
**Serious and Other Selected Adverse Events
Reported for Human Gene Transfer Protocols
Recombinant DNA Advisory Committee Meeting
March 2011**

Protocol Number: 542

Protocol Title: AdV-tk therapy in combination with surgery and chemoradiation for pancreas cancer

DocID#	Receipt Date	Event Description
11056	12/30/2010	Subject had baseline abdominal pain and nausea that increased approximately three days after intratumoral injection of the gene transfer agent. Subject was hospitalized and a computed tomography scan demonstrated inflammation in the area near the injection of the study agent. The subject was discharged after being treated for his symptoms and remains on the study.

Protocol Number: 622

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

DocID#	Receipt Date	Event Description
11063	01/05/2011	Subject developed elevations in Troponin I, a blood test that is used in diagnosing cardiac ischemia (decreased blood flow to the heart). However, other tests did not show evidence of cardiac ischemia. The rise in this blood test may be related to the procedure, or less likely the gene transfer agent.

Protocol Number: 624

Protocol Title: Phase I Trial of Conditionally Replication-Competent Adenovirus (Delta-24-RGD) for Recurrent Malignant Gliomas.

DocID#	Receipt Date	Event Description
11028	11/23/2010	Subject had surgery and the second injection into the tumor cavity (i.e. where the tumor was removed). Almost three weeks after this surgery and injection of the gene transfer agent, subject was admitted to the hospital for a fever of unknown origin and a subgaleal (the potential space between the outer layer of the skull and the scalp) fluid collection was identified. The etiology of the fever was investigated. The fluid was sampled but no infectious agent was identified. The exact etiology for the fever remains unknown but after an investigation the principal investigator concluded that it was unlikely to have been related to the gene transfer agent.

Protocol Number: 674

Protocol Title: A Phase IIa Study of ADV-TK + Valacyclovir Gene Therapy in Combination with Standard Radiation Therapy for Malignant Gliomas

DocID#	Receipt Date	Event Description
11013	11/02/2010	Approximately two weeks after intracranial injection of the study agent, the subject unexpectedly died while at a rehabilitation facility. The cause of death could not be determined but subject had been doing well with no signs of treatment related problems. However, due to the timing of the death a possible role of the gene transfer cannot be ruled out.
11018	11/02/2010	Subject admitted due to altered mentation and fever seven days after study agent injection. This was the sixth day of valacyclovir administration. The subject received the first day of radiation therapy and later that night returned to an urgent care center with altered mentation and fever. A blood test showed an elevated white blood cell count. The surgical site did not appear infected. Aside from the fever and altered mentation, there were no other clinical signs of meningitis (infection in the cerebral spinal fluid). A computed tomography scan of the head showed left sided edema producing a midline shift in the brain structures. A lumbar puncture was not performed due to this finding. The subject was treated with intravenous steroids and antibiotics. Symptoms resolved and no source of infection was identified. The subject was discharged three days later on antibiotics, steroids and anti-seizure medication.

Protocol Number: 794

Protocol Title: Dose-Intensive Chemotherapy in Combination with Chemoprotected Autologous Stem Cells for Patients with Malignant Gliomas

DocID#	Receipt Date	Event Description
11041	12/02/2010	The subject received an autologous transplant of gene-modified cells following chemotherapy. Subject has received one cycle of combination chemotherapy with 06-benzylguanine and temozolomide. Approximately two months post transplant, the subject was found to have low blood counts, including low white and red blood cells and platelets. The subject was admitted and treated with a platelet transfusion as well as recombinant human granulocyte colony-stimulating factor (G-CSF). The blood counts began to recover. The subject also developed a fever and radiologic imaging indicated possible pneumonia so the subject was treated with antibiotics as well. Per the principal investigator given the time frame since administration of 06-benzylguanine and temozolomide chemotherapy (15 days), the observed low blood counts are most likely due to the administration of these agents. This was the first cycle of this combination chemotherapy following receipt of the gene-modified cells.

Protocol Number: 829

Protocol Title: **A Phase II Study of HyperAcute Pancreatic Cancer Vaccine in Combination with Chemotherapy and Chemoradiotherapy in Subjects with Surgically Resected Pancreatic Cancer**

DocID#	Receipt Date	Event Description
11021	11/17/2010	Approximately seven months after last dose of study agent vaccine, subject presented to the clinic and was found to have a low hemoglobin level (oxygen carrying blood cells) for which he received a blood transfusion. After the second unit of blood was given, subject developed raised lesions (hives) and redness at the site of the previous vaccine injections. Subject was treated with antihistamines and steroids and the symptoms resolved the next day. Of note, the subject had a similar reaction to the injections in the past.

Protocol Number: 868

Protocol Title: **A Phase 1 Safety Study of Heat/Phenol-Killed, E. coli-Encapsulated, Recombinant Modified Peanut Proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) in Normal Volunteers Followed by Subjects Allergic to Peanuts (Protocol NO. APA-001)**

DocID#	Receipt Date	Event Description
11086	02/09/2011	Subject had a mild to moderate anaphylactic reaction after receiving highest dose of the study agent. Subject recovered completely after one dose of epinephrine intramuscularly.
11062	01/05/2011	The subject presented for a scheduled dosing visit and received the study agent in the rectum per protocol. Approximately ten minutes after receiving the dose, the subject complained of stomach upset and went to the bathroom and had a liquid stool. The subject was flushed, had fine hives (small raised skin lesions) on the chest and complained of dry, itchy eyes. Subject received antihistamines. The subject then complained of feeling short of breath, but wasn't sure if it was due to anxiety. Upon examination, lungs were clear to auscultation, and spirometry (a measure of lung function) was the same as baseline. The subject's voice began to sound hoarse and the subject complained of throat tightness. Epinephrine was administered intramuscularly. All of the symptoms resolved within ten minutes. The subject was observed for three hours without further symptoms.

