ClinSphere Journals
International Peer-Reviewed Open Access Journal
Advancing Healthcare, Clinical Research & Innovation
DOI: 10.5281/zenodo.23806863

Review Article

Cell and Gene Therapies: Emerging Pharmacotherapeutic Strategies for Rare Diseases

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Acknowledgments: None.

ABSTRACT

Rare diseases are individually uncommon but collectively impose substantial clinical, social and economic burdens. Many are monogenic disorders in which a pathogenic variant disrupts a protein, enzyme, structural component or regulatory pathway. Cell and gene therapies (CGTs) offer the possibility of addressing disease mechanisms more directly than conventional symptom-directed pharmacotherapy. Therapeutic strategies include in vivo gene addition using viral or non-viral vectors; ex vivo genetic modification of autologous haematopoietic stem and progenitor cells; genome editing; and cell replacement or engineered-cell approaches. Clinical translation has progressed from proof-of-concept studies to authorised products for selected disorders, including spinal muscular atrophy, inherited retinal dystrophy, haemophilia B, metachromatic leukodystrophy, sickle cell disease and transfusion-dependent β-thalassaemia in certain jurisdictions. However, the evidence, eligibility criteria, durability and benefit-risk profile differ by product and disease. Important constraints include immune responses, off-target or insertional effects, conditioning toxicity, manufacturing complexity, limited long-term data, high costs and unequal access. This narrative review summarises the biological rationale, platforms, representative clinical evidence, clinical implementation, safety, regulatory considerations and emerging directions in rare-disease CGTs, with attention to the Indian context. It emphasises multidisciplinary care, transparent communication and long-term pharmacovigilance.

Keywords: rare diseases; gene therapy; cell therapy; genome editing; CRISPR-Cas9; haematopoietic stem cells; adeno-associated virus; pharmacovigilance; precision medicine.

1. Introduction

Rare diseases comprise a heterogeneous group of conditions, many of which are genetic, progressive, life-limiting or associated with substantial disability. Although prevalence thresholds differ across jurisdictions, the cumulative population affected is large. Conventional treatment may manage symptoms or slow progression without correcting the underlying molecular defect. Advances in genomic sequencing, vector engineering, cell processing and genome editing have enabled therapies designed to restore gene function, modify disease-associated pathways or replace dysfunctional cells.

CGTs are not a single pharmacological class. They are complex biological products whose active components may be nucleic acids, genetically modified cells, unmodified cells, or engineered tissues. Their clinical effect may be transient or durable, local or systemic, and dependent on cell division, tissue tropism, immune status and developmental timing. The term 'potentially disease-modifying' is therefore more appropriate than assuming that every CGT is curative.[1,2]

2. Methodology / Literature Search Strategy

A narrative literature review was developed using targeted searches of PubMed/MEDLINE-indexed literature, major peer-reviewed journals, clinical-trial publications, regulatory product information and government guidance. Search concepts included 'rare disease', 'gene therapy', 'cell therapy', 'AAV', 'lentiviral', 'haematopoietic stem cell gene therapy', 'CRISPR', 'genome editing', 'long-term follow-up', 'safety' and 'India regulation'. Priority was given to pivotal clinical trials, systematic or state-of-the-art reviews, and primary regulatory sources. The evidence was synthesised thematically across therapeutic platforms, clinical applications, safety and implementation.

This is a narrative review, not a systematic review. No protocol registration, exhaustive duplicate screening, formal risk-of-bias assessment or meta-analysis was undertaken. Product authorisations and labels change over time and are jurisdiction-specific; the examples below should be checked against current local regulatory information before clinical use or manuscript submission.

3. Background

Monogenic disorders can arise from loss-of-function, gain-of-function, dominant-negative or regulatory variants. The optimal intervention depends on the disease mechanism. Gene addition may be appropriate when supplying a functional copy can compensate for a deficient gene. Gene silencing or editing may be needed for toxic gain-of-function variants. Ex

vivo correction can be useful when a patient's cells can be harvested, modified and returned. Cell replacement may be considered when the relevant tissue can be repopulated or supported by transplanted cells.

