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Landscape of *ex vivo* gene therapies: Technological trends and future prospects

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***Ex vivo* gene therapy, a revolutionary approach involving extraction, genetic modification, and infusion of cells, is rapidly evolving, making it difficult to track its advancements. Strategic foresight methodologies play a crucial role in understanding the future of technology, anticipating trends, and making informed decisions. This study pioneers the use of strategic foresight methodology to understand technological trends of *ex vivo* gene therapies, leveraging data mining to generate and analyze a database of 1,491 products. Notably, 79.78% of *ex vivo* gene therapies target neoplasms, with T cells as the primary cell type (75.26%) and chimeric antigen receptor (CAR) as the most common genetic modification (83.19%). Although stem cells constitute a relatively small proportion (2.41%), they have demonstrated significant clinical promise. It was also observed that CD19 and BCMA (B-cell maturation antigen) are consolidated targets, although new targets (GPC3 [Glypican-3], mesothelin, CLDN18 [Claudin-18], KRAS [Kirsten rat sarcoma viral oncogene homolog], and others) as well as multispecific products are emerging. Vector analysis indicates that CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-based modifications are expanding (25.66%), although lentivirus vector (40.12%) remains the dominant platform. Significantly, 22 products have advanced to the pre-registration or registration phase, underscoring their potential as viable treatments. This study provides a comprehensive overview of the current landscape and future directions in *ex vivo* gene therapy.**

INTRODUCTION

Innovations achieved in the field of molecular biology since the 1950s have allowed recombinant DNA technology to flourish, opening the door for high-efficiency gene transfer tools to be established. These possibilities founded the field of transgenesis for therapeutic purposes in humans. More recently, gene-editing tools such as zinc-finger nucleases, TALENs (Transcription Activator-Like Effector Nucleases), and CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) have allowed changes to gene sequences within the cell nucleus, representing a step forward in terms of refinement and potential safety of gene therapy approaches.[1–5]

Currently, gene therapies represent a safe and effective treatment option for a variety of conditions, including inherited diseases and certain types of cancer. They are classified as a subset of advanced therapy medicinal products (ATMPs), which also encompasses somatic cell therapy medicinal products and tissue-engineered therapies.[1,6] There are two main delivery procedures in gene therapy. *In vivo* gene therapy delivers new or corrected genes using a vector directly into the body, either systemically or locally. The second approach, *ex vivo* gene therapy, involves the removal of cells from the individual, their genetic modification, and reinfusion into the patient, and it is the primary focus of this work.[1,2,5,7]

There are two main strategies in *ex vivo* gene therapies. The first, known as gene-target therapy (GTTs), has been developed for monogenic diseases, and it is used to deliver a working copy of the defective gene into the genomic DNA of the patient's cells, which are infused back into the patient. There are several products of this category approved for sickle cell disease (SCD) and beta-thalassemia

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(BTB), demonstrating the therapeutic potential of *ex vivo* GTTs in addressing genetic disorders at their source.[7,8]

The second approach delivers immunotherapy to the patient as personalized medicine for cancer and other diseases. The most preeminent example of this approach is the chimeric antigen receptor (CAR)-T cell therapy that has achieved successful outcomes in hematological malignancies. After isolation via leukapheresis, T cells are harvested and genetically modified *ex vivo* using viral or non-viral transfection approaches, introducing genes that encode fusion proteins designed to recognize specific antigens on the surface of target cells. CARs are more straightforward if compared to conventional T cell receptors (TCRs) due to the absence of major histocompatibility complex (MHC) restriction to identify antigens and deliver the effector function against the tumor cell. Despite the great success in hematological malignancies, CAR-T cells and other genetically modified immunological approaches still encounter substantial limitations when applied to solid tumors.[9,10]

Despite the significant advancements in *ex vivo gene* therapies, several challenges persist in their development and clinical application (including difficulties in the patient journey and manufacturing). The inherent complexity of *ex vivo* gene therapies leads to high costs that create difficulties in affordability and accessibility. To mitigate these issues, both industry and academic researchers are actively seeking innovative strategies to reduce manufacturing costs.[11,12]

Another significant challenge is the occurrence of adverse events associated with novel therapeutic mechanisms, necessitating long-term patient follow-up, often extending to at least 15 years. One risk associated with *ex vivo* gene therapy is the development of secondary malignancies due to the treatment. The FDA (Food and Drug Administration), so far, has identified over 30 cases of T cell cancers after treatment with CAR-T, though causality remains unclear. As the field continues to evolve, understanding the implications of these adverse events will be crucial for improving therapeutic strategies and ensuring patient safety.[12–14]

Several technologies are emerging to overcome all these challenges and bring new solutions, driving the rapid evolution of this field. Understanding how these technologies can be integrated into *ex vivo* gene therapies will foster innovation and lead to more powerful therapeutic strategies.

Strategic foresight methodologies play a crucial role in understanding the future of technology and its application. They enable policymakers, companies, and R&D to identify and anticipate trends to support informed decision-making.[15–18] Although previous studies have explored the technological or clinical trends in *ex vivo* gene therapy,[1,5,9,19–32] to our knowledge, this is the first published study based on strategic foresight to develop a comprehensive database of *ex vivo* gene therapies based on data mining exploring cell types and sources, genetic modifications, vectors, molecular targets, and clinical aspects to understand the trends of the field.

RESULTS

Overview of the cell and gene therapy database

Data were collected in July of 2024, and after data cleaning, qualitative validation, transformation, and enrichment, the final database contained 3,427 advanced therapies currently under development. Most products were in earlier development stages (Figure 1). Gene therapy dominated the landscape, with *ex vivo* (43.55%) and *in vivo* (30.81%) modalities accounting for 74.31% of all therapies. Among cell therapies, stem cell-based treatments (10.81%) and immunotherapy (7.3%) represented most of the products of this approach (Figure 1A).

The next step was the systematic evaluation of indications using the disease taxonomy established by the World Health Organization (WHO), the International Classification of Diseases, 11th Revision (ICD-11)[33] (Figure 1B). Advanced therapies were employed to address a diverse spectrum of diseases: 25 different medical fields and 151 disease families. In contrast to *in vivo* gene therapies and non-modified cell therapies, which were applied to a wide variety of conditions (data not shown), *ex vivo* gene therapies were predominantly focused on treating neoplasms, accounting for 79.78% of products, followed by diseases of the immune system (6.27%). All other medical fields collectively represented less than 15% of the applications (Figure 1B).

The ICD-11 disease families of *ex vivo* gene therapies are illustrated in Figure 1C. While solid tumors were investigated, hematological malignancies emerged as the predominant focus. Therapies targeting neoplasms of hematopoietic or lymphoid tissues have demonstrated significant advancement into late-stage clinical trials and registration phases. In contrast, although non-organ-specific systemic autoimmune disorders have been extensively studied for *ex vivo* gene therapy, the products developed thus far have primarily reached early clinical trial stages. Additionally, notable progress has been observed in fields such as anemias or other erythrocyte disorders, as well as inborn errors of metabolism, where several therapeutic products have successfully advanced to late clinical trials and registration.

The subsequent sections will provide a detailed analysis of *ex vivo* gene therapies, exploring cell types and sources, genetic modifications, vectors, molecular targets, and clinical aspects.

T cells as primary cells and CAR technology as the leading genetic modification in *ex vivo* gene therapy

The primary cell types utilized in *ex vivo* gene therapy applications were T cells (75.26%), followed by natural killer (NK) cells (12.02%) and stem cells (7.69%). Regardless of the cell type, most of the products remain in the pre-clinical stage of development. *Ex vivo* gene therapies based on T cells and stem cells have demonstrated significant clinical progress (Figure 2A). T cells, NK cells, and other immune cells were primarily employed for neoplasms, while stem cells were studied for a great variety of diseases (Figure 2B).

