient, genetically modifying them outside the body using viral vectors (often lentiviruses or gamma-retroviruses), and then reinfusing the corrected or engineered cells. This strategy has been especially transformative in oncology, where genetically modified T cells expressing chimeric antigen receptors (CARs) have redefined treatment paradigms for relapsed or refractory hematologic cancers, as well as in rare genetic diseases requiring systemic hematopoietic correction. This classification is not merely academic; it reflects important differences in vector selection, manufacturing complexity, regulatory pathways, safety profiles, and immunogenicity concerns. For example, in vivo gene therapy often requires immunosuppressive regimens to mitigate host immune responses to viral vectors or the transgene product, while ex vivo therapies require robust cell-processing facilities and quality control protocols to ensure cellular identity, potency, and sterility. Additionally, the persistence of transgene expression (whether episomal or through genome integration) plays a critical role in therapeutic durability and informs long-term patient monitoring strategies. As of 2025, over two dozen GTMPs have gained formal market authorization in the US and EU, Table 5 summarizes the available commercial products in order of approval date, including therapies that were withdrawn from the market.

In vivo gene therapies involve direct delivery of genetic material into the patient's body. Glybera (alipogene tiparvovec) was the first gene therapy approved in the EU in 2012 for lipoprotein lipase deficiency. It utilizes an AAV serotype 1 (AAV1) vector to deliver the lipoprotein lipase (LPL) S447X gene variant (where a Serine (S) at position 447 is replaced by a premature stop codon (X)) into muscle cells, enabling the production of functional lipoprotein lipase to metabolize chylomicrons, thereby reducing triglyceride levels and preventing pancreatitis episodes. However, it was withdrawn in 2017 due to limited demand [77]. Imlygic (talimogene laherparepvec), approved in 2015, is an oncolytic herpes simplex virus type 1 engineered to selectively replicate in tumor cells and express granulocyte-macrophage colony-stimulating factor (GM-CSF), promoting systemic anti-tumor immunity [78]. Luxturna (voretigene neparvovec), approved in 2017 (US) and 2018 (EU), delivers a functional retinal pigment epithelium-specific 65-kDa protein (RPE65) gene via an AAV2 vector to retinal pigment epithelial cells, restoring the visual cycle in patients with biallelic RPE65 mutation-associated retinal dystrophy [82]. Zolgensma (onasemnogene abeparvovec), approved in 2019 (US) and 2020 (EU), uses an AAV9 vector to deliver the Survival motor neuron 1 (SMN1) gene to motor neurons, addressing the genetic cause of spinal muscular atrophy by enabling production of the survival motor neuron (SMN) protein [83]. Upstaza (eladocagene exuparvovec), approved in the EU in 2022, delivers the dopa decarboxylase (DDC) gene via an AAV2 vector to the putamen, restoring dopamine synthesis in patients with aromatic L-amino acid decarboxylase deficiency [91]. Roctavian (valoctocogene roxaparvovec), approved in 2022 (EU) and 2023 (US), uses an AAV5 vector to deliver the B-domain deleted coagulation factor 8 (F8) gene to hepatocytes, enabling endogenous production of F8 in hemophilia A patients [92]. Hemgenix (etranacogene dezaparvovec), approved in 2022 (US) and 2023 (EU), employs an AAV5 vector to deliver the Padua variant of the coagulation factor 9 (F9) gene to hepatocytes, facilitating sustained factor IX expression in hemophilia B patients [94]. Vyjuvek (beremagene geperpavec), approved in the US in 2023, is a topical gel containing a modified herpes simplex virus type 1 vector encoding the Collagen, Type VII, Alpha-1(COL7A1) gene, promoting type VII collagen

Table 5
EMA and FDA approved gene therapy medicinal products (GTMPs) illustrating how targeted gene addition or editing can achieve durable disease modification in severe genetic and oncologic conditions, while highlighting clinically validated delivery platforms, manufacturing strategies, and regulatory pathways that inform future GTMP development.

Name	Approval Date	Approved Regions	Composition	Mechanism	Indications	Status	Company	Description	Ref
Glybera (alipogene tiparvovec)	Oct 2012	EU	AAV1 vector carrying the LPL gene	Delivers a functional LPL gene to muscle cells, restoring enzyme activity	Lipoprotein lipase deficiency with recurrent pancreatitis	EU marketing authorization not renewed (Oct 2017, commercial decision)	uniQure	A pioneering gene therapy that uses an AAV vector to deliver the LPL gene into muscle tissue to reduce pancreatitis episodes in patients with LPL deficiency.	[77]
Imlygic (talimogene laherparepvec)	Oct 2015	EU, US	Genetically modified HSV-1 oncolytic virus	Selectively infects and lyses tumor cells while stimulating an anti-tumor immune response	Unresectable metastatic melanoma	Active	Amgen Inc.	A novel oncolytic virus therapy that directly lyses tumor cells and primes the immune system to attack cancer cells in advanced melanoma patients.	[78]
Strimvelis	May 2016	EU	Autologous $CD34^+$ HSCs transduced with a retroviral vector encoding the ADA gene	Modified stem cells express ADA to restore immune function	ADA-SCID	Active	GlaxoSmithKline	The first approved ex vivo gene therapy that collects a patient's stem cells, genetically modifies them to express ADA, and reintroduces them to treat ADA-SCID.	[79]
Kymriah (tisagenlecleucel)	Aug 2017	EU, US	Autologous T cells modified with an anti-CD19 CAR	CAR-T cells recognize and kill CD19-positive leukemia/lymphoma cells	Pediatric/young adult ($\leq$25 yrs) B-cell ALL; Adult DLBCL.	Active	Novartis Pharmaceuticals	A breakthrough CAR-T cell therapy that reprograms a patient's own T cells to target and eliminate CD19-positive blood cancers.	[80]
Yescarta (axicabtagene ciloleucel)	Oct 2017	EU, US	Autologous T cells engineered with an anti-CD19 CAR	CAR-T cells target and eliminate malignant B-cells	Relapsed/refractory large B-cell lymphoma	Active	Kite Pharma, Inc. (now under Gilead)	A CAR-T cell therapy that genetically modifies T cells to target and kill CD19-expressing lymphoma cells in aggressive B-cell cancers.	[81]
Luxturna (voretigene neparvovec)	Dec 2017	EU, US	AAV2 vector carrying the RPE65 gene	Subretinal injection delivers a functional RPE65 gene to retinal cells, restoring the visual cycle	Inherited retinal dystrophy due to biallelic RPE65 mutations	Active	Spark Therapeutics, Inc.	A gene therapy for inherited retinal dystrophy that delivers the RPE65 gene via an AAV2 vector to improve vision.	[82]
Zolgensma (onasemnogene abeparvovec)	May 2019	EU, US	AAV9 vector carrying the SMN1 gene	One-time intravenous infusion delivers the SMN1 gene to motor neurons, restoring SMN protein levels	Spinal muscular atrophy in children <2 years old	Active	Novartis Gene Therapies, Inc.	A one-time gene therapy that delivers a functional SMN1 gene via an AAV9 vector to treat SMA in young children.	[83]
Zynteglo (betibeglogene autotemcel)	May 2019	EU, US	Autologous $CD34^+$ HSCs transduced ex vivo with a lentiviral vector encoding HbA^{T87Q}	Genetically modified stem cells produce functional adult hemoglobin containing the HbA^{T87Q} β-globin variant, which compensates for defective or absent β-globin, reducing transfusion dependence	Transfusion-dependent β-thalassemia	EU withdrawn (Mar 2022, commercial decision) US Active	bluebird bio, Inc.	A gene therapy that modifies autologous $CD34^+$ HSCs to produce functional β-globin, reducing or eliminating the need for regular transfusions in patients with β-thalassemia.	[84]
Tecartus (brexucabtagene autoleucel)	Jul 2020	EU, US	Autologous anti-CD19 CAR-T cells	CAR-T cells target and eliminate CD19-expressing malignant B cells	Relapsed/refractory mantle cell lymphoma	Active	Kite Pharma, Inc.	A CAR-T cell therapy that targets CD19 on malignant B cells, providing a treatment option for patients with mantle cell lymphoma.	[85]
Libmeldy (atidarsagene autotemcel)	Dec 2020	EU, US	Autologous $CD34^+$ cells transduced	Gene-corrected stem cells produce ARSA to slow disease progression	Metachromatic leukodystrophy (MLD)	Active		A gene therapy for MLD that uses a patient's autologous stem	[86]

(*continued on next page*)

Table 5 (*continued*)

Name	Approval Date	Approved Regions	Composition	Mechanism	Indications	Status	Company	Description	Ref
			with a lentiviral vector encoding the ARSA gene				Orchard Therapeutics (Europe) Limited	cells modified to express ARSA, aiming to halt or slow disease progression.	
Breyanzi (lisocabtagene maraleucel)	Feb 2021	EU, US	Autologous anti-CD19 CAR-T cells with a defined CD4/CD8 ratio	CAR-T cells with a balanced CD4/CD8 composition target CD19 to eliminate malignant cells	Relapsed/refractory large B-cell lymphoma	Active	Juno Therapeutics, Inc., a BMS Company	A refined CAR-T cell therapy with a controlled CD4/CD8 ratio designed to enhance safety and efficacy in treating large B-cell lymphoma.	[87]
Abecma (idecabtagene vicleucel)	Mar 2021	EU, US	Autologous *anti*-BCMA CAR-T cells	CAR-T cells target BCMA on multiple myeloma cells, eliminating them	Relapsed/refractory multiple myeloma	Active	Celgene Corp, a BMS Company	A CAR-T cell therapy targeting BCMA, providing treatment for patients with advanced multiple myeloma.	[88]
Skysona (elivaldogene autotemcel)	Jul 2021	EU, US	Autologous $CD34^+$ HSCs cells transduced with a lentiviral vector carrying the ABCD1 gene	Modified stem cells produce Adrenoleukodystrophy Protein (ALDP) to slow neurological decline	Early active CALD in boys in the 4–17 age range	EU Withdrawn (Nov 2021, commercial decision) US Active	bluebird bio, Inc.	A gene therapy for CALD that uses autologous $CD34^+$ HSCs modified to express ABCD1; withdrawn in the EU for commercial reasons.	[89]
Carvykti (ciltacabtagene autoleucel)	Feb 2022	EU, US	Autologous CAR-T cells targeting BCMA	Dual-epitope CAR-T cells target BCMA on myeloma cells to induce cell death	Relapsed/refractory multiple myeloma	Active	Janssen Biotech, Inc.	A next-generation CAR-T cell therapy featuring dual-epitope targeting of BCMA for improved specificity and efficacy in advanced multiple myeloma.	[90]
Upstaza (eladocagene exuparvovec)	Jul 2022	EU, US	AAV2 vector expressing the AADC gene	Delivers the AADC gene directly to striatal cells via brain infusion, restoring enzyme activity	aromatic L-amino acid decarboxylase (AADC) deficiency in pediatric patients	Active	PTC Therapeutics	A gene therapy for AADC deficiency that delivers the AADC gene via an AAV2 vector directly into the brain, enhancing neurotransmitter production.	[91]
Roctavian (valoctocogene roxaparvovec)	Aug 2022	EU, US	AAV5 vector carrying the Factor VIII gene	Increases liver production of Factor VIII, reducing bleeding episodes	Severe hemophilia A in adults	Active	BioMarin Pharmaceutical Inc.	A gene therapy for hemophilia A that uses an AAV5 vector to deliver a high-activity Factor VIII gene, thereby reducing bleeding risk.	[92]
Adstiladrin (nadofaragene firadenovec)	Dec 2022	US	Adenoviral vector encoding IFNα2b gene	Intravesical delivery transduces bladder cells to produce IFNα2b, enhancing local immune response	BCG unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS).	Active	Ferring Pharmaceuticals A/S	An adenoviral gene therapy for bladder cancer that induces local production of IFNα2b to stimulate an anti-tumor immune response.	[93]
Hemgenix (etranacogene dezaparvovec)	Feb 2023	EU, US	AAV5 vector carrying a high-activity F9 gene (Padua variant)	Delivers a high-activity F9 gene to liver cells via AAV5, boosting F9 production	Hemophilia B (congenital F9 deficiency)	Active	CSL Behring LLC	A gene therapy for hemophilia B that uses an AAV5 vector to deliver a high-activity F9 gene (Padua variant), reducing bleeding episodes.	[94]
Vyjuvek (beremagene geperpavec)	May 2023	US	Modified HSV-1 vector expressing COL7A1 gene	Topically delivers COL7A1 to skin cells, boosting collagen VII production	Dystrophic epidermolysis bullosa	Active	Krystal Biotech, Inc.	A topical gene therapy that uses a modified HSV-1 vector to deliver COL7A1, strengthening	[95]

(*continued on next page*)

Table 5 (*continued*)

Name	Approval Date	Approved Regions	Composition	Mechanism	Indications	Status	Company	Description	Ref
					(DEB) for wound treatment			skin adhesion and aiding wound healing in patients with DEB.	
Elevidys (delandistrogene moxeparvovec)	Jun 2023	US	AAVrh74 vector encoding a micro-dystrophin gene	Delivers a truncated dystrophin gene to muscle cells to produce functional protein	Duchenne muscular dystrophy in ambulatory pediatric patients	Active	Sarapata Therapeutics, Inc.	A gene therapy for Duchenne muscular dystrophy (DMD) that uses an AAVrh74 vector to deliver a micro-dystrophin gene, aiming to improve muscle strength and function in affected children.	[96]
Lyfgenia (lovotibeglogene autotemcel)	Dec 2023	US	Autologous $CD34^+$ HSCs transduced with a lentiviral vector encoding the βA-T87Q-globin gene	Genetically modified patient's HSCs to produce HbA^{T87Q}, reducing sickling of red blood cells	SCD in patients ≥12 years with a history of vaso-occlusive events	Active	Bluebird bio, Inc.	A one-time gene therapy aiming to alleviate SCD symptoms by enabling production of anti-sickling hemoglobin	[97]
Casgevy (exagamglogene autotemcel)	Feb 2024	EU, US	Autologous $CD34^+$ HSCs edited using CRISPR-Cas9 technology targeting the BCL11A gene	Disrupts BCL11A gene to increase HbF production, mitigating sickling of red blood cells	SCD with recurrent vaso-occlusive crises; Transfusion-dependent β-thalassemia in patients ≥12 years	Active	Vertex Pharmaceuticals & CRISPR Therapeutics	First FDA-approved CRISPR-based gene therapy, offering a potential cure for SCD and β-thalassemia by reactivating HbF production	[98]
Beqvez (fidanacogene elaparvovec)	Jul 2024	EU, US	Recombinant AAVRh74 vector encoding the FIX-Padua gene variant	Delivers a high-activity FIX gene to hepatocytes, enabling endogenous production of FIX	Moderate to severe Hemophilia B in adults without neutralizing antibodies to AAVRh74	Active	Pfizer Inc.	A one-time intravenous gene therapy designed to reduce or eliminate the need for regular Factor IX infusions in Hemophilia B patients	[99]
Aucatzyl (obecabtagene autoleucel)	Nov 2024	EU, US	Autologous T cells genetically modified to express a CD19-directed chimeric antigen receptor (CAR)	Engineered T cells target and eliminate CD19-positive B-cell precursor acute lymphoblastic leukemia cells	Relapsed or refractory B-cell precursor acute lymphoblastic leukemia in adults	Active	Autolus Therapeutics	A CAR-T cell therapy offering a novel treatment option for adult patients with relapsed or refractory B-cell ALL	[100]

Table 6
Approved somatic cell therapy medicinal products (sCTMPs) illustrating how ex vivo–manipulated autologous and allogeneic cells can modulate immune responses, restore physiological function, or support tissue repair while highlighting the clinical, manufacturing, and efficacy-validation challenges that shape sustainable sCTMP development.

