Serious and Other Selected Adverse Events
Reported for Human Gene Transfer Protocols
Recombinant DNA Advisory Commitee Meeting
September 2006

Protocol Number: **337**

Protocol Title: **Transduction of CD34+ Cells from the Umbilical Cord Blood of Infants or the Bone Marrow of Children with Adenosine Deaminase (ADA)-Deficient Severe Combined Immunodeficiency (SCID)**

DocID#	Receipt Date	Event Description
8633	07/14/2006	Subject experienced prolonged pancytopenia following administration of Busulfan. Subject received the gene transfer 3 days after the Busulfan. Subject was diagnosed with trisomy 8 mosaicism which contributed to the low blood counts. Subject underwent a unrelated bone marrow transplant and was taken off the active phase of the study and placed on long-term follow-up. The low blood counts were not felt to be related to the gene transfer.

Protocol Number: **412**

Protocol Title: **A Phase III, Multi-Center, Open-Label, Randomized Study to Compare the Effectiveness and Safety of Intratumoral Administration of RPR/INGN 201 in Combination with Chemotherapy Versus Chemotherapy Alone in 288 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN).**

DocID#	Receipt Date	Event Description
8582	05/11/2006	Subject had a history of Li Fraumeni syndrome and several tumors including metastatic brain lesions. The study agent was administered under a "compassionate use" protocol. Although there were some responses at some tumor sites, subject's disease progressed at other sites and subject died of metastatic cancer.

Protocol Number: **530**

Protocol Title: **A Randomized, Phase II, Study of TNFerade™ Biologic with 5-FU and Radiation Therapy for First-Line Treatment of Unresectable Locally Advanced Pancreatic Cancer.**

DocID#	Receipt Date	Event Description
8522	05/12/2006	Subject, in the hours following the third dose of study agent, developed a fever reported as 102.7 F and was subsequently hospitalized for evaluation. Blood and urine cultures, computed tomography (CT) scans of the chest and abdomen and standard laboratory tests showed no evidence of infection. The event resolved after 4 days and the subject was discharged from hospital. Subject received the next dose of study agent without any recorded side effects. The investigator assessed this event as possibly related to study agent, possibly due to administration procedure and possibly due to previous dental work received.
8725	08/25/2006	About 1 1/2 months after receiving the gene transfer, the subject was admitted to the hospital for nausea and vomiting after having a jejunal stent replaced. The subject was discharged several days later.

Protocol Number: **543**

Protocol Title: **Phase I Study to Evaluate the Safety of Cellular Immunotherapy for CD19+ Follicular Lymphoma Using Autologous T Cell Cytolytic Clones Genetically Modified to be CD19-Specific and Express HyTK**

DocID#	Receipt Date	Event Description
8546	05/24/2006	The discharge diagnosis summary provided by the investigator was neutropenic fever and the subject was discharged on oral antibiotics. Cultures and chest x-ray were negative for infectious etiology.

DocID#	Receipt Date	Event Description
8576	05/31/2006	During the administration of the investigational agent, subject's left ventricle was perforated. The subject underwent pericardiocentesis and then required a pericardial window. Subject recovered.
8631	07/12/2006	Five months after receiving the gene transfer, the subject collapsed, was transported to hospital, and died. The investigator originally was unable to assess whether the death was related to the investigational agent but subsequently determined that it was not associated with the investigational agent or procedure.
8511	05/05/2006	Six months after receiving gene transfer, the subject was admitted with angina and discovered to have a low blood count. Subject reported history of "red" stool. A colonoscopy revealed a fungating ulcerated mass in the colon that biopsy showed adenocarcinoma.
8512	05/05/2006	Subject had an in-hospital cardiac arrest and died 5 days after surgery to resect colon cancer. Per the hospital's record of death, an autopsy was not performed. The death due to cardiac arrest was felt to not be related to the gene transfer.
8583	06/06/2006	The subject was admitted to the hospital with vasodepressive syncope nine months after receiving the gene transfer. The subject reported having syncopal episodes for the past three months, with two episodes over the last several days. The subject reported that the syncopal episodes are usually accompanied by right-sided headaches and left arm and leg numbness and weakness before the syncopal episodes. A tilt table test revealed episodes of vasodepressive syncope. Subject was discharged with appropriate therapy. The event was considered resolved with sequelae. The investigator judged the event as an unknown association to the study drug, device, or procedure. The event of vasodepressive syncope is unexpected for this patient population.
8606	06/27/2006	A baseline ophthalmologic exam was negative for proliferative retinopathy and age related macular degeneration. Subject received study agent, and one month later, subject complained of seeing "floaters", a symptom that had been reported by the subject at screening. Subject scheduled an appointment with an ophthalmologist and the subject was referred for laser treatment to right eye for proliferative diabetic retinopathy and reported being back to baseline at 3 month visit. In the opinion of the Principal Investigator, this is an important medical event and it is unknown if this is related to the study drug, device, or procedure.
8613	06/27/2006	Six months after receiving the gene transfer, the subject was admitted to the hospital with diverticulitis and worsening angina. An electrocardiogram (ECG) revealed sinus bradycardia but was otherwise normal. Cardiac enzymes were negative. A colonoscopy revealed normal underlying mucosa, mild sigmoid diverticulosis without evidence of active inflammation and random biopsies were obtained throughout the entire colon. The events of diverticulitis and worsening angina were considered resolved. The Investigator judged the events of diverticulitis and worsening angina as not associated with the study drug, device or procedure.

