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

Protocol Number: **4**

Protocol Title: **Autologous Bone Marrow Transplant for Children with Acute Myelogenous Leukemia in First Complete Remission: Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and the Mechanism of Relapse.**

DocID#	Receipt Date	Event Description
8284	01/17/2006	Over ten years after gene transfer, subject was diagnosed with moderate to severe avascular necrosis (death of bone tissue) (AVN) in hips and shoulders. Subject underwent bone grafting of hips and shoulder replacement. AVN is an expected post transplant complication; however AVN is typically found to be more common in patients who received radiation treatment and long term, high dose steroids. Subject did not receive radiation treatment for leukemia and received only rare, intermittent steroids. Follow up Investigator: This event of severe AVN requiring multiple surgeries and persistent disability is unexpected in the context of the autologous transplant and gene marking and the relationship can only be considered unknown at this time.

Protocol Number: **359**

Protocol Title: **Phase I Trial of Adenoviral Vector Delivery of the Human Interleukin-12 cDNA by Intratumoral Injection in Patients with Primary or Metastatic Colorectal Cancer to the Liver.**

DocID#	Receipt Date	Event Description
8093	11/21/2005	Eight days after gene transfer, subject had an elevated APTT (coagulation blood test) that was noted on routine study blood tests. Subject denied nausea, vomiting, chills, shortness of breath, bleeding, or pain. These results suggest that APTT elevation may be due to development of an antiphospholipid antibody. The adverse event is assessed as a grade 2 (Common Toxicity Criteria) coagulation, possibly related to intratumoral injection of the gene product. The subject experienced no adverse clinical outcomes associated with this lab abnormality.

Protocol Number: **400**

Protocol Title: **Transfer of the Multidrug Resistance Gene, MDR-1, to Hematopoietic Progenitors from Patients with High Risk Lymphoma.**

DocID#	Receipt Date	Event Description
8097	08/31/2005	Nine months after gene transfer, subject was hospitalized with complaints of shortness of breath and lower extremity swelling. Subject was diagnosed with myocardial infarction and a Computed Tomography (CT) scan of the lungs showed bilateral ground glass appearance and scattered interstitial (between the tissue) infiltrates. Subject had no clinical improvement despite appropriate antibiotic therapy and was intubated. Ventilator support was eventually discontinued because subject did not improve and subject expired. The principle investigator does not believe the pulmonary toxicity experienced by this subject to be secondary to the gene transfer, but may have been related to the chemotherapy and radiation preparative regimens received prior to the stem cell transplants, and the long-standing immune suppression post transplant. The cardiac toxicities may be the result of coronary disease found during autopsy, and possibly, the cumulative consequences of chemotherapy received as part of the subject's initial therapy a few years ago, and the high dose cyclophosphamide with the second transplant.

Protocol Number: **452**

Protocol Title: **A Multicenter, Randomized, Double-Blind, Placebo Controlled, Dose-Response Study to Evaluate the Efficacy and Safety of Ad5.1FGF-4 in Patients with Stable Angina.**

DocID#	Receipt Date	Event Description
8080	11/10/2005	Almost two years after gene transfer, subject expired. No additional information available.

Protocol Number: **480**

Protocol Title: **A Phase II, Open-Label, Ascending Dose Study of the Safety and Efficacy of Trinam™ (EG004) in Stenosis Prevention at the Graft-Vein Anastomosis Site in Dialysis Patients.**

DocID#	Receipt Date	Event Description
8067	09/22/2005	Nine months after the gene transfer, subject experienced an outflow vein rupture at site of dialysis graft. This event resolved.
8062	09/22/2005	The subject experienced an AV graft site complication. No information provided on date of gene transfer.
8065	09/22/2005	Subject experienced a thrombosis of dialysis graft. No information provided on date of gene transfer.

Protocol Number: **520**

Protocol Title: **Transplantation of Unrelated or Mismatched Related Donor T cells Containing the HSV-TK Suicide Gene to Facilitate Engraftment and Control Graft-versus-Host Disease in Patients with Fanconi Anemia. A Phase I Trial.**

DocID#	Receipt Date	Event Description
8108	10/11/2005	Approximately one month after gene transfer, subject had a fatal arrhythmia while in the hospital receiving treatment for infection with associated complications including renal insufficiency and hematologic abnormalities. Per the investigator, the infection and multi-organ system failure experienced by this subject is expected and unlikely to be related to gene transfer. The arrhythmia experienced by this subject was "unusual and unexpected and possibly related to gene transfer." A detailed summary of infusion toxicity, blood test results, tumor staging, data related to subject's infections and the clinical course of respiratory decline was provided.

