AMENDMENTS AND UPDATES TO HUMAN GENE TRANSFER PROTOCOLS
RECOMBINANT DNA ADVISORY COMMITTEE MEETING
December 8-10, 1999

August 10, 1999 (letter date)	**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:** Three new investigators/sites have been added. (1) Christoph Zielinski, M.D.; University of Vienna; Vienna, Austria; (2) Brian Link, M.D.; University of Iowa Hospital and Clinics; Iowa City, Iowa; and (3) John Truelson, M.D.; University of Texas Southwestern Medical School; Dallas, Texas.
August 13, 1999	**9805-245 Moss and Moira**	**A Phase I Study of Aerosolized tgAAVCF for the Treatment of Cystic Fibrosis Patients with Mild Lung Disease** **Amendments:** One new investigator/site is added. Dr. David Waltz, M.D.; Harvard Medical School; Boston, Massachusetts. Clinical protocol has been amended to allow for the inclusion of a fourth cohort of three patients. This new cohort will receive a dose of $1x10^{13}$ DNAase Resistant Particles (previous highest dose cohort received $1x10^{12}$). Purpose of additional cohort is to generate additional safety and kinetic data. In addition, the bronchoscopy schedule has been altered to attempt to obtain "...gene transfer data at time points to supplement data obtained on previous patients."
August 18, 1999	**9904-306 Vieweg**	**Safety and Feasibility Study of Active Immunotherapy in Patients with Hormone Refractory Prostate Cancer Using Autologous Dendritic Cells Pulsed with RNA Encoding Prostate Specific Antigen, PSA** **Amendments:** Additional blood draws have been added during the vaccination cycle. Also, the testing for delayed hypersensitivity will now include PSA RNA transfected dendritic cells.

August 23, 1999	**9901-280 Buller *et al.***	**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** **Amendment:** Eleven new investigators/sites are added. The new investigators are: (1) McClure L. Smith, M.D.; University of Nebraska Medical Center; Omaha, Nebraska; (2) Susan A. Davidson, M.D.; University of Colorado Health Sciences Center; Denver, Colorado; (3) John C. Gutheil, M.D.; Sharp HealthCare, Sidney Kimmel Cancer Center; San Diego, California; (4) Jeffrey D. Bloss, M.D.; University of Missouri; Columbia, Missouri; (5) Allan J. Jacobs, M.D.; Beth Israel Medical Center; New York, New York; (6) Larry E. Puls, M.D.; Greenville Hospital System; Greenville, South Carolina; (7) Nelson Nan-Hsiung Teng, M.D., Ph.D.; Stanford University School of Medicine; Stanford, California; (8) Mark D. Pergram, M.D.; University of California, Los Angeles; Los Angeles, California; (9) Holly Gallion, M.D.; University of Kentucky Medical Center; Lexington, Kentucky; (10) Michael Rodriguez, M.D.; University Hospitals of Cleveland Cleveland, Ohio; and (11) John H. Malfetano, M.D.; Albany Medical College; Albany, New York.
August 23, 1999	**9905-318 Venook and Warren**	**A Phase II Study of SCH 58500 in Combination with Chemotherapy Alone in Patients with Colorectal Cancer Metastatic to the Liver** **Amendment:** Five new investigators/sites are added. The new investigators are: (1) Heinz-Josef Lenz, M.D.; University of Southern California; Los Angeles, California; (2) Thanjavur S. Ravikumar, M.D.; Montefiore Medical Center; Bronx, New York; (3) Edwin A. McElroy, Jr., M.D.; Alton Ochsner Medical Foundation; New Orleans, Louisiana; (4) Mark S. Roh, M.D.; Allegheny General Hospital; Pittsburgh, Pennsylvania; and (5) Margaret Kemeny, M.D.; Stony Brook University Hospital; Stony Brook, New York.
August 24, 1999	**9709-210 Gonzales and Hersh**	**Compassionate Use Protocol for Retreatment with Allovectin-7 Immunotherapy for Metastatic Cancer by Direct Gene Transfer** **Amendment:** One new site/investigator is added. Albert Deisseroth, M.D.; Yale University; New Haven, Connecticut.

