
**Gene Transfer Safety Assessment Board
Adverse Event Report
NIH Office of Biotechnology Activities
March 2012**

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
	12/07/2011	Subject developed a fever and was admitted into the hospital for antibiotic treatment. Blood and urine cultures were done, but no source of infection found. At the time of admission, the subject also had an inflamed area on the right side of the face that appeared to be infected. An ultrasound of the area did not reveal any significant findings. The inflamed area on the cheek improved markedly after several days of antibiotic treatment. However, the antibiotic treatment made the subject neutropenic (low white blood cell count), and the subject was kept in the hospital until the neutropenia resolved. At the last follow-up the cheek inflammation had almost completely resolved, and subject's absolute neutrophil count was improving. This adverse event is related to the study intervention (withdrawal of PEGylated adenosine deaminase).

Protocol Number: **622**

Protocol Title: **Adenyl Cyclase VI Gene Transfer for Congestive Heart Failure**

DocID#	Receipt Date	Event Description
11345	11/10/2011	Four hours after administration of the gene transfer agent by cardiac catheterization, the subject's laboratory studies showed an increase in a blood test used to measure cardiac muscle injury. The subject was kept in the hospital for one additional night as a precaution. The blood test levels returned to normal prior to discharge. The subject had no chest pain or electrocardiogram changes.

Protocol Number: 793

Protocol Title: **Pilot Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR ζ and 4-1 BB Signaling Domains in Patients with Chemotherapy Resistant Or Refractory CD19+ Leukemia and Lymphoma**

DocID#	Receipt Date	Event Description
11351	11/21/2011	Subject had fevers following the first administration of the T-cells, leading to a prolongation of the hospitalization. During the hospitalization, the subject also developed hospital acquired pneumonia (infection of the lungs) that responded to antibiotics.
11385	01/10/2012	The subject was admitted to the hospital for chills, rigors and chest pain which developed following the second infusion of T cells engineered to express a chimeric antigen receptor targeting CD19. The subject was receiving packed red blood cells (PRBC) for profound asymptomatic anemia when rigors developed. The PRBC transfusion was stopped five minutes after start of infusion and the subject was found to have an elevated blood pressure. The subject received Demerol for rigors and complained of tightness in his throat and pain in the left side of chest (no palpitations reported). After receiving Demerol, the rigors resolved, but the subject continued to complain of mild pain in his left upper chest and tightness in his upper throat. Electrocardiogram showed sinus tachycardia (rapid heart rate) without any obvious changes indicating abnormal blood flow to the heart or heart attack. All symptoms resolved. The events of chills and rigors were felt to be related and expected. The event of chest pain was felt to be unlikely related to the gene transfer and unexpected.
11384	01/10/2012	Four days after the second infusion of T cells engineered to express a chimeric antigen receptor targeting CD19, the subject was readmitted to the hospital for recurrent chills and chest pain. While in the hospital, the electrocardiogram was normal, and a blood test for cardiac tissue injury, troponin, was slightly elevated. The subject was monitored and discharged in stable condition.
11354	11/21/2011	Approximately two weeks after receiving the gene modified cells, the subject developed "tumor lysis syndrome", a syndrome in which the rapid destruction of the tumor cells can lead to complications, including kidney problems. The subject recovered.

Protocol Number: 843

Protocol Title: **A Phase I Study of Autologous T-Cells Genetically Modified at the CCR5 Gene by Zinc Finger Nuclease SB-728 in HIV-Infected Patients**

DocID#	Receipt Date	Event Description
11399	02/13/2012	Subject developed fever and chills within one day of receiving the gene modified cells. The subject also developed myalgias and joint pain that was unexpected and persisted for several days. About two weeks after receiving the cells, the subject continued to have joint pain and presented to an emergency room for treatment. The symptoms largely resolved by a month following infusion of the T-cells. Of note subject had joint pain upon enrollment and prior to dosing. The symptoms gradually resolved and subject is considered to be at baseline.

Protocol Number: **951**

Protocol Title: **An open label phase I study to evaluate the safety and tolerability of a vaccine consisting of whole, heat-killed recombinant *Saccharomyces cerevisiae* (yeast) genetically modified to express CEA protein in adults with metastatic CEA-expressing carcinoma**

DocID#	Receipt Date	Event Description
11397	02/09/2012	Subject developed increased fluid around the lung approximately eight months after receiving the gene transfer vaccine. While initially thought to be possible progression of disease or infection, further analysis revealed it was likely from an immune response against the tumor in the lung. The subject was given steroids to reduce this immune response and did not receive any additional gene transfer vaccines.