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
8187	12/21/2005	After completion of the fourth injection of the investigational agent and radiation treatment, the subject complained of dizziness and "seeing stars" and appeared to lose consciousness for less than a minute. Fluids and oxygen were administered and the subject was immediately responsive. Subject noted chills and confusion but did not have nausea, vomiting, pain or fever. Symptoms resolved rapidly with hydration and oxygen. The principal investigator and sponsor's medical monitor have agreed to not administer the fifth dose of the investigational agent in light of the escalating post dosing complications. The Investigator deemed the event as probably related to study drug, possibly related to the administration procedure and unrelated to chemotherapy or to radiation therapy.

Protocol Number: **549**

Protocol Title: **A Phase II, Multi-Center, Single Arm Evaluation of Preoperative Chemoradiation plus TNFerade™ Biologic (AdgvEGR.TNF.11D) Prior to Esophagectomy for Locally Advanced Esophageal Cancer.**

DocID#	Receipt Date	Event Description
8146	12/13/2005	Subject had five weeks of chemotherapy and radiation therapy combined with gene transfer. Subject then underwent a thoracoscopic esophageal mobilization, laparascopic gastric mobilization with esophago-partial gastrectomy, gastric pull-up and jejunostomy tube placement. Post-op course was complicated by an anastomotic leak with empyema. The leak ultimately sealed and subject was discharged. Subject subsequently underwent repeated esophageal dilatations and applications of Indermil Tissue glue to the fistula site. A follow-up endoscopy confirmed the fistula was closed. The Investigator considered the delayed recovery from surgery as possibly related to the study drug and definitely related to the underlying disease and surgery.
8127	12/02/2005	This is an informational report of a long term thrombotic complication in a subject treated on a currently inactive study. The subject, with adenocarcinoma of the esophagus, received gene transfer more than one year ago. The subject had a computed tomography scan (per protocol) that revealed an asymptomatic right middle lobe pulmonary embolus. The investigator felt that this pulmonary embolism was incidental and anticoagulation was not initiated. A successful esophagectomy was performed. The CT findings of pulmonary emboli were again noted. The subject relapsed with disease found in the upper esophagus and liver and was treated with ongoing chemotherapy. A recent evaluation suggested persistent but slightly decreased metastases. Subject was admitted with acute abdominal pain. The work up, including chest CT, revealed a new pulmonary emboli, again without respiratory symptoms. The abdominal CT did not reveal a clear source for the abdominal pain and subject's discomfort resolved with analgesia and anticoagulation. The subject was started on and continues on coumadin and enoxaparin. Subject's physician feels that the abdominal pain may have been a consequence of abdominal deep vein thrombosis that subsequently embolized to lung. The subject continues to be asymptomatic from the pulmonary emboli after the event. The Investigator deemed these events as possibly related to the study drug because subject was unable to completely exclude a relationship but, the investigator felt it was and probably related to underlying disease. The Medical Monitor disagrees with the possible attribution to study drug, as these events occurred over 1 year after completion of treatment with TNFerade in the setting of metastatic esophageal adenocarcinoma with ongoing Megace therapy. Sponsor considers the event to have an unlikely relationship to study drug or to the administration procedure and probable relationship to underlying disease and Megace therapy.

Protocol Number: **552**

Protocol Title: **A Phase I/II Study of An Antitumor Vaccination using α(1, 3) Galactosyltransferase Expressing Allogeneic Tumor Cells in Patients with Refractory or Recurrent Non-Small Cell Lung Cancer.**

DocID#	Receipt Date	Event Description
8110	11/29/2005	One day after gene transfer, subject was noted to have a low absolute lymphocyte count . Pre-study lymphocyte counts were within normal limits. The Investigator reports " It is uncertain if the lymphopenia is a late reaction to the extensive radiation therapy that the subject previously received (for multiple bone and brain metastases) or an acute effect of the vaccine". The subject had no adverse symptoms, and the event resolved completely without specific intervention.

