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**Preliminary Data from the First Hematopoietic Stem Cell Gene Therapy Trial with Lentiviral Vector Demonstrate Expression of the Therapeutic Protein in High Percentage of Lymphocytes and Monocytes in Two Patients with X-Linked Adrenoleukodystrophy**

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We report preliminary results in two children with cerebral X-linked adrenoleukodystrophy (ALD) who received in September 2006 and January 2007 hematopoietic stem cell (HSC) gene therapy using a HIV1-derived lentiviral vector. We have previously shown that the cerebral demyelination associated with cerebral ALD can be stopped or reversed within 18 months by allogeneic HSC transplantation. For the current HSC gene therapy procedure, mobilized peripheral blood CD34_ cells were transduced *ex vivo* for 18 hr with a non-replicative HIV1- derived lentiviral vector (provided by Cell Genesys, Inc.) expressing the ALD cDNA under the control of the MND promoter, and in the presence of Il-3, SCF, Flt3-ligand, MGDF, and CH-296 retronectine. Transduced cells were frozen to perform replication-competent lentivirus (RCL) assays. After thawing and prior to reinjection, 50% and 30%, respectively, of transduced CD34_ cells expressed the ALD protein with a mean of 0.7 and 0.6 copies of integrated provirus/cell. Transduced CD34_ cells were infused to ALD patients after full myeloablation with cyclophosphamide and busulfan.

Hematopoietic recovery occurred at day 15 post-transplant, and the procedure was uneventful. The percentage of corrected lymphocytes and monocytes in the peripheral blood of treated patients remained stable from day 30 to the last follow-ups. From 25% to 30% (Patient P1, 9 months after transplant) and 20% (Patient P2, 4 1/2 months after transplant) of CD14_, CD3_, CD19_, and CD3_CD56_ cells expressed the ALD protein (0.4 integrated provirus copy/cell). Tests assessing vector-derived RCL and vector mobilization were negative up to the last follow-ups. These early results support that: (1) *ex vivo* HSC gene therapy using HIV1-derived lentiviral vector is not associated with the emergence of RCL and vector mobilization; (2) a high percentage of hematopoietic progenitors were transduced expressing ALD protein in the short term; (3) no early evidence of selective advantage of the transduced ALD cells or clonal expansion was observed; and (4) HSC gene therapy appears to have short-term neurological effects comparable with allogeneic HSC transplantation.

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