SERIOUS, POSSIBLY ASSOCIATED AND UNEXPECTED ADVERSE EVENTS REPORTED FOR HUMAN GENE TRANSFER PROTOCOLS
REPORTING PERIOD: 02/01/01 -- 05/01/01
RECOMBINANT DNA ADVISORY COMMITTEE MEETING
June 2001

Event #	OBA Date	Event Date	Protocol #	Event Description
			9707-198	**A Phase I/II Study of Autologous CC49-Zeta Gene-Modified T Cells and alpha-Interferon in Patients with Advanced Colorectal Carcinomas Expressing the Tumor-Associated Antigen, TAG-72. Sponsor: Cell Genesys, Inc.**
3387	2/23/2001	2/21/1998		FU1 to event # 3237. Sponsor reply to questions from OBA Medical Officer. Of note is that the subject had experienced a similar central retinal artery thrombosis occurrence 5 years previous to this event. The previously reported erythrocyte sedimentation rate (ESR) value of 199 was in error. The correct value is 119.
			9802-238	**Phase 1/2 Study of the Effects of Ascending Doses of Adenovirus Mediated Human FGF-4 Gene Transfer in Patients with Stable Exertional Angina. Sponsor: Berlex Laboratories, Inc.**
3424	3/13/2001	10/23/2000		Initial. Subject developed worsening angina 8 months after the initial experimental treatment. The subject was taking up to 20 sublingual nitroglycerin tablets per day and opted for a repeat coronary artery bypass graft (CABG) to relieve anginal symptoms. CABG was performed uneventfully 9 months after administration of the experimental agent. The PI considers the event as possibly related to the gene transfer product.
3514	4/26/2001	4/18/2001		Initial. Subject was admitted for weakness secondary to a left temporoparietal glioblastoma. Subject was unable to maintain balance. The event was deemed by the PI to be possibly related to the study drug.
			9804-243	**Phase I Study of Direct Administration of a Replication Deficient Adenovirus vector (AdGVVEGF121.10) Containing the VEGF121 cDNA to the Ischemic Lower Limb of Individuals with Peripheral Vascular Disease. Sponsor: Parke-Davis Pharmaceutical Research**
3349	1/28/2000	1/18/2000		FU1 to event # 171. Report from PI following bladder biopsy. Biopsy showed transitional cell carcinoma grade I/III. Event was considered possibly related to study drug.

Event #	OBA Date	Event Date	Protocol #	Event Description
			9806-255	**Phase I Trial of Intraperitoneal Adenoviral p53 Gene Therapy in Patients with Advanced Recurrent or Persistent Ovarian Cancer. Sponsor: National Cancer Institute - Cancer Therapy Evaluation Program (NCI-CTEP)**
3361	2/ 7/2001	2/ 6/2001		Initial. Subject developed mild abdominal cramping and diarrhea 3 days post-administration of study drug. Event is believed to be possibly related to study drug or to the intraperitoneal (IP) catheter port. The PI states that such symptoms are commonly observed with carcinomatosis and advanced disease.
3406	3/ 6/2001	11/29/2000		FU5 to event # 3129. Final autopsy report giving the Cause of Death as: "Metastatic Clear Cell Carcinoma of the Ovary Complicated by Peritonitis and Respiratory Failure."
3415	3/ 9/2001	3/ 5/2001		Initial, (same subject as Event # 3416). Subject presented with complaints of increased nausea and vomiting occurring over a 3-day period. Subject was only able to tolerate oral liquids. Lab results indicated serum sodium level= 134, and potassium= 3.5. Subject was rehydrated and given intravenous (IV) antiemetics and IV potassium. Subject's symptoms subsequently improved. Investigator felt the suspected cause of the event to be carcinomatosis ileus secondary to hemorrhagic ascites possibly exacerbated by the dose escalation of the experimental therapy.
3416	3/ 9/2001	2/27/2001		Initial, (same individual as event # 3415). Within 7.5 hours post injection of study drug, subject spiked a fever of 38.4C. Subject was afebrile 9.5 hours after administration of Tylenol without recurrence of fever. There were no signs of clinical infection or clinical peritonitis. Event was felt to be possibly related to the experimental therapy.
3477	3/16/2001	11/29/2000		FU6 to event # 3129. Sponsor's compilation of all reports submitted by PI. No new information provided.
3463	3/30/2001	2/ 6/2001		Initial. Two days post-injection of study drug, subject developed mild intermittent abdominal cramping with diarrhea. Pt also found to be anemic and received 3 Units of packed red blood cells. The PI believes the event to be possibly related to study drug; the sponsor believes it not related.
3462	3/30/2001	3/ 5/2001		FU1 to event # 3415. CTEP report; no change in event information or attribution. The subject chose to withdraw from study on 3/9/01 and return home.
			9808-263	**Phase I Trial of Adenovirus-Mediated Wild Type p53 Gene Therapy for Malignant Gliomas. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)**
3428	3/13/2001	2/10/2001		Initial. Subject had been complaining of intermittent nausea, vomiting and low-grade fever since discharge following open craniotomy and Ad-P53 intrathecal injection. A lumbar puncture was attempted without success to rule out viral meningitis on the 2 week post-op visit. Subject was admitted 15 days post-injection for observation. Events were considered possibly related to the gene transfer product.