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
11408	11/08/2011	The subject, who had metastatic melanoma, died just over two months after receiving the gene modified T-cells. His post transfusion course was complicated by hypotension (low blood pressure), hypoxemia (low blood oxygen levels) and liver failure. Of note, he had an elevated Epstein-Barr virus titer and a serum ferritin level that was greater than 40,000mcg/liter (normal < 200 mcg/liter). Autopsy revealed a Epstein-Barr virus lymphoproliferative disorder, diffuse B-cell lymphoma. There were also signs of disseminated infection that likely caused sepsis. Finally, there was evidence of thrombotic microangiopathy. The immunocompromised state was a significant factor in this case but the T-cell infusion possibly contributed.

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
11386	01/12/2012	<p>Subject is an approximately 50 year old male with metastatic melanoma with metastases to the brain, axilla, lungs, and mesentery who was enrolled on this protocol which administers T-cells engineered to express a T-cell receptor against MAGE A3/12, a cancer testis antigen often highly expressed on tumor. After receiving interleukin-2 per protocol, the subject developed changes in alertness, cognition and low blood pressure. He was transferred to the intensive care unit for decreasing mental status, hypotension - (systolic blood pressure in the 80's) - despite normal saline boluses, with heart rate in the 120's. He was intubated for airway protection. Hospital course was complicated by continued low blood pressure and decreased heart function. During recovery from these events, the subject had a seizure. Despite anti-seizure medications, the subject continued to have seizures and an MRI showed extensive changes in the white matter of the brain. Subject had minimal level of consciousness and a subsequent brain MRI showed extensive leukomalacia involving the white matter of both cerebral hemispheres consistent with an acute and subacute toxic metabolic or autoimmune demyelinating process. A brain biopsy showed micro-vacuolation of the white matter with relative sparing of the gray matter. Of note, tumor burden was also significantly decreased. Subject died approximately two months later. Autopsy showed white matter spongy vacuolation and necrosis and evidence of cross reactivity of the gene modified T cells to MAGE antigen expressed on brain tissue. This finding was discussed by Dr. Rosenberg at the June 19, 2012 meeting of the RAC.</p> <p>http://oba.od.nih.gov/oba/RAC/meetings/June2012/RAC_Minutes_06-12.pdf</p>

Protocol Number: 1097

Protocol Title: Phase I/II Study of Metastatic Cancer that Expresses NY-ESO-1 Using Lymphodepleting Conditioning Followed by Infusion of Gene Engineered Lymphocytes Cotransduced with Genes Encoding IL-12 and Anti-NY ESO-1 TCR

DocID#	Receipt Date	Event Description
11383	01/12/2012	<p>In the days following administration of the gene modified tumor infiltrating cells, the subject experienced fevers treated with acetaminophen. Laboratory reports showed elevated liver enzyme blood tests, so the acetaminophen was changed to an anti-inflammatory medication. Subject began to experience shortness of breath and oxygen was administered. A chest x-ray and chest CAT scan was performed. It showed patchy "ground glass" abnormalities. A repeat chest x-ray showed worsening congestion, and the subject became progressively more short of breath with exertion. Subject experienced intermittent episodes of asymptomatic hypotension (low blood pressure). Subject was transferred to the intensive care unit for worsening respiratory status and anuria (failure to urinate). Subject developed acute respiratory distress and was intubated. She began having worsening kidney failure and was started on continuous veno-venous hemofiltration (CVVH). Subject was started on methylprednisolone every eight hours and alemtuzumab - a recombinant monoclonal antibody that binds to CD52 which is present on mature lymphocytes to decrease the effect of the gene modified T-cells. A rash was noted over a significant portion of her body. A bronchoalveolar lavage was performed which showed evidence of a fungal pneumonia, therefore an anti-fungal was started. Despite continued care, subject's condition worsened with development of liver and kidney failure. Subject died about a month after receiving the cells. Autopsy confirmed bacterial sepsis and fungal pneumonia.</p>