The therapeutic window is often narrow. Early intervention may prevent irreversible neuronal, retinal, muscular or organ damage, but presymptomatic treatment requires reliable newborn or family-based diagnosis and careful assessment of genotype and phenotype. Genetic confirmation, variant interpretation, functional testing and counselling are foundational to patient selection.

4. Current Evidence

4.1 In vivo gene addition

In vivo gene therapy administers a vector directly to the patient to deliver a functional genetic sequence to target cells. Recombinant adeno-associated virus (AAV) vectors are widely used because selected serotypes can transduce particular tissues and generally persist episomally in many post-mitotic cells. Onasemnogene abeparvovec delivers an SMN1 transgene for spinal muscular atrophy; voretigene neparvovec delivers RPE65 to retinal cells in biallelic RPE65-associated retinal dystrophy; and etranacogene dezaparvovec delivers a functional factor IX sequence for haemophilia B.[3–5]

AAV-based approaches face constraints including pre-existing neutralising antibodies, capsid-directed immune responses, limited ability to redose, payload capacity, variable tissue distribution and potential liver toxicity. Non-viral delivery systems, including lipid nanoparticles, are being explored to improve tissue targeting and repeat dosing, although delivery to many extrahepatic tissues remains challenging.

4.2 Ex vivo gene-modified haematopoietic stem-cell therapy

In ex vivo approaches, autologous CD34-positive haematopoietic stem and progenitor cells are collected, genetically modified outside the body, characterised and reinfused after a conditioning regimen. Lentiviral gene addition has been used in selected disorders such as metachromatic leukodystrophy, cerebral adrenoleukodystrophy and haemoglobinopathies. Atidarsagene autotemcel (Libmeldy/Lenmeldy) is an example for eligible presymptomatic or early symptomatic metachromatic leukodystrophy in authorised markets. Long-term outcomes in early-onset disease support the importance of treatment before advanced neurological injury.[6]

The approach requires mobilisation or marrow collection, specialised manufacturing, product release testing and often myeloablative busulfan conditioning. Conditioning-associated cytopenias, infection, infertility and organ toxicity are clinically important. Autologous products reduce graft-versus-host disease risk but do not eliminate manufacturing failure, clonal expansion or insertional genotoxicity concerns.

4.3 Genome editing

Genome editing aims to modify DNA at a defined genomic locus. CRISPR-Cas systems use guide RNA to direct a nuclease to a target sequence; repair outcomes may disrupt a regulatory element, correct a variant or insert a sequence. Exagamglogene autotemcel (exa-cel; Casgevy) edits the erythroid-specific enhancer of BCL11A in autologous CD34-positive cells, increasing fetal haemoglobin. In a phase 3 study of transfusion-dependent β-thalassaemia, 32 of 35 evaluable patients (91%) achieved transfusion independence for at least 12 consecutive months at the reported interim analysis.[7] In severe sickle cell disease, the pivotal study reported freedom from severe vaso-occlusive crises for at least 12 consecutive months in most evaluable patients.[8]

These results are clinically important but must be interpreted with the study design, follow-up duration and conditioning burden in mind. Potential editing-related risks include off-target changes, large deletions, chromosomal rearrangements, mosaic editing and clonal selection. Long-term surveillance remains essential.

4.4 Cell replacement and engineered-cell approaches

Cell therapies may replace damaged cells, provide a missing biological function or deliver a therapeutic molecule. Haematopoietic stem-cell transplantation is established for selected inherited immunodeficiencies and metabolic disorders, while engineered immune-cell therapies are more established in oncology than in most inherited rare diseases. Encapsulated or locally delivered genetically modified cells may provide sustained local protein production. For rare diseases, the key questions include cell persistence, functional integration, immune compatibility, product consistency and whether the intended biological function is maintained over time.