Name	Approval Date	Approved Regions	Composition	Mechanism	Indications	Active/Withdrawal	Company	Description	Ref
Provenge (sipuleucel-T)	Apr 2010	EU, US	Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF	Activates the patient's immune cells to recognize and attack cancer cells	Metastatic castration-resistant prostate cancer	EU Withdrawn (May 2015, never granted full EU marketing authorization) US Active	Dendreon Corp	An autologous immunotherapy that uses a patient's own immune cells—collected and activated ex vivo—to target and kill prostate cancer cells.	[101]
Laviv (Azficel-T)	Jun 2011	US	Autologous fibroblasts cultured from the patient's skin	Fibroblasts produce collagen and ECM, improving skin structure	Correction of moderate-to-severe nasolabial fold wrinkles	Active	Fibrocell Technologies	A cell therapy that uses a patient's own cultured fibroblasts to enhance skin appearance by increasing collagen production and improving facial structure.	[102]
Zalmoxis	Aug 2016	EU	Allogeneic T lymphocytes modified with a "suicide gene" (HSV-TK Mut2)	Provides immune reconstitution with a built-in safety switch for controlled elimination	Adjunct treatment following HSCT in high-risk patients	EU Withdrawn (Oct 2019, commercial decision)	MolMed S.p.A.	An allogeneic T-cell therapy engineered with a safety "suicide" gene to support immune reconstitution after transplant, allowing controlled elimination if needed.	[103]
Alofisel (darvadstrocel)	Mar 2018	EU	Expanded allogeneic adipose-derived mesenchymal stem cells	MSCs modulate inflammation and promote tissue repair	Complex perianal fistulas in Crohn's disease	EU Withdrawn (Dec 2024, efficacy not confirmed)	TiGenix	An allogeneic MSCs therapy designed to reduce inflammation and promote healing in perianal fistulas associated with Crohn's disease; later withdrawn in Europe.	[104]
Omisirge (omidubicel-onlv)	Apr 2023	US	Allogeneic cord blood–derived hematopoietic progenitor cells, expanded ex vivo	Accelerates engraftment and neutrophil recovery after transplant	Hematologic malignancy patients undergoing cord blood transplantation	Active	Gamida Cell Ltd.	An allogeneic cell therapy that utilizes cord blood–derived PCs to reduce the time needed for neutrophil recovery in transplant patients.	[105]
Lantidra (donislecel)	Jun 2023	US	Allogeneic pancreatic islet cells	Islet cells engraft in the liver and secrete insulin to control blood glucose	Type 1 diabetes with recurrent severe hypoglycemia	Active	CellTrans Inc.	An allogeneic islet cell therapy intended to restore insulin production and stabilize blood glucose levels in patients with type 1 diabetes.	[106]
Amtagvi (lifileucel)	Feb 2024	US	Autologous TIL expanded ex vivo	Expanded TILs target and kill tumor cells	Unresectable or metastatic melanoma	Active	Iovance Biotherapeutics, Inc.	A personalized therapy that expands a patient's own tumor-infiltrating lymphocytes ex vivo, then reinfuses them to specifically target melanoma cells.	[107]
Ryoncil (remestemcel-L)	Dec 2024	US	Allogeneic bone marrow–derived MSCs	MSCs modulate immune responses and support tissue repair	Pediatric steroid-refractory acute graft-versus-host disease	Active	Mesoblast, Inc.	An allogeneic MSCs therapy designed to reduce the severity of acute graft-versus-host disease in pediatric patients following transplant.	[108]

Table 7
Clinically authorized TEPs demonstrating how ex vivo–constructed cellular tissues can restore structural and functional integrity in skin, cartilage, and eye, while revealing the critical importance of manufacturing robustness, clinical durability, and reimbursement alignment for long-term regulatory and commercial success.

Name	Approval Date	Approved Regions	Composition	Mechanism	Indications	Status	Developer	Description	Ref
Epicel	Clinically used since the late 1980s. 2007, FDA humanitarian authorization February 2016 as biologics	US	Autologous ex vivo expanded epidermal keratinocyte sheets	Replaces epidermis by providing cultured autologous epithelial tissue	Severe deep dermal or full-thickness burns (≥30% TBSA)	Active	Vericel	Cultured epidermal autograft representing one of the earliest clinically used tissue-engineered products; formally authorized by FDA under humanitarian provisions, following decades of clinical use.	[109]
Carticel	Aug 1997	US	Autologous cultured chondrocytes	Cartilage repair through implantation of expanded chondrocytes	Symptomatic cartilage defects of the knee	Discontinued (superseded by MACI)	Vericel	First FDA-licensed autologous chondrocyte implantation product for cartilage repair.	[110]
Apligraf	May 1998	US	Living bilayered skin substitute (keratinocytes and fibroblasts in collagen matrix)	Supports re-epithelialization and dermal matrix formation	Chronic venous leg ulcers; diabetic foot ulcers	Active	Organogenesis	A bilayered, human skin equivalent composed of viable allogeneic keratinocytes and dermal fibroblasts embedded within a bovine collagen matrix, designed to promote re-epithelialization and dermal repair	[111]
Dermagraft	Jan 2001	US	Allogeneic human dermal fibroblasts seeded on a bioabsorbable polyglactin scaffold	Promotes wound healing via viable fibroblasts producing extracellular matrix and growth factors	Chronic full-thickness diabetic foot ulcers	Active (authorization maintained; commercialization intermittent)	Organogenesis	A tissue-engineered human dermal substitute composed of living allogeneic fibroblasts cultured on a resorbable scaffold to stimulate regeneration and accelerate healing	[112]
OrCel	Sep 2001	US	Allogeneic keratinocytes and fibroblasts on collagen matrix	Temporary biologically active wound coverage	Burn donor sites; RDEB hand surgery	Active	Ortec	A bilayered, skin substitute composed of viable allogeneic human keratinocytes and fibroblasts cultured on a collagen matrix, designed to provide a temporary dermal–epidermal construct that promotes wound healing and epithelialization	[113]
ChondroCelect	Oct 2009	EU	Autologous cartilage cells expanded ex vivo	Repairs damaged cartilage by replacing lost tissue	Cartilage defect in the knee	EU Withdrawn (July 2016, commercial decision)	TiGenix	A tissue-engineered therapy using autologous chondrocytes cultured in vitro to form an implant that repairs and regenerates damaged knee cartilage.	[114]
Gintuit	Mar 2012	US	Allogeneic cultured keratinocytes and fibroblasts on a bovine collagen scaffold	Provides a living cellular skin substitute to support tissue regeneration	Oral soft tissue regeneration in dental surgery	Active	Organogenesis Incorporated	A tissue-engineered skin substitute designed to promote regeneration of gingival tissue in patients undergoing dental surgery.	[115]
MACI	Jun 2013	EU, US	Autologous chondrocytes seeded on a porcine collagen membrane	Restores articular cartilage through the biological activity of autologous chondrocytes delivered on a collagen membrane	Full-thickness cartilage defects of the knee	EU Marketing authorization not renewed (June 2018, commercial decision) US Active	Vericel Corporation	A tissue-engineered product that applies cultured autologous chondrocytes on a collagen membrane to restore damaged knee cartilage.	[116]
Holoclar	Feb 2015	EU	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	Replaces damaged corneal tissue by supplying limbal stem cells	LSCD due to burns	Active	Holostem Terapie Avanzate S.R.L.	A regenerative therapy for the eye that uses a sheet of autologous corneal epithelial cells to restore the corneal surface in patients with LSCD.	[50]
Spherox	Jul 2017	EU				Active	Co.don AG		[117]

(*continued on next page*)

Table 7 (*continued*)

Name	Approval Date	Approved Regions	Composition	Mechanism	Indications	Status	Developer	Description	Ref
			Spheroids of autologous matrix-associated chondrocytes	Forms self-assembling cell clusters that integrate to regenerate cartilage	Cartilage defects of the knee (up to 10 cm^2)			A novel therapy using spheroidal aggregates of autologous chondrocytes to repair cartilage defects in the knee with improved integration and durability.	
StrataGraft	Jun 2021	US	Allogeneic keratinocytes and fibroblasts in collagen construct	Promotes durable wound closure and regeneration	Deep partial-thickness thermal burns	Active	Stratatech (Mallinckrodt)	An allogeneic human skin substitute composed of viable keratinocytes and dermal fibroblasts organized within a collagen-based scaffold, designed to provide a permanent skin-like tissue that supports re-epithelialization and dermal regeneration	[118]
Rethymic	Oct 2021	US	Allogeneic processed thymus tissue (cultured pediatric thymus slices)	Restores thymic tissue function by providing viable thymic epithelial cells that support T-cell development	Pediatric congenital athymia (e.g., DiGeorge syndrome)	Active	Enzyvant Therapeutics GmbH	A tissue-engineered product that uses cultured thymus tissue slices to restore immune function in infants with congenital athymia, such as DiGeorge syndrome.	[119]

expression and wound healing in dystrophic epidermolysis bullosa [95]. Adstiladrin (nadofaragene firadenovec), approved in 2022 (US), utilizes a non-replicating adenoviral vector to deliver the human Interferon alpha-2b (IFNα2b) gene to urothelial cells, inducing local interferon production and anti-tumor activity in Bacillus Calmette-Guérin (BCG) unresponsive non-muscle invasive bladder cancer [93]. Elevidys (delandistrogene moxeparvovec), conditionally approved by the FDA in 2023, employs an AAVrh74 vector to deliver a micro-dystrophin gene to muscle cells, aiming to restore dystrophin expression in Duchenne muscular dystrophy [96]. Beqvez (fidanacogene elaparvovec), approved in both the EU and US in 2023, uses an AAV vector to deliver a functional F9 gene to hepatocytes, providing sustained factor IX expression in hemophilia B patients [99].

Ex vivo gene therapies involve modifying cells outside the patient's body and then reinfusing them. Strimvelis, approved in 2016 by the EMA for ADA-SCID, modifies autologous HSCs, characterized by the presence of the Cluster of Differentiation 34 ($CD34^+$) surface antigen, ex vivo using a γ-retroviral vector encoding the *ADA* gene to restore immune function. [79]. Kymriah (tisagenlecleucel), approved in 2017 (US) and 2018 (EU), is a CD19-directed CAR-T cell therapy for ALL and later diffuse large B-cell lymphoma (DLBCL), where autologous T cells are genetically modified to express a chimeric antigen receptor targeting CD19, enabling them to identify and destroy CD19-expressing malignant B cells [80]. Yescarta (axicabtagene ciloleucel), approved in 2017 (US) and 2018 (EU), is another CD19-directed CAR-T therapy for DLBCL and other B-cell malignancies, following a similar mechanism of action [81]. Tecartus (brexucabtagene autoleucel), approved in 2020, is the first CAR-T therapy indicated for mantle cell lymphoma and also used for ALL; it features a CD28 costimulatory domain for enhanced T cell activation and proliferation [85]. Breyanzi (lisocabtagene maraleucel), approved in 2021 (US), is a CD19-directed CAR-T therapy for large B-cell lymphoma, uniquely formulated with a defined 1:1 ratio of $CD8^+$ and $CD4^+$ CAR-T cells, which is intended to reduce variability and improve product consistency [87]. Abecma (idecabtagene vicleucel), approved in 2021 (US), was the first CAR-T therapy targeting B-cell maturation antigen (BCMA), used in multiple myeloma to selectively eliminate malignant plasma cells expressing BCMA [88]. Carvykti (ciltacabtagene autoleucel), approved in 2022 (US and EU), is also BCMA-directed and employs a dual-epitope binding CAR, which enhances binding avidity and cytotoxic activity against multiple myeloma cells, even with low antigen density [90]. Aucatzyl (obecabtagene autoleucel), approved in 2024 (US), is a CD19-targeting CAR-T therapy for relapsed/refractory B-cell ALL in adults, and notable for being developed entirely outside of the US, reflecting the globalization of CAR-T innovation [100].

Outside of oncology, Zynteglo (betibeglogene autotemcel) is a lentiviral gene therapy for transfusion-dependent β-thalassemia, approved in the EU in 2019 and later in the US in 2022 (the EU marketing authorization was withdrawn in 2021 for commercial reasons). It involves autologous $CD34^+$ HSCs transduced with a lentiviral vector encoding a modified β-globin gene (HbA^{T87Q}), in which threonine-87 is replaced by glutamine to mimic fetal hemoglobin function, allowing for endogenous production of adult hemoglobin and reducing or eliminating the need for transfusions [84]. Skysona (elivaldogene autotemcel), approved in 2021 (EU) and 2022 (US), is a lentivirus-based therapy for early cerebral adrenoleukodystrophy (CALD), a neurodegenerative disorder caused by mutations in the adenosine triphosphate (ATP) - binding cassette subfamily D member 1 (ABCD1). In this case, patient-derived $CD34^+$ HSCs cells are modified to express functional ABCD1 protein, potentially halting disease progression [89]. Libmeldy (atidarsagene autotemcel), approved in 2020 (EU) and 2023 (US), is a lentiviral-modified autologous HSCs product for metachromatic leukodystrophy (MLD), where the ARSA gene is delivered to enable long-term enzymatic correction in the central and peripheral nervous systems [86]. Two landmark therapies for sickle cell disease (SCD) were approved in 2023: Lyfgenia (lovotibeglogene autotemcel) is an autologous, lentiviral vector–based gene therapy in which the patient's own $CD34^+$ HSCs are transduced ex vivo to express HbA^{T87Q}, producing anti-sickling hemoglobin [97], and Casgevy (exagamglogene autotemcel) is the first approved gene therapy to utilize CRISPR-Cas9 genome editing [98]. It introduces a targeted disruption of the erythroid-specific enhancer of the B-cell lymphoma/-leukemia 11A (BCL11A) gene in autologous $CD34^+$ hematopoietic stem and progenitor cells, reactivating fetal hemoglobin (HbF) production and thereby reducing hemoglobin polymerization and red blood cell sickling. Casgevy was concurrently approved for both SCD and transfusion-dependent β-thalassemia in the US and EU, representing a critical milestone in the clinical translation of genome editing technologies [98].