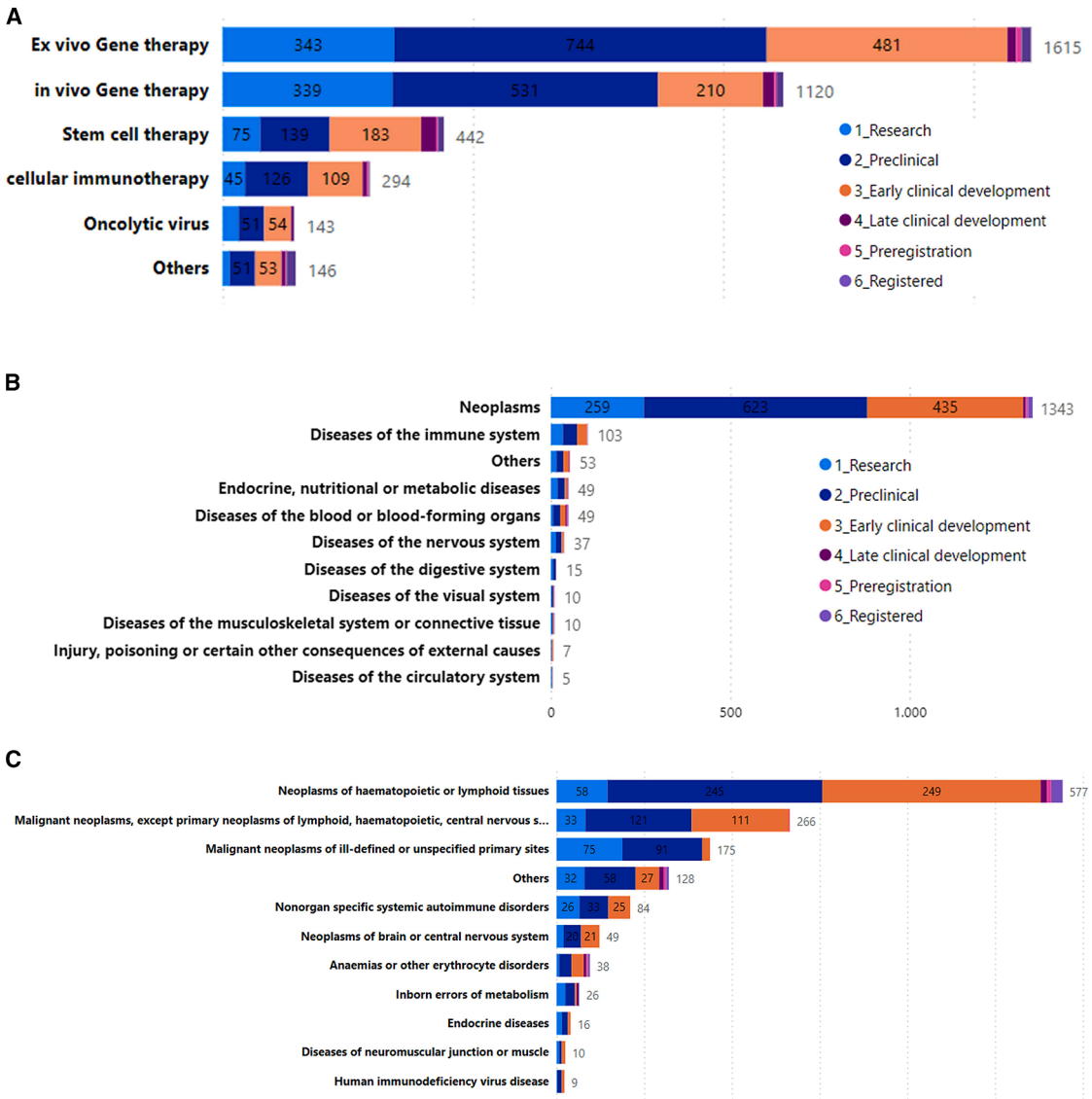


Figure 1. Overview of cell and gene therapy database and indications of *ex vivo* gene therapies

(A) Overview of cell and gene therapies by technology detail and development phase group. (B) Overview of *ex vivo* gene therapies by technology detail and indication group (ICD disease fields). "Others" in (B) include the following ICD disease fields: certain infections or parasitic diseases; diseases of the skin; extension codes; diseases of the genitourinary; system; developmental anomalies; external causes of morbidity or mortality; mental, behavioral, or neurodevelopmental disorders; symptoms, signs, or clinical findings, not elsewhere classified. (C) Overview of *ex vivo* gene therapies by technology detail and indication group (ICD disease families). "Others" in (C) includes around 50 different diseases families. Note: There may be duplications as a drug may be in more than one phase simultaneously in different countries or for different indications. Early clinical development includes phase 1, phase 1/2, or phase 2; late clinical development includes phase 2/3 or phase 3.

Across all three cell types, the primary genetic modification was the introduction of CAR, accounting for 83.19% of products. In addition, TCR modifications were also commonly utilized (10.84%). Other constructs for antigen recognition, antibody-coupled T cell receptor (ATCR), dimeric antigen receptor T (DAR-T), specific peptide enhanced affinity receptor (SPEAR), T cell antigen coupler, antigen-receptor complex-T cells (ARC-T), and TCR, are less frequently applied. Other genetic modifications were mostly applied for stem cells as gene-target therapies (GTTs) (Figure 2C). Cell source information was primarily available for products in late-stage clinical trials or more advanced phases of development. Notably, over 90% of these products were autologous, with only three allogeneic therapies identified (Figure 2D).

The predominant targets in *ex vivo* gene therapy and emerging alternatives

Data regarding the molecular target were available for almost half of the *ex vivo* gene therapies (Figure 3). The most frequently

