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Gene Therapy: Mechanisms, Clinical Translation, Challenges, and Future Perspectives

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ABSTRACT

Gene therapy has progressed from a speculative concept to a clinically validated therapeutic modality, transforming the management of monogenic disorders, hematologic malignancies, and ocular, neuromuscular, and cardiovascular diseases. Following nearly five decades of preclinical refinement and a turbulent early clinical history marked by serious adverse events, the field has matured into a regulated discipline supported by over 3,900 clinical trials worldwide. This review synthesizes the current state of gene therapy, with emphasis on viral and non-viral delivery platforms—particularly adeno-associated viral (AAV) vectors, lentiviral vectors, and ionizable lipid nanoparticles (LNPs)—as well as somatic versus germline and in vivo versus ex vivo classifications. Landmark regulatory approvals, including voretigene neparvovec (Luxturna), onasemnogene abeparvovec (Zolgensma), etranacogene dezaparvovec (Hemgenix), exagamglogene autotemcel (Casgevy), and chimeric antigen receptor (CAR)-T cell therapies, are critically appraised. Genome-editing innovations—CRISPR-Cas9, base editing, and prime editing—are discussed in the context of expanding therapeutic precision. Persistent challenges encompass immunogenicity, off-target editing, insertional mutagenesis, durability of expression, manufacturing scalability, and equitable access. The review concludes with future perspectives on next-generation vectors, in vivo CAR-T engineering, and global access frameworks essential to realizing the curative promise of genetic medicine.

Keywords: Gene therapy; adeno-associated virus; lentiviral vectors; CRISPR-Cas9; base editing; prime editing; CAR-T cell therapy; lipid nanoparticles; insertional mutagenesis; precision medicine

1. INTRODUCTION

Gene therapy refers to the deliberate introduction, modification, removal, or repair of nucleic acid sequences within human cells with the intent of preventing or treating disease. After three decades of promise tempered by setbacks, gene therapies have become indispensable tools in the contemporary therapeutic armamentarium for both inherited and acquired disorders (Dunbar et al., 2018). The rationale is conceptually straightforward: when a genetic lesion causes the loss, dysfunction, or aberrant expression of a protein, the introduction of a functional copy of the gene—or precise correction of the underlying mutation—can restore physiological function, often after a single administration (High & Roncarolo, 2019). What was once experimental has now entered routine clinical practice, with

approvals spanning inherited retinal dystrophies, spinal muscular atrophy, hemophilia B, β-hemoglobinopathies, Duchenne muscular dystrophy, and B-cell hematologic malignancies (Ginn et al., 2024).

The translation from concept to bedside has not been linear. Early enthusiasm in the 1990s gave way to caution following the death of Jesse Gelsinger in 1999 from a fatal innate immune response to an adenoviral vector, and subsequent leukemias in X-linked severe combined immunodeficiency (SCID-X1) trials due to insertional oncogenesis (Naldini, 2015). The subsequent two decades witnessed iterative engineering of safer vector platforms—particularly self-inactivating lentiviral and AAV vectors—coupled with regulatory and ethical frameworks that have permitted gene therapy to reach the standard of evidence required for regulatory approval (Cavazzana et al., 2019). Concurrently, the discovery of programmable nucleases—zinc finger nucleases, transcription activator-like effector nucleases, and most consequentially CRISPR-Cas9—has reframed gene therapy from gene addition to genome editing, opening avenues for direct correction of pathogenic variants in situ (Porteus, 2019).

This review provides a comprehensive synthesis of contemporary gene therapy, outlining the historical development of the field, mechanisms underlying viral and non-viral vector systems, classifications of gene therapy approaches, clinical applications across disease domains, challenges and safety considerations, and emerging frontiers including base editing, prime editing, and lipid nanoparticle-mediated nucleic acid delivery.

2. HISTORICAL BACKGROUND AND DEVELOPMENT

The intellectual foundations of gene therapy date to the early 1970s, when visionary scientists hypothesized that exogenous DNA might be used to treat inherited disease (Dunbar et al., 2018). The first authorized human gene transfer experiment was performed in 1990 by W. French Anderson and colleagues, who treated a four-year-old patient with adenosine deaminase (ADA)-deficient SCID using retrovirally transduced autologous lymphocytes. Although this trial yielded modest clinical benefit, it established the procedural feasibility of ex vivo gene transfer (Naldini, 2015).