Protocol Number: **567**

Protocol Title: **A Multicenter, Randomized, Double-Blind, Dose Ranging Placebo-Controlled Study Evaluating Defined Doses of Percutaneously Delivered Via Boston Stiletto™ Endocardial Direct Injection Catheter System pVGI.1 (VEGF2) (placebo, 20, 200, or 800µg) in Patients with Class III or IV Angina.**

DocID#	Receipt Date	Event Description
8090	11/17/2005	During administration of the gene product or placebo, the subject's electrocardiogram began to show ST-segment elevation and subject developed chest pain. The decision was made to stop treatment. Subject discharged the next day.
8081	11/14/2005	Per the family, subject was admitted to local hospital for a pacemaker implant for third degree block. Family stated that subject was disoriented when subject arrived home from hospital. Subject was found dead the next morning. A local cardiologist believed cause of death to be complete heart block. The Principal Investigator assessed the causality as unknown until more records have been obtained.
8191	12/23/2005	About three weeks after gene transfer, the subject presented to the ER complaining of inability to move right leg for approximately 30 minutes. The subject was admitted for further evaluation, and continued to experience difficulty moving toes on right foot. The subject was discharged with a diagnosis of transient ischemic attack. The investigator judged the relationship as unknown to study drug and not related to the device or procedure.
8432	03/13/2006	Several hours after injection of the study agent, subject became hypotensive and short-of-breath and was discovered to have a collection of fluid around the heart (pericardial effusion) that required pericardiocentesis. During the pericardiocentesis, the subject developed a ventricular arrythmia requiring defibrillation. The subject was taken to surgery for a pericardial window and evacuation of clots and was discovered to have a posteriolateral perforation of the left ventricle. The subject was admitted to the intensive care unit and required pressors to maintain hemodynamic stability. Subject did recover and was discharged from the hospital.

Protocol Number: **600**

Protocol Title: **A Phase II Randomized, Double Blind, Controlled Study to Evaluate the Safety and Efficacy of PROSTVAC®-VF/TRICOM™ in Combination with GM-CSF in Patients with Androgen-Independent Adenocarcinoma of the Prostate.**

DocID#	Receipt Date	Event Description
8188	12/19/2005	About one month after gene transfer, subject was admitted with epigastric pain, shortness of breath, and diaphoresis. Subject had a myocardial infarction. Subject also diagnosed with thrombotic thrombocytopenic purpura and acute renal failure. Subject was discharged and continued dialysis and plasmaphoresis as an outpatient.
7959	10/20/2005	One month post administration of the study agent or placebo, subject presented to the clinic because nephrostomy tube was leaking and not draining. The nephrostomy tube was removed after a negative antegrade contrast study. Approximately 2 to 3 hours after the procedure, subject experienced fevers and chills. Subject recorded a fever at home of 104.0 F degrees and returned to the ER for evaluation. Laboratory results showed subject to have possible bacteremia. Subject treated with antibiotics and intravenous fluids. Blood cultures showed no growth at 2 days. A urine culture was positive for bacteria. The subject remained hospitalized. The investigator classified the event of fever as possibly related to the study drug administration.

Protocol Number: **611**

Protocol Title: **Modulation of Vascular Endothelial Growth Factor (VEGF) Using an Engineered Zinc-finger Transcription Factor to Treat Lower Limb Intermittent Claudication.**

DocID#	Receipt Date	Event Description
8145	12/14/2005	Nine months after gene transfer, subject admitted to hospital for catheterization and placement of a stent pursuant to clinical evaluations that were scheduled as follow up to previous myocardial infarction.
8147	12/14/2005	Ten months after gene transfer, subject diagnosed with prostate cancer and was scheduled for radiation therapy. The cancer was detected by a routine physical exam.