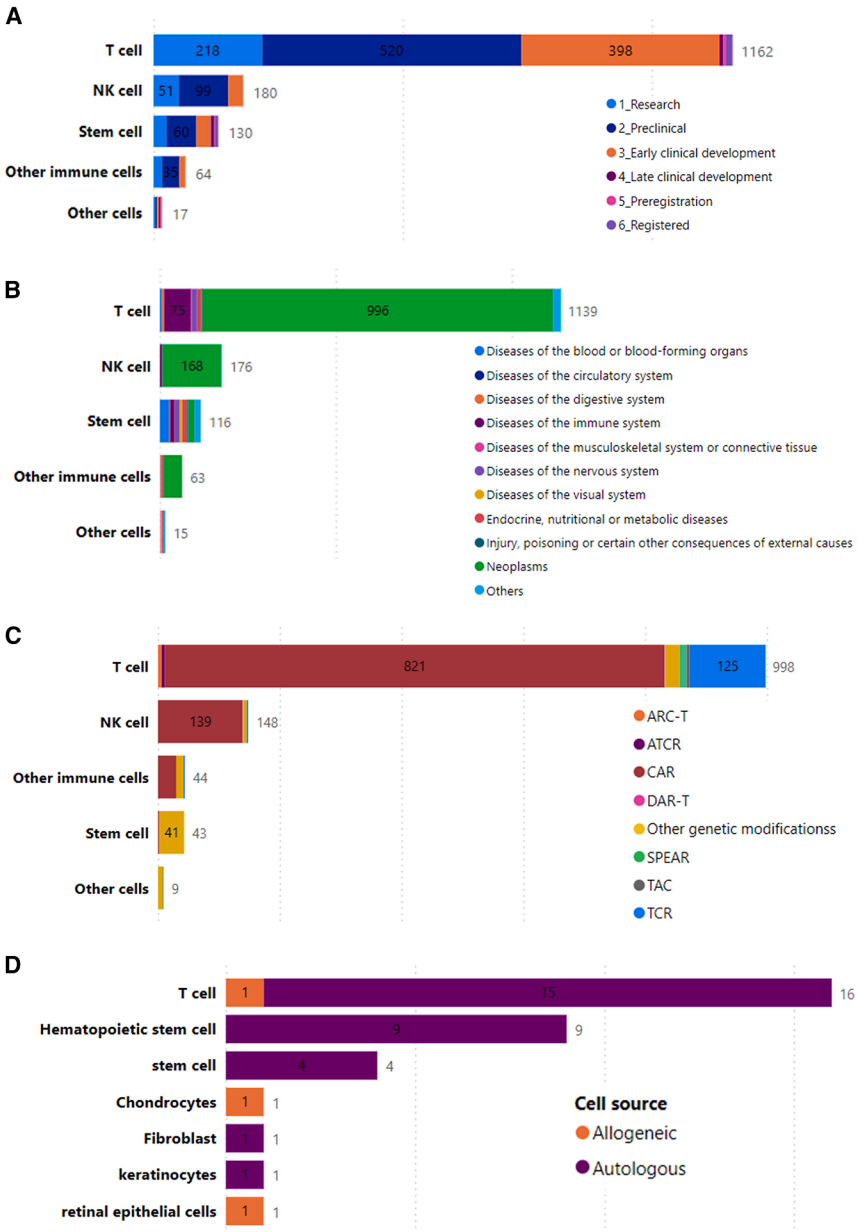


Figure 2. Cell types and genetic modifications of *ex vivo* gene therapy

(A) Cell types by development phase. (B) Cell types by indication. (C) Cell types by genetic modifications applied in *ex vivo* gene therapies. (D) Cell types and cell sources (allogeneic or autologous) of products in late clinical trials (pre-registration or registered). Note: There may be duplications as a drug may be in more than one phase simultaneously in different countries or for different indications. Early clinical development includes phase 1, phase 1/2, or phase 2; late clinical development includes phase 2/3 or phase 3. Other cells include fibroblasts, chondrocytes, endothelial cells, epithelial cells, keratinocytes, muscle cells, and retinal epithelial cells. Abbreviations are as follows: ATCR, antibody coupled T cell receptor; DAR-T, dimeric antigen receptor T; SPEAR, specific peptide enhanced affinity receptor; TAC, T cell antigen coupler; ARC-T, antigen-receptor complex-T cells; TCR, T cell receptor.

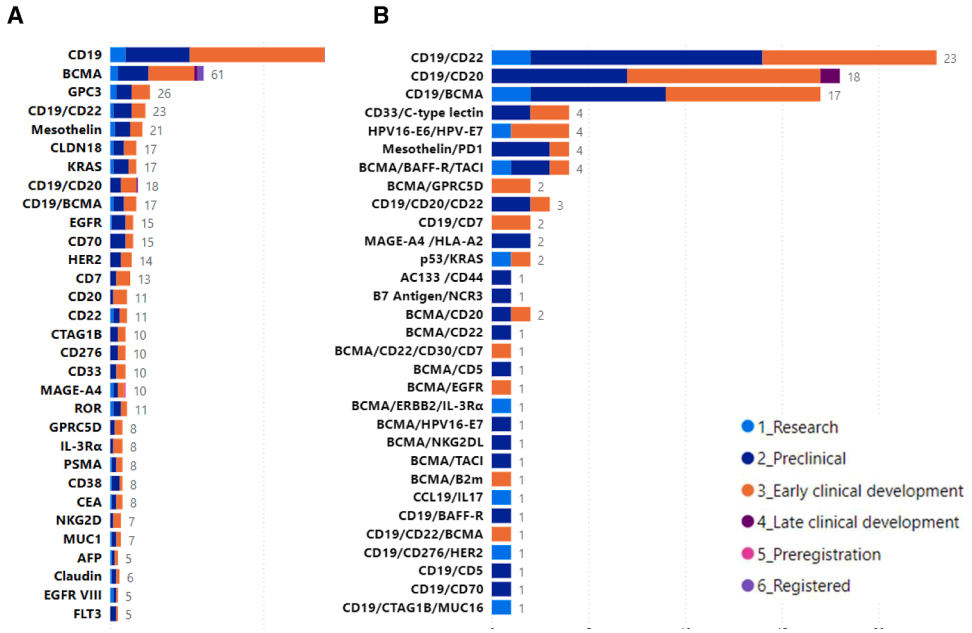
targeted molecules were CD19, accounting for 16.01% of therapies, followed by BCMA (B-cell Maturation Antigen), GPC3 (Glypican-3), mesothelin, CLDN18 (Claudin-18), KRAS (Kirsten rat sarcoma viral oncogene homolog), and others. Among these most frequent targets, CD19 and BCMA were the only ones to advance to late clinical development and registration (Figure 3A).

An emerging innovative trend observed is the development of multi-targeted therapies, with 143 products incorporating multi-target approaches, predominantly CD19 and/or BCMA combined with additional antigens (Figure 3B). Most bispecific products are at the research or pre-clinical stage (around 57%), 65 products advanced to early clinical development, and the most advanced product is a CD19/CD20 CAR (zantocabtagene autoleucel) that reached phase 3. The database also contained 16 trispecific CARs and 6 reached early clinical development (Figure 3B).

Approximately 20 different molecular targets were investigated concurrently for neoplasms of hematopoietic or lymphoid tissue and ICD-11 classifications associated with solid tumors (Figure 3C). Notably, several targets initially developed for hematological malignancies, such as CD19, BCMA, CD19/CD20, CD7, BCMA/BAFF-R/TACI, and CD19/TIGIT, are now being investigated for non-organ-specific systemic autoimmune disorders, both as monotherapies and in combination. NKG2D is being studied across all neoplastic disease groups, while CD70, ROR, CTAG1B, CD276, EGFR, and CD19/BCMA are being studied in three of the four neoplastic disease families (Figure 3C).

Viral vectors dominate the current landscape, with CRISPR and other alternatives on the horizon

The availability of vector information varied significantly across different development stages. Specifically, this information was accessible for only 30% of products in earlier development stages, while it was comprehensive for all products that progressed to late clinical trials. The results presented here showed the prevalence of viral vectors in *ex vivo* gene therapy, especially in late clinical development (Figure 4).



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Lentiviral vectors were the predominant choice among the various delivery systems for *ex vivo* gene therapies (40.12%), followed by CRISPR technology (25.66%) (see Figure 4A). Among the candidates in late-stage clinical development, the majority utilized viral vectors, including lentiviral (69.7%), retroviral (18.2%), and adenoviral vectors (3.03%), as illustrated in Figure 4B. Transposons, RNA-based vectors, DNA plasmids, ZNF, and TALENs were also present in our database, but were less frequently used.

Our data also reveal a decline in the use of retroviral vectors over the past few years, accompanied by a consolidation of lentiviral vectors (Figure 4C). CRISPR is steadily gaining traction in recent years, which is an emerging tool, and was more commonly applied in the earlier stages of development. Other technologies, such as TALEN and transposons, are also emerging and have reached early clinical development.