The early 2000s represented a watershed moment for the field. Cavazzana-Calvo and colleagues demonstrated that γ-retroviral gene transfer of the IL2RG gene to autologous $CD34^+$ hematopoietic stem cells restored immunity in children with SCID-X1, providing the first unequivocal evidence of a curative gene therapy in a previously fatal disease (Cavazzana et al., 2019). However, four of the treated patients subsequently developed T-cell acute lymphoblastic leukemia due to vector-mediated activation of the LMO2 proto-oncogene, prompting a critical re-evaluation of vector design (Bushman, 2020). This catalyzed the transition to self-inactivating lentiviral vectors with deleted long terminal repeat enhancers and physiological internal promoters, which exhibit a far more favorable integration profile (Naldini, 2015).

In parallel, AAV vectors emerged as the preferred platform for in vivo gene therapy because of their broad tissue tropism, low immunogenicity relative to adenoviruses, predominantly episomal persistence, and excellent safety profile (Hastie & Samulski, 2015; Wang et al., 2019). The first FDA-approved in vivo gene therapy, voretigene neparvovec (Luxturna), was authorized in December 2017 for biallelic RPE65-mediated inherited retinal dystrophy (Russell et al., 2017). This was followed in 2019 by onasemnogene abeparvovec (Zolgensma) for spinal muscular atrophy (Mendell et al., 2017), in 2022 by etranacogene dezaparvovec (Hemgenix) for hemophilia B (Pipe et al., 2023), and in 2023 by exagamglogene autotemcel (Casgevy)—the first CRISPR-Cas9 gene-edited therapy—for sickle cell disease and transfusion-dependent β-thalassemia (Frangoul et al., 2021).

3. MECHANISMS OF GENE THERAPY: VIRAL AND NON-VIRAL VECTORS

Effective gene therapy requires the delivery of therapeutic nucleic acid payloads—DNA, mRNA, short interfering RNA, antisense oligonucleotides, or ribonucleoprotein editing complexes—into target cells in sufficient quantity, with adequate persistence, and with minimal immunogenicity or genotoxicity. Delivery vehicles fall into two principal categories: viral vectors and non-viral systems (High & Roncarolo, 2019).

3.1 Viral Vectors

Adeno-associated viruses (AAVs) are non-enveloped, single-stranded DNA parvoviruses with a packaging capacity of approximately 4.7 kilobases. Their multiple naturally occurring and engineered serotypes display differential tropism for tissues including liver, retina, central nervous system, skeletal muscle, and cardiac muscle, allowing rational selection for organ-specific gene transfer (Wang et al., 2019). Recombinant AAVs predominantly persist as extrachromosomal episomes, minimizing the risk of insertional mutagenesis, although low-frequency integration events have been documented (Hastie & Samulski, 2015). Six AAV-based gene therapies have received FDA approval to date, underscoring the platform's clinical maturity (Ginn et al., 2024).

Lentiviral vectors, derived predominantly from human immunodeficiency virus type 1, can transduce both dividing and non-dividing cells and stably integrate up to 8–10 kilobases of therapeutic cassette into the host genome. Modern self-inactivating lentiviral vectors preferentially integrate into transcriptionally active regions but exhibit a substantially reduced propensity for activation of nearby proto-oncogenes compared to first-generation γ-retroviral systems (Cavazzana et al., 2019; Naldini, 2015). Lentiviruses are the workhorse for ex vivo modification of hematopoietic stem cells and T lymphocytes, including the manufacture of CAR-T cell products (June & Sadelain, 2018; Sadelain et al., 2017). Adenoviral vectors afford high transduction efficiency and large packaging capacity but elicit potent innate and adaptive immune responses, restricting their use largely to oncolytic and vaccine applications (Dunbar et al., 2018).

