AMENDMENTS AND UPDATES TO
HUMAN GENE TRANSFER PROTOCOLS
RECOMBINANT DNA ADVISORY COMMITTEE MEETING
SEPTEMBER 24-25, 1998

May 27, 1998 (letter date)	**9701-173 Williams**	**A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine (PCV) for Poor Prognosis Pediatric and Adult Brain Tumors Utilizing Fibronectin-Assisted, Retroviral-Mediated Modification of CD34+ Peripheral Blood Cells with O^6-Methylguanine DNA Methyltransferase** **Amendments:** Several minor amendments to note changes made in pre-treatment screening for antibodies to fibronectin. In addition, changes were made to note alteration in transduction procedure. Two four hour transductions will now be performed separated by at least 20 hours. Finally, Dr. James Croop will serve as the primary investigator. Dr. Williams will be a co-investigator.
June 1, 1998	**9406-081 Lotze**	**IL-12 Gene Therapy Using Direct Injection of Tumor with Genetically Engineered Autologous Fibroblasts** **Update:** A total of 29 patients have been treated (for a total of 39 treatment cycles, five patien received two treatment cycles). The vast majority of tumor types treated were melanoma and breast cancer. No toxicities beyond Grade 1 were observed. In addition, the maximum tolerated dose was determined to be 7, 000 ng/24 hours.
June 3, 1998	**9709-212 Gonzalez *et. al.***	**Phase I Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) with IL-2 Plasmid DNA/DMRIE/DOPE Lipid Complex (Leuvectin) as an Immunotherapeutic Regimen in Patients with Metastatic Melanoma** **Amendments:**

		Inclusion criteria have been altered to allow patients who have chosen to decline conventional therapies. In addition, the section concerned with dose limiting toxicity has been altered to repeat the dose (if a dose-limiting or WHO Grade 3 or higher drug-related toxicity is encountered) where at most one, instead of no toxicity, dose-limiting or severe drug-related toxicity was observed. Finally, an alteration has been made concerning handling of patients who are remove from the study. If a patient is removed before the final visit, the study procedures scheduled to be performed at the final visit should be done the last time the patient is seen.
June 17, 1998	**9605-159 Heslop *et al.***	**A Comparative Evaluation of the Utility of Hematopoietic Progenitor Cells Derived from Peripheral Blood vs Bone Marrow** **Amendment:** Protocol has been transferred to the Baylor College of Medicine; Houston, Texas from St. Jude's Children's Research Hospital.
June 18, 1998	**9806-259 Figlin**	**Phase II Study of Direct Gene Transfer of IL-2 Plasmid DNA/DMRIE/DOPE Lipid Complex (Leuvectin) as an Imunotherapeutic Regimen in Patients with Metastatic Renal Cell Carcinoma** **Amendment:** Two new investigators/sites have been added. 1) John A. Thompson, M.D. at the University of Washington, Seattle Washington and 2) Evanthia Galanis, M.D. at the Mayo Clinic, Rochester, Minnesota
June 19, 1998	**9806-259 Figlin *et al.***	**Phase II Study of Direct Gene Transfer of IL-2 Plasmid DNA/DMRIE/DOPE Lipid Complex (Leuvectin) as an Imunotherapeutic Regimen in Patients with Metastatic Renal Cell Carcinoma** **Amendments:**

		The first amendment clarifies the inclusion and exclusion criteriaFor inclusion, patients must have had resection of the primary tumor.And are excluded if they have a single tumor mass that is greater than 10 x 10 cm.In addition, if a patient is removed from the study before the week 19 visit, the week 19 study procedures are t be completed at the final visit. The second amendment substitutes the NCI Common Toxicity Criteria for the WHO Recommendations for Grading of Toxic Effects. The sponsor; Vical, Inc.; states that the NCI criteria "...are more representative of the symptoms commonly seen with biologics."
June 1, 1998(received June 22, 1998)	**9406-081 Lotze**	**IL-12 Gene Therapy Using Direct Injection of Tumor with Genetically Engineered Autologous Fibroblasts** **Amendment:** Protocol amendment to treat pediatric patients.Patients must have been less than 18 years old at diagnosis. Five cohorts are proposed with three patients in each cohort. The PI of this study is Dr. StevenNeudorf. Dr. Lotze, the PI of 9406-081, is listed as a Co-PI. The revised protocol, IRB approval, and IRB-approved informed consent document were submitted.
June 29, 1998	**9709-214 Breau *et al.***	**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)** **Amendment:** One new investigator/site has been added. Dirk Eber, M.D. at the Ear, Nose and Throat Clinic, Erfurt, Germany.
June 29, 1998	**9712-226 Dreicer *et al.***	**A Phase II, Multi-Center, Open Label, Study to Evaluate Effectiveness and Safety of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 39 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)**

		Amendment: One new investigator/site has been added. Heikki Minn, M.D. at Turku University Central Hospital, Turku Finland.
July 24, 1998	**9706-196 Smith and Dinauer**	**Fibronectin-Assisted, Retroviral-Mediated Transduction of CD34+ Peripheral Blood Cells with gp91 phox in Patients with X-Linked Chronic Granulomatous Disease: A Phase I Study** **Amendments:** Very minor amendments have been made to the protocol. Modifications include clarification of the timing for blood draws, the amount of blood to be drawn, and other editorial changes.
July 29, 1998	**9804-250 Swisher**	**An Efficacy Study of Adenoviral Vector Expressing Wildtype p53 (Ad5CMV-p53) Administered Intralesionally as an Adjunct to Radiation Therapy in Patients with Non-Small Cell Lung Cancer** **Amendments:** Two amendments were made to the clinical protocol. 1) The viral dose has been changed throughout the protocol from plaque forming units to particle forming units. 2) Tests to assess the adenoviral vector biodistribution have been deleted. These tests were included in this protocol prior to completion of a Phase I study employing this vector and a similar patient population. In addition, data have been analyzed from approximately 100 patients that have been treated under similar studies.
July 15, 1998(received July 31, 1998)	**9804-247 Roth**	**A Phase I Safety and Dose Escalation Trial of Autologous Transfected Human Fibroblasts Producing Human Factor VIII in Patients with Severe Hemophilia A** **Amendments:** 1) Change has been made in the number of cohorts. Now there will be four dose groups with three patients in each group. Either 100 x 10^6 or 400 x 10^6 autologous cells expressing human factor VIII will be administered in either of two different