4.5 Selected clinical examples

Therapy / platform	Disease area	Therapeutic principle	Evidence / practical note
Onasemnogene abeparvovec; in vivo AAV	5q spinal muscular atrophy	SMN1 gene replacement	Single-dose IV gene transfer; benefit is time-sensitive and eligibility/label-specific.[3]
Voretigene neparvovec; subretinal AAV	RPE65-associated inherited retinal dystrophy	RPE65 gene delivery to viable retinal cells	Phase 3 randomised trial demonstrated improved functional vision-related mobility outcomes.[4]
Etranacogene dezaparvovec; AAV5	Haemophilia B	Hepatocyte-directed factor IX expression	Phase 3 evidence supports sustained factor IX activity in many participants; monitor liver enzymes and factor levels.[5]

Atidarsagene autotemcel; lentiviral HSC	Metachromatic leukodystrophy	ARSA gene addition to autologous HSCs	Early treatment is critical; long-term non-randomised data support disease modification in selected early disease.[6]
Exagamglogene autotemcel; CRISPR-edited HSC	Sickle cell disease / β-thalassaemia	BCL11A enhancer editing to raise fetal haemoglobin	High response rates reported in pivotal studies; requires myeloablative conditioning and specialist transplant care.[7,8]

5. Clinical Applications

Clinical application begins with molecular diagnosis and assessment of whether the causal variant and disease mechanism match the product's mechanism of action. Eligibility may depend on age, genotype, disease stage, organ function, neutralising antibodies, prior therapies and ability to tolerate conditioning or surgery. A multidisciplinary team should assess expected benefit against irreversible disease burden, treatment risks and available alternatives.

Treatment pathways differ. Systemic AAV infusion may require pre-treatment assessment, immunomodulation and frequent liver, platelet and cardiac monitoring. Ocular gene therapy requires specialised vitreoretinal surgery and postoperative surveillance. Ex vivo HSC products require collection, bridging care, conditioning, infusion and prolonged haematological monitoring. Genome-edited HSC therapy additionally requires counselling on fertility preservation, transfusion support, infection prevention and long-term malignancy surveillance.

6. Safety & Limitations

Safety is platform- and product-specific. AAV products can cause transaminase elevations, immune-mediated hepatotoxicity, thrombocytopenia, complement activation and, rarely, severe systemic complications. Pre-existing antibodies may exclude patients, and redosing can be difficult. Lentiviral integration is intended to be stable but creates a theoretical and observed risk of insertional oncogenesis or clonal dominance; product-specific long-term follow-up is therefore required. Genome editing introduces additional uncertainties related to off-target activity and structural genomic changes.

Ex vivo therapies may cause complications from conditioning, including severe cytopenias, mucositis, infection, infertility and organ toxicity. Surgical delivery can cause procedure-related injury. Cell products can vary in potency, viability, identity and purity. Small rare-disease populations, single-arm trials, surrogate endpoints, short follow-up and heterogeneous natural history complicate efficacy assessment. A single-dose intervention should not be assumed to have lifelong benefit.

7. Emerging Advances

Emerging directions include base editing and prime editing, which may alter DNA without conventional double-strand breaks; RNA editing and antisense approaches; tissue-targeted non-viral delivery; improved AAV capsids; in vivo editing; allogeneic and induced-pluripotent-stem-cell-derived products; and personalised, mutation-specific therapies. Better natural-history cohorts, newborn screening, patient-derived organoids and computational variant interpretation may improve target validation and trial design. These approaches remain at different stages of preclinical and clinical development and should not be conflated with authorised therapies.

8. Pharmacist's Role

Pharmacists contribute across the CGT lifecycle. Before treatment, they can reconcile medicines, assess interactions, verify eligibility-related medication restrictions, support vaccination and infection-prevention planning, and counsel patients about realistic expectations. During preparation and administration, they can oversee cold-chain integrity, chain of identity and custody, handling requirements, dose verification, premedication and management of infusion or immune-mediated reactions.

After treatment, pharmacists support adherence to immunosuppressive or prophylactic medicines when prescribed, monitor laboratory parameters and adverse events, identify interactions, reinforce reproductive and vaccination advice, and coordinate long-term follow-up. They also contribute to pharmacovigilance by documenting product identifiers, lot numbers, traceability information, suspected adverse reactions and outcomes. Clear communication is essential because CGTs are often administered once but require prolonged surveillance.