4.2. *Commercial somatic cell therapy medicinal products (sCTMP)*

As of 2025, a growing number of sCTMPs have been authorized for clinical use in the US and Europe, addressing a diverse range of conditions through mechanisms involving immunomodulation, immune stimulation, and cellular replacement. A summary of the available products is shown in Table 6. Among the earliest approved therapies, sipuleucel-T (Provenge) was authorized by the FDA in 2010 for metastatic castration-resistant prostate cancer. It consists of autologous peripheral blood mononuclear cells activated ex vivo with a recombinant fusion protein containing prostatic acid phosphatase (PAP) linked to GM-CSF (PAP- GM-CSF), designed to elicit a tumor-targeted immune response via antigen-presenting cell activation and T-cell priming [120,101]. Another autologous product, azficel-T (Laviv), approved in the US in 2011, involves the intradermal injection of autologous fibroblasts cultured from a patient's skin biopsy. These fibroblasts produce ECM components such as collagen, thereby improving dermal integrity and reducing facial wrinkles [102]. Several therapies have utilized allogeneic or donor-derived cell sources. Darvadstrocel (Alofisel), composed of expanded adipose-derived mesenchymal stem cells, was approved in Europe in 2018 for the treatment of complex perianal fistulas in adult patients with Crohn's disease. The cells exert local immunosuppressive effects by inhibiting pro-inflammatory cytokines and promoting tissue repair, although the product was withdrawn from the market in 2024 [121,104]. Similarly, remestemcel-L (Ryoncil) was approved by the FDA in 2024 for pediatric steroid-refractory acute graft-versus-host disease (GVHD). This allogeneic bone marrow-derived mesenchymal stromal cell therapy acts through paracrine immunomodulatory effects, including suppression of effector T-cell proliferation and secretion of anti-inflammatory mediators such as prostaglandin E2 and Interleukin-10 (IL-10) [122, 108].

Another notable product, omidubicel-onlv (Omisirge), approved in the US in 2023, consists of allogeneic umbilical cord blood–derived hematopoietic PCs expanded ex vivo with nicotinamide to improve cell viability and homing. When used following myeloablative conditioning in patients undergoing transplantation for hematologic malignancies, Omisirge accelerates neutrophil recovery and reduces infection rates by promoting rapid hematopoietic reconstitution [123,105]. In the field of metabolic disease, donislecel (Lantidra) was authorized by the FDA in 2023 for adults with type 1 diabetes and severe hypoglycemia unawareness. The product consists of allogeneic pancreatic islet cells infused into the portal vein, where they engraft in the liver and secrete insulin in response to glucose, potentially restoring glycemic control and reducing or eliminating the need for exogenous insulin [124,106]. Most recently, two therapies have expanded the application of autologous and allogeneic cell therapy to cancer and transplant-related complications. Lifileucel (Amtagvi), an autologous tumor-infiltrating lymphocyte (TIL) therapy approved in 2024 for unresectable or metastatic melanoma, involves harvesting TILs from a patient's tumor, expanding them ex vivo in IL-2, and reinfusing them to mediate direct cytotoxicity against tumor cells. Unlike genetically engineered products, TIL therapy leverages naturally tumor-reactive T cells and has shown durable responses in patients with heavily pretreated melanoma [125,107]. Lastly, nalotimagene carmaleucel (Zalmoxis), which received conditional approval in Europe in 2016 but was later withdrawn, consisted of donor-derived T cells engineered with the Herpes Simplex Virus-Thymidine Kinase (HSV-TK) suicide gene. Designed for patients undergoing haploidentical stem cell transplantation, the therapy allowed immune reconstitution while preserving the option to eliminate the cells pharmacologically in cases of GVHD, using ganciclovir [103].

4.3. Commercial tissue engineered products (TEP) and combined therapy medicinal products (cATMPs)

Under EU regulation TEPs and cATMPs are both ATMPs distinguished by their composition and mode of action. TEPs consist solely of engineered cells or tissues and are intended to regenerate, repair, or replace a human tissue. In contrast, cATMPs combine an ATMP (which may itself be a TEP, sCTMPs, or GTMPs) with a medical device that is an integral part of the product, for example an ATMP in which cells are cultivated on a scaffolding structure should be considered as an cATMP. This section combines data from commercial TEPs and commercial cATMPs, categories that are underrepresented within the expanding field of ATMPs. Table 7 summarizes the available commercial TEP and cATMPs in order of approval date, including therapies that were withdrawn from the market.

From a clinical perspective, skin and soft-tissue regeneration represents the earliest, most mature, and most populated application area of tissue-engineered products (TEPs). This reflects both the accessibility of the skin as a target tissue and the long-standing clinical need for effective solutions to extensive burns, chronic wounds, and complex surgical defects. One of the earliest and most emblematic examples is Epicel, which consists of autologous ex vivo expanded epidermal keratinocyte sheets derived from a small patient skin biopsy. After extensive expansion, these sheets are transplanted to cover large full-thickness burn areas, providing epidermal replacement in patients with limited donor sites [109]. Although Epicel lacks a dermal component and does not fully reconstitute native skin architecture, it has demonstrated life-saving potential in patients with massive burns and represents a foundational milestone in clinical tissue engineering [126]. Subsequent developments aimed to more closely mimic native skin structure by incorporating both epidermal and dermal cellular components. Apligraf is a bilayered living skin equivalent composed of allogeneic keratinocytes and fibroblasts embedded within a collagen matrix, designed to reproduce key biological features of human skin [111]. Rather than acting as a permanent graft, Apligraf functions as a biologically active temporary tissue, releasing cytokines, growth factors, and extracellular matrix components that stimulate host cell migration, angiogenesis, and re-epithelialization. Its clinical use in chronic venous leg ulcers and diabetic foot ulcers has highlighted the importance of paracrine signaling and cell–matrix interactions in wound healing [127]. Dermagraft represents a complementary dermal-focused strategy, consisting of allogeneic human dermal fibroblasts cultured on a bioabsorbable polymer scaffold. Upon application to chronic wounds, the viable fibroblasts produce extracellular matrix proteins and growth factors that modulate inflammation and promote granulation tissue formation [112]. Unlike bilayered constructs, Dermagraft primarily targets dermal regeneration, relying on host keratinocytes for epidermal closure. Its development underscored the therapeutic relevance of fibroblast-mediated matrix remodeling in non-healing wounds [128]. Other skin TEPs were developed to address more specialized surgical indications. OrCel is a bilayered construct of allogeneic keratinocytes and fibroblasts cultured on a collagen matrix, intended as a temporary biologically active wound covering [113]. It has been applied in burn donor site wounds and in reconstructive surgery for recessive dystrophic epidermolysis bullosa, where it supports epithelialization and reduces surgical morbidity without permanently engrafting [129]. More recently, StrataGraft has advanced the field by aiming to provide a durable, skin-like tissue rather than a transient biological stimulus [118]. Composed of allogeneic keratinocytes and dermal fibroblasts organized within a collagen-based scaffold, StrataGraft is designed to integrate with host tissue and restore both epidermal and dermal layers in deep partial-thickness thermal burns, potentially reducing or eliminating the need for autologous skin grafting [130].

Another wide category of TEPs is intended for cartilage regeneration. Carticel, approved in the United States in 1997, represents the first commercially approved autologous chondrocyte implantation therapy for cartilage regeneration, consisting of ex vivo–expanded patient-derived chondrocytes implanted to repair focal articular cartilage defects [110]. ChondroCelect was the first TEP for cartilage repair to receive market approval in Europe. It is an autologous chondrocyte implantation (ACI) therapy designed to repair full-thickness cartilage lesions of the knee. ChondroCelect is based on the use of characterized chondrocytes expanded ex vivo and implanted into the defect site, where they facilitate hyaline cartilage formation and improve joint function [131]. MACI (Matrix-Induced ACI) represents the next generation of ACI therapies and is one of the two ever approved cATMP. Unlike ChondroCelect, which requires periosteal suturing, MACI involves the use of a porcine-derived collagen membrane seeded with autologous chondrocytes, simplifying the surgical procedure and improving cell retention. This technique enhances cartilage regeneration, leading to better functional outcomes [132]. Is worth noticing that MACI is often reported incorrectly as cATMPs while in its European public

assessment report (EPAR) is indicated as follows "MACI is an advanced therapy medicinal product called a 'tissue engineered product'" clearly positioning MACI as TEP. Spherox is a newer cartilage repair therapy that utilizes spheroid technology, where chondrocytes form self-organized spheroids before implantation. This method enables the cells to maintain their ECM, improving their integration and cartilage regeneration capabilities. Spherox is particularly effective in treating small to medium-sized cartilage defects [133].

Other therapies tackle the regeneration of different other damaged tissues. Holoclar is a pioneering ex vivo expanded autologous limbal stem cell therapy designed for patients with severe limbal stem cell deficiency (LSCD), often caused by burns or chemical injuries. This treatment involves harvesting limbal stem cells from a small unaffected area of the patient's eye, expanding them in vitro, and transplanting them back onto the damaged ocular surface to restore corneal integrity [51]. Gintuit is an allogeneic cell therapy product composed of keratinocytes and fibroblasts cultured on a bovine collagen matrix. This is the second product that can be classified as cATMP, it is indicated for oral soft tissue regeneration, particularly in cases where gingival augmentation is necessary for periodontal reconstruction. Gintuit provides a scaffold for cellular integration and promotes tissue regeneration [134]. Rethymic is an innovative tissue-engineered thymus graft used for immune reconstitution in children with congenital athymia, such as those with complete DiGeorge syndrome. Rethymic consists of cultured thymic epithelial cells that are implanted into the recipient, facilitating T-cell development and immune system restoration [135].

4.4. Commercialization bottlenecks across ATMP categories

The commercialization of Advanced Therapy Medicinal Products (ATMPs) continues to face challenges, specifically the "valley of death," where early innovations are hindered by manufacturing, regulatory, financial, and reimbursement obstacles. Consequently, a significant portion of EU-approved ATMPs (30%, or 8/27, based on our analysis of commercial products) have been withdrawn due to commercial, rather than safety, issues [136]. These challenges are category-specific yet share common threads: exorbitant per-patient costs (often €300K–€1.8M), fragile supply chains, immature potency assays, limited long-term data from small orphan trials, and payer skepticism over cost-effectiveness, amplified by the one-time curative paradigm that demands upfront payment for deferred benefits [137,138]. GTMPs, sCTMPs, and TEPs each face distinct hurdles that precipitate failure, underscoring the need for harmonized regulations, manufacturing innovation, and novel reimbursement models to enable sustainable market translation.

GTMPs, relying on viral/non-viral vectors for sustained genetic correction, grapple with vector production scalability (e.g., AAV/lentiviral titers), genotoxicity risks (insertional mutagenesis, hepatotoxicity), immune neutralization of re-dosing, and proving durable transgene expression sans off-target effects, necessitating costly specialized GMP facilities prone to low yields and contamination [139,140]. Preclinical demands for extensive animal genotoxicity models compound timelines, while reimbursement collapses under payers' insistence on decades-long follow-up for rare diseases [140]. To date over twenty GTMPs commercialized in the EU, only three have been retired from the market. Glybera (alipogene tiparvovec) exemplifies GTMP pitfalls: the first EMA-approved GTMP (2012) for lipoprotein lipase deficiency via AAV1-LPL gene delivery achieved only one €1M sale amid ultra-rare prevalence (1–2 EU cases/year), cumbersome multi-injection administration, and payer rejection of uncertain long-term data, prompting voluntary 2017 withdrawal [141]. Similarly, Zynteglo (betibeglogene autotemcel), a 2019-approved lentiviral HSCT product for beta-thalassemia (€1.575M/dose), delivered transfusion independence in 80% of patients but succumbed to manufacturing disruptions, chemotherapy risks, and failed German reimbursement talks, leading to 2022 EU withdrawal [142].

sCTMPs, featuring ex vivo expanded/manipulated non-genetically modified cells, contend with autologous "vein-to-vein" logistics (4–6 weeks), donor variability, cryopreservation viability loss, and severe adverse events such as CRS/neurotoxicity demanding specialized centers, alongside contamination risks during expansion and elusive in vivo potency metrics [138,143]. High per-patient costs (€300K–€500K) erode viability in heterogeneous oncology settings lacking real-world evidence [138,143]. Zalmoxis (nicotinamide-expanded allogeneic T cells), conditionally approved in 2015 as a leukemia HSCT adjunct, boosted engraftment but missed Phase III leukemia-free survival endpoints, coupled with low uptake and reimbursement barriers, yielding 2019 suspension [144]. An interesting point to consider is that Europe currently lacks available sCTMPs, stemming from the fact that all three of the pertinent products have been removed from the market.

TEPs and cATMPs, fusing living cells with scaffolds/matrices for structural regeneration, confront scaffold integration failures, vascularization deficits in avascular cores, mechanical mismatches, and hyper-complex manufacturing blending cell culture, biomaterial sterilization, and 3D maturation under bioreactor automation deficits, yielding short shelf-lives (hours–days) that mandate just-in-time logistics and skyrocket costs. Regulatory device/ATMP hybrid ambiguity and durability doubts versus synthetics stall reimbursement in niche orthopedic/wound markets. Two emblematic failure cases illustrate these issues. Dermagraft, a fibroblast-seeded bioabsorbable scaffold for diabetic foot ulcers developed by ATS, achieved FDA approval but failed commercially in the early 2000s due to unscalable manufacturing, unsustainable production costs, and inadequate reimbursement pathways that prevented the company from achieving profitability [128,145]. Despite clinical efficacy, ATS filed for bankruptcy in 2002, selling Dermagraft to Smith & Nephew for approximately $12 million after struggling with the complex logistics of cell culture, cryopreservation, and quality control [145]. ChondroCelect, the first approved ATMP at the EMA in 2009, consisted of autologous expanded cartilage chondrocytes for knee cartilage repair with demonstrated clinical benefit and a positive benefit-risk profile, yet the manufacturer (TiGenix) voluntarily withdrew from the EU market in 2016 due to limited market uptake and unfavorable reimbursement conditions across key EU countries consistently questioned cost-effectiveness against cheaper alternatives such as microfracture, and the complex, patient-specific autologous approach could not compete economically despite regulatory approval [146].