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
8180	12/19/2005	Eight days after gene transfer subject admitted after a siezure. Subject had another siezure in the hospital and medications were adjusted. Imaging done showed resolution of post operative pneumocephalus. Prior medical records and lab values provided by investigator in follow-up report.
8181	12/20/2005	Six months after gene transfer, an update received on the subject's recent seizure activity at the suggestion of the subject's local pediatric neurologist. The mother reported that the subject was experiencing clusters of brief seizures while attempting to fall asleep in the evening or for an afternoon nap. These episodes were characterized by a stiffening of the body and a deviation of the head to the left, lasting a few seconds each, and resolving without intervention. Following each episode, the subject would cry for approximately 20 minutes, and then experience another similar episode while re-attempting to fall asleep. Anti-epileptic medications were adjusted. Per the investigator "this is being reported as a SAE because it is medically significant event. The intensity is mild. 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
8058	11/02/2005	About three months after starting gene transfer with cancer vaccine, subject was hospitalized for fever, chills, vomiting, nausea, abdominal pain, and dehydration. A Computed Tomography scan performed just prior to admission confirmed disease progression, manifested by an increase in the size of liver, lower chest, and abdominal lesions, as well as the primary pancreatic head carcinoma. After receiving intravenous (IV) hydration, subject developed a fever of 101 degrees Fahrenheit, had chills and began to vomit. The subject was treated with antibiotics for a suspected in-dwelling catheter infection. The nausea and vomiting improved with anti-emetics. Subject continued to require intravenous hydration and pain control treatment. The subject's dehydration, fever, and chills all resolved without sequelae at discharge. The subject was withdrawn from the study due to disease progression. The fever and chills were considered to be possibly related to study drug administration; all other events were considered not related to study drug administration, but rather to progressive pancreatic cancer. This is the first report of possibly vaccine-related serious adverse events of pyrexia and rigors in the study.
8075	11/04/2005	Approximately two months post gene transfer, the subject developed a blood clot in right leg and was placed on Fragmin. Subject was initially managed as an outpatient until left leg began to swell, and subject was subsequently hospitalized. This information within this report is based on a phone call from the subject's family. No medical documents were available at the time of this report. The subject has not yet received a primary evaluation from the investigator. This is the first report of a possibly vaccine-related serious adverse event of deep vein thrombosis in this study.

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
8104	11/18/2005	Investigator changed the adverse events and attribution to joint pain and muscle pain/aches, related to gene transfer vaccine with associated events of aggravated atrial fibrillation, related to gene transfer vaccine. Urinary tract infection and pneumonia were clearly unrelated events. Events occurred approximately ten days after gene transfer.

Protocol Number: **657**

Protocol Title: **A Phase II Trial Using a Universal GM-CSF-Producing and CD40L-Expressing Bystander Cell Line (GM.CD40L) in the Formulation of Autologous Tumor Cell-Based Vaccines for Patients with Malignant Melanoma.**

DocID#	Receipt Date	Event Description
	10/21/2005	Subject experienced slow heart and low blood pressure immediately following a punch biopsy three days after gene transfer vaccine. Blood pressure went as low as 40/20 and pulse into the 40's. Subject recovered after about twenty minutes with intravenous fluids and being placed in a prone position. Subject was admitted to the medical center and monitored for 24 hours. Cardiac enzymes were negative. Subject reported a similar incident approximately 4 months ago that occurred while flying. Subject was instructed to hold beta blocker medication and an appointment with subject's cardiologist was arranged the week of discharge.

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
8261	01/12/2006	Approximately one month after receiving gene transfer the subject was admitted to the hospital for acute ischemia (decrease in blood flow) to the right leg that required a revascularization procedure. The subject was known to have underlying peripheral vascular disease that is characterized by decreased blood flow to the extremities due diseased arteries. This acute ischemic event was unexpected and there may have been an acute atherothrombotic event (i.e. arterial clot) associated with a vulnerable arterial atherosclerotic plaque, but this could not be confirmed. Although this subject's event was likely due to underlying peripheral arterial disease, a relationship to study treatment could not be ruled out. Therefore, the event was considered possibly related to the gene product.

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
8125	12/01/2005	Less than one month after receiving gene transfer, subject contacted investigational site complaining of a low grade fever. The subject appeared short of breath (SOB) to coordinator. Subject had a Tenckhoff intraperitoneal catheter in place as part of the study, but subject denied symptoms at the catheter site. On physical examination by a physician, the subject had abdominal rebound and guarding. Subject was admitted for intravenous antibiotics and abdominal computed tomography scan due to suspected peritonitis. Upon admission subject was afebrile with normal vital signs. Subject was awake, alert and oriented with no signs of distress. Lungs were clear to auscultation bilaterally with a regular heart rate and rhythm. White blood cell count was within normal limits. Treatment consisted of IV antibiotics and removal of Tenckhoff catheter. Subject did have some low grade fevers during hospitalization with a maximum temperature of 100.6 degrees Fahrenheit. Abdominal computed tomography scan showed that the cancer had spread to many areas (carcinomatosis) and moderate ascites. Blood cultures and cultures from the ascites had no growth to the date of discharge. Plans were made for a follow up computed tomography scan after discharge.