9. Research Gaps

Priority gaps include durability beyond the current follow-up periods; genotype- and age-specific response prediction; management of pre-existing and treatment-induced immunity; safe redosing; off-target and insertional risk quantification; optimal conditioning with less gonadotoxicity; scalable manufacturing; validated potency assays; and meaningful patient-reported outcomes. Evidence is particularly limited for ultra-rare disorders, older patients, advanced disease, diverse ancestries and health systems with constrained specialist infrastructure.

10. Future Perspectives

Future progress will depend on matching the modality to disease biology rather than applying a single platform broadly. More accessible genomic diagnosis, interoperable registries, adaptive trial designs and harmonised long-term follow-up can strengthen evidence generation.

Manufacturing innovation and regional production may reduce delays and costs, but quality systems must remain rigorous. Innovative payment models may help address upfront costs, yet reimbursement should be linked to transparent evidence, measurable outcomes and sustained patient support.

11. Indian Regulatory and Access Considerations

In India, development and clinical use of cell- and gene-based products must be considered within the applicable framework for new drugs, clinical trials and biological products, together with national stem-cell research guidance and institutional ethics oversight. The New Drugs and Clinical Trials Rules, 2019 and subsequent amendments provide the broader regulatory framework for clinical research and new drugs. ICMR lists the National Guidelines for Stem Cell Research (2017), National Guidelines for Haematopoietic Cell Transplantation (2021) and other relevant guidance.[9,10] The precise classification, permissions and requirements depend on the product and proposed use; investigators and sponsors should obtain current advice from CDSCO, ICMR/DBT and the relevant ethics and biosafety committees.

Access barriers include limited genetic testing, specialist centres, manufacturing infrastructure, affordability, travel burden and the absence of mature long-term registries for many products. India's National Policy for Rare Diseases (2021) provides a policy context for rare-disease care, but it does not itself establish universal access to every internationally authorised CGT. Availability, approval and reimbursement should be verified individually; foreign approval does not equal Indian marketing authorisation.

12. Conclusion

Cell and gene therapies are reshaping the pharmacotherapeutic landscape for selected rare diseases by enabling gene replacement, ex vivo cell modification, genome editing and cellular restoration. Clinical evidence is strongest for a limited number of genetically defined conditions and demonstrates meaningful disease modification in appropriately selected patients. These benefits must be balanced against platform-specific toxicities, conditioning burden, uncertain durability, manufacturing complexity, cost and unequal access. Molecular diagnosis, specialist multidisciplinary care, transparent consent, rigorous product traceability and long-term pharmacovigilance are essential. Pharmacists have an important role in safe handling, medication management, patient education and post-treatment monitoring.

13. Declarations

Funding: [To be completed by the authors; state 'No external funding' only if accurate].

Conflicts of interest: [To be completed by all authors].

Ethics approval: Not applicable for a narrative review that does not involve new human-participant research; confirm journal requirements.

Informed consent: Not applicable.

Data availability: No new datasets were generated or analysed.

Author contributions: [Insert CRediT contribution statement for each author].

Acknowledgements: [Optional; obtain permission where required].

AI-use disclosure: If AI-assisted tools were used for drafting, language editing or figure preparation, disclose the tool and the nature of assistance in accordance with the target journal's policy. Authors remain responsible for source verification, accuracy and final content.

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14. Tables & Figures

Table 1. Representative cell and gene therapy platforms and clinical examples.