Protocol Number: 881

Protocol Title: **Phase 1b, Open Label Trial to Define the Safety, Tolerance, Transgene Function, and Immunological Effects of Intratumoral Injection(s) of Adenoviral Transduced Autologous Dendritic Cells Engineered to Express hIL-12 Under Control of The RheoSwitch® Therapeutic System in Subjects With Stage III and IV Melanoma**

DocID#	Receipt Date	Event Description
11068	01/19/2011	Subject received the third dose of the gene modified cells after receiving the activator drug that leads to the expression of interleukin-12 by the gene modified cells. The activator drug dose for this cycle was increased as per the protocol. Subject developed diarrhea that was possibly related to the activator drug and evidence of gastrointestinal bleeding. Subject subsequently fell and after declining medical attention experienced muscle injury from the fall and subsequent impairment of renal function. Subject continues to be treated in the hospital. The event was considered a dose limiting toxicity and the dose escalation of the activator drug was modified.

Protocol Number: 901

Protocol Title: **Adoptive Transfer of MART-1 F5 TCR Engineered Peripheral Blood Mononuclear Cells (PBMC) after a Nonmyeloablative Conditioning Regimen, with Administration of MART-126•35-Pulsed Dendritic Cells and Interleukin-2, in Patients with Advanced Melanoma**

DocID#	Receipt Date	Event Description
11067	12/20/2010	Subject received lymphodepleting chemotherapy followed by gene modified cells and the peptide pulsed dendritic cells. Subject was admitted approximately three weeks after administration of the gene modified cells with low blood cell counts, including low white blood cells. Treatment was begun with steroids, cyclosporine and anti-thymocyte globulin. The blood counts improved slowly. Tests to determine the etiology of this event did not indicate that the gene modified T cells played a role. As the lymphodepleting chemotherapy may have contributed to this event the protocol was modified to reduce the dose of fludarabine prior to cell transfer. In addition, the number of doses of IL-2 given after cell administration will also be reduced as this may lead to hematologic toxicities. Recent evidence indicates that a smaller number of IL-2 doses may be as efficacious.

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
11024	11/17/2010	Subject had myelodysplastic syndrome and had a stem cell transplant followed by enrollment into this trial. After two doses of vaccine, subject was noted to have mild graft versus host disease (GVHD). Approximately, two months after the second vaccine subject developed very low platelet counts that did not come back to normal despite treatment with steroids, intravenous immunoglobulin infusions and rituximab. Subject has however had an improvement in platelet count levels with romiplostin. While low platelet counts can be a rare complication of stem cell transplants, a contributory role of the gene transfer vaccine can not be ruled out.

Protocol Number: 947

Protocol Title: **A Randomized Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of a Treatment with OncoVEXGM-CSF Compared to Subcutaneously Administered GM-CSF in Melanoma Patients with Unresectable Stage IIIb, IIIc and IV Disease**

DocID#	Receipt Date	Event Description
11069	07/23/2009	The subject developed a cellulitis (redness in the skin indicating possible infection) in the right arm and chest, 24 days after the first injection of the gene transfer vaccine. The cellulitis responded to antibiotics and source of infection was not identified. Injections were received in a chest wall tumor near the right clavicular bone.

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
11094	02/11/2011	Subject had been receiving vaccines on the study for several months when she presented with severe shoulder pain, shortness of breath, and low oxygen levels. Subject was noted to have an increase in fluid around the lung. She was treated with antibiotics and pain medications and recovered.
11020	11/16/2010	One day after the second dose of the vaccine, subject reported severe upper back pain and left shoulder pain requiring hospitalization. No cause was found. Of note, subject has a history of lymph node dissection near the clavicle. The subject was discharged from the hospital the next day.

Protocol Number: 1013

Protocol Title: **A Phase III Study of Chemotherapy and Chemoradiotherapy With or Without HyperAcute®-Pancreatic Cancer Vaccine in Subjects with Surgically Resected Pancreatic Cancer**

DocID#	Receipt Date	Event Description
11065	01/07/2011	Subject was on the study receiving vaccines for six months when subject presented to the emergency room with difficulty breathing and a fever. The subject was admitted to the intensive care unit and required a breathing tube. Images of the lungs showed evidence of possible infection and edema. This etiology of this acute respiratory distress syndrome was never determined but subject recovered.

Protocol Number: 1064

Protocol Title: **Phase I/II Study: 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 Using a Modified Administration Method.**

DocID#	Receipt Date	Event Description
11043	12/15/2010	Three days post vector administration, the subject's parents noticed new bilateral facial movements (dyskinesias) that abated with sleep. Magnetic resonance imaging showed stable post surgery changes and the electroencephalogram (EEG) did not show a new seizure focus. The investigator noted that "dyskinesia" is an unexpected development after delivery of the gene transfer, which requires a surgical procedure. This adverse event which required hospitalization was probably related to the surgical procedure but possibly related to the study drug. These abnormal movements decreased over one month but did not completely resolve.
