Serious and Other Selected Adverse Events
Reported for Human Gene Transfer Protocols
Recombinant DNA Advisory Commitee Meeting
September 2007

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
9101	05/02/2007	Two weeks after busulfan administration, the patient's absolute neutrophil count fell and reached a level that constituted a Grade 3 toxicity event according to the pediatric Division of AIDS (DAIDS) toxicity scale. The event resolved. About one month later the subject then had an apparent ear infection and about two weeks later the absolute neutrophil count once again fell to a level that constituted a Grade 3 toxicity in the pediatric DAIDS toxicity scale. Decreased production of blood cells from the bone marrow is an expected consequence of the administration of busulfan. The principal investigator noted that a respiratory tract infection may have stimulated an increase in neutrophil production by the bone marrow, which may have consumed the patient's bone marrow of reserve of granulocytes and caused the decrease in the absolute neutrophil count below the Grade 3 toxicity threshold.

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
9171	07/02/2007	The first dose of TNFerade was administered via percutaneous administration. The second dose of TNFerade was administered one week later; but upon arriving for the third dose, the subject was noted to have an irregular heart rate. The subject was admitted to the hospital for further evaluation. An electrocardiogram confirmed atrial fibrillation with a ventricular rate of approximately 100 beats per minute. A beta blocker was prescribed. During the hospitalization, subject also experienced stomatitis (felt to be related to concomitant chemotherapy), weakness, anemia, and abdominal pain. An abdominal CAT scan revealed new small pleural effusions, and a hematoma anterior to the left lobe of the liver. Due to the hematoma, subsequent doses of the gene transfer are being discontinued. An echocardiogram confirmed mitral valve prolapse.

Protocol Number: **545**

Protocol Title: **A Phase I Escalating Dose, Open Label Evaluation of Safety, Feasibility and Tolerability of Transgenic Lymphocyte Immunization Vaccine (TLI) in Subjects with Histologically Proven Prostate Adenocarcinoma.**

DocID#	Receipt Date	Event Description
9099	05/03/2007	Subject underwent gene transfer in 2004. Subject complained of rash starting in early 2006 with itching. The rash was not painful. Upon inspection of the skin, the surrounding right hip demonstrated a dermatomal-like rash originating in the lower back and extending laterally anteriorly to the umbilicus. The rash was slightly raised with no sign of any papules which had crusted. The history and physical exam were consistent with shingles. Subject was prescribed Famvir. The principal investigator assessed this incident as unlikely to be treatment related, but not definitely unrelated due to the possible relationship to immune function.

Protocol Number: **591**

Protocol Title: **An Open-Label Safety Study of Escalating Doses of SGT-53 for Systemic Injection in Patients with Advanced Solid Tumor Malignancies.**

DocID#	Receipt Date	Event Description
9213	08/07/2007	Subject received the first infusion of the gene transfer intravenously, via a venous central line. The subject was being monitored for eight hours post infusion in an outpatient setting as specified per study protocol. Prior to the infusion, the blood pressure (BP) was elevated (above 160 mmHg systolic). During the infusion, the subject did not have any complaints and BP, varied between 140-150 systolic with normal diastolic pressure and normal pulse. Five hours post-infusion, the subject's BP started to rise and it peaked with a systolic blood pressure above 200mmHg and diastolic above 100 mmHg. The subject developed chills and a low grade fever. Subject's outpatient antihypertensive medication was administered. At the same time, the subject complained of left sided abdominal cramps and slight headache. The subject was given Tylenol. Eight hours post infusion, blood glucose went up above 200 mg/dl, and temperature increased to above 40.7 degrees Celsius. The BP remained elevated and a new hypertensive drug was administered orally. The subject was admitted for management of hypertension and fever. Over the next few hours, blood work was done showing a decline in white blood cell and red blood cell count along with elevation in D-dimer, decrease platelets and increase in partial thromboplastin time. A chest x-ray showed infiltrates and pleural effusion, which resolved over the next week. The subject's clinical status improved over the next 48 hours and the subject was discharged. Because the first subject to receive the study agent was hospitalized the trial was placed on voluntary hold per protocol pending further review of event by the data safety monitoring board.