3.2 Non-Viral Vectors

Non-viral systems offer reduced immunogenicity, simpler manufacturing, and the capacity to deliver large or repeatedly dosed payloads. Lipid nanoparticles have emerged as the most clinically advanced non-viral platform, exemplified by the success of patisiran for hereditary transthyretin amyloidosis and LNP-formulated mRNA vaccines against SARS-CoV-2 (Hou et al., 2021). LNPs are typically composed of an ionizable cationic lipid, a structural phospholipid, cholesterol, and a polyethylene glycol-conjugated lipid; their physicochemical tunability permits encapsulation of mRNA, siRNA, and CRISPR ribonucleoprotein complexes with high efficiency. Although intravenously administered LNPs predominantly accumulate in the liver, recent advances in selective organ targeting and ligand-conjugated formulations have expanded their reach to extrahepatic tissues including lung, spleen, bone marrow, and tumor microenvironments (Hou et al., 2021). Other non-viral approaches include electroporation, polymeric nanoparticles, virus-like particles, engineered exosomes, and direct injection of naked DNA, each offering a distinct trade-off between delivery efficiency, persistence, and immunogenicity (High & Roncarolo, 2019).

4. TYPES OF GENE THERAPY

4.1 Somatic versus Germline Gene Therapy

Somatic gene therapy modifies non-reproductive cells, restricting any genetic alteration to the treated individual without transmission to offspring. All currently approved gene therapies are somatic.

Germline gene therapy, by contrast, alters the DNA of gametes or embryos, with edits inheritable across generations. Germline modification remains prohibited or strongly discouraged in most jurisdictions because of unresolved safety concerns, the potential for irreversible heritable harm, and unresolved ethical questions about the consent of future generations (Porteus, 2019). The 2018 disclosure by He Jiankui of germline editing of two human embryos was widely condemned by the scientific community and led to a moratorium reaffirmed by the Third International Summit on Human Genome Editing in 2023.

4.2 In Vivo versus Ex Vivo Gene Therapy

In vivo gene therapy delivers the therapeutic agent directly to the patient by intravenous, subretinal, intrathecal, intramuscular, or intratumoral routes. Approved in vivo therapies include voretigene neparvovec (subretinal AAV2), onasemnogene abeparvovec (intravenous AAV9), and etranacogene dezaparvovec (intravenous AAV5) (Pipe et al., 2023; Russell et al., 2017). In vivo approaches simplify clinical logistics but face challenges including pre-existing neutralizing antibodies to AAV capsids, hepatic sequestration, and innate immune activation (Wang et al., 2019). Ex vivo gene therapy involves harvesting target cells, genetically modifying them in culture, and reinfusing them after conditioning. This strategy enables rigorous quality control, dose titration, and reduced systemic exposure to vector. Ex vivo platforms underpin CAR-T cell therapies, lentiviral correction of β-hemoglobinopathies, and CRISPR-Cas9 editing in Casgevy for sickle cell disease and β-thalassemia (Cavazzana et al., 2019; Frangoul et al., 2021).

5. CLINICAL APPLICATIONS

5.1 Cancer

Cancer was the first major indication targeted by gene therapy and remains the largest single category of clinical trials globally (Ginn et al., 2024). The most transformative success has been the development of chimeric antigen receptor T-cell (CAR-T) therapy, in which autologous T lymphocytes are engineered ex vivo with a synthetic receptor combining an antigen-recognition domain with intracellular CD3ζ and costimulatory signaling motifs (Sadelain et al., 2017). Tisagenlecleucel was approved by the FDA in 2017 for relapsed or refractory pediatric and young adult B-cell acute lymphoblastic leukemia, achieving complete remission rates of approximately 81% in pivotal trials (Maude et al., 2018). Additional CD19-directed CAR-T products are now licensed for diffuse large B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma. BCMA-targeting CAR-Ts have demonstrated durable responses in multiple myeloma (June & Sadelain, 2018). Despite these successes, challenges persist with antigen escape, T-cell exhaustion, immune-mediated toxicities, limited efficacy in solid tumors, and the substantial cost and manufacturing complexity of autologous platforms.