Platform	Key risks / limitations	Monitoring priorities
AAV in vivo gene addition	Pre-existing antibodies, immune-mediated hepatotoxicity, thrombocytopenia, complement activation, limited redosing	Liver enzymes, platelets, clinical status, vector-specific label monitoring
Lentiviral ex vivo HSC modification	Conditioning toxicity, insertional genotoxicity, clonal expansion, infertility, infection	Blood counts, engraftment, clonal surveillance where indicated, long-term malignancy follow-up
CRISPR genome editing	Off-target edits, structural variants, clonal selection; conditioning-related harms	Engraftment, cytopenias, malignancy surveillance, long-term genomic safety follow-up
Cell replacement / engineered cells	Immune rejection, graft-versus-host disease (depending on product), variable persistence and potency	Cell function, immune complications, product-specific biomarkers and long-term follow-up

Figure 1. Conceptual translational pathway for cell and gene therapies in rare diseases.

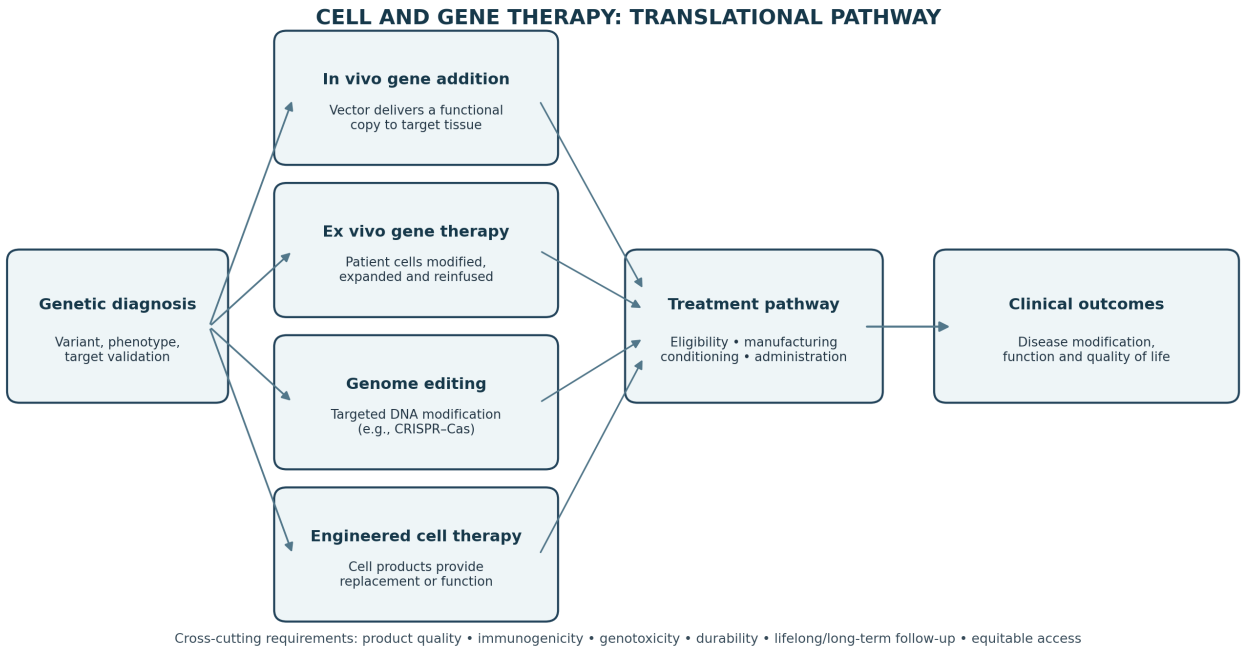


Figure note: This is an original conceptual illustration. It is not a validated clinical algorithm and does not replace product-specific prescribing information.

Table 2. Practical pharmacist-led checkpoints across the CGT pathway.

Stage	Pharmacist contribution
Pre-treatment	Medication reconciliation; review contraindications/interactions; support vaccination, infection prevention and patient counselling
Product receipt	Verify patient/product identity, chain of identity and custody, lot/batch details, storage conditions and expiry
Preparation and administration	Confirm handling and thawing instructions, dose, premedication, administration route and emergency readiness
Post-treatment	Support prophylaxis and concomitant medicines; monitor laboratory tests and adverse reactions; counsel on follow-up
Long-term surveillance	Maintain traceability, document outcomes and suspected adverse events, support registry participation and pharmacovigilance