Protocol Number: **631**

Protocol Title: **A Pilot Trial of a CEA-TRICOM Based Vaccine and Radiation to Liver Metastasis in Adults with CEA Positive Solid Tumors**

DocID#	Receipt Date	Event Description
9113	05/08/2007	Subject was admitted to hospital with abdominal pain and shortness of breath about one week after a dose of the gene transfer vaccine. The subject had been receiving the gene transfer vaccine for almost 4 months. Radiologic imaging showed extensive abdominal metastatic disease. Subject had an elevated bilirubin, (The Common Terminology Criteria for Adverse Events, Grade level 3) and elevated liver enzymes. The differential diagnosis includes possible radiation induced hepatitis/ cholangitis versus low grade bowel obstruction or ileus attributed to radiation or metastatic disease. The investigator cannot rule out an association between the gene transfer and the changes in the liver blood tests but believes these changes are more likely related to the underlying colon cancer.
9147	06/01/2007	Follow-up received on the subject who developed abdominal pain and elevated liver blood tests. A magnetic resonance cholangiopancreatography revealed a lymph node causing extrinsic compression over common bile duct resulting in gross intrahepatic and extrahepatic biliary duct dilitation. The subject was scheduled for a biliary stent to relieve the obstruction. In light of this finding, the principal investigator concluded that the event was related to the target disease and not the study agent.

Protocol Number: **653**

Protocol Title: **A Phase III Randomized, Open-Label Study of CG1940 and CG8711 Versus Docetaxel and Prednisone in Patients with Metastatic Hormone-Refractory Prostate Cancer Who are Chemotherapy-Naïve**

DocID#	Receipt Date	Event Description
9109	05/08/2007	Subject's status deteriorated from cerebral ischemia caused by progression of thromboembolic disease, resulting in death. The event was reported by the investigator as grade 5 cerebral vascular ischemia, related to CG1940/CG8711, with associated event of grade 1 anorexia, unrelated to CG1940/CG8711.
9158	06/13/2007	The subject presented to the hospital complaining of a several week history of dyspnea that worsened with exertion. The subject reported that dyspnea episodes usually lasted 30 minutes and stopped when subject discontinued activity. Subject also reported occasional chest pressure at rest. Subject was subsequently admitted to evaluate for cardiac disease, and was administered Plavix and full-dose aspirin. Upon initial examination, the subject was afebrile with normal vital signs and was found to have diminished breath sounds at lung bases bilateral. Initial laboratory evaluations were unremarkable with normal white blood cell (WBC) count (4.8 K/mm3) and normal cardiac enzymes and coagulation studies. The subject subsequently underwent a left heart catheterization that showed diffuse, but non-critical coronary artery disease, with normal ventricular function and no significant mitral regurgitation. A 2-D echocardiogram was also performed, showing preserved left ventricular function with no significant valvular lesions and/or pericardial effusion. A ventilation-perfusion lung scan showed multiple perfusion defects corresponding to a high probability of pulmonary embolism that was later confirmed by chest CAT scan, which showed an embolus in the right lower lobe. The subject was started on heparin and, once stabilized, was discharged with continued anti-coagulation 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
9186	07/23/2007	Subject developed stage T1c adenocarcinoma of the prostate six months after receiving the gene transfer. The patient's screening serum prostatic specific antigen (PSA) level was slightly above normal range. The screening digital rectal prostate exam was normal. The PSA level at Week 26 had risen and subject was referred to a urologist. In the opinion of the investigator, the adenocarcinoma was of severe intensity and possibly related to study treatment.
9159	06/15/2007	Subject diagnosed with prostate cancer eight months after receiving the investigational gene transfer. Baseline prostate specific antigen blood test and digital rectal exam were within normal limits.

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
9231	08/20/2007	Subject died approximately 3 weeks after receiving second dose of gene transfer. Subject had multiorgan failure and final autopsy results showed evidence of dessiminated histoplasmosis infection. Case discussed at Recombinant DNA Advisory Meeting on September 1, December 5, 2007, and January 14, 2008.

