SAFETY REPORTS AND ADVERSE EVENTS FOR HUMAN GENE TRANSFER PROTOCOLS RECOMBINANT DNA ADVISORY COMMITTEE MEETING MARCH 6 AND 7, 1997

10-24-96	**9406-077 Deisseroth, et.al.**	**Use of Safety-Modified Retroviruses to Introduce Chemotherapy Resistance Sequences into Normal Hematopoietic Cells for Chemoprotection During the Therapy of Breast Cancer: A Pilot Trial.** **Safety Report:** An episode of herpes zoster was diagnosed in a patient following the 8th course of Taxol post transplant chemotherapy; the acquisition of the zoster occurred over a month following the administration of the drug. The patient was given supportive care, acyclovir, and zoster immune globulin. The lesions were restricted to a single dermatome and crusted and healed over. The patient is doing well. Another patient had two hospitalizations that occurred following the mobilization chemotherapy and following the pre-transplant intensive chemotherapy (followed by the transplantation of peripheral blood stem cells). The patient was given antibiotics for neutropenic fever during this hospitalization. These two hospitalizations were anticipated outcomes of this therapy. The Principal Investigator (PI) mentions the 5 courses of zoster on protocols #9306-044 and #9406-077. The first patient mentioned above is the sixth patient of the two post transplant Taxol treatment programs in whom herpes zoster was acquired.
11-04-96	**9403-069 Walker**	**A Phase I/II Pilot Study of the Safety of the Adoptive Transfer of Syngeneic Gene-Modified Cytotoxic T-Lymphocytes in HIV-Infected Identical Twins.** **Safety Report:** One patient was hospitalized for 2 days (9-3-96 to 9-5-96) for severe dehydration, and recovered with treatment. This patient received 3 infusions of genetically engineered cytotoxic T cells beginning in March 1995. He was recently reported to the IRB when he was diagnosed with PML by brain biopsy (8/96). The patient was administered IV fluids, stabilized, and was discharged. The second hospitalization began 9-29-96 and as of this report was continuing. The patient was admitted for aspiration pneumonia, and treated with IV antibiotics, with resolution, but the patient remains hospitalized due to declining neurologic status and to receive IV Cidofavir. The PI states that these hospitalizations are not felt to be related to the investigational product. Another patient has received 2 cell infusions since September 1995 and was hospitalized (9-22-96 to 9-30-96) by his private physician for ophthalmic VZV infection. The PI states the infection and hospitalization are not felt to be related to the investigational product.
11-14-96	**9409-087 Whitley**	**Retroviral-Mediated Transfer of the Iduronate-2-Sulfates Gene Into Lymphocytes for Treatment of Mild Hunter Syndrome (Mucopolysaccaridosis Type II).** **Safety Report:** The first patient was enrolled in this clinical trial on October 25, 1996, and donated lymphocytes by apheresis. The patient had the expected, tender skin at the site of IV placement but no other complications.
11-17-96	**9303-037 Van Gilder, et.al**	**Gene Therapy for the Treatment of Recurrent Glioblastoma Multiforme with In Vivo Tumor Transduction with the Herpes Simplex Thymidine Kinase Gene/Ganciclovir System.** **Safety Report:** *ORDA received the following update/safety report for this protocol in the submission of an amendment for protocol #9608-157.* "Accrual into the study was completed in January 1996. A total of 30 patients were enrolled. Although final analysis is not yet available on this study, evidence of anti-tumor effect has been identified. As of October 1996, preliminary safety data on the patients enrolled into this study showed that