Overall, these cases are not anomalies; across approved ATMPs in Europe, a substantial portion have been withdrawn, with the majority driven primarily by commercial reasons rather than safety failures, and several directly linked to negative Health Technology Assessment (HTA) and reimbursement outcomes highlighting that regulatory clearance does not guarantee market viability [136].

5. A sight into the future: ATMPs in clinical trials

A comprehensive analysis of combined clinical trial data from both the US (https://clinicaltrials.gov/) and the EU (https://euclinicaltrials.eu/) reveals distinct trends in intervention types, targeted diseases, study phases, geographic dispersion, and sponsorship models. The lists of the clinical trials extrapolated by both registers are available as supplementary data.

5.1. A general overview of clinical trials

We summarized the merged results of the US and EU clinical trial datasets in Fig. 6 and, stratified by ATMP category, in Table 8. From a geographical perspective, ATMP clinical activity shows a strong concentration in Asia, North America, and Europe, as illustrated in Fig. 6A and B. When multinational trials are assigned to each participating continent, Asia accounts for the largest share of ATMP trials (40.3%), followed by North America (33.6%) and Europe (22.6%), while South America (1.7%), Oceania (1.3%), and Africa (0.4%) contribute only marginally. At the country level, the United States and China emerge as the dominant contributors within North America and Asia, respectively, with substantial additional activity from major European countries such as Germany,

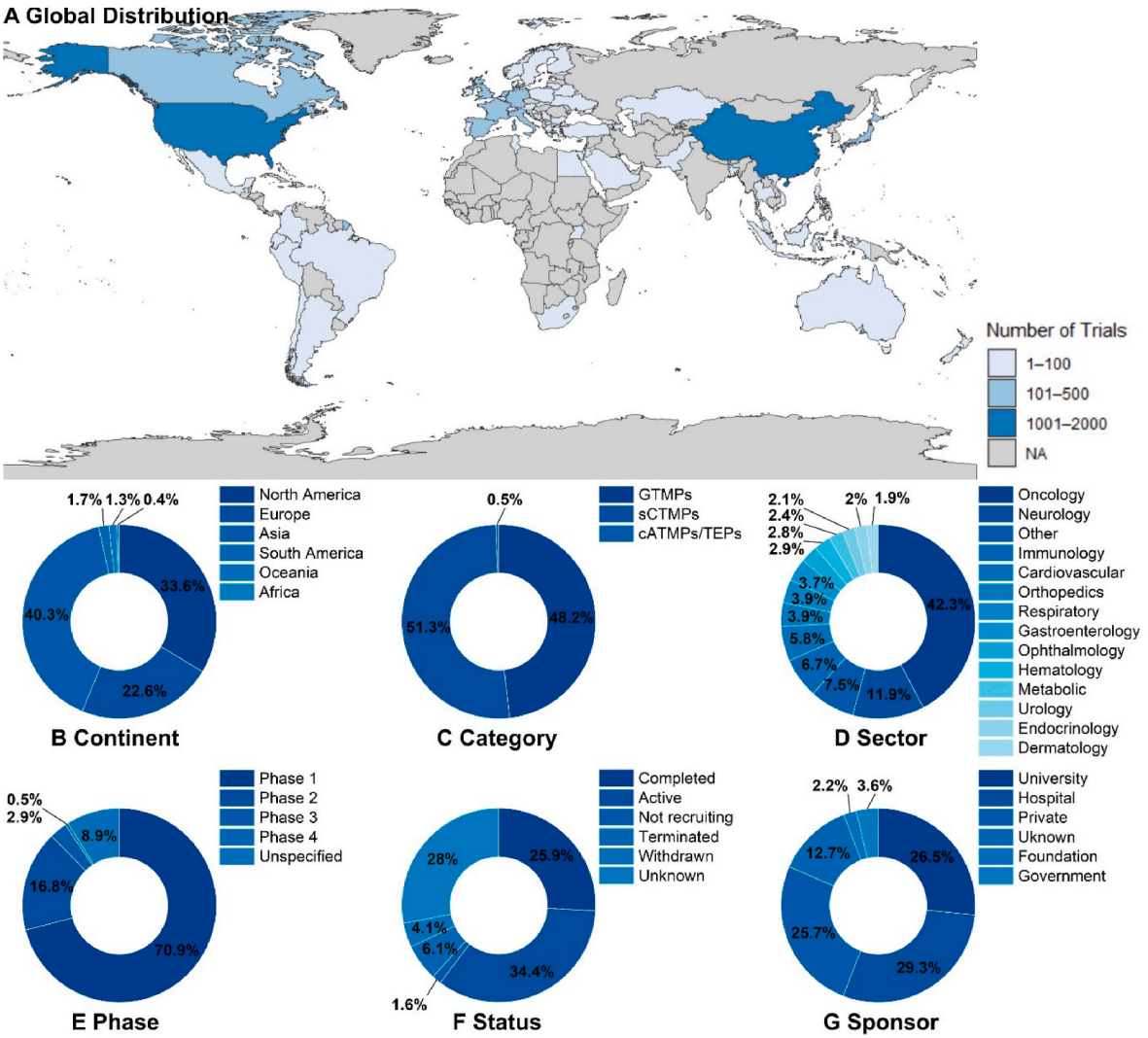


Fig. 6. Infographic summarizing the global landscape of advanced therapy medicinal product (ATMP) clinical trials based on data extracted from ClinicalTrials.gov and the EU Clinical Trials Information System (CTIS). The figure integrates harmonized data from both registries and illustrates multiple dimensions of ATMP clinical development: (A) global geographical distribution of ATMP clinical trials by country, with countries not represented in the analyzed registries shown in grey; (B) distribution of trials by continent; (C) distribution across ATMP categories (GTMPs, sCTMPs, and TEPs/cATMPs); (D) main therapeutic sectors; (E) clinical trial phases; (F) trial status; and (G) sponsor type. Percentages are calculated on the basis of the aggregated EU and US datasets.

Table 8
Summary of the data divided by ATMP category. It should be noted that the combined category TEPs/cATMPs is fundamentally different from the other two because it relies on smaller clinical studies in single nations.

Feature	GTMPs	sCTMPs	cATMPs/TEPs
Number of Trials	1838	1958	19
Typical Interventions	Predominantly gene transfer and gene-editing approaches using viral vectors (AAV, lentivirus, retrovirus) and genome-editing platforms (CRISPR-Cas9, ZFN). A substantial fraction consists of CAR-T and other genetically modified immune cells, as well as in vivo gene replacement for monogenic diseases.	Mainly cell-based immunomodulatory interventions, including mesenchymal stromal/stem cells (MSCs), dendritic cells, NK cells, macrophages, and bone-marrow–derived mononuclear cells. A significant number of trials involve autologous or allogeneic cell infusions without genetic modification.	Interventions are dominated by tissue-engineered constructs combining cells with structural matrices or scaffolds. Materials include collagen, decellularized extracellular matrix, alginate- or PLGA-based scaffolds, and bioactive membranes, typically implanted surgically.
Common Indications	Strong focus on inherited genetic disorders (β-thalassemia, sickle cell disease, hemophilia), hematologic malignancies, and rare pediatric syndromes. Oncology remains the dominant indication group due to CAR-T and oncolytic gene strategies.	Broadly distributed across inflammatory and immune-mediated diseases (Crohn's disease, ulcerative colitis, graft-versus-host disease), cardiovascular ischemic conditions, metabolic complications (e.g. diabetic ulcers), and neurological injury such as stroke.	Almost exclusively localized regenerative indications, including cartilage defects, bone regeneration, corneal repair, chronic wounds, and reconstructive applications following trauma or tumor resection.
Study Phases	Trials span the full clinical spectrum from Phase I to post-marketing studies. Advanced Phase II/III programs are common, reflecting regulatory maturity and established development pipelines.	Predominantly early- to mid-stage (Phase I–II), with fewer late-phase confirmatory trials. Some large observational and pragmatic studies contribute to the high total trial count.	Largely confined to feasibility, pilot, and early Phase I/II studies. Late-phase trials are extremely rare, reflecting manufacturing complexity, regulatory uncertainty, and indication-specific challenges.
Most Active Countries/ Regions	The United States dominates GTMP activity, followed by China. Within the EU, activity is concentrated in Germany, France, Spain, and Italy, largely driven by academic gene-therapy centers.	The US accounts for the majority of sCTMP trials, with additional strong contributions from China and selected EU countries (Germany, Spain, France). Many trials are single-center or investigator-initiated.	Trial activity is sparse overall. The US hosts slightly more studies, while EU contributions come mainly from Italy, Germany, and France, reflecting strong biomaterials and regenerative medicine research hubs.
Technologies Used	Viral vector engineering, ex vivo cell modification, CAR-T manufacturing platforms, genome editing, and gene-silencing technologies. Combination strategies integrating cell therapy with gene transfer are increasingly observed.	Cell isolation and expansion platforms, immune-cell priming, MSC-derived secretomes/exosomes, and minimally manipulated cellular products. Genetic modification is largely absent by definition.	Advanced biomaterials, decellularization processes, scaffold fabrication (including 3D-manufactured matrices), and surgical implantation techniques tightly coupled to product delivery.
Sample Size Range	Ranges from single-patient precision or compassionate-use trials to large multicenter studies enrolling several thousand participants, particularly in oncology and hemoglobinopathies.	Mostly small- to medium-sized trials (tens to hundreds of patients), but with some very large observational or registry-type studies contributing to outliers in sample size.	Typically, very small cohorts, often fewer than 50 patients, with some larger post-market or observational studies. This reflects bespoke manufacturing and indication-specific deployment.

France, Italy, and the United Kingdom. The pronounced geographic skew highlights persistent disparities in access to ATMP clinical development and underscores the need for greater international harmonization of regulatory frameworks and trial reporting practices.

Across ATMP categories (Fig. 6C), sCTMPs constitute the largest fraction of trials (51.3%), followed closely by GTMPs (48.2%), while TEPs and combined ATMPs together represent approximately 0.5% of registered studies. This near parity between sCTMPs and GTMPs reflects the parallel maturation of cell-based and gene-based therapeutic strategies, while the extremely limited representation of TEPs/cATMPs highlights the ongoing translational challenges associated with tissue engineering approaches.

The therapeutic focus of ATMP trials (Fig. 6D) further illustrates this landscape. Oncology is the dominant therapeutic sector, accounting for 42.3% of trials, driven by both GTMPs (e.g., gene-modified immune cells and CAR-T therapies) and sCTMPs (e.g., adoptive and immunomodulatory cell therapies). Neurology (11.9%) and musculoskeletal disorders (7.5%) followed, with additional contributions from immunology (6.7%), cardiology (5.8%), and respiratory diseases (3.9%). Smaller but still relevant fractions target gastroenterology (3.9%), ophthalmology (3.7%), hematology (2.9%), metabolic disorders (2.1%), urology (2.0%), endocrinology (2.0%), and dermatology (1.9%), highlighting the expanding clinical breadth of ATMP applications beyond oncology.

Analysis of clinical development phases (Fig. 6E) reveals a strong skew toward early- and mid-stage development. Phase II trials account for 70.9% of studies, followed by Phase I (16.8%), while Phase III (8.9%) and Phase IV (2.9%) trials remain comparatively limited. When clinical development phases are stratified by ATMP category, a clear differentiation in developmental maturity becomes apparent. sCTMPs are predominantly concentrated in early and mid-stage development, with the majority of studies falling within Phase I and Phase II, reflecting their widespread use in exploratory, proof-of-concept, and investigator-initiated trials. Nevertheless, a non-negligible subset of sCTMP programs has progressed into Phase III confirmatory studies, indicating increasing regulatory acceptance of selected cell-based platforms, particularly allogeneic MSCs and immune cell therapies, and growing confidence in scalable manufacturing and quality control frameworks. In contrast, GTMPs display a broader and more balanced phase distribution, spanning Phase I through Phase IV, including post-marketing and long-term follow-up studies. This reflects both the higher regulatory maturity of gene therapy in defined indications, such as monogenic disorders and hematologic malignancies, and the necessity for extended safety monitoring inherent to permanent or semi-permanent genetic modification. The presence of advanced-phase and post-authorization studies among GTMPs underscores their transition from experimental interventions to established therapeutic modalities within selected clinical contexts. TEPs and combined ATMPs remain overwhelmingly confined to early-phase development, with most trials categorized as Phase I, feasibility, or pilot studies, and only sporadic progression into later phases. This persistent early-phase clustering highlights ongoing translational barriers unique to tissue-engineered products, including manufacturing reproducibility, batch-to-batch variability of biomaterials, integration with surgical procedures, and the absence of universally accepted clinical endpoints for structural tissue regeneration. Collectively, this phase-stratified analysis reinforces the existence of a maturity gradient across ATMP classes, with GTMPs occupying the most advanced position, sCTMPs demonstrating broad but still predominantly exploratory development, and TEPs/cATMPs remaining largely pre-confirmatory.

The distribution of trial status (Fig. 6F) reflects the dynamic and high-risk nature of ATMP development. Completed trials account for 25.9%, while 34.4% are active or ongoing, and 1.6% are active but not recruiting. A substantial fraction of trials (28.0%) is reported with unknown status, reflecting limitations in registry updating and reporting practices. Regulatory and logistical difficulties in developing ATMPs, particularly for novel products without standardized processes or facing difficulties in scaling up production, are highlighted by the fact that approximately 10.2% of trials are either terminated (6.1%) or withdrawn (4.1%), representing definitive discontinuation.

Finally, the sponsorship landscape (Fig. 6G) reveals a heterogeneous ecosystem. Hospitals (29.3%) and universities (26.5%) together sponsor more than half of ATMP trials, reflecting the central role of academic and clinical institutions, particularly in sCTMP development and investigator-initiated studies. Private industry sponsors account for 25.7% of trials and are especially prominent in GTMP development, where capital-intensive manufacturing, proprietary platforms, and intellectual property considerations favor industrial leadership. Smaller contributions arise from foundations (12.7%), government bodies (3.6%), and trials with unknown sponsorship (2.2%), highlighting the complementary role of public and non-profit funding in early-stage and rare-disease ATMP research.

