Development of a pCCLChim Lentiviral Vector for Gene Therapy of Patients with Chronic Granulomatous Disease (CGD) due to p47^{-phox} Deficiency

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Rationale: Chronic Granulomatous Disease (CGD) is an inherited primary immunodeficiency disorder caused by defective components of the NADPH oxidase. CGD patients are susceptible to severe and recurrent infections. We propose to use a lentiviral gene therapy strategy to restore the expression of the p47^{-phox} NADPH oxidase component, coded by the *NCF1* gene. Mutations in p47^{-phox} cause the second most common form of CGD.
Methods: We have made a lentiviral vector, pCCLChimp47^{-phox}, that contains the chimeric cathepsin G/c-fes myeloid promoter and a codon optimized version of the human p47^{-phox} gene. We have introduced the lentiviral vector in a myeloid leukemia cell line deficient for p47^{-phox}, in primary monocytes-derived macrophages taken from p47^{-phox} CGD patients and in a mouse model of p47^{-phox} CGD.
Results: The lentiviral gene therapy efficiently restores p47^{-phox} expression and NAPDH oxidase function in all models tested. Notedly, p47^{-phox}-/- mice transplanted with gene therapy treated stem cells (bearing ~1 copy of vector) recovered an average of ~85% functional granulocytes with levels of oxidase activity comparable to wild type.
Conclusions: Overall our study shows that the pCCLChimp47^{-phox} vector is a promising tool for the clinical application of p47^{-phox} CGD gene therapy.

Financial Support: FAPESP (process number: 2015/13110-4).