5.2 Monogenic Diseases

Monogenic disorders—particularly those affecting hematopoietic, hepatic, retinal, and neuromuscular systems—offer the clearest mechanistic rationale for gene therapy. Hemoglobinopathies have been transformed by both lentiviral gene addition and CRISPR-mediated editing. Betibeglogene autotemcel introduces a modified β-globin gene into autologous hematopoietic stem cells and has eliminated transfusion dependence in most patients with transfusion-dependent β-thalassemia (Cavazzana et al., 2019). Exagamglogene autotemcel employs CRISPR-Cas9 to disrupt the erythroid-specific BCL11A enhancer, derepressing fetal hemoglobin and largely abolishing vaso-occlusive crises in sickle cell disease (Frangoul et al., 2021). Etranacogene dezaparvovec (Hemgenix), an AAV5 vector encoding the high-activity Padua variant of factor IX, produced a 64% reduction in annualized bleeding rate and sustained mean factor IX activity of approximately 37 IU/dL at 18 months in the HOPE-B trial (Pipe et

al., 2023). For SCID, long-term follow-up demonstrates sustained immune reconstitution in the majority of recipients with substantially improved safety relative to first-generation approaches (Cavazzana et al., 2019).

5.3 Neurological and Neuromuscular Disorders

Spinal muscular atrophy type 1, historically the leading genetic cause of infant mortality, has been redefined by onasemnogene abeparvovec (Zolgensma), an AAV9-vectored gene replacement therapy that delivers a functional SMN1 transgene across the blood–brain barrier when administered intravenously. In pivotal and real-world studies, it markedly improved event-free survival, motor milestone achievement, and ventilator independence with benefits maintained for at least five years (Mendell et al., 2017). Delandistrogene moxeparvovec (Elevidys) for Duchenne muscular dystrophy, an AAVrh74 vector delivering a truncated microdystrophin transgene, received expanded FDA approval in 2024. In the central nervous system, AAV-mediated gene delivery has progressed in clinical trials for aromatic L-amino acid decarboxylase deficiency, lysosomal storage disorders, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Porteus, 2019).

5.4 Ophthalmic Diseases

The eye is an attractive target for gene therapy because of its compartmentalization, immune privilege, accessibility, and amenability to non-invasive monitoring. Voretigene neparvovec (Luxturna), an AAV2 vector encoding RPE65 delivered by subretinal injection, was the first directly administered gene therapy approved in the United States. Pivotal trial data demonstrated durable improvements in functional vision in patients with biallelic RPE65 mutations (Russell et al., 2017). Additional programs in clinical development target X-linked retinitis pigmentosa, choroideremia, Stargardt disease, and inherited optic neuropathies, and include CRISPR-Cas9 in vivo editing trials for Leber congenital amaurosis type 10. The subretinal and intravitreal delivery routes, combined with the eye's immunological privilege, facilitate effective gene delivery with limited systemic exposure.

5.5 Cardiovascular Disease

Gene therapy for cardiovascular disease is rapidly expanding. Investigational AAV-based therapies target genetic cardiomyopathies, heart failure, and inherited arrhythmias. A particularly active area involves single-administration in vivo CRISPR base-editing inactivation of PCSK9 delivered by LNPs, which has demonstrated durable reductions in low-density lipoprotein cholesterol in early-phase clinical trials and represents a paradigm shift toward preventive cardiology.

6. CHALLENGES AND SAFETY CONCERNS

6.1 Immunogenicity

Pre-existing humoral immunity to AAV capsids—prevalent in 30–70% of adults depending on serotype—can neutralize systemically administered vector and exclude patients from therapy (Wang et al., 2019). Post-administration anti-capsid $CD8^+$ T-cell responses can eliminate transduced hepatocytes, abolishing transgene expression. Strategies to mitigate immunogenicity include immunosuppressive prophylaxis, capsid engineering to evade neutralizing antibodies, plasmapheresis, and IgG-cleaving endopeptidases. Innate immune sensing of vector components can produce complement activation, thrombotic microangiopathy, and—in the case of high-dose intravenous AAV—severe hepatotoxicity and fatal events in certain clinical contexts (High & Roncarolo, 2019).

6.2 Off-Target Effects

Genome-editing technologies introduce the possibility of unintended modifications at sequences with partial homology to the on-target site. CRISPR-Cas9 nucleases may generate off-target double-strand

breaks yielding insertions, deletions, chromosomal translocations, or structural variants (Porteus, 2019). High-fidelity Cas9 variants, paired nickases, anti-CRISPR proteins, transient delivery as ribonucleoprotein, and unbiased genome-wide detection methods have substantially mitigated but not eliminated this risk. Base editors can produce guide RNA-independent genome-wide deamination, and prime editors, while avoiding double-strand breaks, introduce their own signature of unintended substitutions and indels at the nick site (Anzalone et al., 2019; Komor et al., 2016).

