

---

---

**Serious and Other Selected Adverse Events  
Reported for Human Gene Transfer Protocols  
NIH Office of Biotechnology Activities  
December 2011**

---

---

Protocol Number: **337**

Protocol Title: **A Phase II Study of the Transduction of CD34+ Cells from the Bone Marrow of Children with Adenosine Deaminase (ADA)-Deficient Severe Combined Immunodeficiency (SCID)**

DocID#	Receipt Date	Event Description
	10/10/2011	Approximately three months post gene transfer administration, the subject was hospitalized for fever and possible infection. This event is expected because the subject was withdrawn from PEGylated adenosine deaminase (PEG-ADA) to undergo the treatment protocol. The chemotherapy in the protocol leads to a low white blood cell count for a period of time. Although it is unlikely that this adverse event was caused by the study agent, it cannot be completely ruled out.

Protocol Number: **819**

Protocol Title: **Registration Phase III Study of Lucanix™ (belagenpumatucel-L) in Advanced Non-small Cell Lung Cancer: An International Multicenter, Randomized, Double-blinded, Placebo-controlled Study Of Lucanix™ Maintenance Therapy for Stages III/IV NSCLC Subjects who have Responded to or Have Stable Disease Following One Regimen of Front-line, Platinum-based Combination Chemotherapy**

DocID#	Receipt Date	Event Description
11312	10/12/2011	The subject experienced an allergic reaction that manifested as a diffuse rash on the upper body. The subject had received the agent for almost six months prior to this event. The rash was moderately severe. The subject recovered.

Protocol Number: 910

Protocol Title: **Closely HLA-Matched Allogeneic Virus Specific Cytotoxic T-Lymphocytes (CTL) to Treat Persistent Reactivation or Infection with Adenovirus, CMV and EBV after Hemopoietic Stem Cell Transplantation (HSCT)**

DocID#	Receipt Date	Event Description
	08/31/2011	About a month after receiving the gene modified cells, the subject's graft versus host disease (GVHD) worsened. The subject had GVHD of the gastrointestinal tract and developed severe gastrointestinal bleeding. The subject required multiple transfusions of red blood cells and platelets. The subject's clinical course was also complicated by a fall and broken leg. The subject declined aggressive care and died about two months after receiving the cells. The death was most likely due to worsening GVHD.

Protocol Number: 930

Protocol Title: **A Double-Blind, Placebo-Controlled (Sham Surgery), Randomized, Multicenter Study Evaluating CERE-110 Gene Delivery in Subjects with Mild to Moderate Alzheimer's Disease**

DocID#	Receipt Date	Event Description
11275	08/08/2011	Almost two months after receiving the blinded study agent (gene transfer agent or placebo) the subject had a possible seizure. Subject had recently discontinued an atypical anti-psychotic medication that was being used for agitation. The subject recovered and was started on anti-seizure medications.

Protocol Number: 937

Protocol Title: **Vaccination With Lethally Irradiated Autologous Myeloblast Admixed With Granulocyte Macrophage-Colony Stimulating Factor Secreting K562 Cells (Gm-K562) In Patients With Advanced MDS Or AML After Allogeneic Hematopoietic Stem Cell Transplantation**

DocID#	Receipt Date	Event Description
11367	12/13/2011	About two months after the first dose of the gene transfer vaccine, the subject died of acute respiratory distress syndrome and complications from a severe eosinophilia that was related to the gene transfer agent. This event was discussed by the Sponsor at the December 13, 2011, meeting of the Recombinant DNA Advisory Committee. <a href="http://oba.od.nih.gov/oba/RAC/meetings/Dec2011/RAC_Minutes_12-11.pdf">http://oba.od.nih.gov/oba/RAC/meetings/Dec2011/RAC_Minutes_12-11.pdf</a>

---

Protocol Number: 940

Protocol Title: **Assessment of the Safety and Feasibility of Administering T cells Expressing an anti-CD19 Chimeric Antigen Receptor to Patients with B cell Lymphoma**

---

DocID#	Receipt Date	Event Description
11341	11/09/2011	The subject who had follicular lymphoma, received his second dose of gene modified T cells almost thirteen months after he received the first dose. Subject had been in remission for ten months following the first dose. The second dose was given without subsequent interleukin-2. About a week after receiving the cells the subject developed worsening kidney function and required dialysis. The subject recovered and by two month follow-up kidney function was back to normal and repeat imaging showed a significant decrease in the disease burden.

