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June 10, 2009

**To:** Principal Investigators for Human Gene Transfer Trials Employing Lentiviral or SIN Retroviral Vectors into Hematopoietic and other Stem Cells

**From:** Jacqueline Corrigan-Curay, J.D., M.D.  
Acting Director  
NIH Office of Biotechnology Activities

**Subject:** Clonal Population of Cells Detected in a Clinical Gene Transfer Study Using a Lentiviral Vector

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The purpose of this memorandum is to notify you of an event that occurred in a gene transfer study of  $\beta$ -thalassemia Major and Sickle Cell anemia being conducted in France by Genetix France. On May 27, 2009, the French Medicine Agency, AFSSAPS, reported in a press release that a “relative clonal dominance” was detected in a subject with  $\beta$ -thalassemia Major, two years after the subject received genetically modified hematopoietic stem cells. The clonal population of cells was detected five months ago and has remained stable since then, and the subject has had no change in clinical status. Prior to the gene transfer administration, the subject required blood transfusions once a month, on average. Since the gene transfer administration, the subject has not required transfusions for more than 11 months. The press release is available in French at: <http://www.afssaps.fr/Infos-de-securite/Points-d-information-Points-d-etape/Essai-clinique-de-therapie-genique-dans-les-hemoglobinopathies-Observation-biologique-chez-un-patient-traite>.

The vector being used in the study is a self-inactivating (SIN) HIV-1 derived lentivirus that contains the gene for  $\beta$ -globin under the control of the  $\beta$ -globin promoter and two safety elements (self-inactivation and chromatin insulators). The clonal population of cells that were detected share a common integration site in a gene coding for the protein HMGA2. HMGA2 is associated with both benign and malignant tumors. The trial investigators are performing further studies to evaluate the consequences of this integration and the capacity of the cells to proliferate. Thus far, only two subjects have received the gene-modified cells. Until these studies are completed and reviewed by AFSSAPS, which is scheduled to occur in September 2009, no additional subjects will receive the gene modified cells.

This event raises important questions about whether the use of lentiviral and modified SIN retroviral vectors containing insulators can, as has been the hope among investigators, decrease the risk of insertional mutagenesis in hematopoietic stem cells. In the coming months, OBA will be gathering additional information about the event, including specifics on the vector used, the dose of cells, transduction conditions and the clinical course of both subjects, and we will organize a discussion at a meeting of the NIH Recombinant DNA Advisory Committee as soon as further data are available.

cc: Gene Transfer Investigators Using Retroviral Vectors  
NIH Recombinant DNA Advisory Committee  
Institutional Biosafety Committees  
Food and Drug Administration Center for Biologics Evaluation and Research  
HHS Office for Human Research Protections