6.3 Insertional Mutagenesis

Integrating retroviral and lentiviral vectors carry an intrinsic risk of insertional mutagenesis. Bushman (2020) summarized four documented mechanisms by which retroviral vector integration can drive clonal expansion in humans: enhancer-mediated activation of proto-oncogenes, aberrant splicing into oncogenes, disruption of tumor-suppressor genes, and stabilization of growth-regulatory transcripts by 3′ truncation. The transition from γ-retroviral to self-inactivating lentiviral vectors with physiological internal promoters has substantially reduced—but not eliminated—this risk. Long-term molecular monitoring is now standard for all integrating gene therapy products (Cavazzana et al., 2019).

6.4 Durability, Manufacturing, and Cost

For non-integrating AAV episomal therapies, gradual loss of transgene expression over years—particularly in dividing tissues—remains a concern, raising questions about the need for redosing in the context of adaptive immunity. Manufacturing of clinical-grade viral vectors at scale is technically demanding, with current cGMP production capacity representing a significant bottleneck. The cost of approved gene therapies—ranging from approximately US$425,000 per eye for Luxturna to US$3.5 million per dose for Hemgenix—has provoked sustained debate about value-based pricing, reimbursement frameworks, and equitable global access (Ginn et al., 2024).

6.5 Ethical Issues

Ethical concerns extend beyond germline editing to encompass informed consent in pediatric populations receiving one-time potentially curative interventions, the management of off-target uncertainty, equitable access across socioeconomic and geographic boundaries, and the moral status of in utero gene therapy. Somatic enhancement applications raise additional concerns about distributive justice and societal coercion, underscoring the need for robust international governance frameworks (Porteus, 2019; Doudna, 2020).

7. RECENT ADVANCES AND FUTURE PERSPECTIVES

7.1 Base Editing and Prime Editing

The advent of programmable RNA-guided nucleases has opened new dimensions in gene therapy. CRISPR-Cas9 and related Cas variants enable site-specific gene knockout, knock-in, and RNA editing (Cox et al., 2017). Base editors, comprising a catalytically impaired Cas9 fused to a deaminase, mediate precise base transitions without inducing double-strand breaks and can theoretically correct approximately 60% of pathogenic point mutations (Gaudelli et al., 2017; Komor et al., 2016). Prime editing, introduced by Anzalone et al. (2019), employs a Cas9 nickase fused to an engineered reverse transcriptase together with a prime-editing guide RNA that templates the desired edit at the target site. Prime editing supports all 12 base-to-base conversions, small insertions, and deletions, and could in principle correct up to 89% of known pathogenic variants. Clinical trials of base editors and prime editors for PCSK9 inactivation and chronic granulomatous disease are already underway.

7.2 In Vivo CAR-T Engineering and Next-Generation Platforms

Conventional autologous CAR-T manufacturing is logistically and economically constrained. In vivo CAR-T engineering—delivery of CAR-encoding mRNA via T-cell-targeted LNPs—obviates the need for ex vivo manipulation, reduces cost, and permits transient dose-tunable expression. Early proof-of-concept studies in cardiac fibrosis and autoimmune disease models suggest broad therapeutic potential extending beyond oncology (Hou et al., 2021). Capsid engineering through directed evolution, machine learning, and rational design is yielding AAV variants with enhanced tissue tropism, reduced seroprevalence, and detargeting from off-target organs (Wang et al., 2019). CRISPR-mediated multiplex editing of T-cell receptor and HLA loci is enabling allogeneic "off-the-shelf" CAR-T products that circumvent the manufacturing limitations of autologous platforms.

7.3 Equitable Access

Despite spectacular scientific progress, gene therapies remain inaccessible to the majority of patients globally, including those in low- and middle-income countries where the burden of monogenic disease is greatest. Innovative financing mechanisms, public–private partnerships, technology transfer agreements, and point-of-care manufacturing are essential to bridge this gap (Ginn et al., 2024). Developing regulatory pathways adapted to resource-limited settings, alongside price negotiation frameworks tied to clinical outcomes, will be critical to ensuring that the curative potential of gene therapy is realized equitably across populations.

