SAFETY REPORTS AND ADVERSE EVENTS FOR
HUMAN GENE TRANSFER PROTOCOLS
RECOMBINANT DNA ADVISORY COMMITTEE MEETING
December 13 and 15, 2000

ID #	OBA Date	Event Date	Protocol	Description
3037	10/26/00	6/12/00	**9409-083** **Sponsor: Targeted Genetics Corporation**	**A Phase I Study of an Adeno-associated Virus-CFTR Gene Vector in Adult CF Patients with Mild Lung Disease.** Follow Up 2 to ID #1715. Event: Subacute exacerbation of Cystic Fibrosis lung disease 3 days post vector instillation believed to be possibly related to study drug. Event resolved after 14 days of IV antibiotics. Patient was discharged.
2723	5/30/00	unk	**9409-089**	**Treatment of Advanced CNS Malignancy with the Recombinant Adenovirus H5.020RSVTK: A Phase I Trial.** Initial; Event: About 8 hours post injection of study drug, pt had generalized seizure. Pt was somnolent for several hours with a worsening of hemiparesis. CT showed increased edema and midline shift. Corticosteroids were increased and pt improved.
2729	5/30/00	unk		Initial; Event: Approximately 4 days post injection, pt experienced headache, lethargy and change in mental status. Pt treated with corticosteroids and diuretics; symptoms resolved. Pt was discharged. Event believed to be probably related to study drug or possibly a delayed response to surgical manipulation
2727	5/30/00	unk		Initial; Event: Pt experienced Grade III elevation of transaminases post-injections. Transaminases returned to baseline without intervention. Pt was asymptomatic. Elevations believed to be possibly related to study drug or ganciclovir.
2728	5/30/00	unk		Initial; Event: Same pt as ID #2723- Pt developed headache and somnolence 3 days post 2nd vector injection. Pt was arousible, but did not respond verbally. Again corticosteroids were increased and pt improved with almost full recovery the following day.
2726	5/30/00	unk		Initial: Event: One week after second injection of study drug, pt experienced increasing headaches. Lumbar puncture showed increased intracranial pressure. The headaches resolved after removal of spinal fluid and did

				not recur. Event believed to be probably related to study drug
2724	5/30/00	4/16/97		Initial; Event: Five days post vector injection, patient experienced increase in liver function tests (ALT rose to 260 from a previous level of 38). No hepatic enlargement or tenderness observed. Transaminase (ALT) gradually decreased. Believed to be secondary to study drug, Ganciclovir, or anesthesia.
2850	6/28/00	3/30/99	**9508-118**	**Accelerated Re-endothelialization and Reduced Neointimal Thickening Following Catheter Transfer of phVEGF165.** Initial; Event: Pt underwent radical nephrectomy following detection of a right renal mass.
2882	9/27/00	9/15/00	**9512-138**	**A Phase I Study of the Safety of Injecting Malignant Glioma Patients with Irradiated TGF-β2 Antisense Gene Modified Autologous Tumor Cells.** Initial; Event: Pt may have received Staphylococcus-contaminated study drug. 72 hrs post injection, study drug tested positive for coagulase negative staph. Pt was prophylactically placed on Keflex and did not exhibit any indications of infection. Event is thought to be a false positive.
2918	5/31/00	11/5/96	**9603-149**	**Ovarian Cancer Gene Therapy with BRCA-1.** Initial; Event: Pt with terminal metastatic ovarian cancer developed sterile peritonitis lasting less than 24 hours; deemed related to study drug.
2923	5/31/00	6/18/96		Initial; Event: Pt with terminal metastatic ovarian cancer developed sterile peritonitis lasting less than 24 hours; deemed related to study drug.
2909	5/31/00	10/21/99		Initial; Event: Pt with terminal ovarian metastatic cancer developed peritonitis; deemed related to study drug.
2925	5/31/00	7/28/96		Initial; Event: Pt with terminal metastatic ovarian cancer developed sterile peritonitis lasting less than 24 hours; deemed related to study drug.
2990	10/11/00	1/21/98	**9709-214** **Sponsor: Aventis (formerly Gencell)**	**A Phase II Multi-Center, Open Label, Randomized Study to Evaluate Effectiveness and Safety of Two Treatment Regimens of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 78 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN).** Follow Up1 to ID #2144. End date of 1st grade 3 hemorrhage event changed to 1/26/98. Pt recovered from the 2nd hemorrhage on 1/28/00. Event still considered possibly related to study drug.
2972	10/10/00	9/30/00	**9712-224**	**Phase I Study of Chemokine and Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using an Adenoviral**