Protocol Number: **615**

Protocol Title: **Phase II Study in metastatic melanoma using lymphocytes reactive with the gp100 antigen following the administration of a nonmyeloablative lymphocyte depleting regimen.**

DocID#	Receipt Date	Event Description
8599	06/20/2006	Subject has a past medical history significant for melanoma from an upper chest wall lesion with metastatic disease involving the neck and chest. One hour following the T cell infusion, the subject complained of shortness of breath (SOB) and chest tightness. Although oxygen was given, subject continued to have SOB, chest tightness, and developed tachycardia, high systolic blood pressure and a persistent non-productive cough with episodes of hemoptysis. Subject was transferred to ICU, intubated and placed on forced ventilation. Subject's pulmonary artery pressure was increased and chest x-ray showed bilateral alveolar infiltrates consistent with increasing pulmonary edema or acute respiratory distress syndrome (ARDS). Blood and tracheal aspirate cultures were negative. Echocardiogram was performed and revealed severe right ventricular (RV) dysfunction. After receiving steroids and other appropriate treatments, subject was extubated and placed on oxygen via aerosol face mask.
8715	08/18/2006	Subject was in the hospital and was recovering from initial event of hypoxemia with pulmonary infiltrates when subject developed rapid performance status deterioration, progressive dyspnea, continuous cough and acute hypotension. Subject was intubated. The chest x-ray showed significantly increased left lung infiltrates and the echocardiogram revealed severe right ventricular dysfunction and moderate pericardial effusion. Peripheral blood cultures were negative, but aspirate cultures grew gram negative rods. Subject was treated aggressively with vasopressors, intravenous antibiotics and other supportive measures, but subject's condition continued to deteriorate despite all supportive measures.

Protocol Number: **619**

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

DocID#	Receipt Date	Event Description
8603	06/23/2006	The mother reported that the subject had a "bad four hour long seizure that required her to take the subject to the emergency room where they gave the subject diazepam." The mother was unable to give further information at that time. Subject received the gene transfer almost one year prior to the event. The investigator noted that there is no way of distinguishing as to whether this event is part of the natural progression of the disease, or due to the study drug and procedures.
8621	07/03/2006	The subject experienced an episode of seizure activity approximately two months post vector administration. This seizure lasted approximately 5 minutes and was characterized by generalized jerking movements of the subject's arm and legs with lips smacking together. Once the seizure stopped, it took 10 minutes before the subject recovered consciousness and then subject became extremely agitated. Subject's antiepileptic medication was adjusted. Since this episode the subject has not had any more seizures. The PI reports " from the information available, we have no way of distinguishing as to whether this event is part of the natural progression of the disease, or due to the study drug and procedures. For this reason, we are reporting this as "possibly" related to the study drug and procedures. It is being reported as an expected serious adverse event."

Protocol Number: **635**

Protocol Title: **A Phase III Randomized, Controlled Study to Evaluate the Safety and Efficacy of PANVAC™-VF in Combination with GM-CSF Versus Best Supportive Care or Palliative Chemotherapy in Patients with Metastatic (Stage IV) Adenocarcinoma of the Pancreas Who Have Failed a Gemcitabine-Containing Chemotherapy Regimen.**

DocID#	Receipt Date	Event Description
8569	05/31/2006	The subject was diagnosed with a non-occlusive portal vein thrombosis four months after the last does of the investigational agent.
8557	05/26/2006	Subject received the gene transfer but was withdrawn from the study about 2 weeks later due to disease progression. Approximately 3 weeks later (5 weeks after dosing), was seen for the end of study visit with complaints of generalized weakness, shortness of breath, anorexia, decreased appetite, mild nausea, and constipation of one months duration. An electrocardiogram (EKG) revealed atrial flutter with rapid ventricular rhythm, with a heart rate of 126 beats per minute. Subject was treated with a beta blocker. Subject's constipation and dehydration were treated and subject was discharged home with hospice care. The investigator considered the event atrial flutter with rapid ventricular rhythm to be possibly related to a known rare side effect of GM-CSF therapy.

