

**Serious and Other Selected Adverse Events
Reported for Human Gene Transfer Protocols
Recombinant DNA Advisory Committee Meeting
September 2009**

Protocol Number: **530**

Protocol Title: **A Randomized, Phase II/III 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 |
|--------|--------------|--|
| 10364 | 05/12/2009 | The subject experienced bleeding from the gastrointestinal tract almost two months after receiving the last dose of the study agent. A scope placed through the mouth looking at the upper digestive tract was negative. A computed tomography (CT) scan revealed that dead tissue from the pancreatic mass had eroded into the stomach and that this may have been the cause of the bleeding. The bleeding stopped the day after subject was hospitalized. |
| 10441 | 07/13/2009 | The subject received the first dose of study agent. The subject was recently discharged from a hospital where a MRI of the spine had been done for complaints of decreased sensation over the abdomen and leg weakness. MRIs showed significant spinal stenosis in the cervical spine (narrowing of the spinal cord) without any metastatic disease. Surgery was performed upon cervical spine after readmission to the hospital for progressive numbness, tingling and weakness in the upper extremities, chest and legs. The subject was discharged after the surgery but readmitted within a day with complaints of worsening upper and lower extremity weakness. While MRIs of the spine were unchanged, an MRI of the brain done after subject developed seizures revealed posterior white and gray matter changes of unclear etiology but possibly related to infectious or a cytotoxic agent. The subject required intubation for recurrent seizures but recovered and subsequent MRI showed clearing of the abnormal changes. The final diagnosis was posterior encephalopathy syndrome of unclear etiology. A possible role of the investigational agent cannot be ruled out. |
| 10366 | 05/15/2009 | On admission for scheduled chemotherapy, the subject was found to have a low red blood cell count. The subject informed the treating physician of vomiting blood 4 days prior to admission. A scope was placed through the mouth to examine the upper digestive tract. There were signs of bleeding. The investigator felt that the bleeding was most likely due to the underlying disease. However, it was unclear whether this alone could account for the decrease in red blood cells, or whether the study agent had a role. |
| 10420 | 06/25/2009 | Two days after the dose of study agent, the subject was admitted to the hospital due to complaints of nausea, vomiting and dehydration. The subject was discharged in two weeks. The subject has not yet recovered and the event is considered to be ongoing. |
| 10458 | 07/22/2009 | While admitted to the hospital for a third injection of study agent, the subject experienced a persistent fever of 100 to 102 degrees Fahrenheit and rigors (shaking). The subject was admitted for overnight observation. It was noted that the subject tolerated the previous two injections well, but also experienced rigors. Upon admission, the subject had no complaints of cough, shortness of breath, chest pain, or urinary symptoms. The next day the subject's fever continued and peaked overnight at 102 degrees Fahrenheit. A preliminary chest x-ray from that day suggested a presence of an infectious process; however, a subsequent chest x-ray did not show this, but did show a possibility of atelectasis (collapse of part of the lung). The subject had complaints of weakness and fatigue, so the subject remained in the hospital as an inpatient and initiated antibiotic therapy. The subject's fever resolved the same day, but the subject remained hospitalized for more observation prior to discharge. It was noted that the subject's symptoms were consistent with possible transient bacteria in the blood that resulted from the intratumoral study agent injection and perhaps related to the procedure or chemotherapy. Therefore, the doctor cannot definitively establish the causality of the event. The subject was discharged from the hospital three days later. The subject has recovered and the event is considered to be resolved. Study agent administration was interrupted. |

10440 07/10/2009 An elderly subject with a history of diabetes and chronic renal insufficiency was admitted to the hospital for bilateral lower extremity edema (swelling), an infected ulcer and cellulitis of the right and left lower extremities over a month after the last dose of the gene transfer agent. The subject was treated with broad-spectrum antibiotics and pills that help remove fluid and reduce edema. The wound was cultured and grew coagulase-negative staphylococcus. The Investigator noted that the cellulitis and edema were most likely a reaction to the study agent. The subject was discharged on antibiotics for ten days.

Protocol Number: 725

Protocol Title: **A Phase I Pilot Study of Safety and Feasibility of Stem Cell Therapy for AIDS Lymphoma Using Stem Cells Treated with a Lentivirus Vector Encoding Multiple anti-HIV RNAs**

| DocID# | Receipt Date | Event Description |
|--------|--------------|---|
| 10358 | 05/07/2009 | Upon evaluation at six months after transplant, the subject was diagnosed with Langerhans Cells Histocytosis (LCH) of the shoulder blade. LCH is a disease in which there are too many of a type of white blood cell called a Langerhans cell. Due to the rarity of this event, the subject was asked to come in for follow-up. Based on the clinical presentation, it was unclear whether this was an inflammatory reaction or malignancy. The possibility of this being related to the subject's underlying disease could not be ruled out. A full body bone survey was conducted and was negative for this process. A second chest CT scan was performed and showed multiple small cysts with thick walls in the upper regions of the lungs. The subject had elevated chlamydia antibodies, a sign of the body fighting infection, and was treated as an outpatient. The subject had a bronchoscopy, a video image of the airways, which did not reveal any significant pathology. The CT scan, however, was consistent with LCH of the lungs. Because there was no tissue confirmation, this is based only on the images. The history of possible chlamydia lung infection and the subject's history of continued smoking, suggest that this is an inflammatory, reactive process rather than malignancy. The investigators have monitored the subject's blood for presence of the vector. There was detectable vector for 3 months after transplant, but the 4 month results did not show any evidence of vector in the blood. |

