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OncoVantage

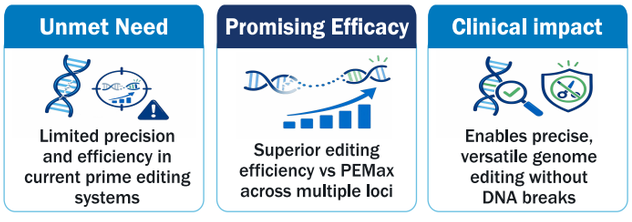
Insights into global breakthroughs in cell-based therapies

NEXT GENERATION GENOME EDITING | CRISPR-CAS12A SCD TRIAL | LAD-I GENE THERAPY APPROVAL | CML BIOMARKER (BCL-XL)

Chimeric Oligonucleotide-Directed Editing Enhances Precision Genome Engineering

This study presents **Chimeric Oligonucleotide-Directed Editing (CODE),** a next-generation genome editing platform designed to enhance the efficiency and precision of prime editing. CODE employs **engineered nCas9–DNA polymerase fusion proteins with a chimeric pegRNA (cpegRNA)** to enable programmable "search-and-replace" editing without inducing double-stranded DNA breaks. It incorporates a modified Bst DNA polymerase with improved thermostability and processivity, while the advanced CODEMax (exo+) variant adds 5′–3′ exonuclease activity to enhance strand invasion and repair, improving edit incorporation.

Pre-clinically, CODE outperformed PEMax across multiple loci in HEK293T cells, enabling efficient insertions, deletions, and substitutions via plasmid and RNP delivery. CODEMax further demonstrated precise editing in mouse and bovine embryos, achieving efficiencies up to 9.3%, highlighting its potential as a safer, high-precision genome engineering platform.



Clinical Implications

- Enables **precise genome editing without generating double-stranded DNA breaks,** potentially improving safety profile.
- Demonstrates **enhanced editing efficiency over existing PEMax prime editing systems.**
- Supports versatile editing applications including insertions, deletions, and substitutions.
- May improve feasibility of genome engineering in challenging systems such as embryos and primary cells.

Why It Matters

- Advances the field of next-generation precision genome editing beyond conventional CRISPR approaches.
- Addresses limitations of current prime editing technologies related to editing efficiency and repair outcomes.
- Expands translational potential for therapeutic gene correction and regenerative medicine applications.
- Strengthens the genome editing toolbox for applications requiring high-fidelity editing without genomic disruption.

Reference: Nguyen, L.T *et al.,* Nat Commun (2026).

CRISPR-Cas12a Gene Editing of HBG1 and HBG2 Promoters to Treat Sickle Cell Disease- A phase I/II clinical trial

The Phase I/II study evaluated renizgamglogene autogedtemcel (reni-cel), a CRISPR-Cas12a-edited autologous hematopoietic stem cell therapy for severe sickle cell disease (SCD). The approach disrupts BCL11A binding sites in HBG1/HBG2 promoters to reactivate fetal hemoglobin (HbF) production. Preclinical studies confirmed effective HbF restoration via targeted genome editing.

In an ongoing multicenter trial, 28 patients received a single infusion following busulfan conditioning, achieving neutrophil and platelet engraftment at 23 and 25 days. At 6 months, total hemoglobin increased to 13.8 g/dL and HbF to 48.1%. Notably, 27/28 patients remained free of vaso-occlusive events, indicating durable clinical benefit with manageable safety. **These findings support reni-cel as a promising gene-editing therapeutic approach with the potential to provide durable disease modification in patients with severe sickle cell disease.**

Clinical Implications

- Demonstrates effective reactivation of HbF through targeted CRISPR-mediated genome editing.
- Shows potential for durable disease modification with marked reduction in vaso-occlusive crises.
- Supports feasibility of CRISPR-Cas12a platform as an alternative to CRISPR-Cas9-based editing strategies.
- Highlights promise of autologous gene-edited stem cell therapies in hereditary hematologic disorders.

Why It Matters

- Enables functional cure potential via sustained HbF reactivation.
- Validates CRISPR-Cas12a for precise clinical genome editing.
- Achieves significant reduction in vaso-occlusive events.
- Expands genome editing toolbox beyond Cas9.