Current landscape of *ex vivo* gene therapy in clinical trials

The landscape of *ex vivo* gene therapies that have progressed to clinical trials is illustrated in Figure 5, while Table 1 details the 22 therapies that have achieved pre-registration or registration status. CAR-T cells dominated the landscape, being applied mostly to neoplastic diseases (Figure 5), including ten CAR-T cell therapies approved, all anti-BCMA or anti-CD19 for hematological maligancies (Table 1).

Other genetic modifications of antigen receptors (such as ATCR, DAR-T, SPEAR, TAC, ARC-T, and TCR) are also mostly applied for neoplastic diseases. Afamitresgene autoleucel, a SPEAR for several solid tumors, is the only product in this category to have reached the pre-registration stage (Figure 5; Table 1).

Other *ex vivo* therapies are evolving to pre-registration and registered stage, such as prademagene zamikeracel (autologous keratinocyte for a genetic and developmental disorder affecting the skin), revakinagene taroretcel (allogeneic retinal epithelial cells for disorders of the retina), nalotimagene carmaleucel (allogeneic T cell modified to express thymidine kinase to treat hematological malignancies), and tonogenchoncel-L (allogeneic chondrocytes for diseases of the musculoskeletal system or connective tissue) (Figure 5; Table 1).

Additionally, genetically modified autologous stem cell therapies are predominantly used to treat blood and blood-forming organ disorders, with multiple therapies reaching pre-registration or registration, including exagamglogene autotemcel, mozafancogene autotemcel, and betibeglogene autotemcel (Figure 5; Table 1).

As we can see in Table 1, most pre-registered or registered products use lentiviral vectors for genetic modification (72,73%). Retroviral vectors are applied to tonogenchoncel-l, strimvelis, prademagene zamikeracel, and nalotimagene carmaleucel. The only approved products with non-viral vectors are exagamglogene autotemcel, which is the first *ex vivo* gene therapy approved using CRISPR technology, and revakinagene taroretcel that utilizes DNA plasmid.

DISCUSSION

The data presented here showed that *ex vivo* gene therapy is an active field of innovation with 1,491 products in different stages of development and the most dynamic and rapidly growing area of advanced therapies, with more products advancing through clinical phases and regulatory approval. The database presented here is built through a structured search and extensive data curation rather than automated algorithms, allowing for careful verification and enrichment. This approach ensures data quality and reliability. This methodology has been previously utilized to explore the landscape of therapeutic antibodies,[34] and also in advanced therapies,[5,21,24,29–31] but it is not clear if they use the same data curation procedure. Most importantly, existing publications rarely focus exclusively on *ex vivo* gene therapies or offer such an integrated analysis covering cell types and sources, genetic modifications, vectors, molecular targets, and clinical dimensions. By providing this multidimensional perspective, our study offers a more comprehensive and nuanced overview of the current landscape of *ex vivo* gene therapy.

The changing landscape of vectors applied in *ex vivo* gene therapy

The results demonstrate a clear predominance of viral vectors in *ex vivo* gene therapies undergoing late-stage clinical development. Among these, lentiviral and retroviral vectors remain the most widely used, reflecting their compatibility with CAR-T cell generation through efficient transduction and stable transgene expression.[26,35] Other viral vectors, such as adenovirus, AAV, herpes simplex virus, and polyomavirus, are much less common. In line with prior reports, AAVs and adenoviral vectors are generally preferred for *in vivo* delivery, as they efficiently introduce payloads into post-mitotic cells and remain episomal.[27,29,36]

The current analysis also reveals a recent shift: retroviral vector usage has declined while lentiviral vectors have become standard, likely due to their ability to transduce non-dividing cells and lower risk of

Figure 3. Molecular targets for *ex vivo* gene therapies

(A) Main molecular targets of *ex vivo* gene therapies by development phase. (B) Multispecific *ex vivo* gene therapies by development phase. (C) Targets (gray) grouped by the top 5 ICD diseases families: neoplasms of hematopoietic or lymphoid tissues (hematopoietic neoplasms, red); malignant neoplasms of ill-defined or unspecified primary sites (unspecified neoplasms, orange); neoplasms of brain or central nervous system (neoplasms of brain, blue); malignant neoplasms, except primary neoplasm of lymphoid, hematopoietic, central nervous system, or ill-defied or unspecified primary sites (other neoplasms, purple); and non-organ-specific systemic autoimmune disorders (autoimmune disorders, green). Note: There may be duplications as a drug may be in more than one phase simultaneously in different countries or for different indications. Early clinical development includes phase 1, phase 1/2, or phase 2; late clinical development includes phase 2/3 or phase 3.

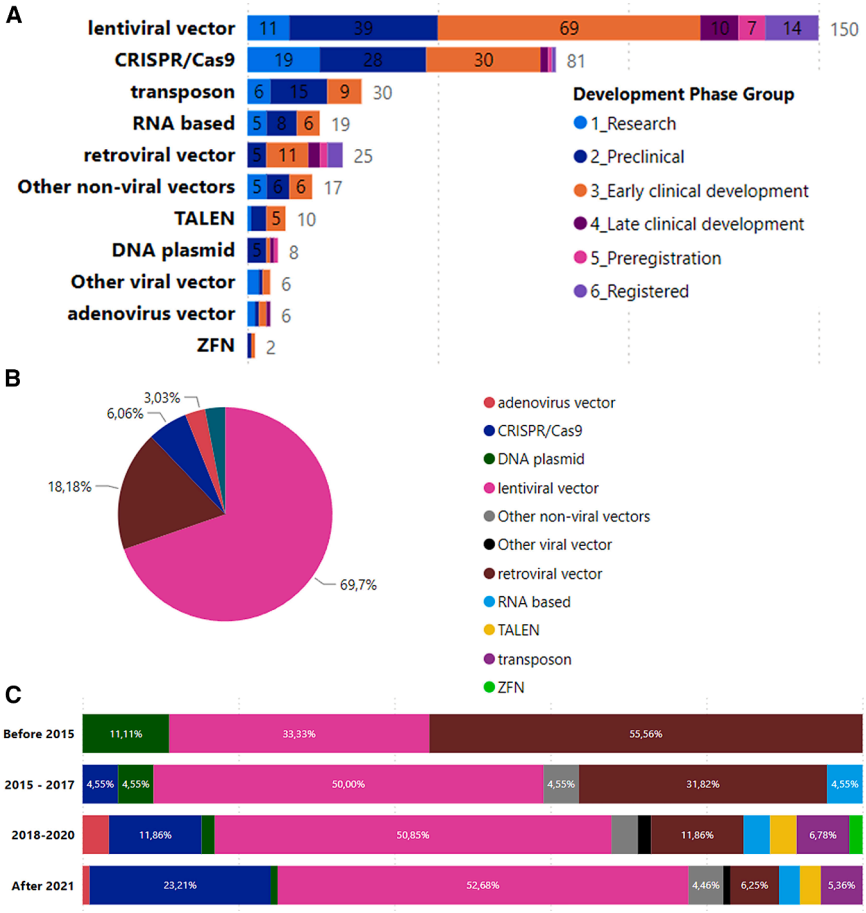

Figure 4. Overview of vectors utilized in *ex vivo* gene therapies

(A) Distribution of vectors categorized by development stage. (B) Vectors used in products that progressed to late-stage clinical development. (C) Vectors applied in different periods of time. Note: There may be duplications as a drug may be in more than one phase simultaneously in different countries or for different indications. Early clinical development includes phase 1, phase 1/2, or phase 2; late clinical development includes phase 2/3 or phase 3.