		the following events which occurred shortly after the administration of vector VPCs were at least possibly related to the VPC administration and/or the surgical resection of the recurrent glioblastoma: - Severe ventricular/meningeal reaction subsequent to direct ventricular/meningeal entry or diffusion was reported in four patients. Three of these patients required treatment in intensive care and all recovered. One of the patients had a less severe reaction which may be due to ventricular entry or diffusion of VPCs, however, the investigator does not believe ventricular entry or diffusion of the VPCs occurred in this case. Each of these episodes followed injection of VPCs into the tumor cavity via an Ommaya catheter. No patient developed ventriculitis after direct intraoperative injection into the wall of the resection cavity. - Less severe reactions or neurological symptoms which occurred within 48 hours following VPC injection and were possibly or probably due to cerebral edema or increased intracranial pressure were reported in six patients. These patients experienced one or more of the following symptoms: mild rigors, fever, nausea, vomiteing, post-operative hemiplegia, convulsion, severe headache, speaking difficulty, somnolence, loss of appetite, and eye swelling. - Symptoms of cerebral edema and/or intracranial hypertension occurring days to weeks after VPC injection which were noted as possibly related to study treatment were reported in six patients. These patients experienced one or more of the following symptoms: headache, hemiparesis, reduced responsiveness, aphasia, dysphasia, lethargy, and vomiting. - One patient experineced headache and fever two days following the VPC injection which was probably related to the study treatment. Additionally, three patients experienced cerebral edema which occured during or shortly after GCV administration which was probably related to the study treatment and responded to steriod treatment. One patient experienced confusion and mild hemiparesis associated with EEG seizure activity during GCV administration. In one of the cases of meningeal irritation, the patient received a single intraoperative HSV-TK1 VPCs into the lateral ventricle on the 7th postoperative day. The patient had significant residual glioblastoma multiforme post-operatively in both the brain and the dura. In addition, tumor was identified on post-operative MR scans. The intraventricular injection resulted in an immediate severe ventriculitis characterized by high fever, hypertension, and severe headache, from which the patient recovered. Fourteen days after the second (and last) HSV-TK1 VPC injection, the patient received 14 days of intravenous GCV. On the 60th post-operative day, the patient died of intracranial hemorrhage. Hickman catheter-related Staphylococcal bacteremia was noted on autopsy. Post-mortem pathologic examination of the brain revealed no evidence of residual tumor. In some patients, an increase in the size of the region of enhancement has been observed on MR scan and seen to persist for variable periods of time. This transient increase is likely to result from a self-limited inflammatory response to foreign cells and/or vector sequences, and/or transduced tumor cells. This inflammation can result in misdiagnosis of progressive disease. Because of the need to definitively establish whether the MR scan was in fact showing only inflammation or an additional element of tumor progression, and because of neurologic symptoms consistent with a mass effect, two patients were taken *(next page)*
-continued-	**-continued-**	back to the operating room. In both patients, histologic confirmation was obtained that the mass effect was a consequence of tumor necrosis which extended 2-3 cm beyond the resection cavity. These findings suggest that these patients had a pronounced local anti-tumor effect. As of October 1996, twenty-three of the thirty patients have died, four from pulmonary embolism (a complication known to be associated with glioblastoma), one from intracranial hemorrhage (with sepsis found on autopsy), and eighteen from disease progression. Among the seven surviving patients, are a (patient) progression-free at 25+ months despite a rapidly progressing glioblastoma at entry with significant residual tumor on the post-operative MR scan, having undergone two cycles of treatment. (Another patient) is alive 23+ months after operation having undergone three cycles of treatment. The additional five surviving patients are alive at 14+, 11+, 10+, 10+, and 9+ months. Patient samples were obtained for biological monitoring in all

		patients. All samples tested for RCR in peripheral blood were negative. Anti-p30 antibodies were detected in the sera of ten patients (one of whom tested positive at baseline). Antibody positive samples are not unexpected in a study using repeated administration. In eight patients, eleven peripheral blood samples were postive for vector by PCR analysis."
11-17-96	**9206-019 Oldfield**	**Gene Therapy for the Treatment of Brain Tumors Using Intra-Tumoral Transduction with the Thymidine Kinase Gene and Intravenous Ganciclovir.** **Safety Report:** *ORDA received the following update/safety report for this protocol in the submission of an amendment for protocol #9608-157.* "Fifteen patients were enrolled into a study using single injection of HSV-TK vector producer cells (GTI-0100).... As of October 1996, the median survival of the 13 evaluable patients after the VPC injection, is 7 months, with two of the patients alive at 34+ months (anaplastic oligodendroglioma) and 44+ months (anaplastic astrocytoma recurring as a glioblastoma)."
11-19-96	**9608-157 Maria, et.al.**	**Prospective, Open-Label, Parallel-Group, Randomized, Multicenter Trial Comparing the Efficacy of Surgery, Radiation, and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir Against the Efficacy of Surgery and Radiation in the Treatment of Newly Diagnosed, Previously Untreated Glioblastoma.** **Adverse Event:** Serious but not life-threatening adverse event of 'cerebral edema, confusion, staring', expected but possibly related to the gene therapy in one patient. In the opinion of the investigator, this event was suspected to be due to surgical and radiation induced cerebral edema compounded by a decrease in his Decadron dose 8 days earlier. The relation to the packaging cells injected and ganciclovir could not be ruled out and this incident was noted to be 'possibly related'.
12-17-96	**9509-127 Welsh, Zabner**	**Cationic Lipid Mediated Gene Transfer of CFTR: Safety of a Single Administration to the Nasal Epithelia.** **Safety Report:** *The following information was enclosed in the submission of protocol #9612-170.* "In Part A of this trial, the lipid 67:DOPE formulation optimized for instillation was administered to the nose of normal volunteers in a single dose, dose escalation study. Lipid 67:DOPE alone was selected for testing in normal volunteers because our preclinical animal toxicity studies indicated that the majority of the toxicity observed with the complex was attributable to the lipid components alone. A total of six normal volunteers were treated in three dosing cohorts. The observed safety profile was as follows: - One of the first two volunteers (0.8 mg dose) developed mild nasal erythema and edema in the treated nostril four days following installation. The second patient complained of sinus discomfort on day 9, -a CT scan of the sinuses was normal. - One of the two volunteers at the next dose level (2 mg) developed erythema and edema in the treated nostril while the other patient developed similar findings in the vehicle control (water for injection) nostril. - One of the two volunteers treated with 4 mg who had a known history of cholinergic urticaria developed urticaria, nasal erythema and rhinnorhea during the installation. The installation was stopped with resolution of (the patient's) urticaria following which the administration was completed. The other volunteer treated at that dose had no new signs or symptoms. The highest tolerated dose was therefore defined as the two (2) mg dose 67:DOPE. In Part B of this trial, the highest tolerated dose of 67:DOPE from Part A i.e., two (2) mg, was complexed to the plasmid pCF1-CFTR at a 0.25:1 molar ratio. Two (2) mg 67:DOPE was complexed with 1.25 mg pCF1-CFTR DNA and administered to the nasal epithelium of CF patients. Nine patients were enrolled in this double blind section of the trial comparing the effect of 67:DOPE:pCF1-CFTR with administration of the plasmid pCF1-CFTR alone (1.25 mg pDNA) in the contralateral nostril. There were no adverse reactions to administration of the investigational material(s). In addition to safety, results of Part B demonstrate that