				Vector. Initial; Event: Eleven days post second injection, pt admitted for fever greater than 102F and decreased oral intake. Treatment consisted of IV antibiotics, hydration and a transfusion of packed red blood cells. Blood cultures were negative. Discharged next day and received third injection without complications. Event was considered possibly related to study drug.
2776	6/8/00	6/11/98	**9802-232**	**Gene Therapy for Myocardial Angiogenesis** Initial; Event: Two days post study drug injection, pt experienced tachycardia and wheezing. Pt went into cardiac arrest and was resuscitated. A pacemaker was placed. Pt had extensive hospital course, but remained mechanically ventilated. Pt discharged to a pulmonary rehabilitation facility two months after arrest still requirin mechanical ventilation, but alert and oriented.
2779	6/8/00	8/9/98		Initial; Event: Same pt as ID #2776 - Pt admitted to pulmonary rehabilitation facility while under mechanical ventilation. Pt was alert and oriented.
2821	6/8/00	8/6/99		Initial; Event: Pt with history of neck pain that was diagnosed as severe discogenic disease was treated with VEGF in 1998. Pain continued and pt hospitalized 1 year later. MRI showed an infiltrating mass involving the C3 vertebral body. The biopsy of the mass was consistent with chordoma. The mass was excised, and bone graft performed.
1408	5/25/00	1/24/00	**9802-238** **Sponsor: Berlex Laboratories, Inc.**	**Phase 1/2 Study of the Effects of Ascending Doses of Adenovirus Mediated Human FGF-4 Gene Transfer in Patients with StableExertional Angina.** Follow-Up3 to ID #438: Pt undergoing treatment for stable exertional agina received an intracoronary dose of Ad5FGF-4. The 6 month follow-up was uneventful. The patient sought medical attention 4 months after the 6 mo. follow up for diarrhea and bloody stools; the diagnosis was colon adenocarcinoma, two masses were noted - one involving a kidney and one involving a lung. Patient underwent a bowel resection and nephrectomy. Sponsor does not believe the neoplasms to be related to study drug, but cannot totally exclude the possibility.
2874	9/19/00	5/22/00		Initial; Event: Pt admitted for cardiac catheterization and stent placement for worsening angina. Investigator considered the event possibly related to study drug.
3001	10/18/00	10/12/00		Initial; Event: Pt complained of a mild speech impedimen that was not confirmed upon on examination. Symptoms of aphasia progressed and patient was admitted 2 weeks