insertional oncogenesis. Notably, there is no definitive pre-clinical or clinical evidence favoring one viral vector platform over another for engineered T cells.[27,30,36] For hematopoietic stem cell applications, clinical trials for SCID highlighted the risk of insertional mutagenesis with gamma retroviruses, a problem mitigated by switching to lentiviral vectors—which maintained efficacy with improved safety.[37,38]

Another important trend observed is the increased adoption of CRISPR, the second most common genetic engineering technology in our dataset. This shift highlights growing interest in non-viral approaches, which could reduce immunogenicity, lower production costs, and simplify scale-up processes. Nevertheless, non-viral vectors—including transposons, RNA-based systems, DNA plasmids, ZFNs, and TALENs—are still emerging and less prevalent in the current database. Their main advantage lies in cost-effectiveness and flexibility, but their efficiency and precision continue to be actively refined[31,39,40]

Genome-editing endonucleases such as CRISPR-Cas9, TALENs, and ZFNs have emerged as an alternative enabling precise, programmable editing.[31,36] Among them, CRISPR-Cas9 stands out for its simplicity—relying on guide RNAs for target recognition and allowing multiplex gene targeting. Accordingly, CRISPR has rapidly expanded its adoption in clinical settings, as evidenced by the recent approval of Casgevy for SCD, an achievement that establishes a framework for future CRISPR-modified CAR-T trials. Early evidence also suggests that CRISPR editing can enhance CAR-T cell function and reduce production costs, though long-term clinical data are still accruing.[39,40]

Evolving targets beyond CD19 and BCMA

BCMA and CD19 are well-established targets for CAR-T cell therapies in hematological malignancies, particularly in B cell leukemias/lymphomas.[5,30–32] Notably, their scope is expanding beyond oncology, as B cells are also crucial in the pathogenesis of autoimmune diseases.[41–43] In addition to these established antigens, recent efforts focus on novel targets such as CD20, BAFF-R, TACI, and TIGIT—some of which, such as TIGIT and CD7, are linked to T and NK cells rather than B cells.[44,45] Although research on these newer targets is promising, especially for autoimmune indications, robust clinical evidence remains limited.

The correlation between molecular target selection, cell type, and genetic modification approach was also assessed (data not shown). Notably, molecular targets utilized in other engineered receptors beyond CAR approaches tend to be more frequently associated with solid tumors than with hematological malignancies, and other genetic modification targets are associated with other diseases. Regarding solid tumors, the field is broadening to include both established (HER2 and EGFR) and emerging (CLDN18, GPC3, and mesothelin) extracellular antigens, many of which are well known from monoclonal antibody therapies.[9,32,46–51] The translation of these targets to CAR T cell platforms leverages their surface accessibility to extend immunotherapeutic reach beyond hematology.

In contrast, intracellular targets such as KRAS and MAGE-A4 require alternative approaches, notably engineered TCRs that recognize intracellular peptide-MHC complexes. Despite their potential,

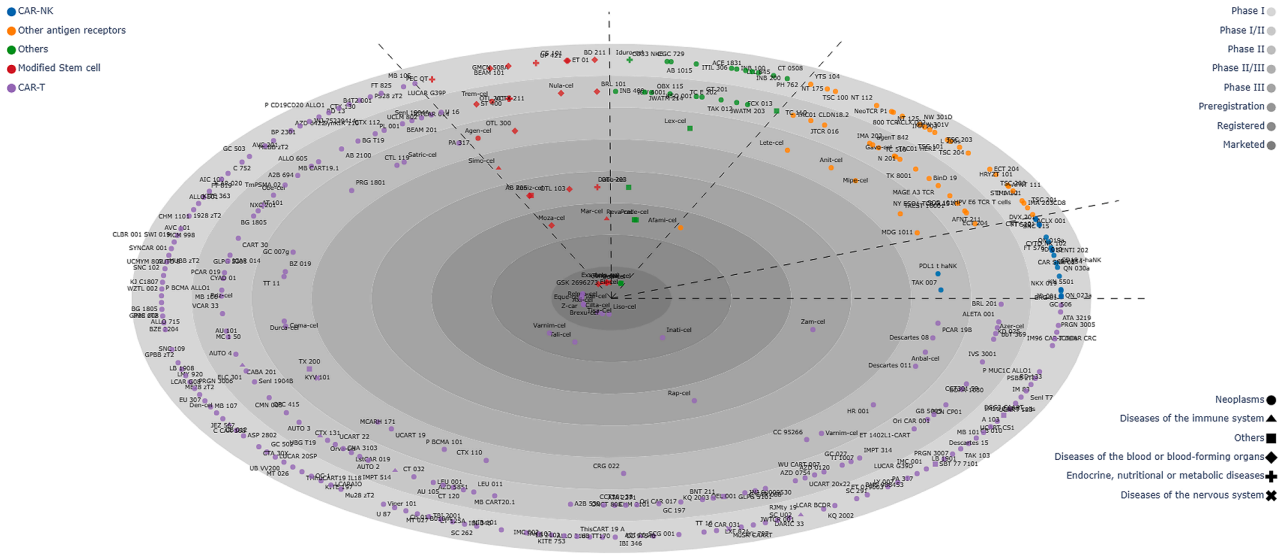

Figure 5. Bullseye of *ex vivo* gene therapies in clinical trials

The rings represent the phases of development, the shapes represent the medical fields of ICD-11, and the colors represent the combination of two attributes genetic modification and cell type. Note: "Others" include the following: NK and T cells with other genetic modifications, other immune cells expressing CAR, and other cell types with other genetic modifications. Abbreviations are as follows: Obe-cel, obecabtagene autoleuce; Eque-cel, equecabtagene autoleucel; Lete-cel, letetresgene autoleucel; Satric-cel, satricabtagene autoleucel; Mar-cel, marnetegragene autotemcel; Reva-cel, revakinagene taroretcel; Cema-cel, cemacabtagene ansegedleucel; Reniz-cel, renizgamglogene autogedtemcel; Cilta-cel, ciltacabtagene autoleucel; Liso-cel, lisocabtagene maraleucel; Brexu-cel, brexucabtagene autoleucel; Afami-cel, afamitresgene autoleucel; Relma-cel, relmacabtagene autoleucel; Prade-cel, prademagene zamikeracel; Durca-cel, durcabtagene autoleucel; Trem-cel, tremtelectogene empogeditemcel; Anit-cel, anitocabtagene autoleucel; Rap-cel, rapcabtagene autoleucel; Moza-cel, mozafancogene autotemcel; Priz-cel, prizloncabtagene autoleucel; Exa-cel, exagamglogene autotemcel; Ide-cel, idecabtagene vicleucel; Nula-cel, nulabeglogene autogedtemcel; Arsa-cel, atidarsagene autotemcel; Gavo-cel, gavocabtagene autoleucel; Z-car, zevorcabtagene autoleucel; ,Azer-cel, azercabtagene zapreleucel; Beti-cel, betibeglogene autotemcel; Simo-cel, simoladagene autotemcel; Tali-cel, talicabtagene autoleucel; Tono-cel, tonogenchoncel-L; Axi-cel, axicabtagene ciloleucel; Inati-cel, inaticabtagene autoleucel; Anbal-cel, anbalcabtagene autoleucel; Tisa-Cel, tisagenlecleucel; Den-cel, denocabtagene Ciloleucel; Eli-cele, livaldogene autotemcel; Orva-cel, orvacabtagene autoleucel; Zam-cel, zamtocabtagene autoleucel; Mipe-cel, mipetresgene autoleucel; Iduro-cel, iduronicrin genleukocel-T; Dabo-cel, dabocemagene autoficel; Nal-cel, nalotimagene carmaleucel; Lex-cel, lexgenleucel-T; Agen-cel, agenmestencel-T.

these therapies face challenges including HLA restriction and the risk of off-target effects.[52,53]

An important trend observed is the development of bispecific or dual-targeting CAR-T constructs—143 candidates in our dataset—aimed at overcoming antigen loss-mediated resistance in hematological malignancies and solid tumors. Such therapies are an emerging innovative approach to address low response rates and relapses due to downregulation of target antigens and have progressed to clinical trials.[54–58] New studies are necessary to understand if they will bring a better clinical response to neoplastic and other diseases.