		administration of the investigational material produced some correction of the CF electrophysiologic abnormality."
12-24-96	**9403-069 Walker**	**A Phase I/II Pilot Study of the Safet of the Adoptive Transfer of Syngeneic Gene-Modified Cytotoxic T-Lymphocytes in HIV-Infected Identical Twins.** **Safety Report:** A patient was recently hospitalized for treatment of presumed Pneumocystis carinii pneumonia. The patient has received 4 infusions of syngeneic CD8 cells that are not genetically modified (this patient is in the control arm of the study). The patients most recent cell infusion was on 10-28-96, and the patient was hospitalized on 12-12-96. The PI states that he believes the patient's clinical condition is a complication of advanced HIV infection and is unlikely to be related to the investigational product.
1-19-97	**9409-087 Whitley**	**Retroviral-Mediated Transfer of the Iduronate-2-Sulfates Gene Into Lymphocytes for Treatment of Mild Hunter Syndrome (Mucopolysaccharidosis Type II).** **Safety Report:** The first patient has enrolled, and this patient received the first two infusions of cells without any complications. The patient had just received the third (and largest) dose of autologous, genetically modified lymphocytes ($5x10^9$); 13 hours later, the subject was found to have a low grade fever (100.8 degrees, orally). The patient also had flu-like symptoms (loss of appetite, malaise, and arthralgia and/or myalgia). These symptoms responded over 12-24 hours with administration of ibuprofen (400-800 mg po q 4-6 hours prn discomfort). During this period, the patient's white count drifted down from 4,700 (pre-infusion) to 3,600 and the platelet count from 188,000 to 114,000 (post-infusion numbers being obtained 36 hours after infusion of cells). Several blood cultures remain "sterile" at the time of writing this report, and liver function enzymes are normal. The PI has reviewed literature and consulted experts regarding this possible adverse drug response, and believes that it may have been a response to administration of activated T-cells, or possible a coincident viral flu-like infection. The PI reports that the patient is comfortable now and is being discharged.
1-24-97	**9608-157 Maria, et.al.**	**Prospective, Open-Label, Parallel-Group, Randomized, Multicenter Trial Comparing the Efficacy of Surgery, Radiation, and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir Against the Efficacy of Surgery and Radiation in the Treatment of Newly Diagnosed, Previously Untreated Glioblastoma.** **Safety Report:** The patient reported here is enrolled at the University of Cincinnati, Ohio, under the care of Dr. Ronald Warnick. The event is cerebral edema (confusion, right-sided weakness, lethargy, and incontinence). It is the opinion of the investigator, with the sponsor agreeing, that this event is probably related to the administration of the vector producing cells. It is thought to be related because the enhancement and edema on MRI correspond with the area of the brain which was injected with the cell suspension. This patient had presented with memory loss, headaches, and weight loss prior to entry into the trial. On 12-30-96, the patient underwent craniotomy with resection of a left frontal tumor and an intracerebral injection of 10 ml of the vector producing cell suspension. The immediate post-operative period was uneventful. On 1-11-97, the patient was hospitalized with confusion, right-sided weakness, lethargy, and incontinence. An MRI was performed on that date which revealed enhancement and edema, and the patient's Decadron dose was increased to 10 mg q6h. On 1-12-97, Mannitol was started at 25 grams IV, q6h. The patients symptoms began to improve on 1-17-97, and Mannitol was discontinued. The Decadron dose began to be decreased as of 1-19-97. Discharge from the hospital was pending at the time of this report. The report notes that on 1-16-97 the patient experienced a pulmonary embolus, which is not regarded as an alert report since it is not considered related to GLI-328 (the vector

	producing cells) and is recognized as an increased risk associated with glioblastoma multiforme.