---

Protocol Number: 977

Protocol Title: **Direct CNS Administration of a Replication Deficient Adeno-Associated Virus Gene Transfer Vector Serotype rh.10 Expressing the Human CLN2 cDNA to Children with Late Infantile Neuronal Ceroid Lipofuscinosis**

---

DocID#	Receipt Date	Event Description
11250	07/28/2011	Approximately six months after administration of the gene transfer agent, diffusion changes were noted on the subject's MRI. The subject was asymptomatic. The significance of these changes on imaging with no apparent clinical effect is not clear. This event and other similar events were discussed by the PI at the March 8, 2012, meeting of the Recombinant DNA Advisory Committee. <a href="http://oba.od.nih.gov/oba/RAC/meetings/mar2012/RAC_Minutes_03-12.pdf">http://oba.od.nih.gov/oba/RAC/meetings/mar2012/RAC_Minutes_03-12.pdf</a>
11293	09/19/2011	Approximately twelve months post vector administration, diffusion changes were noted on the subject's MRI. The subject was asymptomatic. The significance of these changes on imaging with no apparent clinical effect is not clear. This event and other similar events were discussed by the PI at the March 8, 2012 meeting of the Recombinant DNA Advisory Committee. <a href="http://oba.od.nih.gov/oba/RAC/meetings/Mar2012_March_7-8_2012agenda_annotated.pdf">http://oba.od.nih.gov/oba/RAC/meetings/Mar2012_March_7-8_2012agenda_annotated.pdf</a>
11303	08/25/2011	On the day of the study drug administration, the subject began having abnormal facial movements in which eyebrows would raise and lower spontaneously. Neurology was called for consult. Family reported that the subject often had similar movements at baseline. Eyebrow movements continued throughout the day and by the next morning the facial twitching was gone, but jerking in the upper extremities was evident. Electroencephalogram confirmed that the movements were not seizures, and the subject was kept overnight in the hospital. The upper body jerking continued throughout the day, but by the following morning all movements had stopped, and the subject was discharged from the hospital.
11304	08/25/2011	Approximately two months after receiving the vector, the subject had a partial complex seizure. The seizure occurred in conjunction with a cold congestion which persisted for a few weeks and the subject was treated with antibiotics. Subject did not have a fever at the time of the seizure.
11326	10/14/2011	Approximately six months post vector administration, diffusion changes were noted on the subject's MRI. The subject was asymptomatic. The significance of these changes on imaging with no apparent clinical effect is not clear. This event and other similar events were discussed by the PI at the March 8, 2012, meeting of the Recombinant DNA Advisory Committee. <a href="http://oba.od.nih.gov/oba/RAC/meetings/mar2012/RAC_Minutes_03-12.pdf">http://oba.od.nih.gov/oba/RAC/meetings/mar2012/RAC_Minutes_03-12.pdf</a>

---

Protocol Number: 1019

Protocol Title: **A Phase IIA Open-Label Study to Assess the Safety and Efficacy of a Single or Multiple Intravenous (IV) Dose of VB- 111 in subjects with Advanced Differentiated Thyroid Cancer (DTC)**

DocID#	Receipt Date	Event Description
11258	08/15/2011	Subject developed a prolonged activated partial thromboplastin time (PTT) (about three times normal) about a month after receiving the gene transfer agent. PTT is one indication of how well blood clots. Subject was also found to have a positive lupus anticoagulant level. This test has been associated with an elevated PTT. The elevated lab had no apparent clinical effect and became negative several months later.
11287	09/16/2011	Subject received the first dose of study agent intravenously. Approximately six hours post dosing, the subject experienced diarrhea, worsening shortness of breath and a rapid heart rate. Subject reported approximately ten loose stools over the next two hours. The subject was admitted to the hospital for observation. No fever or chills were noted. Upon admission, subject was found to have a good blood pressure and pulse and most of the symptoms had already resolved. The diarrhea stopped and bowel and bladder function were normal. The subject was observed overnight and had no further symptoms. Subject was discharged from the hospital in good condition the following day.