Neoplastic diseases: The foremost focus of *ex vivo* gene therapy

CAR-T cell therapies have revolutionized the treatment of B cell malignancies since the approval of tisagenlecleucel for ALL in 2017.[59] Since then, the majority of *ex vivo* gene therapy development has focused primarily on neoplastic indications, with hematological malignancies at the forefront. This is reflected in our current results, which show that hematological malignancies account for the highest number of approved products (11) and of clinical trials (over 250). These findings are consistent with the broader literature that underscores the significant clinical success achieved in this area.[10,59–62] Most of these therapies employ CAR-T constructs, with a smaller (yet increasing) share utilizing TCR or other approaches. Recent approvals and studies—including those targeting CD19 and BCMA—have demonstrated high remission rates and manageable safety profiles, reinforcing the clinical impact of these platforms.[53,60–63] Despite these advances, substantive challenges remain. Disease relapse post-CAR-T, often linked to antigen escape or loss, continues to be a major concern, and cytokine release syndrome remains a significant, potentially life-threatening toxicity.[64,65]

Even though the results presented here show a great number of *ex vivo* gene therapies being developed for solid tumors, few products have advanced to later clinical trials. There are several challenges associated with CAR-T in solid tumors, such as restricted trafficking and infiltration into the tumor, hypotoxic and immunossupressive tumor microenvironment, antigen escape and heterogeneity, among others difficulties.[9,59,66]

Notably, our database showed the recent accelerated approval of afamitresgene autoleucel (Tecelra), a SPEAR TCR-T therapy targeting MAGE-A4 in synovial sarcoma, signals new opportunities for

Table 1. *Ex vivo* gene therapies that reached pre-registration or registration stage

Drug name	Vector	Cell type/source	Genetic modification/target	Indications	Developers	Countries/territories
Afamitresgene autoleucel (TECELRA)	lentiviral vector	T cell/autologous	SPEAR (specific peptide enhanced affinity receptor) anti- MAGEA4	synovial sarcoma	Adaptimmune, University of Texas M. D. Anderson Cancer Center	**Registered:** USA (Accelerated approval)
Atidarsagene autotemcel (Lenmeldy/ Libmeldy)	lentiviral vector	hematopoietic stem cell/autologous	genetically engineered to express functional arylsulfatase A (ARSA) genes	metachromatic leukodystrophy	Orchard Therapeutics, The San Raffaele Telethon Institute for Gene Therapy (JV)	**Marketed:** United Kingdom, France, Iceland, Germany, European Union, Norway
					Orchard Therapeutics	**Marketed:** Italy **Registered:** Switzerland, USA
Brexucabtagene autoleucel (Tecartus)	lentiviral vector	T cell/autologous	CAR-T anti-CD19	mantle-cell lymphoma	Kite Pharma, Cabaret Biotech	**Marketed:** Netherlands, Poland, USA, United Kingdom **Registered:** Canada, European Union, Iceland, Liechtenstein, Norway
				precursor B cell lymphoblastic leukaemia-lymphoma		**Marketed:** USA **Registered:** European Union, Iceland, Liechtenstein, Norway **Preregistration:** United Kingdom
Ciltacabtagene autoleucel (CARVYKTI)	lentiviral vector	T cell/autologous	CAR-T anti-BCMA	multiple myeloma	Janssen Biotech	**Marketed:** Austria, Germany, USA **Registered:** China, European Union, Iceland, Japan, Liechtenstein, Norway, United Kingdom
					Legend Biotech USA	**Marketed:** Canada **Registered:** Brazil, United Kingdom
					Nanjing Legend Biotech	**Registered:** China
Elivaldogene autotemcel (SKYSONA)	lentiviral vector	hematopoietic stem cell/autologous	genetically engineered to express drenoleukodystrophy protein (ALDP)	adrenoleucodystrophy	Bluebird Bio, Genetix Pharmaceuticals	**Marketed:** USA,Iceland, European Union, Norway, Liechtenstein **Preregistration Submission Withdrawal:** United Kingdom
Equecabtagene autoleucel (FUCASO)	lentiviral vector	T cell/autologous	CAR-T anti-BCMA	multiple myeloma	Innovent Biologics	**Marketed:** China
					Nanjing IASO Biotherapeutics	**Marketed:** China
Exagamglogene autotemcel (CASGEVY)	CRISPR-Cas9 technology	hematopoietic stem cell/autologous	genetically engineered to block BCL11A increasing γ-globin and fetal hemoglobin (HbF)expression	beta-thalassaemia	CRISPR Therapeutics, Vertex Pharmaceuticals	**Marketed:** Bahrain, United Kingdom* **Registered:** USA, Norway, Liechtenstein, Iceland, European Union, Canada
					Vertex Pharmaceuticals	**Registered:** Saudi Arabia, Switzerland
				sickle cell anemia	CRISPR Therapeutics, Vertex Pharmaceuticals	**Marketed:** Bahrain, United Kingdom, USA
						Registered: Norway, Liechtenstein, Iceland, European Union, Canada

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Table 1. ***Continued***

Drug name	Vector	Cell type/source	Genetic modification/target	Indications	Developers	Countries/territories
					Vertex Pharmaceuticals	**Registered:** Saudi Arabia, Switzerland
GSK 2696273 (Strimvelis)	retroviral vector	hematopoietic stem cell/autologous	genetically engineered to express the human adenosine deaminase (ADA)	adenosine deaminase deficiency	Orchard Therapeutics, The San Raffaele Telethon Institute for Gene Therapy	**Marketed:** Finland, Ireland, Italy, Netherlands, Poland, United Kingdom **Registered:** Iceland, European Union, Liechtenstein, Norway
Idecabtagene vicleucel (Abecma)	lentiviral vector	T cell/autologous	CAR-T anti-BCMA	multiple myeloma	Bluebird bio	**Marketed:** USA **Registered:** Switzerland, Canada, Japan
					Bristol-Myers Squibb	**Marketed:** USA **Registered:** Israel, United Kingdom, Switzerland, Japan
					Celgene Corporation	**Registered:** Canada, Japan, European Union, Iceland, Liechtenstein, Norway
					2seventy bio	**Registered:** Israel, United Kingdom
Lisocabtagene maraleucel (Breyanzi)	lentiviral vector	T cell/autologous	CAR-T anti-CD19	chronic lymphocytic leukemia	Celgene Corporation	**Marketed:** USA
				diffuse large B cell lymphoma	Bristol-Myers Squibb	**Marketed:** USA **Registered:** Canada, European Union, Iceland, Japan, Liechtenstein, Norway, Switzerland
				follicular lymphoma	Celgene Corporation	**Marketed:** USA
					Bristol-Myers Squibb	**Registered:** European Union, Iceland, Japan, Liechtenstein, Norway
				mantle-cell lymphoma		**Marketed:** USA
				non-Hodgkin's lymphoma	Juno Therapeutics	**Preregistration:** USA
Lovotibeglogene autotemcel (LYFGENIA)	lentiviral vector	hematopoietic stem cell/autologous	β-globin gene	beta-thalassaemia	Bluebird Bio, Genetix Pharmaceuticals	**Marketed:** USA, Denmark, Netherlands, Poland **Registered:** Norway, European Union, Liechtenstein, United Kingdom, Iceland **Market Withdrawal:** Germany
				sickle cell anemia		**Marketed:** USA
Marnetegragene autotemcel (KRESLADI)	lentiviral vector	hematopoietic stem cell/autologous	deliver of ITGB2 gene, encoding for the human CD18 receptor	leukocyte-adhesion deficiency syndrome	Rocket Pharmaceuticals, CIEMAT	**Preregistration (fast-track):** USA
Mozafancogene autotemcel (RP-L102)	lentiviral vector	hematopoietic stem cell/autologous	genetically engineered to expresses a functional copy of the FANC-A gene	Fanconi's anemia	Rocket Pharmaceutical, CIEMAT	**Preregistration:** Europe, USA (phase II, fast track), United Kingdom (Phase II), Spain
Nalotimagene carmaleucel (Zalmoxis)	retroviral vector	T cell/allogeneic	genetically engineered to express thymidine kinase (TK)	leukemia	AGC Biologics	**Marketed:** Germany, Italy **Registered:** Iceland, European Union, Norway, Liechtenstein

