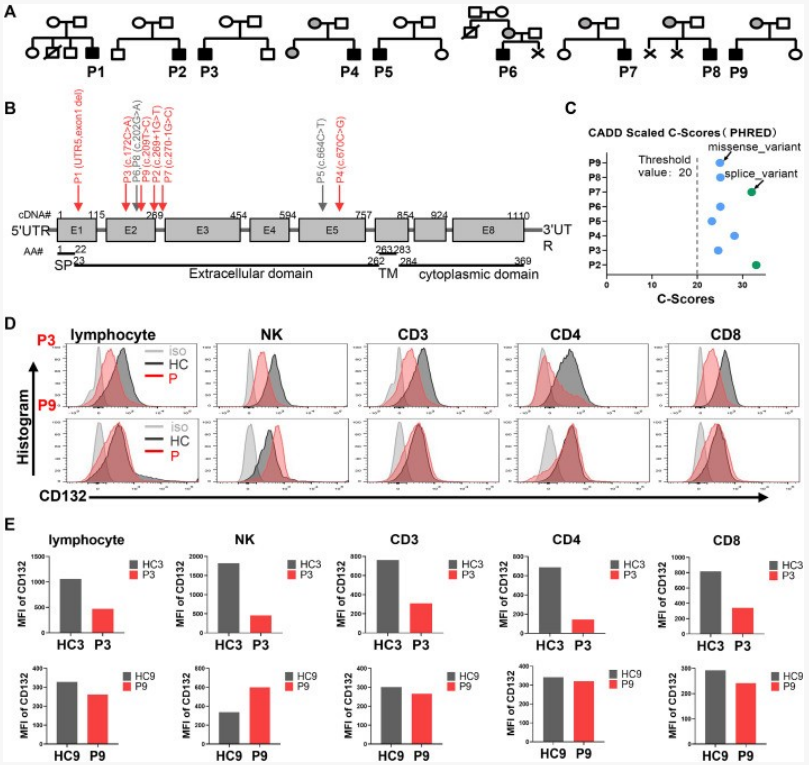
IL2RG Gene Therapy for X-SCID

Pre-clinical validation of SIN-EFS-IL2RG.co vector-based gene therapy for X-SCID



(A) Family pedigrees of the patients. The black solid symbols indicate the affected patients (P1–P9), the grey solid symbols indicate carriers of the same gene mutation, and the open symbols indicate unaffected family members. The squares indicate male su

CHINA, March 13, 2025 /EINPresswire.com/ -- X-linked severe combined immunodeficiency disease (X-SCID) is a rare genetic disorder characterized by profound defects in T-cell, B-cell, and natural killer (NK) cell function, caused by mutations in the interleukin-2 receptor γ-chain (IL2RG) gene. Current treatment options that restore immune functions include hematopoietic stem cell transplantation (HSCT) and gene therapy; however, the clinical application of HSCT is limited by the shortage of suitably matched donors. With 300 births per year, China has seen a rising incidence of X-SCID, highlighting the urgent need to develop gene therapy protocols tailored to the Chinese cohort.

In a recent study published in the Genes and Diseases journal, researchers at the Children's Hospital of Chongqing Medical University, UCL Great Ormond Street Institute of Child Health, Ubrigene (Beijing) Biosciences Co. Ltd, and Westlake Laboratory of Life Sciences and Biomedicine report a pre-clinical study that evaluates the safety and efficacy of SIN-IL2RG-LV vector-based gene therapy for X-SCID.

