GENE THERAPY FOR X-LINKED DYSKERATOSIS CONGENITA

A research team from CIEMAT, Fundación Jiménez Díaz and CIBER has developed a novel *ex vivo* gene therapy approach for X-linked dyskeratosis congenita caused by pathogenic *DKC1* variants.

The Need

Dyskeratosis congenita (DC) is a rare inherited telomere biology disorder characterized by critically short telomeres, progressive bone marrow failure, pulmonary and liver complications, and increased cancer susceptibility. X-linked dyskeratosis congenita (X-DC), caused by pathogenic variants in the *DKC1* gene, accounts for up to 25% of DC cases.

Current therapeutic options for DC, and particularly for X-DC, remain limited. Allogeneic hematopoietic stem cell transplantation may restore hematopoiesis in selected patients, but it does not correct the underlying molecular defect or prevent the progression of non-hematological complications.

There is currently no approved gene therapy that directly addresses *DKC1* deficiency in patients with X-DC. Therefore, there is a clear unmet need for a therapeutic strategy capable of restoring dyskerin function and correcting the telomeric and extratelomeric defects associated with the disease.

The Solution

The present invention provides a novel *ex vivo* gene therapy approach for the potential treatment of X-linked dyskeratosis congenita caused by pathogenic DKC1 variants.

The technology is based on the *ex vivo* transduction of autologous hematopoietic stem and progenitor cells with a third-generation lentiviral vector designed to achieve controlled expression of a functional *DKC1* gene. By using autologous cells, this strategy may reduce the risk of immune incompatibility and other complications associated with allogeneic transplantation.

Preclinical studies have demonstrated correction of telomeric and extratelomeric defects, improved progenitor-cell function, and maintenance of gene-modified human cells in vivo, supporting the further development of this approach toward clinical translation.

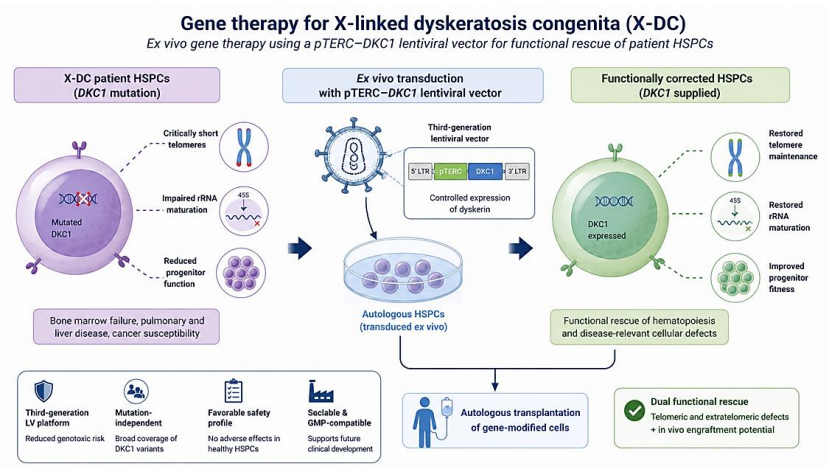
Innovative Aspects

- **Use of *TERC* regulatory elements** to achieve **controlled DKC1 expression** in hematopoietic stem and progenitor cells.
- A **third-generation lentiviral vector** designed to restore dyskerin function while **maintaining expression within a functionally tolerated range.**
- Coordinated **correction of telomeric and extratelomeric defects**, including telomere maintenance, rRNA maturation and progenitor-cell function.
- A **mutation-independent** gene supplementation strategy with potential applicability across **a broad range of pathogenic *DKC1* variants.**
- Favorable preclinical **safety profile**, with no detectable adverse effects in healthy human HSPCs under the conditions tested.
- Compatibility with scalable *ex vivo* manufacturing processes and future development under good manufacturing practice conditions.
- To our knowledge, this is **the first DKC1 gene supplementation approach** to demonstrate **coordinated rescue of telomeric, extratelomeric and progenitor-function defects** in human X-DC models.

Stage of Development: Preclinical proof of concept established through in vitro studies and in vivo validation in mouse xenotransplantation models.
Functional rescue of telomeric and extratelomeric defects, maintenance of gene-modified human cells over time, and in vivo engraftment have been demonstrated.

Intellectual Property:

PCT application in 2025



Aims

Seeking partners interested in licensing and/or co-development agreements to advance this technology toward clinical translation and commercialization.

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