Event #	OBA Date	Event Date	Protocol #	Event Description
			9812-274	**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. Sponsor: Aventis (formerly Gencell).**
3322	2/ 1/2001	8/10/2000		FU2 to event # 2880. Subject 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. Sponsor comment: "There is no information that would suggest a definitive causal relationship between the reported events and treatment of study drug....there is a possibility that the hypodensities in liver might be metastases." Causality has been revised by the PI as not related to the study agent.
3320	2/ 1/2001	7/25/2000		FU2 to event # 2879. Subject 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. Additional review of April 2000 Chest X-ray was performed: - according to the treating physician, the nodular lung density may have been present although not quite as pronounced. The sponsor concludes that "the fact that the density was more pronounced on an X-ray in July 2000 may well have been due to technical factors." Causality has been revised by the PI as not related to the study agent.
3382	2/22/2001	8/10/2000		FU5 to event # 2880. Same subject as Event #3322. This report is of the subject's follow-up with the pulmonologist. A recent chest x-ray and a CT scan of the chest done 20 weeks after dosing were reviewed. There was no significant change in the pleural-based density. The subject has no pleuritic symptoms. A follow-up chest radiograph and CT scan in 4 months were recommended.

Event #	OBA Date	Event Date	Protocol #	Event Description
			9901-280	**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. Sponsor: Schering Corporation**
3375	2/20/2001	2/15/2001		Initial. Subject admitted after complaining of four days of nausea, vomiting, epigastric discomfort and pain. Symptoms began 9 days post study drug injection. Subject was treated for dehydration and pain management. Event deemed possibly related to study drug.
3393	2/26/2001	2/23/2001		Initial. Subject admitted for observation after complaining of pain/discomfort at catheter port site, fever, redness, induration, swelling with increased warmth on skin over area of intraperitoneal port. Four days prior to admission, which was Day 1 of second cycle, the port was difficult to access requiring multiple punctures. Cultures were taken from port on admission. Culture results are pending.
3395	2/27/2001	2/26/2001		Initial, (same subject as # 3375). Subject admitted with complaints of vomiting, decreased appetite, constipation and bloating. Subject noted to have increased abdominal girth. Diagnosed with small bowel obstruction and to rule out recurrent disease. Relationship to study drug is presently unknown.
3441	3/23/2001	3/21/2001		Initial, (same subject as # 3393). Two to three hours post-injection of study drug, subject suffered a prolonged period of abdominal pain and frequent vomiting. Continued to vomit every 2-3 hours. Admitted for observation, IV fluids and electrolytes.
			9901-281	**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. Sponsor: Genzyme Molecular Oncology**
3447	3/26/2001	2/21/2001		Initial. On routine ophthalmic exam, per protocol, subject was noted to have new internal limiting membrane changes in the posterior pole and mid-periphery of the retina. Retinal pigment epithelium mottling in the same location was reported in both eyes. The changes in pigmentation were assessed by the ophthalmologist as mild and they did not appear to impact the subject's vision. The subject will have additional follow-up. The PI indicated that it is not clear how this event is related to gene transfer since the subject is at risk for retinitis due to recent immunotherapy. The PI assessed the relationship between the events and modified dendritic cells as "possibly related."