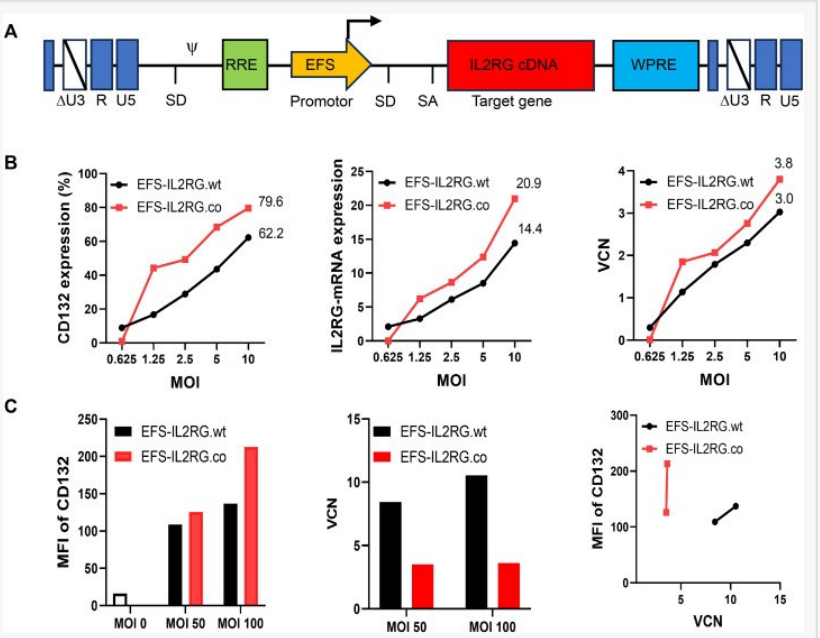
Using next-generation screening and Sanger sequencing, the authors identified six novel IL2RG mutations in a Chinese cohort of nine X-SCID patients. Of the nine patients, two adolescent patients with an atypical immunotype were confirmed by analyzing IL-2-JAK-STAT5 signaling, T cell proliferation, and T cell receptor excision circles (Trecs).

Self-inactivating lentiviral vectors (SIN-LV) comprising either the naive/wild-type (IL2RG.wt) or

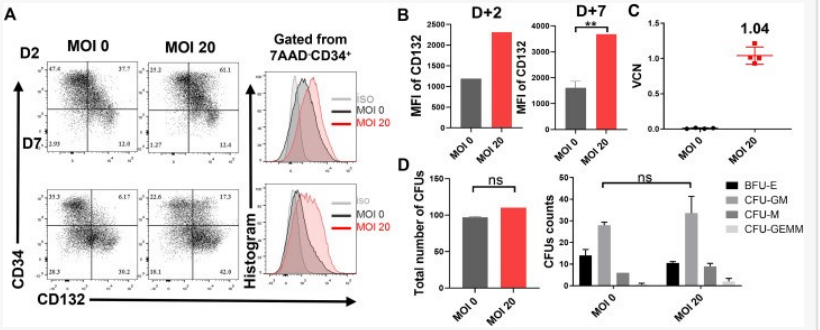
codon-optimized (IL2RG.co) IL2RG cDNA sequences placed under the transcriptional control of an EFS promoter and incorporated with a mutated WPRE were constructed and subsequently transfected into ED7R cells deficient in IL2RG and human BM CD34+ cells. In both cells, the EFS-IL2RG.co vector increased the expression of IL2RG mRNA and CD132 protein compared to the EFS-IL2RG.wt.

Transduction of the EFS-IL2RG.co vector in large-scale cultures of human mobilized CD34+ cells in a GMP workshop increased CD132 protein levels without compromising cell viability or purity. Additionally, in vivo studies showed that SIN-EFS-IL2RG.co vector-transduced CD34+ cells lacked oncogenicity. Finally, the authors demonstrated the successful ex vivo transduction of CD34+ cells from patients with X-linked severe combined immunodeficiency disease (X-SCID).

In conclusion, this study demonstrates the safety and efficacy of the SIN-EFS-IL2RG.co vector for gene therapy in X-SCID. Furthermore, the authors affirm its GMP compliance and its potential to facilitate further clinical trials in X-SCID gene therapy in China.



(A) Scheme of the self-inactivating (SIN) lentiviral vector containing the deleted long terminal repeats (LTRs) (Δ), the short EF1α promoter (EFS), the codon-optimized or wild type version of the IL2RG (IL2RG.co/IL2RG.wt), the HIV-1 Rev Responsive Element



(A) CD132 expression in IL2RG defect or corrected CD34+ cells at 2 days and 7 days after transduction. (B) MFI of CD132 in CD34+ cells. (C) Mean VCNs (± standard deviation) in the bulk population of transduced CD34+ cells. (D) The total numbers of colony-

Reference

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