SERIOUS, POSSIBLY ASSOCIATED AND UNEXPECTED ADVERSE EVENTS
REPORTED FOR HUMAN GENE TRANSFER PROTOCOLS
REPORTING PERIOD: 11/01/01 -- 02/01/02
RECOMBINANT DNA ADVISORY COMMITTEE MEETING
March 2002

Event ID	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)**
4059	01/16/2002	05/29/2001		Approximately 4 hours after receiving gene transfer agent via bronchoalveolar lavage, subject experienced grade 3 pleuritic pain with cough, fever, rigors and chills. Pain decreased to grade 2 after use of MS Contin. Full recovery 15 days after start of event. This was subject's second course of gene transfer agent.
4096	01/31/2002	05/29/2001		Follow-up from sponsor. Radiology reports provided. Adverse event details and causality not changed from prior report.
			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)**
4086	01/29/2002	03/28/2001		Subject experienced grade 3 pleural effusion 12 days after receiving last intralesional injection of gene transfer product. CT scan done, showing new onset moderate sized right pleural effusion possibly neoplastic or inflammatory in etiology. Thoracentesis done - negative for malignancy on cytologic examination.

Event ID	OBA Date	Event Date	Protocol #	Event Description
			9910-346	**A Phase II, Randomized, Multicenter, 26-Week Study to Assess the Efficacy and Safety of CI-1023 Delivered Through Minimally Invasive Surgery Versus Maximum Medical Treatment in Patients with Severe Angina, Advanced Coronary Artery Disease, and No Options for Revascularization. Sponsor: Parke-Davis Pharmaceutical Research**
4018	12/05/2001	11/18/2001		Evening after receipt of investigational agent, subject became tachycardic with pulmonary congestion. Based on cardiac enzyme level elevations, believed to have suffered a myocardial infarct (MI). MI led to the development of congestive heart failure (CHF), leading to renal failure with a significant decrease in urine output and an increase in Creatinine and blood urea nitrogen. Pulmonary compromise developed as well. Pulmonary artery catheter inserted and treated aggressively with inotropes, albumin and diuretics. Subject improved and was discharged 11/26/01, (8 days after start of event). MI deemed by both the PI and study sponsor to be due to either the study therapy and/or procedure (mini-thoracotomy) and the CHF and renal failure due to the MI.
4034	12/18/2001	11/18/2001		Nine hours post study agent administration, subject developed tachycardia and "wet lungs". Chest X-ray showed atelectasis, ECG showed sinus tachycardia, ST and T wave changes suggestive of anterolateral ischemia and an inferior MI of unknown age. Subject's O_2 saturation decreased, developed hypotension, decreased consciousness and oliguria which progressed into anuria. An echocardiogram showed ejection fraction of 35-40% (which was decreased from previous reading), inferior wall scar and a severely hypokinetic lateral wall. The aortic and mitral valves were sclerotic with insufficiency. Subject treated with inotropics and aggressive diuretics and began to improve. Though not stated, most likely this is a repeat submission of SAE # 4018.
4060	01/17/2002	11/18/2001		Follow-up (to report 4018) A chronology of cardiac enzyme measurements was provided. The subject recovered and was discharged 11/26/01. No change in PI or sponsor attribution of causality.
			9912-360	**Treatment of Patients with Metastatic Melanoma Using Cloned Lymphocytes Following the Administration of a Nonmyeloablative But Lymphocyte Depleting Regimen.**
4055	01/11/2002	12/19/2001		Subject developed grade 2 anterior uveitis. Treated with steroid and atropine eye drops with punctal occlusion. Sight returning to baseline and uveitis resolving at time of report.

Event ID	OBA Date	Event Date	Protocol #	Event Description
			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.**
3806	08/07/2001	07/31/2001		A 48 year old male with stage IV non-small-cell lung cancer received three autologous vaccines with cells transduced with the GM-CSF gene. The total number of transduced cells per vaccine was 6.3 X 10^6 with a GM-CSF secretion of 407 ng/10^6 cells/24 hours (or 2.6 μg/dose). The last vaccine was administered on 7-17-01. The next day the subject returned to the emergency room due to lower back and sacral pain, with extension of his cancer noted in that area. While in the hospital, subject developed significant pericardial effusion with tamponade physiology, progressive respiratory distress, and after refusing mechanical ventilation, ultimately respiratory failure and death. Due to the recognized correlation of GM-CSF use and the development of pericardial effusions, the investigator deemed this adverse event as "possibly associated" with the vaccines.
4032	12/17/2001	07/31/2001		Follow-up final autopsy report. Immediate cause of death - respiratory failure due to extensive tumor involvement, pneumonia and fibrosis involving both lungs. Causality (possible exacerbation of the subject's already compromised pulmonary and pericardial pathology by the gene transfer product) not changed by PI/Sponsor.
			0002-388	**A Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, 26-Week Study to Assess the Safety and Efficacy of CI-1023 ($AD_{GV}VEGF_{121.10}$) in Peripheral Arterial Disease Patients with Severe, Disabling Intermittent Claudication. Sponsor: Parke-Davis Pharmaceutical Research**
4045	12/31/2001	12/18/2001		Subject hospitalized after an apparent transient ischemic attack. Subject has history of cerebro-vascular accident and cardiovascular disease. Details regarding if and when gene transfer product was given are not provided.
			0005-396	**A Phase I, Open-Label, Dose-Escalating Study of the Safety, Tolerability, and Anti-Tumor Activity of a Single Intrahepatic Injection of a Genetically Modified Herpes Simplex Virus NV1020, in Subjects with Adenocarcinoma of the Colon with Metastasis to the Liver and the associated, long-term follow-up protocol: Long-Term Follow-Up of the Safety and Survival of subjects with Adenocarcinoma of the Colon with Metastasis to the Liver Who Enrolled in a Phase I Dose-Escalating Study Evaluating a Genetically Engineered Herpes Simplex Virus, NV1020. Sponsor: NeuroVir Therapeutics, Inc.**
4078	01/28/2002	01/19/2002		Subject given single study infusion on 1/15/02 and on 1/18/02 had hepatic infusion pump placed. On 1/19/02 the subject had decrease in urine output, tachycardia and hemoglobin/hematocrit fell from 13.7/38.6 to 9.7/28.5. Naso-gastric lavage drained "coffee-ground" fluid that irrigated clear. CT scan of abdomen without contrast showed no evidence of retroperitoneal bleed. Endoscopy pending at time of report but it was felt that the subject had a self-limited upper GI bleed.