8. CONCLUSION

Gene therapy has transitioned from aspiration to clinical reality, offering potentially curative interventions for an expanding catalogue of previously intractable diseases. The convergence of refined viral vectors—particularly AAV and self-inactivating lentivirus—with non-viral lipid nanoparticle platforms and programmable genome-editing tools has produced a therapeutic toolkit of unprecedented versatility. Approved products such as Luxturna, Zolgensma, Hemgenix, Casgevy, and the CAR-T cell therapies have validated the paradigm and reshaped clinical expectations across hematology, neurology, ophthalmology, and oncology. Persistent challenges—immunogenicity, off-target editing, insertional mutagenesis, durability, manufacturing scalability, cost, and ethical governance—must be addressed through continued multidisciplinary research and thoughtful policy. As base editing, prime editing, in vivo CAR-T engineering, and next-generation delivery systems mature, gene therapy is positioned to evolve from a treatment of last resort for rare monogenic disorders into a mainstream modality applicable to common cardiovascular, neurodegenerative, and metabolic diseases. Realizing this potential will require not only scientific innovation but also equitable global access, robust long-term safety surveillance, and sustained public engagement to maintain the social license that has been so painstakingly earned.

DECLARATIONS

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REFERENCES

Anzalone, A. V., Randolph, P. B., Davis, J. R., Sousa, A. A., Koblan, L. W., Levy, J. M., Chen, P. J., Wilson, C., Newby, G. A., Raguram, A., & Liu, D. R. (2019). Search-and-replace genome editing without double-strand breaks or donor DNA. *Nature*, 576(7785), 149–157. https://doi.org/10.1038/s41586-019-1711-4

Bushman, F. D. (2020). Retroviral insertional mutagenesis in humans: Evidence for four genetic mechanisms promoting expansion of cell clones. *Molecular Therapy*, 28(2), 352–356. https://doi.org/10.1016/j.ymthe.2019.12.009

Cavazzana, M., Bushman, F. D., Miccio, A., André-Schmutz, I., & Six, E. (2019). Gene therapy targeting haematopoietic stem cells for inherited diseases: Progress and challenges. *Nature Reviews Drug Discovery*, 18(6), 447–462. https://doi.org/10.1038/s41573-019-0020-9

Cox, D. B. T., Gootenberg, J. S., Abudayyeh, O. O., Franklin, B., Kellner, M. J., Joung, J., & Zhang, F. (2017). RNA editing with CRISPR-Cas13. *Science*, 358(6366), 1019–1027. https://doi.org/10.1126/science.aaq0180

Doudna, J. A. (2020). The promise and challenge of therapeutic genome editing. *Nature*, 578(7794), 229–236. https://doi.org/10.1038/s41586-020-1978-5

Dunbar, C. E., High, K. A., Joung, J. K., Kohn, D. B., Ozawa, K., & Sadelain, M. (2018). Gene therapy comes of age. *Science*, 359(6372), eaan4672. https://doi.org/10.1126/science.aan4672

Frangoul, H., Altshuler, D., Cappellini, M. D., Chen, Y.-S., Domm, J., Eustace, B. K., Foell, J., de la Fuente, J., Grupp, S., Handgretinger, R., Ho, T. W., Kattamis, A., Kernytsky, A., Lekstrom-Himes, J., Li, A. M., Locatelli, F., Mapara, M. Y., de Montalembert, M., Rondelli, D., … Corbacioglu, S. (2021). CRISPR-Cas9 gene editing for sickle cell disease and β-thalassemia. *New England Journal of Medicine*, 384(3), 252–260. https://doi.org/10.1056/NEJMoa2031054

Gaudelli, N. M., Komor, A. C., Rees, H. A., Packer, M. S., Badran, A. H., Bryson, D. I., & Liu, D. R. (2017). Programmable base editing of A•T to G•C in genomic DNA without DNA cleavage. *Nature*, 551(7681), 464–471. https://doi.org/10.1038/nature24644

Ginn, S. L., Mandwie, M., Alexander, I. E., Edelstein, M., & Abedi, M. R. (2024). Gene therapy clinical trials worldwide to 2023—an update. *The Journal of Gene Medicine*, 26(8), e3721. https://doi.org/10.1002/jgm.3721