(*Continued on next page*)

Table 1. ***Continued***

Drug name	Vector	Cell type/source	Genetic modification/target	Indications	Developers	Countries/territories
Prademagene zamikeracel (Pz-cel)	retroviral vector	keratinocytes/autologous	genetically engineered to express the missing type VII collagen protein	epidermolysis bullosa dystrophica	Abeona Therapeutics	**Preregistration:** USA
Relmacabtagene autoleucel (Carteyva)	lentiviral vector	T cell/autologous	CAR-T anti-CD19	follicular lymphoma	JW Therapeutics	**Marketed:** China
				mantle-cell lymphoma		**Marketed:** China
				diffuse large B cell lymphoma		**Preregistration:** China
				non-Hodgkin's lymphoma	JW Therapeutics, Shanghai Ming Ju Biotechnology	**Marketed:** China
Revakinagene taroretcel (Rexenus)	DNA plasmid	retinal epithelial cells/allogeneic	genetically engineered to express ciliary neurotrophic factor (CNTF)	retinal telangiectasis	Neurotech USA	**Registration:** USA (fast track)
Talicabtagene autoleucel (NexCAR19)	lentiviral vector	T cell/autologous	CAR-T anti-CD19	B cell lymphoma, precursor B cell lymphoblastic leukaemia-lymphoma	ImmunoACT	**Registered:** India
Tisagenlecleucel (Kymriah)	lentiviral vector	T cell/autologous	CAR-T anti-CD19	diffuse large B cell lymphoma	Novartis	**Marketed:** Ireland, USA, Belgium, Poland, Australia, Spain, France, Norway, Czech Republic, Switzerland, Netherlands, United Kingdom, Finland, Greece, Denmark **Registered:** Singapore, Japan, Canada, Liechtenstein, Iceland, European Union
				follicular lymphoma	Novartis	**Marketed:** Denmark, France, Greece, Spain, Poland, Czech Republic, Belgium, Netherlands, Ireland, Norway, Finland, USA **Registered:** Liechtenstein, European Union, Iceland **Preregistration:** Japan
				precursor B cell lymphoblastic leukaemia-lymphoma	Novartis	**Marketed:** Switzerland, Czech Republic, Ireland, Belgium, Norway, Denmark, Poland, Finland, Greece, Spain, United Kingdom, Australia, Netherlands, France, USA (Novartis, University of Pennsylvania) **Registered:** Iceland, European Union, Singapore, Japan, Canada, Liechtenstein
Tonogenchoncel-L (Invossa)	retroviral vector	chondrocytes/allogeneic	genetically modified to produce TGF-beta 1	osteoarthritis	Kolon Life Science, TissueGene	**Marketed:** South Korea
Varnimcabtagene Autoleucel (Qartemi)	lentiviral vector	T cell/autologous	CAR-T anti-CD19	precursor cell lymphoblastic leukaemia-lymphoma	Institut d Investigacions Biomediques	**Registered:** Spain
Zevorcabtagene autoleucel (CARsgen)	lentiviral vector	T cell/autologous	CAR-T anti-BCMA	multiple myeloma	CARsgen	**Marketed:** China

engineered TCR-based approaches in solid tumors. Tecelra's early results highlight both the promise and the remaining limitations of TCR therapies: responses have been observed in HLA-restricted settings, but durability and broader applicability are still being evaluated.[67]

Advancing the application of *ex vivo* gene in non-oncological diseases

Beyond neoplastic indications, immune system disorders and genetic diseases—especially metabolic and blood disorders—are prominent targets for *ex vivo* gene therapy in our dataset, though most developments remain preclinical. Despite representing only a small fraction of *ex vivo* therapy candidates, stem cell-based interventions have yielded outsized clinical impact, with several products now approved or in advanced trials.

The field has seen remarkable progress with therapies for SCD and BTB, utilizing diverse strategies such as lentiviral β-globin gene addition (e.g., betibeglogene autotemcel and lovotibeglogene autotemcel) and CRISPR-based genome editing (e.g., exagamglogene autotemcel). These approaches have consistently demonstrated high rates of transfusion independence and reduction of disease manifestations, sustaining recent regulatory approvals.[68–71]

For immune-mediated diseases, *ex vivo* gene therapy progress has centered on refractory rheumatic and systemic autoimmune disorders, where current treatment options are often limited. Most clinical progress to date has leveraged CD19 or CD19/BCMA-targeted CAR-T therapies, which have produced rapid and durable remissions in case series and early-phase trials. Nevertheless, long-term surveillance remains essential, as uncertainties persist around risks of insertional mutagenesis and off-target effects.[41–44,72]

Besides immune-mediated diseases and blood disorders, the current database also demonstrated *ex vivo* gene therapies in registration or approval phase for genetic immunodeficiencies and degenerative genetic disorders. These emerging indications underscore the expanding potential of *ex vivo* gene therapies beyond oncology, demonstrating promising advances in treating a broad spectrum of genetic and inherited disorders such as epidermolysis bullosa dystrophica, adenosine deaminase deficiency, adrenoleukodystrophy, and metachromatic leukodystrophy, highlighting the versatility and transformative impact of gene correction strategies in regenerative medicine and rare diseases.[73–77]

Challenges and perspectives of *ex vivo* gene therapies

The widespread implementation of *ex vivo* gene therapies continue to face notable challenges beyond clinical performance. The results presented here demonstrated notable uneven distribution regarding the availability of pre-registered and registered products among high-income countries (HICs), upper-middle countries, and low-middle income countries. The overwhelming concentration of approved and pre-registered products in HICs is shaped not only by purchasing power but also by corporate strategies, R&D localization, and regulatory factors. Thus, the global landscape is characterized by stark differences in both therapy availability and trial activity.[78–81]