Event ID	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**
4074	01/23/2002	01/10/2002		Subject admitted with increasing frequency of anginal chest pain 5 months after study injection. Angiography done, found 95% lesion in proximal LAD, stent placed. Lesion reduced to 0%. No further
			0006-404	**A Multicenter, Double-Blind, Placebo-Controlled, Phase II Study of Aerosolized AAVCF in Cystic Fibrosis Patients with Mild Lung Disease. Sponsor: Targeted Genetics**
3985	11/07/2001	10/18/2001		Follow-up report. Subject admitted for sub-acute pulmonary exacerbation of CF lung disease and nasal congestion approximately 1 month after receiving first course of gene transfer agent. Received IV antibiotics and discharged home after 2 weeks in-house.
4047	12/27/2001	12/11/2001		Subject developed chest tightness, shortness of breath, increased cough and sinusitis 2 days after third and final dose of study drug given. Started on IV antimicrobials and hospitalized for ease of administration. Discharged after 6 days in-house on additional oral antimicrobials.
4049	12/27/2001	12/10/2001		Approximately one week after completing third and final dose of study drug, subject presented to clinic with symptoms of pulmonary exacerbation. Started on oral antibiotics and TOBI (aerosolized tobramycin) treatment at home. Due to failure on oral antibiotics, hospitalized and received IV antibiotics, albuterol nebulizer treatments and chest physiotherapy. Discharged home after 10 days in-house.
4048	12/27/2001	12/11/2001		Approximately 30 days after receiving third and final dose of study drug, subject admitted with a history of increased cough and sputum production with hemoptysis and fever. Diagnosed with CF pulmonary exacerbation and admitted for IV antibiotics, albuterol nebulizer treatments and chest physiotherapy. Discharged after 8 days in-house.

Event ID	OBA Date	Event Date	Protocol #	Event Description
			0009-412	**A Phase III, Multi-Center, Open-Label, Randomized Study to Compare the Effectiveness and Safety of Intratumoral Administration of RPR/INGN 201 in Combination with Chemotherapy Versus Chemotherapy Alone in 288 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN). Sponsor: Aventis Pharmaceuticals - Gencell Division**
4007	11/27/2001	11/11/2001		Nine days after administration of study agent, subject admitted after unable to be aroused by family. On admission noted to have elevated liver enzymes and altered mental status and somnolence. Narcan administered resulting in a withdrawal response and some improvement in mental status. Within 24 hours subject was more alert and liver enzyme (AST & ALT) levels decreased.
4118	02/11/2002	02/04/2002		Follow-up from Sponsor. SAE listed in safety report has been modified to reflect a grade III neuro-cortical event and a grade III transaminase elevation (no longer ongoing). Subject's hospital records indicate subject took 2 extra dilaudid doses on day prior to admission with ongoing use of fetanyl patch. Transferred out of ICU on 13 November 2001. Subject continued to improve. Discharged 19 November 2001. Etiology of neuro-cortical event was felt to be secondary to narcotics overusage. Transaminase elevation felt to be secondary to hypotension, shock liver related to over usage of narcotics.
			0107-481	**An Open-Label, Phase Ib/II Study of the Safety, Tolerability and Efficacy of G207, a Genetically Engineered Herpes Simplex Type-1 Virus, Administered Intracerebrally to Subjects with Recurrent Malignant Glioma. Sponsor: MediGene, Inc.**
4081	01/29/2002	01/20/2002		This event involves the first subject enrolled into the first cohort of the study. The subject underwent tumor resection and injection of gene transfer product on 1-17-01. On the third day post-op the subject was found confused and apparently post-ictal on the floor of his bathroom. He developed grade 3/3 expressive dysphasia and dense (3/3) right hemiparesis. CT and MRI scans were done and these showed no significant change compared to a post-op day 1 MRI. Tegretol and phenobarbital levels were checked and found to match pre-surgery levels. Sodium levels were within normal limits. The subject has a prior history of glioblastoma multiforme and is status post multiple previous surgical resections. Additionally, the subject has a history of a seizure disorder, grade 1/3 expressive dysphasia and grade 1/3 right hemiparesis. The cause of the worsening of the dysphasia and hemiparesis is believed to be due to the seizure, though cause of seizure is not discussed (On 2-12-02 OBA received a follow-up report (#4124) where causality of events changed to "possibly related to study". Subject seen in follow-up and slowly improving.