Together, these results represent a strategic shift in the ATMP field. sCTMPs have moved from an adjunctive research tool to a front-line development category, driven by their flexibility, lower manufacturing barriers (compared to gene therapy or tissue engineering), and wide-ranging indications. Meanwhile, GTMPs continue their advance in high-profile genetic and oncologic domains, supported by a maturing regulatory framework. TEPs and cATMPs remain conceptually promising yet underrepresented, reflecting a misalignment between scientific investment in tissue engineering and its clinical translatability.

5.2. Success rates and failure mechanisms of ATMP clinical trials

The integrated analysis of ATMP clinical trials across the combined US and EU datasets reveals that apparent development success is highly dependent on trial status reporting and is strongly conditioned by early operational feasibility. To ensure a conservative and reproducible assessment, all trials with unknown or non-reported status were excluded from the analysis. Trial success was defined at the registry level: trials classified as withdrawn (discontinued prior to patient enrollment) or terminated (discontinued after enrollment began) were considered non-successful, whereas trials classified as completed, active (recruiting or ongoing), or active but not recruiting were considered successful. Using this definition and restricting the analysis to trials with explicitly reported status, the overall success rate across all ATMPs was 85.9% (Table 9).

Stratification by patient enrolment (Table 10 and Fig. 7) demonstrates that this success rate masks a critical structural vulnerability concentrated at the earliest stages of clinical development. Across all ATMP categories, trials enrolling zero patients exhibited a 0%

Table 9
Registry-level success rates of advanced therapy medicinal product (ATMP) clinical trials stratified by ATMP category. Only trials with explicitly reported status were included. Trials classified as withdrawn or terminated were considered non-successful, while completed, active, or not-recruiting trials were considered successful.

ATMP category	Trials	Non-successful	Successful	Success rate
GTMPs	1386	147	1239	**89.4%**
sCTMPs	1350	238	1112	**82.4%**
TEPs/cATMPs	12	3	9	**75.0%**
All ATMPs	**2748**	**388**	**2360**	**85.9%**

Table 10
Enrollment-stratified registry-level success of ATMP clinical trials across GTMPs, sCTMPs, and TEPs/cATMPs. Analyses include only trials with explicitly reported status. Success was defined as trials not classified as withdrawn or terminated. Zero-enrollment trials uniformly failed, while success rates increased sharply once patient enrollment exceeded 10 participants.

ATMP	Enrolled patients	Trials	Successes	Success rate (%)
GTMPs	0	54	0	0.0
	1–10	369	308	83.5
	11–50	715	691	96.6
	51–100	159	154	96.9
	101–500	74	72	97.3
	>500	7	7	100.0
sCTMPs	0	99	0	0.0
	1–10	339	253	74.6
	11–50	620	579	93.4
	51–100	165	159	96.4
	101–500	112	107	95.5
	>500	4	4	100.0
TEPs	0	1	0	0.0
	1–10	4	2	50.0
	11–50	4	4	100.0
	51–100	2	2	100.0
	101–500	1	1	100.0

success rate, indicating that withdrawal prior to first patient treatment represents a dominant failure mode. In contrast, trials enrolling more than 10 participants consistently showed success rates exceeding 93%, revealing a sharp inflection point beyond which clinical continuation becomes highly probable. These findings indicate that most ATMP trial failures occur before or immediately after trial initiation, rather than as a consequence of late-stage clinical inefficacy or safety failure.

GTMPs exhibited the highest success rate among ATMP categories, with 89.4% of trials with known status classified as successful. Enrollment-stratified analysis clarifies this performance. All GTMP trials enrolling zero patients were non-successful, reflecting feasibility-level failure rather than biological or safety-driven discontinuation. Among trials enrolling 1–10 patients, success decreased to 83.5%, highlighting early operational vulnerability. However, once enrollment exceeded 10 participants, GTMP success rates consistently exceeded 96% and reached 100% in large-scale studies. This pattern indicates that the principal risks in GTMP development reside upstream of clinical execution, particularly in manufacturing readiness, vector supply, and site activation, while true clinical failure after patient exposure is comparatively rare. sCTMPs, which represent the numerically dominant ATMP category, displayed a lower success rate of 82.4% when restricted to trials with known status. As observed for GTMPs, all sCTMP trials enrolling zero patients were non-successful, confirming that a substantial proportion of attrition occurs before treatment initiation. Notably, early-enrollment trials (1–10 patients) exhibited a success rate of only 74.6%, reflecting increased operational complexity, variability in cell sourcing, and sensitivity to manufacturing logistics. Importantly, once enrollment exceeded 10 participants, sCTMP success rates rapidly converged with those of GTMPs, exceeding 93–96% across subsequent enrollment strata. These results indicate that sCTMP development is not primarily constrained by intrinsic clinical inefficacy, but rather by early translational and operational challenges. Tissue-engineered products and combined ATMPs (TEPs/cATMPs) exhibited the lowest success rate, 75.0%, when unknown-status trials were excluded, although interpretation is limited by the small cohort size. Enrollment-stratified analysis nonetheless revealed a consistent pattern. Trials withdrawn prior to enrollment uniformly failed, whereas all trials enrolling more than 10 patients were successful. In contrast, trials enrolling 1–10 patients showed a markedly reduced success rate (50%), underscoring the exceptional vulnerability of TEP development at the interface between bespoke manufacturing, surgical implementation, and regulatory classification. The reliance on integrated devices or scaffolds and specialized surgical infrastructure likely amplifies early feasibility risks relative to GTMPs and sCTMPs. Importantly, the absence of late-phase failures among enrolled TEP trials suggests that, once early operational barriers are overcome, clinical continuation is highly likely.

Taken together, this conservative analysis demonstrates that ATMP clinical development exhibits high continuation rates once patient enrollment is achieved, but that this success is preceded by a pronounced and systematic vulnerability at the pre-enrollment and very early enrollment stages. Excluding trials with unknown status reveals lower overall success rates than registry-inclusive

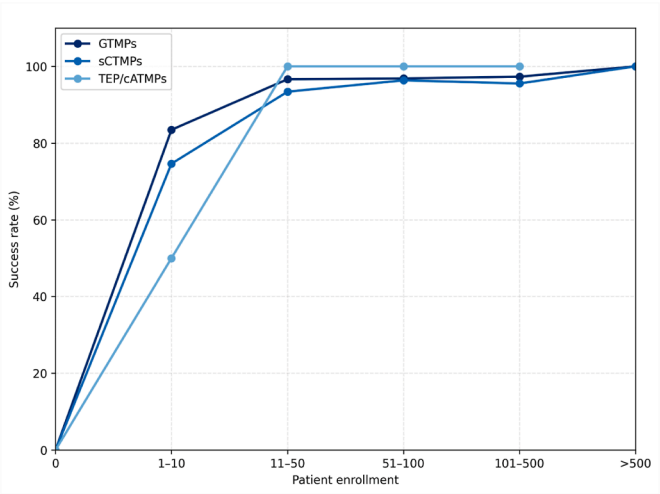


Fig. 7. Success-vs-enrollment curves for GTMPs, sCTMPs, and TEPs/cATMPs, excluding trials with unknown or non-reported status. Trial success was defined as any study not classified as withdrawn or terminated. All ATMP categories show complete failure at zero enrollment and a rapid convergence to >93% success once enrollment exceeds 10 patients, indicating that attrition is concentrated at the pre-enrollment and very early enrollment stages.

analyses and highlights that early attrition, particularly for sCTMPs and TEPs, is driven predominantly by operational, manufacturing, and regulatory feasibility constraints rather than intrinsic scientific or biological failure. These findings emphasize that improving ATMP development outcomes will depend less on incremental biological innovation alone and more on early, rigorous integration of manufacturing strategy, clinical operations planning, and regulatory engagement, especially during early-phase development where the risk of silent pre-enrollment failure remains highest.

6. Future directions

Building on the quantitative analysis of ATMP clinical development presented above, it is evident that future progress in the field will depend less on incremental proof of biological concept and more on the ability to address early translational bottlenecks, including delivery strategies, manufacturing robustness, regulatory alignment, and integration into standard clinical workflows. The success-versus-enrollment and phase-stratified analyses highlight that once ATMP programs overcome early feasibility and operational barriers, clinical continuation becomes highly likely, underscoring the importance of innovative development paradigms that couple scientific ambition with pragmatic execution. In this context, emerging therapeutic strategies and enabling technologies that explicitly integrate delivery, potency, risk management, and clinical usability offer particularly instructive models for next-generation ATMP development. The following case studies exemplify such approaches, illustrating how advanced gene therapy and biofabrication platforms may shape the future trajectory of precision regenerative and immunogene therapies.

6.1. Dual gene therapy for glioma: the Ad-TK/Ad-Flt3L case study

Dual-vector gene therapies, which deliver complementary transgenes via separate viral vectors to synergistically combine cytotoxic and immunostimulatory mechanisms, remain investigational and are not commercially available, with several candidates having progressed through phase I clinical evaluation but requiring further efficacy trials prior to regulatory approval. Within this context, dual-vector adenoviral gene therapy combining thymidine kinase (Ad-TK) with Feline McDonough Sarcoma (FMS)-like tyrosine kinase 3 ligand (Ad-Flt3L) in high-grade glioma exemplifies a clinically translated immunogene strategy that couples tumor-selective cytotoxicity with immune activation [147–149].

In the phase I trial (NCT01811992) [150], both vectors were injected directly into the resection cavity wall immediately following maximal safe tumor debulking in adults with newly diagnosed glioblastoma, optimizing transduction of residual tumor cells at the resection margin while minimizing systemic exposure and requiring no specialized neurosurgical equipment beyond standard neuronavigation. Patients then received oral valacyclovir (the prodrug analog of ganciclovir) for 2–4 weeks alongside standard-of-care radiotherapy and temozolomide, with no dose-limiting toxicities observed and transgene persistence confirmed up to 17 months post-administration in recurrent tumor samples from re-operated patients [150]. Early clinical evaluation revealed immune activation signals, including enhanced $CD8^+$ T-cell infiltration with effector markers, increased plasmacytoid dendritic cells in the tumor microenvironment, and reduced regulatory T cells in a subset of patients, consistent with conversion of immunosuppressive “cold” tumors to inflamed “hot” phenotypes and mirroring preclinical data in rodent glioma models [148,151–153]. Mechanistically,

TK-mediated apoptosis releases damage-associated molecular patterns such as high mobility group box 1 (HMGB1), calreticulin, and ATP, which enable dendritic cell maturation, while Flt3L recruits and expands.

This glioma example also illustrates how a gene therapy medicinal product can be embedded within existing quality and regulatory frameworks in both the EU and the US. [154–157]. Potency testing, defined as the specific capacity to achieve therapeutic effect, is implemented through quantitative assays that measure infectious titre (e.g. 50% Tissue Culture Infectious Dose ($TCID_{50}$)), transgene expression (Herpes Simplex Virus type 1 Thymidine Kinase (HSV1-TK) and Flt3L protein), and functional activity (ganciclovir-dependent killing for TK and dendritic-cell expansion for Flt3L) for every manufactured lot [154–157]. Product release incorporates a full Safety, Identity, Strength, Purity, and Quality (SISPQ) panel (sterility, endotoxin, replication-competent adenovirus, vector identity and purity, and stability-indicating potency assays) supported by in-process controls on cell substrate, infection parameters, downstream purification, and post-thaw performance of the final drug product [154–157]. Procedure-related risks are mitigated by intratumoral delivery during neurosurgical resection, which confines vector to the tumor bed, leverages the non-integrating adenoviral genome to minimize insertional mutagenesis risk, and limits systemic biodistribution compared with intravenous administration. Long-term follow-up follows FDA and EMA guidance for non-integrating viral vectors, with at least 5 years of planned surveillance including periodic clinical assessment, Magnetic Resonance Imaging (MRI), and quantitative polymerase chain reaction (qPCR)-based monitoring of vector sequences in blood to detect delayed adverse events such as late-onset malignancy, neuroinflammation, or unexpected infections. Taken together, Ad-TK/Ad-Flt3L gene therapy for glioma provides a clinically relevant case study in which a dual-vector immunogene approach is coupled to potency-driven manufacturing, structured product release, neurosurgical risk management, and harmonized long-term safety monitoring in EU and US settings [147,148,154,157–159].

Further development of dual-vector gene therapies such as Ad-TK/Ad-Flt3L depends on overcoming central nervous system delivery limitations, particularly through optimization of convection-enhanced delivery and focused ultrasound–mediated blood–brain barrier opening to extend vector distribution beyond resection margins [160]. Clinical combination strategies integrating these approaches with immune checkpoint inhibitors (antibodies against programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) (*anti*-PD-1/PD-L1)), CAR-T cells targeting glioma antigens, or next-generation oncolytic viruses hold promise to amplify systemic anti-tumor immunity while addressing tumor heterogeneity and immune escape [151,152,161,162]. Critically, long-term outcome monitoring remains paramount in brain tumor patients, where 5–15 years survival data will clarify durability of immune memory, risk of late neurotoxicity, and potential for re-dosing in recurrent disease, ultimately informing phase II/III trial designs and regulatory pathways.

6.2. *Bioprinting: the LIGŌ system case study*

The LIGŌ system is a first-in-class regenerative biodelivery device developed by Inventia Life Science to enable precision, in-situ soft tissue reconstruction directly in the operating room. Rather than relying on extensive grafting or long ex vivo culture times, the system integrates surgical robotics with bioengineering to deliver cell- and biomaterial-based formulations in a controlled manner, reconstructing natural tissue layers at the treatment site and aiming to advance regenerative medicine into routine clinical practice. Inventia describes LIGŌ as a platform that "brings precision bioengineering from the lab to the operating room," emphasizing standardized, reproducible reconstruction of soft tissues and positioning it as a transformational leap beyond traditional graft-based approaches [163].

In its current clinical focus, LIGŌ targets skin regeneration for deep partial-thickness and full-thickness wounds, where current standards of care often require flap procedures or split-thickness skin grafts harvested from donor sites, adding surgical complexity and donor-site morbidity [164]. By enabling in-situ reconstruction of all layers of the skin in a more physiological manner, the system is designed to enhance integration of the regenerated tissue, potentially accelerate recovery, and reduce or even eliminate the need for autologous grafts [165]. Inventia highlights several anticipated benefits: simplified surgical workflows through standardized biodelivery, reduced variability compared with fully manual techniques, and the prospect of lowering healthcare costs by minimizing donor site requirements and shortening recovery times [163]. These attributes are complemented by a configurable output, allowing surgeons to adjust dose and biodelivery complexity to personalize treatment for individual patients and wound types, which aligns with broader trends in precision regenerative medicine and personalized surgery.