Event #	OBA Date	Event Date	Protocol #	Event Description
			9902-287	**Phase I Pilot Trial of Adenovirus p53 in Bronchioloalveolar Cell Lung Carcinoma (BAC) Administered by Bronchoalveolar Lavage. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)**
3423	3/ 9/2001	4/ 5/2000		Initial. Subject experienced pneumonitis associated with fatigue 1 day after third course of study drug. No evidence of pneumonia was seen by chest X-ray (CXR) on day of receipt, but post obstructive pneumonia noted on CXRs post-treatment days 1 and 2. The condition was verified by CTscan on post-treatment day 3. Blood cultures were negative. The subject was treated with antibiotics. A possible causal relationship was attributed to the investigational agent and the subject's disease.
			9902-288	**Phase I Pilot Trial of Adenovirus p53 and Radiotherapy on Non-Small Cell Lung Cancer. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)**
3461	3/30/2001	3/ 6/2001		Initial. One day post-injection of study drug, the subject experienced a sudden onset of sharp chest pain. The chest X-ray (CXR) showed evidence for a right lower lung lobe infiltrate. The subject's maximum temperature was 38.7C, O2 saturation decreased to 90% and became short of breath. Subject was given O2, antibiotics and monitored. CXR on the following day was back to baseline.
			9903-296	**Phase I Trial of Immunotherapy with Adenovirus-Interferon-Gamma (TG1041) in Patients with Malignant Melanoma. Sponsor: Transgene, Inc.**
3439	3/22/2001	3/12/2001		Initial. Within 4 hours following study drug injection (3rd cycle), subject experienced grade 3 flu-like syndrome with fever, chills, muscle aches in the right leg, nausea, injection site inflammation and mild face flushes. A mild upper respiratory infection with productive cough, right earache, left ear congestion and rhinitis were also noted but believed to be unrelated to the study drug. The subject was admitted for observation and treated with Tylenol, potassium chloride and cefepime. The event resolved the next day. Blood and urine cultures were negative. Subject had a similar syndrome about 6 hours after the second injection, but was at home and did not inform the PI until the day of the third injection.
3446	3/23/2001	3/12/2001		FU1 to event # 3439. Clarification that the location of the injected tumor site for the subject in Event #3439 was a left axillary nodule and that the event (grade 3 flu-like syndrome) was probably related to the study drug.
			9910-345	**A Phase I/II Dose Finding Trial of the Intravenous Injection of Calydon CV787, a Prostate-Specific Antigen Cytolytic Adenovirus, in Patients with Hormone Refractory Metastatic Prostate Cancer. Sponsor: Calydon, Inc.**
3515	4/26/2001	4/10/2001		Initial. Hospitalization was extended due to severe fatigue. Subject developed fever about 4 hours post-administration of study drug and also transient, but more severe than expected, fatigue. Hospitalization was extended approximately 8 hours due to the fatigue. The subject recovered from the fatigue without event and was back at his baseline when released. The fatigue was felt to be related to the study agent.