Protocol Number: 741

Protocol Title: **A Phase 2 Double-Blind, Placebo Controlled, Multi-center Adjuvant Trial of the Efficacy, Immunogenicity, and Safety of GI-4000; an Inactivated Recombinant Saccharomyces cerevisiae Expressing Mutant Ras Protein Combined with a Gemcitabine Regimen Versus a Gemcitabine Regimen with Placebo, in Patients with Post-resection R0/R1 Pancreatic Cancer with Tumor Sequence Confirmation of Ras Mutations.**

| DocID# | Receipt Date | Event Description |
|--------|--------------|--|
| 10406 | 06/12/2009 | On Day 212 of the study, the subject presented to the clinic for the study drug dose (GI-4000 or Placebo). Blood pressure at the time of the visit was elevated. The subject has a history of hypertension and had an increase in blood pressure two weeks prior for which treatment with daily diltiazem was started. The kidneys began to show signs of damage. As the kidneys became progressively worse, the subject was hospitalized for further evaluation and treatment. On admission, the subject was also noted to have a 20 lb weight gain along with swelling of the face and extremities. A kidney biopsy was done and was consistent with hemolytic uremic syndrome (HUS). The event was considered unexpected, of severe intensity, possibly related to blinded study therapy and definitely related to gemcitabine chemo therapy. The subject is receiving treatment with plasma exchange and steroids and kidney function is slowly recovering. Blinded study therapy has been stopped as a result of this event. The investigator describes the case as hemolytic uremic syndrome in which the gemcitabine is definitely a contributing factor and in which the blinded study drug cannot be ruled out as a possible contributing factor. |

Protocol Number: 838

Protocol Title: **A Randomized Double-Blind Placebo-Controlled Parallel Group Study of the Efficacy And Safety Of XRP0038/NV1FGF On Amputation Or Any Death In Critical Limb Ischemia Patients With Skin Lesions**

| DocID# | Receipt Date | Event Description |
|--------|--------------|---|
| 10363 | 05/12/2009 | At the six month visit, examination of the subject's eye revealed active macular (region of the eye responsible for high acuity vision and central vision) hemorrhage and atrophy of the left eye around the region where the visual nerve leaves the retina. No abnormalities of the right eye were noted. The event was considered by the Investigator as involving persistent or significant disability or incapacity. The subject was diagnosed with neo-vascular macular degeneration and received treatment that stabilized the lesion. At the time of this report, the subject had not yet recovered. The code was broken and the subject had received the study agent, not the placebo. |

Protocol Number: 882

Protocol Title: **Phase II Study of Metastatic Melanoma Using Lymphodepleting Conditioning Followed by Infusion of Anti-MART-1 F5 TCR-Gene Engineered Lymphocytes and ALVAC Virus Immunization**

| DocID# | Receipt Date | Event Description |
|--------|--------------|---|
| 10431 | 07/02/2009 | Approximately 11 days after administration of vaccine and cells, subject complained of fullness in ears and was evaluated by an audiologist and otolaryngologist. Subject was found to have severe hearing loss and received a transtympanic steroid injection. The subject subsequently received 3 more steroid injections. Subject received a fourth transtympanic steroid injection due to profound hearing loss with a recommendation of a hearing device. Subject was also found to have uveitis (inflammation of the eye), now improving and dizziness. Subject will return in two weeks for further evaluation. These toxicities are possibly related to the cells and vaccine. This event is being reported because treatment related toxicities prolonged hospitalization. |

Protocol Number: 939

Protocol Title: **Phase II Study of Metastatic Melanoma Using a Chemoradiation Lymphodepleting Conditioning Regimen Followed by Infusion of Anti-Mart-1 and Anti-gp100 TCR-Gene Engineered Lymphocytes and Peptide Vaccines**

| DocID# | Receipt Date | Event Description |
|--------|--------------|---|
| 10446 | 07/15/2009 | Subject was transferred to the intensive care unit (ICU) for mental status changes and renal failure after receiving the study agent six days earlier, followed by 2 doses of IL-2, stopping for shortness of breath. Subject remains in the ICU with status improving. Mental status changes, cardiac arrhythmias, neutropenic fevers and renal failure are all listed in the consent and are related to IL-2. |

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 |
|--------|--------------|---|
| 10443 | 07/14/2009 | The subject experienced cellulitis over the right arm and chest 24 days after the first intratumoral injection of the gene transfer vaccine. The gene transfer was injected into a lesion in the right front portion of the chest wall and the right upper arm. The cellulitis responded to antibiotics and an organism was not identified. |