The development of LIGŌ may be viewed as progressing through conceptual, preclinical, and clinical translation phases, even in the absence of formal designations on the official site. During the initial concept and engineering phase, Inventia leveraged its existing competency in droplet-based bioprinting and bioink formulation from the RASTRUM platform [166] and adapted it into a surgical format integrating a medical-grade collaborative robotic arm (KUKA LBR Med) capable of safe operation around patients. Technical descriptions from KUKA Innovation Award features and partner case studies show that this phase focused on integrating a compact printhead or biodelivery tool, developing robust motion control and user interfaces, and designing bioinks that retain printability and cell viability while supporting in-situ tissue reconstruction [167]. In a subsequent preclinical phase, LIGŌ-like articulated systems were validated in animal models, with related scientific work on commercial articulated in situ skin bioprinters and advanced soft-robotic in situ bioprinting platforms demonstrating that robot-guided biodelivery can improve deposition fidelity and wound healing outcomes in full-thickness skin defects [168]. The most recent phase is characterized by clinical translation and first-in-human evaluation, particularly the world-first 3D-printed skin trial underway at Concord Hospital's Burns Unit in Sydney, supported by the New South Wales health system and reported by NSW Health and multiple international media outlets. In this trial, clinicians prepare a "skin-growing ink" from the patient's own cells and proprietary biomaterials and then use the LIGŌ Surgical Robot to deposit this formulation directly onto burn wounds, aiming to accelerate healing, reduce pain, and lessen the need for extensive grafting [163,164].

7. Conclusions

The evolution of ATMPs over the past two decades has marked a transformative period in biomedicine, offering the potential to treat previously incurable conditions by targeting the root biological causes of disease. Among the four regulatory categories defined by the EU (GTMPs, sCTMPs, TEPs and cATMPs) a clear maturity gradient has emerged. GTMPs and sCTMPs have achieved substantial clinical and commercial success, as evidenced by their robust pipelines, multiple regulatory approvals, and integration into standard-of-care protocols for indications ranging from hematologic malignancies to genetic disorders. Conversely, the relative stagnation of TEPs and cATMPs remains a puzzling discrepancy, particularly considering the extensive scientific and technological advances in the field of tissue engineering. The disparity is striking, while tissue engineering has long captivated researchers with its promise of functional tissue regeneration and organ replacement, TEPs still represent a minority within the ATMP approvals landscape. Despite decades of foundational research, cutting-edge biofabrication methods, and innovations in biomaterials and stem cell biology, few TEPs have advanced past the clinical trial phase. Even fewer have achieved regulatory authorization. This bottleneck is not due to a lack of effort or creativity but appears to arise from complex translational barriers, primarily the challenges of manufacturing reproducible, robust, and clinically effective constructs that meet stringent regulatory standards. The technical requirements for ensuring a consistent cell phenotype, scaffold integration, and host-tissue remodeling are inherently more demanding than those associated with ex vivo cell manipulation or genetic vector delivery. Furthermore, the therapeutic mechanisms of TEPs (based heavily on structural restoration and complex cell-matrix interactions) are harder to quantify and validate in preclinical and early clinical settings, limiting their eligibility for fast-track regulatory pathways. This underdevelopment is particularly concerning when one considers the volume of scientific literature, investment, and innovation in tissue engineering. Fields such as 3D bioprinting, bioresorbable scaffolds, and stem cell-derived tissue models have experienced exponential growth, producing vast data on construct biocompatibility, functional integration, and regenerative potential. However, the translation of these insights into successful clinical products remains limited. In contrast, GTMPs and sCTMPs have benefited from more straightforward therapeutic paradigms (correcting a single gene, restoring an immune function, or targeting malignant cells) and from the availability of well-defined endpoints, which align more clearly with current regulatory expectations.

From a regulatory perspective, both the EU and US frameworks have taken important steps to accommodate the complexity of ATMPs, but their approaches diverge in meaningful ways. The EU's classification system, as codified in Regulation (EC) No 1394/2007, offers clarity by assigning products to GTMP, sCTMP, TEP, or cATMP categories based on MoA, level of manipulation, and inclusion of device components. This structured categorization facilitates development planning but also enforces rigid distinctions that may not always reflect therapeutic reality, particularly for multi-mechanistic or hybrid constructs. Because of its straightforward design, the EU model may prove restrictive, especially for those complex products, such as TEPs and cATMPs, that defy easy categorization. Conversely, the US FDA has embraced a more flexible, risk-based framework that evaluates products under the broader biologics umbrella, applying different levels of regulatory review based on the extent of manipulation and homologous use. This system allows for greater adaptability and the possibility of innovative designation programs such as the RMAT pathway, which supports expedited development for products addressing serious unmet medical needs. However, this high degree of flexibility introduces uncertainty on the correct regulatory pathway to be followed for developers attempting to navigate classification and premarket requirements (particularly for complex products such as cATMPs, where both the biologic and device components must satisfy distinct standards).

The distinction of substantial versus minimal manipulation is particularly critical in both EU and US jurisdictions that require that TEPs and sCTMPs include “substantially manipulated” cells or tissues to qualify as ATMPs. However, the interpretation of what constitutes substantial manipulation can vary. The EU provides a list of non-substantial procedures, effectively classifying all other processes as substantial. The US FDA similarly distinguishes minimal from more-than-minimal manipulation under 21 Code of Federal Regulation (CFR) Part 1271, but the implications for regulatory pathway and oversight are context-dependent. Moreover, the regulatory treatment of combined products adds another layer of complexity. In the EU, cATMPs are defined as ATMPs containing a medical device as an integral component, and these are jointly assessed under medicinal and device regulations. In the US, combination products are managed through the Office of Combination Products and must satisfy the requirements of both biologics and device oversight bodies, potentially delaying development and complicating approval processes. These challenges are particularly acute for TEPs incorporating biodegradable scaffolds or smart biomaterials with embedded sensing or release capabilities, technologies that increasingly represent the state of the art in regenerative medicine. Another important regulatory consideration is post-market surveillance. Given the long-lasting biological activity and potential for delayed adverse events, GTMPs, sCTMPs, and especially TEPs require extended follow-up periods to assess safety and therapeutic durability. The EU mandates risk management plans and patient registries for ATMPs, while the FDA enforces post-marketing commitments and real-world evidence collection. These strategies, while essential for safeguarding patients, place significant expenses on sponsors (particularly on smaller developers with limited resources).

In light of these considerations, the continued maturation of ATMPs (particularly TEPs and cATMPs) will require regulatory evolution that progresses in parallel with scientific innovation. Concrete steps toward international regulatory harmonization between the EU and US could play a pivotal role in addressing current translational bottlenecks. These include the expansion of joint scientific advice programs and parallel early-stage consultations to align expectations on product classification, manufacturing controls, and clinical endpoints from the outset of development. Greater convergence in the interpretation of substantial manipulation and homologous use, supported by shared case studies and decision frameworks, would reduce ambiguity for developers of complex tissue-engineered and hybrid products. Harmonized acceptance of adaptive clinical trial designs, incorporating surrogate functional endpoints, imaging-based biomarkers, and staged approval models, would better reflect the regenerative and structural mechanisms underlying TEPs. Alignment of CMC standards for advanced biofabrication platforms, including bioprinting and scaffold-based

constructs, could facilitate global scalability and mutual recognition of quality data. Finally, coordinated post-market surveillance strategies, such as interoperable patient registries and shared real-world evidence infrastructures, would strengthen long-term safety monitoring while minimizing duplicative regulatory burdens. Ultimately, while GTMPs and sCTMPs have advanced to the forefront of clinical practice, the underrepresentation of TEPs and cATMPs highlights a persistent misalignment between scientific investment and translational outcomes. Bridging this gap will require sustained, coordinated efforts across academic, industrial, and regulatory stakeholders to ensure that the full promise of tissue engineering and regenerative medicine is realized in clinical practice.

CRediT authorship contribution statement

Alessio Bucciarelli: Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **Antonella Motta:** Writing – review & editing, Supervision, Funding acquisition.

Data availability statement

Gathered data from clinical trial registries is available in Zenodo repository "Filtered Datasets of Clinical Trials on Advanced Therapy Medicinal Products (ATMPs) from European and US Registries" (https://zenodo.org/records/18818095).

Declaration of generative AI in scientific writing

During the preparation of this work the authors used GPT 4.0 in order to screen the clinical trials downloaded from the US and European databases and eliminate all the non-relevant trials (accordingly with the EU definition of ATMPs). After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Funding source

This work was supported by the SHIFT Project, funded by the European Union's Horizon 2020 Research and Innovation Programme under the Maria Sklodowska-Curie grant agreement no. 101008041.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that may influence the work reported in this article.

References

[1] Doudna JA, Charpentier E. The new frontier of genome engineering with CRISPR-Cas9. Science 2014;346:1258096. https://doi.org/10.1126/science.1258096.
[2] Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, Levy JM, et al. Search-and-replace genome editing without double-strand breaks or donor DNA. Nature 2019;576:149–57. https://doi.org/10.1038/s41586-019-1711-4.
[3] Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med 2017;377:1713–22. https://doi.org/10.1056/NEJMoa1706198.
[4] Brudno JN, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for lymphoma. Nat Rev Clin Oncol 2018;15:31–46. https://doi.org/10.1038/nrclinonc.2017.128.
[5] Murphy SV, Atala A. 3D bioprinting of tissues and organs. Nat Biotechnol 2014;32:773–85. https://doi.org/10.1038/nbt.2958.
[6] Advanced therapy medicinal products: overview | European Medicines Agency (EMA) n.d. https://www.ema.europa.eu/en/human-regulatory-overview/advanced-therapy-medicinal-products-overview (accessed March 26, 2025).
[7] Cellular & gene therapy products n.d. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products (accessed March 26, 2025).
[8] Chen G, Wang Y, Xie R, Gong S. A review on core–shell structured unimolecular nanoparticles for biomedical applications. Adv Drug Deliv Rev 2018;130:58–72. https://doi.org/10.1016/j.addr.2018.07.008.
[9] ARM Home. Alliance for regenerative Medicine n.d. https://alliancerm.org/(accessed March 27, 2025).
[10] Cuende N, Ciccocioppo R, Forte M, Galipeau J, Ikonomou L, Levine BL, et al. Patient access to and ethical considerations of the application of the European Union hospital exemption rule for advanced therapy medicinal products. Cytotherapy 2022;24:686–90. https://doi.org/10.1016/j.jcyt.2022.03.007.
[11] Gomes KLG, Da Silva RE, Da Silva JB, Bosio CGP, Novaes MRCG. Post-marketing authorisation safety and efficacy surveillance of advanced therapy medicinal products in Brazil, the European Union, the United States and Japan. Cytotherapy 2023;25:1113–23. https://doi.org/10.1016/j.jcyt.2023.06.005.
[12] European Parliament and the Council of the European Union. Regulation - 1394/2007 - EN - EUR-Lex 2019. https://eur-lex.europa.eu/eli/reg/2007/1394/oj/eng. [Accessed 15 October 2025].
[13] Committee for Advanced Therapies (CAT). Reflection paper on classification of advanced therapy medicinal products n.d.
[14] Congress of United States. Public and healh service act 2025. https://www.govinfo.gov/content/pkg/COMPS-8773/pdf/COMPS-8773.pdf. [Accessed 10 December 2025].
[15] Food and Drug Administration. Food, drugs and cosmetics act. https://uscode.house.gov/view.xhtml?edition=prelim&path=/prelim@title21. [Accessed 10 December 2025].
[16] Food and Drug Administration (FDA). Tissue establishment registration. 2021. https://www.fda.gov/vaccines-blood-biologics/biologics-establishment-registration/tissue-establishment-registration. [Accessed 5 March 2025].
[17] Food and Drug Administration (FDA). Biologics License Applications (BLA) process (CBER). https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biologics-license-applications-bla-process-cber. [Accessed 12 October 2025].
[18] Food and Drug Administration (FDA). Biologics Regulated Products 2021. https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/biologics-regulated-products. [Accessed 10 December 2025].
[19] Food and Drug Administration (FDA). Office of combination products. 2024. https://www.fda.gov/about-fda/office-chief-medical-officer/office-combination-products. [Accessed 7 March 2025].