		omental implantation sites. The previously proposed dose of 200 x 10^6 cells has been dropped. The number of total patients is also increased, from nine to twelve, to reflect the change in the number of cohorts. In addition, the title of the study has been modified. The words "...and Dose Escalation Trial..." have been replaced by the word "Study" to reflect the fact that this is no longer a dose escalation trial. 2) An interim safety analysis has been added after the first 6 patients are treated. No additional patients will be enrolled until the interim safety analysis has been reviewed by the FDA. Also, additional patient evaluations have been added to increase patient monitoring and to ensure patient safety. 3) Inclusion criteria have been changed. The minimum age limit has been changed from 13 years or older to 15 years or older. This change was made to make the protocol consistent with the institutional policies where the study is taking place. In addition, the inclusion criteria have been amended to state that patients must have received conventional factor VIII replacement therapy for at least 50 days. This will help to ensure that patients have had adequate exposure to factor VIII and therefore the risk of generation of human factor VIII antibodies will be reduced. 4) A protocol stopping rule has been added. The protocol will be temporarily halted and discussed with the FDA if two or more patients develop antibodies to factor VIII equal to or greater than ten Bethesda units. The RAC; after the June 19, 1998 public discussion of this protocol; made a recommendation that the trial should be terminated if two or more patients develop antibodies.
August 7, 1998	**9512-142 Gluckman**	**Allovectin-7 in the Treatment of Squamous Cell Carcinoma of the Head and Neck** **Amendment:** Change in the inclusion criteria to allow treatment of patients with primary or recurrent cancer of the upper airway and digestive tract and patients with obstructing non-small cell respiratory tract cancer. Patients with squamous cell carcinoma of the

		head and neck are still eligible.
August 7, 1998	**9802-234 Thompson**	**A Controlled, Randomized Phase III Trial Comparing the Response to Decarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:** One new investigator/site has been added. Robert Dreicer, M.D. at the University of Iowa Hospitals and Clinics; Iowa City, Iowa.
August 17, 1998	**9803-241 Bensinger *et al.***	**A Phase I/II Outpatient, Multicenter, Intrapatient, Multiple Dose Escalation Study of Herpes Simplex Virus Thymidine Kinase (HSV-TK) Transduced Mononuclear Cells in Subjects with Persistent or Relapsed Chronic Myleogenous Leukemia, Chronic Lymphocytic Leukemia, Multiple Myeloma, and Non-Hodgkin's Lymphoma after HLA-Mediated Sibling Allogeneic Stem Cell Transplant** **Amendment:** One new investigator/site has been added. Matthew Carabasi, M.D. at the University of Alabama at Birmingham; Birmingham, Alabama.
August 21, 1998	**9712-226 Dreicer *et al.***	**A Phase II, Multi-Center, Open Label, Study to Evaluate Effectiveness and Safety of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 39 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)** **Amendment:** Two new investigators/siteshve been added. 1) Louis Gueertin, M.D. at CHUM - Pavilion Notre-Dame; Montreal, Quebec. 2) Fei-Fei Liu, M.D. at Princess Margaret Hospital; Toronto, Ontario.
August 24, 1998	**9709-214 Breau *et al.***	**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)**

		Amendment: The Dana-Farber Cancer Institute, with Dr. Marshall Posner as the principal investigator, will no longer be a clinical site for this protocol.
August 24, 1998	**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** **Update:** Since the last update, the principal investigator, Dr. Walker, reports that Period 3, which was completed since the last continuing review, involved administration of 3 infusions of gene modified CD4 and CD8 cells at 2 week intervals. Of the 33 sets of twins who participated on period 2, 18 enrolled and 17 participated on period 3. 3 of the recipient twins also received IL-2 with the third of the 3 cell infusions.
August 25, 1998	**9802-234 Thompson and Dreicer**	**A Controlled, Randomized Phase III Trial Comparing the Response to Decarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:** One new investigator/site has been added. Hilliard Seigler, M.D. at Duke University Medical Center; Durham, North Carolina.
August 25, 1998	**9802-233 Dreicer**	**Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Immunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives** **Amendment:** One new investigator/site has been added. Hilliard Seigler, M.D. at Duke University Medical Center; Durham, North Carolina.
September 1, 1998	**9802-234 Thompson *et al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Decarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma**

		Amendment: Two new investigators/sites have been added. 1) Evanthia Galanis, M.D. at the Mayo Clinic; Rochester, Minnesota and 2) RobertDeConti, M.D. at the H. Lee Moffitt Cancer Center; Tampa, Florida.
September 1, 1998	**9802-233 Dreicer and Seigler**	**Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Immunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives** **Amendment:** Two new investigators/sites have been added. 1) Joseph Rubin, M.D. at the Mayo Clinic; Rochester, Minnesota and 2) RobertDeConti, M.D. at the H. Lee Moffitt Cancer Center; Tampa, Florida.