Protocol Number: **661**

Protocol Title: **A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Dose-Selection Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 in Patients with Intermittent Claudication.**

DocID#	Receipt Date	Event Description
8586	06/06/2006	Subject was diagnosed with adenocarcinoma of the prostate eight months after receiving the blinded study treatment. The patient's screening prostatic specific antigen (PSA) level done before administration of the investigational agent was slightly above normal range. In the opinion of the Investigator, the adenocarcinoma was possibly related to study treatment.

Protocol Number: **682**

Protocol Title: **Treatment of Lower Extremity Critical Limb Ischemia via Modulation of VEGF-A Using an Engineered Zinc-Finger Transcription Factor (EW-A-401) to Evaluate Safety and the Effects on Progenitor Cells.**

DocID#	Receipt Date	Event Description
8547	05/24/2006	About one month after receiving the gene transfer, the subject was admitted to the hospital for lower limb pain in the non-treated leg. The arteriogram did not reveal an emboli in the leg. The subject was treated with intravenous heparin and discharged on Coumadin.
8548	05/24/2006	Four months after receiving the gene transfer, the subject was admitted to the hospital for an elective revascularization of leg. It was attempted twice, and the graft clotted each time. Due to increased infection and gangrene to the limb a "below the knee" amputation was performed.
8552	05/24/2006	Subject was on anticoagulation for peripheral vascular disease. Four months after receiving the gene transfer, subject was admitted to the local hospital to treat a bleeding episode in the lower gastrointestinal tract. Subject received two units of packed red blood cells and recovered completely from the episode.
8555	05/24/2006	Approximately two months after receiving the gene transfer, the subject began showing symptoms of expressive aphasia and was admitted to the local hospital for observation. Imaging studies revealed a left parietal infarct. Subject was also found to be heterozygous for a Factor V Leiden mutation. The Principal Investigator's assessment as to causality was not included in the report. The Sponsor assessed the stroke as being "unlikely" related to the gene transfer.

Protocol Number: **692**

Protocol Title: **A Phase I, Open Label, Dose Escalation Study of the Safety, Tolerability and Preliminary Efficacy of Intraperitoneal EGEN-001 in Patients with Recurrent Epithelial Ovarian Cancer.**

DocID#	Receipt Date	Event Description
8526	05/12/2006	Approximately two weeks after administration of the gene transfer, the subject was admitted to the hospital for peritonitis (inflammation of peritoneum). The subject was treated with appropriate antibiotics. Computer tomography (CT) results pending.

Protocol Number: **698**

Protocol Title: **A Phase I/II Study of Rituximab, High Dose Cyclophosphamide, and GM-CSF Based Immunotherapy for Relapsed Hodgkin's Lymphoma.**

DocID#	Receipt Date	Event Description
8618	06/30/2006	About one week after receiving the gene transfer and 10 days after high dose cyclophosphamide, subject was admitted to the hospital for neutropenic fever. Subject was completing a platelet transfusion when subject developed a fever to 39.9 C with rigors (shivering/chills). A platelet reaction workup was done. Central line blood culture grew gram positive cocci. Subject received intravenous antibiotics with red cell and platelet support as required. The suspicion is that the platelet product may have been contaminated by bacteria and the neutropenia is a result of the chemotherapy.

Protocol Number: **700**

Protocol Title: **MC044C-Phase I Evaluation of Safety of Intravenous Infusion of a Pathotropic Retroviral Vector Bearing a Cytocidal Cyclin G1 Construct (Rexin-G) as Intervention for Locally Advanced and Metastatic Pancreatic Cancer Refractory to Standard Chemotherapy.**

DocID#	Receipt Date	Event Description
8566	05/30/2006	Two days after receiving the gene transfer, the subject was admitted to the hospital with fever, hemoptysis and back pain. The subject was on low molecular weight heparin for a pulmonary embolism. The hemoptysis was felt to be related to the anticoagulation. The fever was felt to be possibly related to the investigational agent. The back pain was attributed to known metastatic lesions to the spine.

Protocol Number: **705**

Protocol Title: **A Phase 1 Dose Escalation Study of Repeat Intra-Articular Administration of tgAAC94, a Recombinant Adeno-Associated Vector Containing the TNFR:Fc Fusion Gene, in Inflammatory Arthritis Subjects with and without Concurrent TNF-α Antagonists.**

DocID#	Receipt Date	Event Description
8598	06/20/2006	Fifteen weeks after study drug injection, subject developed sudden onset of severe left knee pain and increased swelling. Joint aspirate revealed a white blood cell count of 135, 000. Gram stain was initially reported as showing Gram positive cocci: the report was later amended to no organisms seen. Crystal examination was negative. The subject was taken to surgery for open irrigation and debridement of the left knee and started on intravenous antibiotics. Cultures of both joint fluid and blood were negative. Subject improved and was discharged from the hospital to complete a course of IV antibiotics as an outpatient. The Principal Investigator considered the event to be probably related to study drug. Sponsor concurs with this assessment. This event is considered unexpected.