[20] Food and Drug Administration (FDA). Regenerative medicine advanced therapy designation. 2025. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation. [Accessed 10 December 2025].
[21] Congress of United States. 21 CFR part 1271 – human cells, tissues, and cellular and tissue-based products. https://www.ecfr.gov/current/title-21/part-1271; 2001.
[22] European Medicines Agency (EMA). PRIME: priority medicines 2015. https://www.ema.europa.eu/en/human-regulatory-overview/research-development/prime-priority-medicines. [Accessed 11 December 2025].
[23] European Medicines Agency (EMA). Conditional marketing authorisation 2016. https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/conditional-marketing-authorisation. [Accessed 11 December 2025].
[24] Detela G, Lodge A. EU regulatory pathways for ATMPs: Standard, accelerated and adaptive pathways to marketing authorisation. Mol Ther, Methods Clin Dev 2019;13:205–32. https://doi.org/10.1016/j.omtm.2019.01.010.
[25] Iglesias-Lopez C, Agustí A, Obach M, Vallano A. Regulatory framework for advanced therapy medicinal products in Europe and United States. Front Pharmacol 2019;10:921. https://doi.org/10.3389/fphar.2019.00921.
[26] Seimetz D, Heller K, Richter J. Approval of first CAR-Ts: have we solved all hurdles for ATMPs? Cell Med 2019;11:2155179018822781. https://doi.org/10.1177/2155179018822781.
[27] Ali S, Kjeken R, Niederlaender C, Markey G, Saunders TS, Opsata M, et al. The European medicines agency review of kymriah (Tisagenlecleucel) for the treatment of acute lymphoblastic leukemia and diffuse large B-Cell lymphoma. Oncologist 2020;25:e321–7. https://doi.org/10.1634/theoncologist.2019-0233.
[28] Del Pozo-Rodríguez A, Rodríguez-Gascón A, Rodríguez-Castejón J, Vicente-Pascual M, Gómez-Aguado I, Battaglia LS, et al. Gene therapy. In: Silva AC, Moreira JN, Lobo JMS, Almeida H, editors. Current applications of pharmaceutical biotechnology, 171. Cham: Springer International Publishing; 2019. p. 321–68. https://doi.org/10.1007/10_2019_109.
[29] Avery OT, MacLeod CM, McCarty M. Studies on the chemical nature of substance inducing transformation of pneumococcal types. J Exp Med 1944;79:137–58. https://doi.org/10.1084/jem.79.2.137.
[30] Watson JD, Crick FHC. Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. Nature 1953;171:737–8. https://doi.org/10.1038/171737a0.
[31] Brooks PJ, Urv TK, Parisi MA. Gene-targeted therapies: overview and implications. American J Med Genetics Pt C 2023;193:13–8. https://doi.org/10.1002/ajmg.c.32033.
[32] Sayed N, Allawadhi P, Khurana A, Singh V, Navik U, Pasumarthi SK, et al. Gene therapy: comprehensive overview and therapeutic applications. Life Sci 2022;294:120375. https://doi.org/10.1016/j.lfs.2022.120375.
[33] Xu Y, Le H, Wu Q, Wang N, Gong C. Advancements in CRISPR/cas systems for disease treatment. Acta Pharm Sin B 2025;15:2818–44. https://doi.org/10.1016/j.apsb.2025.05.007.
[34] Wang N, Liu C, Li Y, Huang D, Wu X, Kou X, et al. A cooperative nano-CRISPR scaffold potentiates immunotherapy via activation of tumour-intrinsic pyroptosis. Nat Commun 2023;14:779. https://doi.org/10.1038/s41467-023-36550-9.
[35] Yang W, Wang N, Yang J, Liu C, Ma S, Wang X, et al. A multifunctional 'golden cicada' nanoplatform breaks the thermoresistance barrier to launch cascade augmented synergistic effects of photothermal/gene therapy. J Nanobiotechnol 2023;21:228. https://doi.org/10.1186/s12951-023-01983-3.
[36] Cavazzana M, Six E, Lagresle-Peyrou C, André-Schmutz I, Hacein-Bey-Abina S. Gene therapy for X-Linked severe combined immunodeficiency: where do we stand? Hum Gene Ther 2016;27:108–16. https://doi.org/10.1089/hum.2015.137.
[37] Komor AC, Badran AH, Liu DR. Editing the genome without double-stranded DNA breaks. ACS Chem Biol 2018;13:383–8. https://doi.org/10.1021/acschembio.7b00710.
[38] Cesur-Ergün B, Demir-Dora D. Gene therapy in cancer. J Gene Med 2023;25:e3550. https://doi.org/10.1002/jgm.3550.
[39] Kohn DB, Chen YY, Spencer MJ. Successes and challenges in clinical gene therapy. Gene Ther 2023;30:738–46. https://doi.org/10.1038/s41434-023-00390-5.
[40] Qin S, Tang X, Chen Y, Chen K, Fan N, Xiao W, et al. mRNA-based therapeutics: powerful and versatile tools to combat diseases. Signal Transduct Targeted Ther 2022;7:166. https://doi.org/10.1038/s41392-022-01007-w.
[41] Baraniak PR, McDevitt TC. Stem cell paracrine actions and tissue regeneration. Regen Med 2010;5:121–43. https://doi.org/10.2217/rme.09.74.
[42] Hoang DM, Pham PT, Bach TQ, Ngo ATL, Nguyen QT, Phan TTK, et al. Stem cell-based therapy for human diseases. Signal Transduct Targeted Ther 2022;7:272. https://doi.org/10.1038/s41392-022-01134-4.
[43] Santos GW. History of bone marrow transplantation. Clin Haematol 1983;12:611–39. https://doi.org/10.1016/S0308-2261(83)80003-4.
[44] Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med 2006;354:1813–26. https://doi.org/10.1056/NEJMra052638.
[45] Henig I, Zuckerman T. Hematopoietic stem cell Transplantation—50 years of evolution and future perspectives. Rambam Maimonides Med J 2014;5:e0028. https://doi.org/10.5041/RMMJ.10162.
[46] Tuthill M. Hatzimichael. Hematopoietic stem cell transplantation. SCCAA 2010;105. https://doi.org/10.2147/SCCAA.S6815.
[47] Giralt S, Bishop MR. Principles and overview of allogeneic hematopoietic stem cell transplantation. In: Bishop MR, editor. Hematopoietic stem cell transplantation, 144. Boston, MA: Springer US; 2009. p. 1–21. https://doi.org/10.1007/978-0-387-78580-6_1.
[48] Snowden JA, Sánchez-Ortega I, Corbacioglu S, Basak GW, Chabannon C, de la Camara R, et al. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. Bone Marrow Transplant 2022;57:1217–39. https://doi.org/10.1038/s41409-022-01691-w.
[49] Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med 1994;331:889–95. https://doi.org/10.1056/NEJM199410063311401.
[50] European Medicines Agency (EMA). Holoclar 2015. https://www.ema.europa.eu/en/medicines/human/EPAR/holoclar. [Accessed 8 August 2025].
[51] Milazzo G, De Luca M, Pellegrini G. Holoclar: first of its kind in more ways than one. Cell Gene Therapy Insights 2016;2:183–97. https://doi.org/10.18609/cgti.2016.023.
[52] Ankrum JA, Ong JF, Karp JM. Mesenchymal stem cells: immune evasive, not immune privileged. Nat Biotechnol 2014;32:252–60. https://doi.org/10.1038/nbt.2816.
[53] El-Kadiry AE-H, Rafei M, Shammaa R. Cell therapy: types, regulation, and clinical benefits. Front Med 2021;8:756029. https://doi.org/10.3389/fmed.2021.756029.
[54] Lee K-W, Yam JWP, Mao X. Dendritic cell vaccines: a shift from conventional approach to new generations. Cells 2023;12:2147. https://doi.org/10.3390/cells12172147.
[55] Lee B-C, Kang K-S. Functional enhancement strategies for immunomodulation of mesenchymal stem cells and their therapeutic application. Stem Cell Res Ther 2020;11:397. https://doi.org/10.1186/s13287-020-01920-3.
[56] Karantalis V, Schulman IH, Balkan W, Hare JM. Allogeneic cell therapy: a new paradigm in therapeutics. Circ Res 2015;116:12–5. https://doi.org/10.1161/CIRCRESAHA.114.305495.
[57] Takahashi J. Stem cell therapy for Parkinson's disease. Expert Rev Neurother 2007;7:667–75. https://doi.org/10.1586/14737175.7.6.667.
[58] Wang J, Deng G, Wang S, Li S, Song P, Lin K, et al. Enhancing regenerative medicine: the crucial role of stem cell therapy. Front Neurosci 2024;18:1269577. https://doi.org/10.3389/fnins.2024.1269577.
[59] Mayani H. A glance into somatic stem cell biology. Arch Med Res 2003;34:3–15. https://doi.org/10.1016/S0188-4409(02)00450-2.
[60] Almouemen N, Kelly HM, O'Leary C. Tissue engineering: understanding the role of biomaterials and biophysical forces on cell functionality through computational and structural biotechnology analytical methods. Comput Struct Biotechnol J 2019;17:591–8. https://doi.org/10.1016/j.csbj.2019.04.008.
[61] Suamte L, Tirkey A, Barman J, Jayasekhar Babu P. Various manufacturing methods and ideal properties of scaffolds for tissue engineering applications. Smart Mater Manufacturing 2023;1:100011. https://doi.org/10.1016/j.smmf.2022.100011.

[62] Mao AS, Mooney DJ. Regenerative medicine: current therapies and future directions. Proc Natl Acad Sci USA 2015;112:14452–9. https://doi.org/10.1073/pnas.1508520112.
[63] Trounson A, McDonald C. Stem cell therapies in clinical trials: progress and challenges. Cell Stem Cell 2015;17:11–22. https://doi.org/10.1016/j.stem.2015.06.007.
[64] Martin I, Wendt D, Heberer M. The role of bioreactors in tissue engineering. Trends Biotechnol 2004;22:80–6. https://doi.org/10.1016/j.tibtech.2003.12.001.
[65] Griffith LG, Naughton G. Tissue Engineering–Current challenges and expanding opportunities. Science 2002;295:1009–14. https://doi.org/10.1126/science.1069210.
[66] Hynes RO. The extracellular matrix: not just pretty fibrils. Science 2009;326:1216–9. https://doi.org/10.1126/science.1176009.
[67] Kular JK, Basu S, Sharma RI. The extracellular matrix: structure, composition, age-related differences, tools for analysis and applications for tissue engineering. J Tissue Eng 2014;5:204173141455711. https://doi.org/10.1177/2041731414557112.
[68] Bucciarelli A, Selicato N, Coricciati C, Rainer A, Capodilupo AL, Gigli G, et al. Modelling methacrylated chitosan hydrogel properties through an experimental design approach: from composition to material properties. J Mater Chem B 2024. https://doi.org/10.1039/D4TB00670D.
[69] Agostinacchio F, Biada E, Gambari L, Grassi F, Bucciarelli A, Motta A. Surfactant-assisted photo-crosslinked silk fibroin sponges: a versatile platform for the design of bone scaffolds. Biomater Adv 2024;161:213887. https://doi.org/10.1016/j.bioadv.2024.213887.
[70] Yoon DM, Fisher JP. Natural and synthetic polymeric scaffolds. In: Narayan R, editor. Biomedical materials. Cham: Springer International Publishing; 2021. p. 257–83. https://doi.org/10.1007/978-3-030-49206-9_6.
[71] Bucciarelli A, Muthukumar T, Kim JS, Kim WK, Quaranta A, Maniglio D, et al. Preparation and statistical characterization of tunable porous sponge scaffolds using UV cross-linking of methacrylate-modified silk fibroin. ACS Biomater Sci Eng 2019;5:6374–88. https://doi.org/10.1021/acsbiomaterials.9b00814.
[72] Hollister SJ. Porous scaffold design for tissue engineering. Nat Mater 2005;4:518–24. https://doi.org/10.1038/nmat1421.
[73] Discher DE, Janmey P, Wang Y. Tissue cells feel and respond to the stiffness of their substrate. Science 2005;310:1139–43. https://doi.org/10.1126/science.1116995.
[74] Ramasubbu K, Venkatraman G, Ramanathan G, Dhanasekar S, Rajeswari VD. Molecular and cellular signalling pathways for promoting neural tissue growth - a tissue engineering approach. Life Sci 2024;346:122640. https://doi.org/10.1016/j.lfs.2024.122640.
[75] Lovett M, Lee K, Edwards A, Kaplan DL. Vascularization strategies for tissue engineering. Tissue Eng B Rev 2009;15:353–70. https://doi.org/10.1089/ten.teb.2009.0085.
[76] Brown BN, Valentin JE, Stewart-Akers AM, McCabe GP, Badylak SF. Macrophage phenotype and remodeling outcomes in response to biologic scaffolds with and without a cellular component. Biomaterials 2009;30:1482–91. https://doi.org/10.1016/j.biomaterials.2008.11.040.
[77] European Medicines Agency (EMA). Glybera 2012. https://www.ema.europa.eu/en/medicines/human/EPAR/glybera. [Accessed 12 October 2025].
[78] European Medicines Agency (EMA). Imlygic 2016. https://www.ema.europa.eu/en/medicines/human/EPAR/imlygic. [Accessed 10 October 2025].
[79] European Medicines Agency (EMA). Strimvelis 2016. https://www.ema.europa.eu/en/medicines/human/EPAR/strimvelis. [Accessed 20 November 2025].
[80] European Medicines Agency (EMA). Kymriah 2018. https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah. [Accessed 22 July 2025].
[81] European Medicines Agency (EMA). Yescarta 2018. https://www.ema.europa.eu/en/medicines/human/EPAR/yescarta. [Accessed 30 September 2025].
[82] European Medicines Agency (EMA). Luxturna 2019. https://www.ema.europa.eu/en/medicines/human/EPAR/luxturna. [Accessed 29 September 2025].
[83] European Medicines Agency (EMA). Zolgensma 2020. https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma. [Accessed 10 October 2025].
[84] European Medicines Agency (EMA). Zynteglo 2019. https://www.ema.europa.eu/en/medicines/human/EPAR/zynteglo. [Accessed 11 June 2025].
[85] European Medicines Agency (EMA). Tecartus 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/tecartus. [Accessed 20 June 2025].
[86] European Medicines Agency (EMA). Libmeldy 2020. https://www.ema.europa.eu/en/medicines/human/EPAR/libmeldy. [Accessed 9 July 2025].
[87] European Medicines Agency (EMA). Breyanzi 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi. [Accessed 14 May 2025].
[88] European Medicines Agency (EMA). Abecma 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/abecma. [Accessed 4 September 2025].
[89] European Medicines Agency (EMA). Skysona 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/skysona. [Accessed 16 October 2025].
[90] European Medicines Agency (EMA). Carvykti 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti. [Accessed 28 June 2025].
[91] European Medicines Agency (EMA). Upstaza 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/upstaza. [Accessed 15 September 2025].
[92] European Medicines Agency (EMA). Roctavian 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/roctavian. [Accessed 10 September 2025].
[93] Food and Drug Administration (FDA). Adstiladrin 2024. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/adstiladrin. [Accessed 18 August 2025].
[94] European Medicines Agency (EMA). Hemgenix 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/hemgenix. [Accessed 1 September 2025].
[95] Food and Drug Administration (FDA). Vyjuve 2023. https://www.fda.gov/vaccines-blood-biologics/vyjuvek. [Accessed 25 August 2025].
[96] Food and Drug Administration (FDA). Elevidys 2025. https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/elevidys. [Accessed 9 October 2025].
[97] Food and Drug Administration (FDA). Lyfgenia 2024. https://www.fda.gov/vaccines-blood-biologics/lyfgenia. [Accessed 5 July 2025].
[98] European Medicines Agency (EMA). Casgevy 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/casgevy. [Accessed 1 September 2025].
[99] European Medicines Agency (EMA). Glybera 2025. https://www.ema.europa.eu/en/medicines/human/EPAR/beqvez. [Accessed 10 October 2025].
[100] Food and Drug Administration (FDA). Aucatzyl 2024. https://www.fda.gov/vaccines-blood-biologics/aucatzyl. [Accessed 22 May 2025].
[101] European Medicines Agency (EMA). Provenge 2013. https://www.ema.europa.eu/en/medicines/human/EPAR/provenge. [Accessed 3 July 2025].
[102] Food and Drug Administration (FDA). Laviv 2022. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/laviv. [Accessed 12 October 2025].
[103] European Medicines Agency (EMA). Zalmoxis 2016. https://www.ema.europa.eu/en/medicines/human/EPAR/zalmoxis. [Accessed 12 August 2025].
[104] European Medicines Agency (EMA). Alofisel 2018. https://www.ema.europa.eu/en/medicines/human/EPAR/alofisel. [Accessed 17 April 2025].
[105] Food and Drug Administration (FDA). Omisirge 2023. https://www.fda.gov/vaccines-blood-biologics/omisirge. [Accessed 9 October 2025].
[106] Food and Drug Administration (FDA). Lantidra 2023. https://www.fda.gov/vaccines-blood-biologics/lantidra. [Accessed 10 September 2025].
[107] Food and Drug Administration (FDA). Amtagvi 2024. https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/amtagvi. [Accessed 16 September 2025].
[108] Food and Drug Administration (FDA). Ryoncil 2025. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/ryoncil. [Accessed 12 November 2025].
[109] Food and Drug Administration (FDA). Epicel (cultured epidermal autografts). https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/epicel-cultured-epidermal-autografts. [Accessed 17 December 2025].
[110] Food and Drug Administration (FDA). Carticel 1997. https://purplebooksearch.fda.gov/productdetails?query=103661. [Accessed 17 December 2025].
[111] Food and Drug Administration (FDA). Apligraf 2001. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P950032S016. [Accessed 18 December 2025].
[112] Food and Drug Administration (FDA). Dermagraft 2001. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=p000036. [Accessed 17 December 2025].
[113] Food and Drug Administration (FDA). OrCel 2001. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P010016. [Accessed 18 December 2025].
[114] European Medicines Agency (EMA). ChondroCelect 2009. https://www.ema.europa.eu/en/medicines/human/EPAR/chondrocelect. [Accessed 15 October 2025].
[115] Food and Drug Administration (FDA). Gintuit. FDA; 2022. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/gintuit-allogeneic-cultured-keratinocytes-and-fibroblasts-bovine-collagen. [Accessed 7 September 2025].
[116] European Medicines Agency (EMA). Maci 2013. https://www.ema.europa.eu/en/medicines/human/EPAR/maci. [Accessed 6 August 2025].
[117] European Medicines Agency (EMA). Spherox 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/spherox. [Accessed 8 June 2025].