Hastie, E., & Samulski, R. J. (2015). Adeno-associated virus at 50: A golden anniversary of discovery, research, and gene therapy success. *Human Gene Therapy*, 26(5), 257–265. https://doi.org/10.1089/hum.2015.025

High, K. A., & Roncarolo, M. G. (2019). Gene therapy. *New England Journal of Medicine*, 381(5), 455–464. https://doi.org/10.1056/NEJMra1706910

Hou, X., Zaks, T., Langer, R., & Dong, Y. (2021). Lipid nanoparticles for mRNA delivery. *Nature Reviews Materials*, 6(12), 1078–1094. https://doi.org/10.1038/s41578-021-00358-0

June, C. H., & Sadelain, M. (2018). Chimeric antigen receptor therapy. *New England Journal of Medicine*, 379(1), 64–73. https://doi.org/10.1056/NEJMra1706169

Komor, A. C., Kim, Y. B., Packer, M. S., Zuris, J. A., & Liu, D. R. (2016). Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. *Nature*, 533(7603), 420–424. https://doi.org/10.1038/nature17946

Maude, S. L., Laetsch, T. W., Buechner, J., Rives, S., Boyer, M., Bittencourt, H., Bader, P., Verneris, M. R., Stefanski, H. E., Myers, G. D., Qayed, M., De Moerloose, B., Hiramatsu, H., Schlis, K., Davis, K. L., Martin, P. L., Nemecek, E. R., Yanik, G. A., Peters, C., … Grupp, S. A. (2018). Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *New England Journal of Medicine*, 378(5), 439–448. https://doi.org/10.1056/NEJMoa1709866

Mendell, J. R., Al-Zaidy, S., Shell, R., Arnold, W. D., Rodino-Klapac, L. R., Prior, T. W., Lowes, L., Alfano, L., Berry, K., Church, K., Kissel, J. T., Nagendran, S., L'Italien, J., Sproule, D. M., Wells, C., Cardenas, J. A., Heitzer, M. D., Kaspar, A., Corcoran, S., … Kaspar, B. K. (2017). Single-dose gene-replacement therapy for spinal muscular atrophy. *New England Journal of Medicine*, 377(18), 1713–1722. https://doi.org/10.1056/NEJMoa1706198

Naldini, L. (2015). Gene therapy returns to centre stage. *Nature*, 526(7573), 351–360. https://doi.org/10.1038/nature15818

Pipe, S. W., Leebeek, F. W. G., Recht, M., Key, N. S., Castaman, G., Miesbach, W., Lattimore, S., Peerlinck, K., Van der Valk, P., Coppens, M., Kampmann, P., Meijer, K., O'Connell, N., Pasi, K. J., Hart, D. P., Kazmi, R., Astermark, J., Hermans, C. R. J. R., Klamroth, R., … Monahan, P. E. (2023). Gene therapy with etranacogene dezaparvovec for hemophilia B. *New England Journal of Medicine*, 388(8), 706–718. https://doi.org/10.1056/NEJMoa2211644

Porteus, M. H. (2019). A new class of medicines through DNA editing. *New England Journal of Medicine*, 380(10), 947–959. https://doi.org/10.1056/NEJMra1800729

Russell, S., Bennett, J., Wellman, J. A., Chung, D. C., Yu, Z.-F., Tillman, A., Wittes, J., Pappas, J., Elci, O., McCague, S., Cross, D., Marshall, K. A., Walshire, J., Kehoe, T. L., Reichert, H., Davis, M., Raffini, L., George, L. A., Hudson, F. P., … Maguire, A. M. (2017). Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: A randomised, controlled, open-label, phase 3 trial. *The Lancet*, 390(10097), 849–860. https://doi.org/10.1016/S0140-6736(17)31868-8

Sadelain, M., Rivière, I., & Riddell, S. (2017). Therapeutic T cell engineering. *Nature*, 545(7655), 423–431. https://doi.org/10.1038/nature22395

Wang, D., Tai, P. W. L., & Gao, G. (2019). Adeno-associated virus vector as a platform for gene therapy delivery. *Nature Reviews Drug Discovery*, 18(5), 358–378. https://doi.org/10.1038/s41573-019-0012-9

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