The challenges begin with the complexity of transitioning from research to clinical and manufacturing-grade. This process requires not only technical adjustments but also strict adherence to good manufacturing practices (GMP) to ensure product quality, safety, and consistency at scale. Ideally, research facilities should perform GMP simulation, in close collaboration between researchers, product developers, and manufacturing experts, thereby, facilitating and accelerating transitions to clinical and registration phases. The steps of cell harvesting and manipulation are considerably more complicated than those encountered in the production of traditional biopharmaceuticals. They require advanced logistics, specialized infrastructure, and highly skilled personnel. The use of non-virus-based vectors can simplify some steps of GMP compliance; however, most of the current system relies on lentiviral or retroviral vectors, which require the production of large quantities of viruses for clinical-grade use, maintaining a high degree of purity and compliance with GMP standard. The complexities in development and manufacturing lead to high cost of *ex vivo* gene therapies, another important hurdle to access. In addition to manufacturing complexities, efficient patient selection and timely delivery processes present further hurdles.[12,80,82,83]

Financial barriers are further compounded by reimbursement models that were not designed for one-time, potentially curative interventions. While outcome-based agreements (such as spread payments or pay-for-performance schemes) have been proposed to balance initial costs and long-term benefits, their implementation remains limited and often insufficient for broad adoption.[84] To mitigate disparities, expanded investment in manufacturing capacity and regulatory infrastructure within emerging economies is crucial. Countries with biotechnological capacity, such as Brazil, are uniquely positioned to develop local solutions, such as leveraging vaccine production experience for vector manufacturing.[79–81]

From a technical perspective, innovative platforms—including *in vivo* CAR-T,[85,86] where chimeric receptor genes are delivered directly to the patient, and universal allogeneic CAR-T cells[87,88]—offer potential paths to improving scalability and reducing costs. However, these next-generation therapies present their own hurdles, including the requirement for highly specific gene delivery and the risk of reduced efficacy or immune rejection. Several universal CAR-T development programs have now advanced to early-phase clinical trials, underlining both promise and remaining uncertainty in realizing broader access to engineered cell therapies. Besides this approaches, several other technological strategies can simplify and reduce production complexity such as gene delivery based on non-viral vectors, new cells sources, shortening cell expansion period, and decentralized point-of-care manufacturing.[83,85–88]

Conclusions

In summary, while *in vivo* gene delivery has seen significant advancements, *ex vivo* genetic modification remains a dominant

platform for many widely used gene therapies, with numerous new products anticipated to be registered in this modality in the coming years. This study offers a comprehensive overview of current trends and future directions in *ex vivo* gene therapy, highlighting the emergence of non-viral vectors, novel targets, dual targeting strategies, expansion into solid tumors and non-oncological diseases. These developments underscore the potential of *ex vivo* gene therapy to continue playing a pivotal role in the treatment landscape, with ongoing innovations poised to address existing challenges and expand access.

MATERIALS AND METHODS

A systematic strategic foresight study focusing on advanced therapies was conducted to analyze the scenario, including, among other things, their status (development phase) and technological attributes. The methodology developed by the Bio-Manguinhos/Fiocruz team enables data integration from various sources for use in competitive intelligence and foresight to gain insights and make data-driven decisions.[34,89] Product pipeline data were extracted, prepared, and analyzed using the private database AdisInsight, a proprietary resource of global pharmaceutical development that consolidates scientifically validated data from multiple sources. The integration of proprietary databases, such as AdisInsight[34,90–92] or other curated sources,[24,29] is a widely adopted practice in pharmaceutical and biomedical research to streamline data collection and curation. The reliance on non-public data sources can limit external reproducibility, to address this, comprehensive data preparation processes—including cleaning, processing, enrichment, and qualitative validation—were rigorously applied in accordance with the study's objectives.[89]

The search terms "cell therapy" and "gene therapy" comprised 5,646 products and over 30,000 records (more than one per product) in July 2024. All collected data underwent a procedure that included the identification of duplicate, incomplete, or inaccurate records. These data were enriched with additional sources and underwent qualifications by experts. Algorithms for data treatment were developed using Python programming language based on international nonproprietary names,[93] as well as drug classifications from the AdisInsight database. Subsequently, all classifications underwent manual review by experts and were further enriched and validated with additional information sourced from scientific publications, other databases, and relevant company websites.

The data were classified into several categories: technology niche, technological details, vector, cell type, cell source, key detail properties (genetic modification applied), and molecular target. The technology niche subcategories were as follows: gene and cell therapies, oligonucleotide therapies, therapeutic antibodies, therapeutic vaccines, and other biological therapies. The technological details subcategories were as follows: bispecific or multispecific, cell-based vaccine, cellular immunotherapy, *ex vivo* gene therapy, exosome therapies, *in vivo* gene therapy, live biotherapeutic products, monoclonal antibody, mRNA, nucleic acid encoded antibody, nucleic acid-based vaccine, oncolytic virus, small RNA, stem cell therapy, subunit vaccine, vector-based vaccine, and others. The phases of development were classified as preclinical (R&D, including both *in vitro* and *ex vivo*), early clinical development (phase 1, 2, or 1/2), late clinical development (phase 2/3 or 3), preregistration (submitted to registration), or commercially available (products registered).

After the exclusion of products without reported development, those in unknown development phases, discontinued products, and those utilizing other technologies such as oligonucleotide therapies and therapeutic vaccines, the dataset was narrowed to 3,427 gene and cell therapies products. These were identified across medical fields and disease families, classified according to the ICD-11 of the WHO.[33]

This study does not aim to make any inference about the future or to present a predictive or prescriptive trend analysis; consequently, no test of hypothesis was conducted. The main goal of this work is to provide a snapshot of the current landscape, identifying technologies involved, and to discuss technological trends, challenges, and opportunities. To achieve this, we applied a descriptive statistical analysis of the database and its features.

The data were presented, classified, and characterized in different groups to generate tables in Microsoft Excel and graphs using visualization software (Microsoft PowerBi) and codes developed in Python language with specific libraries such as Pandas, NumPy, and Plotly allowing better visualization of results and analysis.

DATA AVAILABILITY

Data for this analysis were made available to the authors through a third-party license from AdisInsight, a commercial database that is part of Springer Nature. In accordance with the corresponding data use agreement, the authors cannot deposit the data extracted for use in this publication in a publicly accessible database. Investigators may access the data by purchasing a license through AdisInsight. Interested individuals may refer to https://adisinsight.springer.com/ for more information on accessing this database.

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AUTHOR CONTRIBUTIONS

A.A.-O. supervised the work, planned the study, prepared the database (collection and enrichment of technological data), analyzed data, discussed the results, and wrote and reviewed the manuscript; M.H.B. interpreted the data, discussed the results, and wrote and reviewed the manuscript; M.S. prepared the database (collection and enrichment of technological data), discussed the results, and wrote and reviewed the manuscript; V.H.V.M. collected data, performed data curation, treatment and visualization, developed codes in Python language, and wrote the manuscript; D.P.B.F. prepared the database (collection and enrichment of technological data), discussed the results, and reviewed the manuscript; A.D. prepared the database (enrichment of clinical data),

discussed the results, wrote and reviewed the manuscript; T.P.C. prepared the database (enrichment of clinical data), discussed the results, and wrote the manuscript; J.d.N.e.S. V. prepared the database (enrichment of clinical data), discussed the results, and wrote the manuscript; M.T.M. analyzed data, discussed the results, and wrote and reviewed the manuscript; C.L.G. prepared the database (enrichment of clinical data), discussed the results, and wrote the manuscript; A.d.M.M. prepared the database (enrichment of clinical data), discussed the results, and wrote and reviewed the manuscript; M.M.B. supervised the work, conceptualized the foresight methodology, discussed the results, and wrote the manuscript; B.d.C.F. supervised the work, conceptualized the foresight methodology, discussed the results, and wrote and reviewed the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used Perplexity, Deepseek, and Copilot in order to improve the language and help in the search along with traditional references databases such as PubMed and Dimensions. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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