Reference: Hanna R., *et., al.,* N Engl J Med 2026 (NCT04853576)

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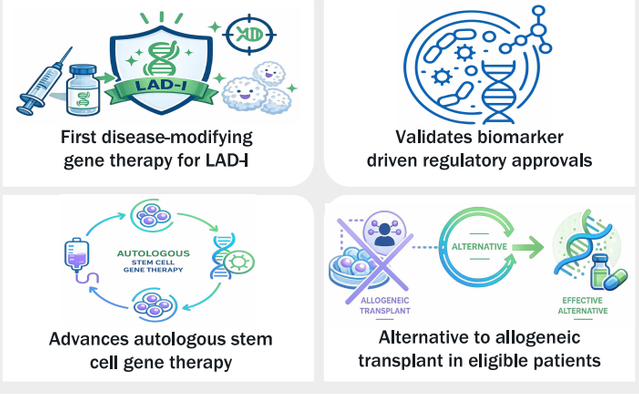
FDA Approves First Gene Therapy for Severe Leukocyte Adhesion Deficiency Type I (LAD-I)

The U.S. FDA has granted accelerated approval to Kresladi (marnetegragene autotemcel), the first gene therapy for pediatric patients with severe Leukocyte Adhesion Deficiency Type I (LAD-I) lacking an HLA-matched sibling donor for stem cell transplantation. The therapy uses autologous hematopoietic stem cells genetically modified to deliver functional ITGB2 copies, restoring CD18/CD11a expression and improving immune cell function. Approval was supported by an open-label multicenter study demonstrating sustained biomarker correction up to 24 months post-infusion, with manageable safety. Confirmatory post-marketing studies are ongoing.

First FDA-approved gene therapy for LAD-I.



Clinical Implications

- **First Disease-Modifying Therapy for LAD-I:** Targets the genetic root cause rather than managing infections symptomatically.
- **Alternative to Allogeneic Transplant:** Provides a treatment option for patients lacking suitable HLA-matched donors and reduces transplant-related risks.
- **Validation of Biomarker-Driven Approvals:** Use of CD18/CD11a restoration as surrogate endpoints highlights regulatory acceptance of mechanistic biomarkers in ultra-rare diseases.
- **Advancement of Autologous HSC Gene Therapy:** Strengthens clinical feasibility of *ex vivo* gene-corrected stem cell approaches for inherited immune disorders.

Why It Matters

- **Major Milestone for Rare Pediatric Gene Therapy:** Represents the first approved gene therapy for LAD-I, addressing a life-threatening unmet medical need.
- **Expands Accelerated Approval Pathways:** Demonstrates regulatory flexibility enabling faster access to therapies for small patient populations.
- **Proof of Curative Potential in Genetic Immunodeficiencies:** Supports gene therapy as a one-time corrective treatment rather than lifelong supportive care.
- **Momentum for Next-Generation Cell & Gene Therapies:** Reinforces growing clinical translation of autologous gene-modified stem cell platforms across rare diseases.

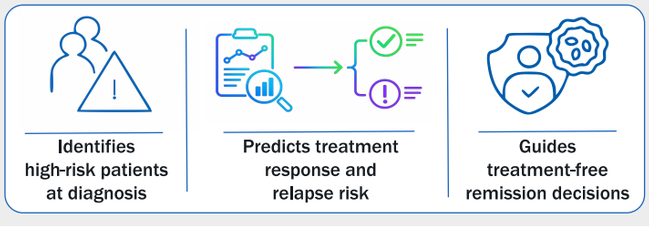
Reference: FDA News Release, March 26, 2026

A Novel CIP2A and BCL-XL Clinical Diagnostic Toolkit to Predict Disease Progression and Treatment-Free Remission in Chronic Myeloid Leukaemia

BCL-XL is being explored as a predictive biomarker for disease progression and treatment-free remission (TFR) outcomes in chronic myeloid leukemia (CML). In the SPIRIT-2 trial, elevated BCL-XL expression at diagnosis was associated with treatment failure, suboptimal early molecular response, and lower rates of achieving MR2/MR3 in patients treated with imatinib.

In the **DESTINY trial,** patients who experienced molecular relapse during treatment de-escalation showed significantly higher BCL-XL levels, detectable 6–8 months prior to relapse. These findings highlight its value as an early predictor of TFR failure and support combining BCL-XL with CIP2A for improved risk stratification in CML.

BCL-XL as a Predictive Biomarker in CML



Clinical Implications

- May enable early identification of CML patients at high risk of treatment failure or disease progression.
- Supports prediction of likelihood of sustained treatment-free remission following TKI discontinuation.
- Provides potential for earlier intervention prior to molecular relapse through dynamic biomarker monitoring.
- Facilitates improved patient stratification and personalized treatment planning in CML management.

Why It Matters

- Addresses a major unmet need for predictive biomarkers in CML treatment optimization.
- Could improve patient selection for safe treatment discontinuation strategies.
- Enhances precision medicine approaches in hematologic malignancies through risk-adapted therapy guidance.
- May reduce relapse risk and unnecessary prolonged therapy exposure in suitable patients.

Reference: Basabrain, A.A *et.al.*, Int. J. Mol. Sci. 2026