Protocol Number: **708**

Protocol Title: **A Phase 3 Randomized, Open-Label Study of Docetaxel in Combination with CG1940 and CG8711 versus Docetaxel and Prednisone in Taxane-Naive Patients with Metastatic Hormone-Refractory Prostate Cancer with Pain.**

DocID#	Receipt Date	Event Description
9169	06/01/2007	Subject presented to the clinic complaining of swelling and erythema in the left arm one week after receiving six intradermal injections of the study agent. Subject was admitted to hospital the same day. Subject had areas of warm, mildly tender patchy redness with mild scaling on left arm consistent with cellulitis. A complete blood count revealed leucopenia with neutropenia. The subject was treated with intravenous antibiotics with considerable improvement in the cellulitis. Subject remained afebrile and hemodynamically stable during hospital course, however, white blood cell count and absolute neutrophil count continued to drop by the time of discharge. This decline was felt to be associated with the nadir of the subject's most recent docetaxel cycle. Discharge medications included 10-day course of oral antibiotics. Subject returned to the clinic for follow up fully recovered with no significant erythema at the previously documented site of cellulitis. Subject's repeat labs showed improved white blood cell and neutrophil counts. The event was reported by the principal investigator as Grade III neutropenic infection, related to study agent and docetaxel.

Protocol Number: **750**

Protocol Title: **A Phase I/II Safety, Tolerability, and 'Proof of Concept' Study of TNFerade™ in Combination with Concomitant Radiotherapy, Fluorouracil, and Hydroxyurea (TNF-FHX) for Patients with Unresectable Recurrent Head and Neck Cancer.**

DocID#	Receipt Date	Event Description
9155	06/12/2007	Subject had a carotid bleed after the 6th dose of study agent. Embolization of the carotid artery was done and subject required admission to the intensive care unit after embolization. Post-operative course was complicated by a pneumothorax requiring pleurodesis due to repeated air leaks and a neck wound infection. The carotid bleed was thought to be caused by the significant tumor reduction leading to erosion into the vessel.
9180	07/10/2007	Subject developed a low-grade fever and a foul smelling, cloudy sputum from tracheostomy approximately one week after receiving the fifth dose of the gene transfer. The subject's family also reported that subject had become "distant and pale, conversing less". The subject was taken to a local emergency room and was admitted to the hospital for further evaluation. A brain MRI was negative for acute stroke and chest x-ray was negative for pneumonia. A complete blood count revealed a normal white blood cell count. No infection was diagnosed and subject continued to receive chemotherapy and radiation therapy during hospitalization.

Protocol Number: **772**

Protocol Title: **A Phase II Study of Direct Tumor Injection of TNFerade™ Followed by KLH-Pulsed Autologous Dendritic Cells in Patients with Unresectable Pancreatic Cancer**

DocID#	Receipt Date	Event Description
9095	05/02/2007	Subject was admitted to the hospital with fever about one week after receiving the gene transfer. The subject was found to have an infection and was treated and discharged. The attribution of this event has been changed and it is no longer considered related to the study agent.

DocID#	Receipt Date	Event Description
8989	05/23/2007	Subject experienced a ischemic stroke resulting in hemiparesis (loss of movement on one side of the body) twenty-eight days after receiving the gene transfer.
9174	07/02/2007	Approximately 29 weeks after commencing the gene transfer vaccines, the subject developed a deep vein thrombosis after reportedly being "housebound" for four days. The study investigator could not rule out a contribution from the study agent.
9175	07/02/2007	Eight days after receiving the gene transfer and interleukin IL-2, subject had a gastric bleed which resulted in haemorrhagic shock. Records indicate the subject was taking two different non-steroidal anti-inflammatory medications for pain in the month prior to the event.
9176	07/02/2007	Subject died from a gastric hemorrhage. The autopsy report raised the possibility that the subject had an undiagnosed chronic stomach ulcer that could have been exacerbated by the administration of interleukin-2.
9179	07/10/2007	Subject admitted with complaints of weakness and melena approximately ten days after receiving first dose of gene transfer and beginning therapy with interferon-alpha. The subject was diagnosed with an upper gastrointestinal bleed and severe anemia (low red blood cell count). Subject remained in the hospital due to a number of complications including a urinary tract infection, pneumonia, and development of jaundice due to a lymph node obstructing the biliary system. Subject's declining health led to a decision to withdraw the patient from the study.