				later. Patient was found to have a lefttempero-parietal brain mass consistent with the presence of a tumor. Biopsy of the mass has been scheduled.
3015	10/19/00	10/13/00		Initial; Event: (see ID #3001) Pt received study drug Ad5FGF-4 on 6/29/00. On 9/6/00 pt complained of speech impediment. MRI on 10/13/00 showed a space occupying lesion in the lefttemporo-parietal region of the brain. Unknown if primary or secondary - biopsy should identify. Sponsor indicates that if the tumor is primary, association with study drug is unlikely; if tumor is secondary (metastatic), possible association with study drug cannot be ruled out.
2880	9/21/00	8/10/00	**9812-274** **Sponsor: Aventis (formerly Gencell).**	**A Phase I, Multi-Center, Open Label, Safety and Tolerability Study of Increasing Single Dose of NV1FGF Administered by Intra-Muscular Injection in Patients with Severe Peripheral Artery Occlusive Disease.** Initial; Event: Pt with peripheral artery occlusive disease was initially dosed on 5/9/00 with NV1FGF. New right lower lung pulmonary mass found on follow-up at week 12. Liver abnormality also detected on follow-up at week 12. Gastroenterology consult pending. Investigator is not certain of possible association with study drug.
2879	9/21/00	7/25/00		Initial; Event: Pt with peripheral artery occlusive disease was initially dosed on 5/9/00 with NV1FGF. New right lower lung pulmonary mass found on follow-up at week 12. Diagnosis is pending. At this time, possible association with study drug is uncertain.
3048	10/31/00	7/25/00		Follow Up 1 to ID #2879. Pt with peripheral artery occlusive disease was initially dosed on 5/9/00 with NV1FGF. New right lower lung pulmonary mass found on follow-up at week 12. Liver abnormality also detected on follow-up at week 12. Gastroenterology consult pending. Investigator is not certain of possible association with study drug. At follow-up, no significant change in the appearance of a pleural based densityanterolaterally within the right lower lobe was observed. The impression is that the density may have been pre-existent and was more pronounced due to technical variability of the previous radiography. CT scans indicate no change in lymph node size; liver densities are consistent with the presence of cysts. Liver and lung scans appear stable. Follow-up continues; possible association with study drug reamins unchanged and is still uncertain.
2732	9/7/00	8/29/00	**9901-280** **Sponsor: Schering Corporation**	**A Phase II/III Trial of Chemotherapy Alone Versus Chemotherapy Plus SCH 58500 in Newly Diagnosed Stage III Ovarian and Primary Peritoneal Cancer Patients with >0.5 cm and <2 cm Residual Disease Following Surgery.**

				Initial; Event: On cycle three of study dosing with rAD/p53, pt with ovarian cancer experienced diarrhea, nausea, vomiting and chills. Symptoms resolved by next morning. Next morning pt started receiving blood transfusion, about 15 min into transfusion pt experienced chills, severe shaking, diaphoresis, tachycardia and shortness of breath. Transfusion stopped, O2 saturation was 86%. Pt treated with O2, benadryl and hydration. Pt recovered fully and was discharged. Hemolysis work-up was negative suggesting that the transfusion was not likely to have been a factor. Investigator believes events probably related to study drug (rAd/p53).
2820	9/11/00	8/29/00		Follow Up1 to ID #2732. Event: On cycle three of study dosing with rAD/p53, pt with ovarian cancer experienced diarrhea, nausea, vomiting and chills. Symptoms resolved by next morning. Next morning pt started receiving blood transfusion, about 15 min into transfusion pt experienced chills, severe shaking, diaphoresis, tachycardia and shortness of breath. Transfusion stopped, O2 saturation was 86%. Pt treated with O2, benadryl and hydration. Pt recovered fully and was discharged. Hemolysis work-up was negative suggesting that the transfusion was not likely to have been a factor. Investigator attributed the event to be probably related to study drug. Because the patient had previously received 6 doses of IND product prior to the onset of this event and due to the temporal association with packed red blood cells, the sponsor believes the event was related to the transfusion, but cannot rule out the possibility of a possible association with the study drug.
2872	9/15/00	7/24/00		Follow Up2 to ID #2336, #2335; Event: Death of pt described in 2335. Autopsy (abdominal only) - no abdominal tumor noted, colonstenosis not seen. Investigator felt the study medication (rAd/p53) may have impacted the pt's immune system thus contributing to the fatal candida sepsis and considered the death as possibly related to the study medication. Sponsor believes events are unlikely to be associated with the study drug, but instead were caused by a subclavian catheter infection and pneumonia exacerbated by immunosuppresion secondary to chemotherapy.
3031	10/27/00	10/12/00	**9901-281** **Sponsor: Genzyme Molecular Oncology**	**Phase I/II Trial of the Safety, Immunogenicity, and Efficacy of Autologous Dendritic Cells Transduced with Adenoviruses Encoding the MART-1 and gp100 Melanoma Antigens Administered With or Without Low Dose Recombinant Interleukin-2 (rIL-2) in Patients with Stage IV Melanoma.** Initial; Event: Female undergoing treatment for cutaneous melanoma received 3rd cycle of modified dendritic cell

