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Stem cell-based gene therapy for recombinae deficient-SCID

Recombinase-activating gene (RAG) deficient SCID patients lack B and T lymphocytes due to the inability to rearrange immunoglobulin and T-cell receptor genes. The two RAG genes are acting as a required dimer to initiate gene recombination. Gene therapy is a valid treatment alternative for RAG-SCID patients, who lack a suitable bone marrow donor, but developing such therapy for RAG1/2 has proven challenging. Hence, we tested clinically relevant lentiviral SIN vectors with different internal promoters (UCOE, PGK, MND, and UCOE-MND) driving codon optimized versions of the RAG1 or RAG2 genes to ensure optimal expression. We used Rag1^{-/-} or Rag2^{-/-} mice as a preclinical model for RAG-SCID to assess the efficacy of the various vectors at low vector copy number. In parallel, the conditioning regimen in these mice was optimized using busulfan instead of commonly used total body irradiation. We observed that B and T cell reconstitution directly correlated with RAG1 and RAG2 expression. Mice receiving low Rag1/2 expression showed poor immune reconstitution; however high Rag1/2 expression resulted in a lymphocyte reconstitution comparable to mice receiving wild type stem cells. Efficiency and safety of our clinical RAG1 lentivirus batch was assessed in Rag1^{-/-} mice model showing that functional restoration of RAG1-deficiency can be achieved with clinically acceptable vectors. Additionally, RAG1-SCID patient CD34⁺ cells transduced with our clinical RAG1 vector and transplanted into NSG mice led to fully restored human B and T cell development. Together with favorable safety data, these results substantiate a clinical trial for RAG1 SCID which is planned for late 2018.

Biography

Frank J T Staal research is Professor at Leiden University and Member of Department of Immunology and Chair for Molecular Stem Biology center. He has done Phd at Stanford school of Medicine and Masters Degree at University of Utrecht. He worked as Associate Professor for Erasmus for Rotterdam. He published nearly 70 articles on Genetics. Translational research leading to novel diagnostic and therapeutic tools is an integral part of his research activities along with Stem cells and Regenerative Medicine

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