Protocol Number: 1028

Protocol Title: **A Phase II Study of Repeat Intranodal Injections of Adenovirus-CD154 (Ad-ISF35) in Patients with Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma**

DocID#	Receipt Date	Event Description
11286	08/29/2011	Subject developed severe hyponatremia (low blood sodium levels) after the third injection of the gene modified cells. This adverse event was considered to be a dose limiting toxicity (DLT). Hyponatremia was associated with nausea, early satiety and a CAT scan which showed increase in the size of lymph nodes. Therefore, this adverse event was considered possibly related to either gene modified cells or disease progression. Based on National Cancer Institute response criteria, the subject was considered to have stable disease. However, because of large lymphadenopathy it was recommended that the subject initiate alternative treatment.

Protocol Number: 1036

Protocol Title: **Phase I/II Study of Metastatic Cancer Using Lymphodepleting Conditioning Followed By Infusion of Anti-VEGFR2 Gene Engineered CD8+ Lymphocytes**

DocID#	Receipt Date	Event Description
11325	10/14/2011	Approximately one week after study agent dosing, the subject's blood liver tests were elevated. A liver ultrasound was performed which did not reveal an etiology for the abnormal tests. Within a week the liver tests improved. Elevated liver function tests are expected events with interleukin-2. Hepatotoxicity is a possible complication of prior chemotherapy and several medications which are a standard component of the current protocol. However it is possible that the gene modified cells contributed to these abnormal blood tests.

---

Protocol Number: 1057

Protocol Title: Phase I study to assess the safety and activity of enhanced TCR transduced autologous T cells against cancer-testis antigens in metastatic melanoma

---

DocID#	Receipt Date	Event Description
11329	10/17/2011	Subject had metastatic melanoma. Four days after receiving the gene modified T-cells, the subject had a fatal myocardial infarction. An autopsy revealed that the subject had a severe occlusion of one of the main cardiac arteries. There was an elevation in the level of cytokines following the administration of cells but there was no evidence of cytokine storm. This event was discussed at the June 13, 2011, meeting of the Recombinant DNA Advisory Committee. <a href="http://oba.od.nih.gov/oba/RAC/meetings/June2011/RAC_Minutes_06-11.pdf">http://oba.od.nih.gov/oba/RAC/meetings/June2011/RAC_Minutes_06-11.pdf</a>

---

Protocol Number: 1065

Protocol Title: Phase II Study of Metastatic Cancer that Expresses MAGE-A3/12 Using Lymphodepleting Conditioning Followed by Infusion of Anti-MAGE-A3/12 TCR-Gene Engineered Lymphocytes

---

DocID#	Receipt Date	Event Description
11333	10/31/2011	Three days after receiving the gene modified cells and interleukin-2 per protocol, subject developed pulmonary edema (fluid in the lungs), resulting in respiratory distress that required a breathing tube. The subject also had a seizure. At the time of the report subject remained in the intensive care unit. This event and other similar events were discussed by the PI at the December 14, 2011, meeting of the Recombinant DNA Advisory Committee. <a href="http://oba.od.nih.gov/oba/RAC/meetings/Dec2011/RAC_Minutes_12-11.pdf">http://oba.od.nih.gov/oba/RAC/meetings/Dec2011/RAC_Minutes_12-11.pdf</a>
11338	11/08/2011	A 70+ year old subject with esophageal cancer received the chemotherapy and gene modified cells followed by a single dose of interleukin before developing hypotension and mental status changes. Subject was admitted to intensive care and continued to have worsening mental status, at one point having minimal or no withdrawal reaction to pain. In addition, subject developed renal failure. Imaging and other testing led to a diagnosis of encephalopathy/leukomalacia. This event was discussed by the PI at the December 14, 2011, meeting of the Recombinant DNA Advisory Committee. <a href="http://oba.od.nih.gov/oba/RAC/meetings/Dec2011/RAC_Minutes_12-11.pdf">http://oba.od.nih.gov/oba/RAC/meetings/Dec2011/RAC_Minutes_12-11.pdf</a>
11292	09/13/2011	Approximately one week after receiving protocol specific chemotherapy followed by study agent dosing, the subject developed an inability to speak. An MRI of the brain showed some abnormalities in the cortex and leptomeninges. Subject was treated with steroids. Subject began to recover and has since returned to baseline.

---