[118] Food and Drug Administration (FDA). Stratagraft 2024. https://www.fda.gov/vaccines-blood-biologics/stratagraft. [Accessed 18 December 2025].
[119] Food and Drug Administration (FDA). Rethymic 2021. https://www.fda.gov/vaccines-blood-biologics/rethymic. [Accessed 9 October 2025].
[120] Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22. https://doi.org/10.1056/NEJMoa1001294.
[121] Scott LJ. Darvadstrocel: a review in treatment-refractory complex perianal fistulas in crohn's disease. BioDrugs 2018;32:627–34. https://doi.org/10.1007/s40259-018-0311-4.
[122] Kebriaei P, Hayes J, Daly A, Uberti J, Marks DI, Soiffer R, et al. A phase 3 randomized study of Remestemcel-L versus placebo added to second-line therapy in patients with steroid-refractory acute graft-versus-host disease. Biol Blood Marrow Transplant 2020;26:835–44. https://doi.org/10.1016/j.bbmt.2019.08.029.
[123] Horwitz M, Tsai SB, Rezvani AR, Maziarz RT, Goshen U, Levy S, et al. Omidubicel-onlv for allogeneic transplantation (allo-HCT) in patients with hematologic malignancies: results of a multicenter open label expanded access program. Blood 2023;142. https://doi.org/10.1182/blood-2023-181167. 6894–6894.
[124] Rios P, Mcgarrigle JJ, Lamonica G, Li Y, Cook J, Joshi I, et al. 35-OR: Lantidra, first FDA-approved cellular therapy to treat type 1 diabetes. Diabetes 2024;73:35–OR. https://doi.org/10.2337/db24-35-OR.
[125] Sarnaik AA, Hamid O, Khushalani NI, Lewis KD, Medina T, Kluger HM, et al. Lifileucel, a tumor-infiltrating lymphocyte therapy, in metastatic melanoma. J Clin Orthod 2021;39:2656–66. https://doi.org/10.1200/JCO.21.00612.
[126] Supp DM. Skin substitutes for burn wound healing: current and future approaches. Expet Rev Dermatol 2011;6:217–27. https://doi.org/10.1586/edm.10.73.
[127] Zaulyanov L, Kirsner RS. A review of a bi-layered living cell treatment (Apligraf) in the treatment of venous leg ulcers and diabetic foot ulcers. Clin Interv Aging 2007;2:93–8. https://doi.org/10.2147/ciia.2007.2.1.93.
[128] Hart CE, Loewen-Rodriguez A, Lessem J. Dermagraft: use in the treatment of chronic wounds. Adv Wound Care 2012;1:138–41. https://doi.org/10.1089/wound.2011.0282.
[129] Ananta M, Brown RA, Mudera V. A rapid fabricated living dermal equivalent for skin tissue engineering: an *in vivo* evaluation in an acute wound model. Tissue Eng 2012;18:353–61. https://doi.org/10.1089/ten.tea.2011.0208.
[130] Centanni JM, Straseski JA, Wicks A, Hank JA, Rasmussen CA, Lokuta MA, et al. StrataGraft skin substitute is well-tolerated and is not acutely immunogenic in patients with traumatic wounds: results from a prospective, randomized, controlled dose escalation trial. Ann Surg 2011;253:672–83. https://doi.org/10.1097/SLA.0b013e318210f3bd.
[131] Vanlauwe J, Saris DBF, Victor J, Almqvist KF, Bellemans J, Luyten FP, et al. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. Am J Sports Med 2011;39:2566–74. https://doi.org/10.1177/0363546511422220.
[132] Gille J, Behrens P, Schulz AP, Oheim R, Kienast B. Matrix-associated autologous chondrocyte implantation: a clinical Follow-Up at 15 years. CARTILAGE 2016;7:309–15. https://doi.org/10.1177/1947603516638901.
[133] Armoiry X, Cummins E, Connock M, Metcalfe A, Royle P, Johnston R, et al. Autologous chondrocyte implantation with chondrosphere for treating articular cartilage defects in the knee: an evidence review group perspective of a NICE single technology appraisal. Pharmacoeconomics 2019;37:879–86. https://doi.org/10.1007/s40273-018-0737-z.
[134] Trubelja A, Kasper FK, Farach-Carson MC, Harrington DA. Bringing hydrogel-based craniofacial therapies to the clinic. Acta Biomater 2022;138:1–20. https://doi.org/10.1016/j.actbio.2021.10.056.
[135] Silva CS, Reis RL, Martins A, Neves NM. Recapitulation of thymic function by tissue engineering strategies. Adv Healthcare Mater 2021;10:2100773. https://doi.org/10.1002/adhm.202100773.
[136] Leong K, Macaulay R. OP73 navigating the advanced therapy medicinal products (ATMPs) conundrum: insights from ATMPs withdrawn in the European market. Int J Technol Assess Health Care 2024;40. https://doi.org/10.1017/S0266462324001326. S32–S32.
[137] De Luca M, Cossu G. Cost and availability of novel cell and gene therapies: can we avoid a catastrophic second valley of death? EMBO Rep 2023;24:e56661. https://doi.org/10.15252/embr.202256661.
[138] Ten Ham RMT, Hoekman J, Hövels AM, Broekmans AW, Leufkens HGM, Klungel OH. Challenges in advanced therapy medicinal product development: a survey among companies in Europe. Mol Ther, Methods Clin Dev 2018;11:121–30. https://doi.org/10.1016/j.omtm.2018.10.003.
[139] Halioua-Haubold C-L, Peyer JG, Smith JA, Arshad Z, Scholz M, Brindley DA, et al. Regulatory considerations for gene therapy products in the US, EU, and Japan. Yale J Biol Med 2017;90:683–93.
[140] Carvalho M, Martins AP, Sepodes B. Hurdles in gene therapy regulatory approval: a retrospective analysis of European marketing authorization applications. Drug Discov Today 2019;24:823–8. https://doi.org/10.1016/j.drudis.2018.12.007.
[141] Senior M. After Glybera's withdrawal, what's next for gene therapy? Nat Biotechnol 2017;35:491–2. https://doi.org/10.1038/nbt0617-491.
[142] Morrison S, Heinz S, Leggat S. POSC275 impact on bluebird's withdrawal from the German market on funding for gene therapies. Value Health 2022;25:S188. https://doi.org/10.1016/j.jval.2021.11.913.
[143] Tsokas K, McFarland R, Burke C, Lynch JL, Bollenbach T, Callaway Ii DA, et al. Reducing risks and delays in the translation of cell and gene therapy innovations into regulated products. NAM Perspectives; 2019. https://doi.org/10.31478/201909d.
[144] Elsallab M, Bravery CA, Kurtz A, Abou-El-Enein M. Mitigating deficiencies in evidence during regulatory assessments of advanced therapies: a comparative study with other biologicals. Mol Ther, Methods Clin Dev 2020;18:269–79. https://doi.org/10.1016/j.omtm.2020.05.035.
[145] Coghill K. Advanced tissue selling interest in dermagraft. Plans Bankruptcy 2002. https://www.bioworld.com/articles/472273. [Accessed 17 December 2025].
[146] Negoro T, Takagaki Y, Okura H, Matsuyama A. Trends in clinical trials for articular cartilage repair by cell therapy. NPJ Regen Med 2018;3:17. https://doi.org/10.1038/s41536-018-0055-2.
[147] Faisal SM, Castro MG, Lowenstein PR. Combined cytotoxic and immune-stimulatory gene therapy using Ad-TK and Ad-Flt3L: translational developments from rodents to glioma patients. Mol Ther 2023;31:2839–60. https://doi.org/10.1016/j.ymthe.2023.08.009.
[148] Umemura Y, Orringer D, Junck L, Varela ML, West MEJ, Faisal SM, et al. Combined cytotoxic and immune-stimulatory gene therapy for primary adult high-grade glioma: a phase 1, first-in-human trial. Lancet Oncol 2023;24:1042–52. https://doi.org/10.1016/S1470-2045(23)00347-9.
[149] Varela M, West M, Faisal SM, Comba A, Castro M, Lowenstein P. CTIM-28. first-in-human transgene detection 17 months post-adenoviral therapy. Neuro Oncol 2023;25. https://doi.org/10.1093/neuonc/noad179.0268. v68–v68.
[150] University of Michigan Rogel Cancer Center. A non-randomized, open-label dose-finding trial of combined cytotoxic and immune-stimulatory strategy for the treatment of resectable primary malignant glioma 2024. https://clinicaltrials.gov/study/NCT01811992. [Accessed 31 December 2025].
[151] King GD, Muhammad AKMG, Curtin JF, Barcia C, Puntel M, Liu C, et al. Flt3L and TK gene therapy eradicate multifocal glioma in a syngeneic glioblastoma model. Neuro Oncol 2008;10:19–31. https://doi.org/10.1215/15228517-2007-045.
[152] Faisal SM, Mendez FM, Nunez F, Castro MG, Lowenstein PR. Immune-stimulatory (TK/Flt3L) gene therapy opens the door to a promising new treatment strategy against brainstem gliomas. Oncotarget 2020;11:4607–12. https://doi.org/10.18632/oncotarget.27834.
[153] Candolfi M, Yagiz K, Foulad D, Alzadeh GE, Tesarfreund M, Muhammad AKMG, et al. Release of HMGB1 in response to proapoptotic glioma killing strategies: efficacy and neurotoxicity. Clin Cancer Res 2009;15:4401–14. https://doi.org/10.1158/1078-0432.CCR-09-0155.
[154] Center for Biologics Evaluation and Research. Guidance for industry potency tests for cellular and gene therapy products. https://www.fda.gov/files/vaccines,%20blood%20%26%20biologics/published/Final-Guidance-for-Industry–Potency-Tests-for-Cellular-and-Gene-Therapy-Products.pdf. [Accessed 31 December 2025].
[155] Center for Biologics Evaluation and Research. Potency assurance for cellular and gene therapy products. 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/potency-assurance-cellular-and-gene-therapy-products. [Accessed 31 December 2025].
[156] Committee for Advanced Therapies (CAT). Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products. 2018.
[157] Salmikangas P, Carlsson B, Klumb C, Reimer T, Thirstrup S. Potency testing of cell and gene therapy products. Front Med 2023;10:1190016. https://doi.org/10.3389/fmed.2023.1190016.
[158] Center for Biologics Evaluation and Research. Long term Follow-Up after administration of human gene therapy products. Guidance Industry 2020.

[159] Follow-up of patients administered with gene therapy medicinal products - scientific guideline. European Medicines Agency (EMA; 2009. https://www.ema.europa.eu/en/follow-patients-administered-gene-therapy-medicinal-products-scientific-guideline. [Accessed 31 December 2025].
[160] Reardon DA, Freeman G, Wu C, Chiocca EA, Wucherpfennig KW, Wen PY, et al. Immunotherapy advances for glioblastoma. Neuro Oncol 2014;16:1441–58. https://doi.org/10.1093/neuonc/nou212.
[161] Puntel M, A.K.M GM, Farrokhi C, VanderVeen N, Paran C, Appelhans A, et al. Safety profile, efficacy, and biodistribution of a bicistronic high-capacity adenovirus vector encoding a combined immunostimulation and cytotoxic gene therapy as a prelude to a phase I clinical trial for glioblastoma. Toxicol Appl Pharmacol 2013;268:318–30. https://doi.org/10.1016/j.taap.2013.02.001.
[162] VanderVeen N, Paran C, Krasinkiewicz J, Zhao L, Palmer D, Hervey-Jumper S, et al. Effectiveness and preclinical safety profile of doxycycline to be used "Off-Label" to induce therapeutic transgene expression in a phase I clinical trial for glioma. Human Gene Therapy Clin Dev 2013;24:116–26. https://doi.org/10.1089/humc.2013.139.
[163] inventialifescience. LIGŌ redefining regenerative surgery. https://inventialifescience.com/ligo. [Accessed 22 December 2025].
[164] Wakefield E. Concord hospital researchers treat burns with 3D printed skin 2025. https://www.voxelmatters.com/concord-hospital-researchers-treat-burns-with-3d-printed-skin/. [Accessed 22 December 2025].
[165] May 2025 P 15. Novel 3D bioprinting device 'prints' skin-growing ink from patient cells in world-first clinical trials. Office Health Med Res 2025. https://medicalresearch.nsw.gov.au/about/news/2025/novel-3d-bioprinting-device-prints-skin-growing-ink-from-patient-cells-in-world-first-clinical-trials. [Accessed 22 December 2025].
[166] inventialifescience. RASTRUM | accessible 3D cell models for research n.d. https://inventialifescience.com/platform/rastrum. [Accessed 22 December 2025].
[167] KUKA Germany. KUKA innovation award 2022 2022. https://www.kuka.com/en-de/future-production/innovation-and-research/kuka-innovation-award/kuka-innovation-award-2022. [Accessed 22 December 2025].
[168] Levin A A, Karalkin P A, Koudan E V, Senatov F S, Parfenov V A, Lvov V A, et al. Commercial articulated collaborative in situ 3D bioprinter for skin wound healing. IJB 2023;9:675. https://doi.org/10.18063/ijb.v9i2.675.