

EX VIVO LENTIVIRAL TRANSDUCED AUTOLOGOUS HEMATOPOIETIC STEM CELL (HSC) GENE THERAPY FOR CHILDHOOD CEREBRAL ADRENOLEUKODYSTROPHY : PRECLINICAL EVALUATION OF SAFETY AND EFFICACY FOR PHASE I/II CLINICAL TRIAL

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Five to ten year old patients with X-linked adrenoleukodystrophy (ALD) suffer from severe cerebral demyelination leading to vegetative state or death within 2-5 years. The only curative treatment today consists of hematopoietic stem cell (HSC) transplantation. The beneficial effect of allogeneic HCT is likely due to the capacity of myelo-monocytic cells derived from bone marrow cells to penetrate into the brain and differentiate into microglia expressing normal ALD protein. Less than 50% of ALD boys who are candidate for HCT can benefit from the procedure due to the lack of related or unrelated HLA-matched donor. In addition, allogeneic HCT is associated with marked morbidity/mortality risk and normal cells have no selective advantage over ALD cells. This justifies clinical attempts to introduce a functional ALD gene into HSC using a lentiviral vector. We have previously shown that transduced CD34⁺ cells from ALD patients with HIV-derived vector mediate long-term engraftment of NOD/SCID mice and expression of functional ALD protein in monocytes/macrophages derived from engrafted cells. We have provided pre-clinical data demonstrating safety and efficacy of ALD gene transfer into HSC with a HIV-based vector. 1/ no vector-mediated insertional abnormal hematopoiesis is observed *in vitro* or *in vivo* in secondary transplanted ALD mice ; 2/ no replication competent lentivirus (RCL) is detectable with a sensitive assay in transduced ALD CD34⁺ cells ; 3/ clinical transduction protocol performed on 40.10⁶ ALD CD34⁺ cells routinely allows to achieve >50% transduction efficacy with < 2 integrated copies per CD34⁺ cell ; 4/ lentiviral transfer of ALD gene into human CD34⁺ or murine SCA1⁺ cells prior to infusion does not modify their differentiation into brain microglia ; 5/ overexpression of ALD gene with the HIV-based vector does not lead to adverse effects *in vitro* and *in vivo* in animal models ; 6/ ALD transgene is not silenced in HSC-derived microglia of ALD mouse after infusion of transduced ALD SCA-1⁺ cells. Based on these results, a clinical protocol was recently submitted to AFSSAPS. This phase I/II clinical trial will evaluate the safety and efficiency of autologous transplantation of ALD CD34⁺ cells corrected with a lentiviral vector. This protocol will be proposed to patients with cerebral ALD, candidates to allogeneic HSC, but with no matched donor.