Event #	OBA Date	Event Date	Protocol #	Event Description
			9910-350	**A Phase I Dose Escalation Study of Intraperitoneal E1A-Lipid Complex (1:3) with Combination Chemotherapy in Women with Epithelial Ovarian Cancer. Sponsor: Targeted Genetics Corporation**
3500	4/13/2001	3/28/2001		Initial. One day-post injection, subject developed fever, nausea, and vomiting. She was admitted, given IV antibiotics and antiemetics. On Day 3 post-injection, she had hypokalemia/hypomagnesemia; both were corrected with treatment. The PI believes the fever, hypokalemia and hypomagnesemia are possibly related to the study drug.
			9912-366	**A Phase III Multi-Center, Open-Label, Randomized Study to Compare the Overall Survival and Safety off Bi-Weekly Intratumoral Administration of RPR/INGN 201 Versus Weekly Methotrexate in 240 Patients with Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN). Sponsor: Aventis Pharmaceuticals - Gencell Division (formerly Rhone-Poulenc Rorer)**
3377	2/20/2001	1/12/2001		FU1 to event # 3288. While hospitalized for an unrelated episode of atrial fibrillation/atrial flutter with 3rd degree heart block and sick sinus syndrome, the subject was found to be "nephrotoxic" with a creatinine level of 1.6. (His creatinine level at screening was 1.4). While other symptoms associated with this event are believed to be not related to the study drug, the nephrotoxicity has been assessed by the investigator as possibly related. Additional information has been requested by the sponsor.
			0001-385	**Phase I/II Study of GM-CSF Gene-Modified Autologous Tumor Vaccines in Early and Advanced Stage Non-Small Cell Lung Cancer (NSCLC). Sponsor: Cell Genesys, Inc.**
3380	2/23/2001	2/ 4/2001		Initial. Subject was hospitalized for treatment of dehydration. One day post receipt of the 6th vaccine dose, subject developed fever, chills, nausea and cough. Subject had unsuccessfully self-medicated for five days prior to admission. The event was believed to be probably related to the study vaccine.
3427	3/14/2001	2/ 4/2001		FU1 to event # 3380. Subject improved and was discharged 4 days after admission. On admission, his potassium (K+) was 3.0 mEq/L, pH 7.487, partial pressure CO2 (pCO2): 33.0 mm Hg, pO2: 72.5 mm Hg while on supplemental O2, and a white blood cell count (WBC) of 8,400. He was treated with IV fluids, IV ceftriaxone, IV and oral potassium. Serum (K+) was 4.7 mEq/L on the day of discharge. The PI considered the event as probably secondary to an inflammatory reaction to the last vaccination. The subject had a history of nausea for several months preceding his entry on the study.

Event #	OBA Date	Event Date	Protocol #	Event Description
			0006-403	**A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Effect of Ad5FGF-4 on Myocardial Perfusion Defect Size and Safety in Patients with Stable Angina. Sponsor: Berlex Laboratories**
3381	2/23/2001	1/10/2001 test		FU1 to ID # 3299; At Week 12, the patient was found to have an asymptomatic elevation of his liver function (LFT) values: Alk Phos 441, ALT 477, AST 363, LDH 390. Lipitor was discontinued and the patient was referred to a gastroenterologist. The patient was found to be Hepatitis C positive by PCR methodology. He is negative for Hepatitis A and B. Baseline serum samples were negative for Hepatitis C RNA by rtPCR followed by PCR analysis. The patient remains asymptomatic and his LFTs are declining. The patient had received active product so the following were tested and found negative for Hepatitis C RNA by rtPCR followed by PCR analysis: Samples of the final product used in the clinical study Reserve samples of the bulk used to produce the final product Reserve samples of the harvest used to produce the final product Master Cell Bank used to produce the final product. The cause of the acute Hepatitis C infection remains unknown.
3503	4/16/2001	1/10/2001		FU2 to event # 3299 (see event # 3381). Additional liver function test results provided. Subject also continues to complain of intermittent nausea, no vomiting. No other clinical symptoms have been observed. Stored serum samples were tested and found positive at weeks 2, 4 and 8 post-administration. Baseline serum test is Hepatitis C negative. Causality of acute Hep. C infection is unknown.
			0007-409	**A Phase I, Multi-Center, Open-Label, Dose-Escalation Study of the Safety and Tolerability of Intravenously Administered VLTS-587 in Patients with Solid Tumors and the Presence of Metastases or Primary Cancer in the Lungs. Sponsor: Valentis, Inc.**
3495	4/12/2001	3/28/2001		Initial. Subject was admitted for nausea, vomiting and dehydration. She was treated with IV fluids and antiemetics. The PI concluded the event was likely due to progression of disease with a superimposed pulmonary infection. A possible relationship with the IND agent could not be ruled out.