				vaccine. Eye exam performed after 3rd cycle showed approximately 100 pin-point areas ofdrusen-like hypo-pigmentation of the retinal epithelium. Macula and vision appear unaffected. Event believed to be probably related to study drug.
2887	9/25/00	9/14/00	**9902-284** **Sponsor: Chiron Corporation**	**Phase I Multi-Center, Single Treatment Dose Escalation Study of Factor VIII Vector [HFVIII(V)] for Treatment of Severe Hemophilia A.** Initial; Event: Pt undergoing experimental treatment for hemophilia A underwent routinePCR screening. Pt's semen tested positive for the presence of vector specific sequences in 1 out of 10 replicates. The positive band was consistent with the expected result for the clinical vector. A subsequent semen sample obtained 3 days later was retested and found negative. The trial was placed on clinical hold.
2780	6/8/00	9/24/99	**9902-294** **Sponsor: Vascular Genetics, Inc.**	**A Multicenter, Open-Label, Dose-Escalating Study of Intramyocardial Vascular Endothelial Growth Factor 2 (VEGF-2) Gene Therapy in Refractory Patients with Stable Exertional Angina Who Are Not Candidates for Revascularization Procedures.** Follow Up1 to ID #2778. Event: Pt entered intoVEGF study with pre-existing lung nodule, thought to be benign. Three days post injection of study drug,xRay of lung mass was qualified as unchanged. Lung nodule was noted to have enlarged by CT scan on same day, and was attached to the pleura, mildly prominentmediastinal lymph nodes were seen. Pt was subsequently diagnosed with cancer and scheduled for non-operative therapy. Open lung biopsy results reported as "positive", but no further specific information provided.
2778	6/8/00	9/24/99		Initial; Event: Pt entered intoVEGF study with pre-existing lung nodule, thought to be benign. Three days post injection of study drug,xRay of lung mass was qualified as unchanged. Lung nodule was noted to have enlarged by CT scan on same day, and was attached to the pleura, mildly prominentmediastinallymph nodes were seen. Pt was subsequently diagnosed with cancer and scheduled for non-operative therapy. Biopsy results pending.
2906	10/3/00	9/14/00	**9905-314** **Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)**	**A Phase I Trial of Intralesional RV-B7.1 Vaccine in the Treatment of Malignant Melanoma.** Initial; Event: Pt reportedstridor due to an almost completely obstructing tracheal mass. Mass was resected, pt recovered withoutsequelae. Event deemed possibly related to study drug and probably related to disease.
3004	10/16/00	9/27/00		Initial; Event: Pt undergoing experimental treatment for

				melanoma, reported fever of 104.5F on the evening after receipt of 3rd and final vaccine of second course. Pt responded to Tylenol. Association withIND agent deemed probable.
1641	6/5/00	1/31/00	**9907-332** **Sponsor: Valentis, Inc.**	**A Multi-Center, Open-Label, Multiple Administration, Rising Dose Study of the Safety, Tolerability, and Efficacy of IL-12 Gene Medicine in Patients with Unresectable or Recurrent/Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN).** Initial; Event: Pt under treatment forsquamous cell carcinoma of the head and neck. EKG on day of second injection showed evidence ofunifocal premature ventricular contractions (PVCs). Subsequent rhythm strips showed monomorphic PVCs lasting approximately 1-2 minutes. Patient remained asymptomatic, no additional intervention required. The consent form was revised to list PVC as a possible side effect of the treatment.