August 25, 1999	**9906-323 Zarrabi *et al.***	**A Multi-Center, Open-Label, Randomized Study of the Safety and Efficacy of Multiple Intratumoral Injections of hIL-2 Plasmid (1.8 mg) Formulated with DOTMA/Cholesterol [Ratio 1:0.5 (-/+)] Liposomes in Patients with Unresectable or Recurrent/Refractory Squamous Cell Carcinoma of the Head and Neck** **Amendment:** One new site/investigator is added. K. Thomas Robbins, M.D.; University of Tennessee; Memphis, Tennessee.
August 26, 1999	**9810-268 Antonia**	**Treatment of Patients with Stage IV Renal Cell Carcinoma with B 7-1 Gene-Modified Autologous Tumor Cells and Systemic IL-2** **Amendments:** A number of minor modifications have been made to the clinical protocol. Two significant changes made to the protocol were that a minimum number of three and a maximum number of five patients will be treated at any dose level regardless of whether significant toxicity was observed. The original protocol stated that three patients would be treated at each dose level with the enrollment of two additional patients at any dose if significant toxicity was encountered. In addition, the third cohort, 12 injections of 10^7 gene-modified autologous tumor cells, was replaced by a cohort that will receive three monthly injections of $5x10^6$ autologous tumor cells. (The PI has discovered that it is not feasible to obtain sufficient quantities of cells in order to treat patients at the highest dose level.) The rationale for this change is that a lower dose maybe as efficacious as the higher doses. Five patients have been treated at doses higher than $5x10^6$ without any toxicity. The doses proposed in the original protocol were arbitrary, according to the PI.
September 1, 1999	**9906-323 Zarrabi *et al.***	**A Multi-Center, Open-Label, Randomized Study of the Safety and Efficacy of Multiple Intratumoral Injections of hIL-2 Plasmid (1.8 mg) Formulated with DOTMA/Cholesterol [Ratio 1:0.5 (-/+)] Liposomes in Patients with Unresectable or Recurrent/Refractory Squamous Cell Carcinoma of the Head and Neck** **Amendment:** One new site/investigator is added. Bert W. O'Malley, M.D.; University of Maryland School of Medicine; Baltimore, Maryland.
	9802-234 Thompson	**A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma**

September 3, 1999	***et al.***	**Amendment:** One new site/investigator isadded.Frank L. Meyskens, Jr., M.D.; University of California, Irvine; Orange, California.
September 8, 1999	**9905-318 Venook *et al.***	**A Phase II Study of SCH 58500 in Combination with Chemotherapy Alone in Patients with Colorectal CancerMetastatic to the Liver** **Amendment:** Two new investigators/sites are added. The new investigators are: (1) Philip J. Gold, M.D.; University of Washington; Seattle, Washington and (2) Charles Staley, III, M.D.; Emory University School of Medicine; Atlanta, Georgia.
September 13, 1999	**9906-323 Zarrabi *et al.***	**A Multi-Center, Open-Label, Randomized Study of the Safety and Efficacy of Multiple Intratumoral Injections of hIL-2 Plasmid (1.8 mg) Formulated with DOTMA/Cholesterol [Ratio 1:0.5 (-/+)]Liposomes in Patients with Unresectable or Recurrent/Refractory Squamous Cell Carcinoma of the Head and Neck** **Amendment:** One new site/investigator is added.Fairooz Kabbinavar, M.D.; University of California, Los Angeles; Los Angeles, California.
September 14, 1999	**9902-286 Stopeck**	**Phase I Study of HLA-B7/b2M Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) by Direct Gene Transfer with Concurrent Low-Dose Subcutaneous IL-2 Protein Therapy as an Immunotherapeutic Regimen in Lung and Head and Neck Cancers.** **Amendment:** The number of cohorts has been reduced from three to two (10 mg and 100 mg, instead of 10 mg, 50 mg, and 100 mg). Change was made to be able to compare the results from this study more easily with other studies for head and neck cancers that employ similar doses of Allovectin-7. However, the same number (18) of patients will be treated in divided into two instead of three dosage groups. Nine patients withmetastaticlung cancer and nine with head and neck cancer.

September 15, 1999	**9901-280 Buller *et al.***	**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** **Amendment:** Six new investigators/sites are added. The new investigators are: (1) Robert P. Edwards, M.D.; University of Pittsburgh; Pittsburgh, Pennsylvania; (2) Janet Rader, M.D.; Washington University; Saint Louis, Missouri; (3) Benedict B Benigno, M.D.; Northside Hospital; Atlanta, Georgia; (4) Joseph T. Santoso, M.D.; University of Texas Medical Branch; Galveston, Texas ; (5) James E. Delmore, M.D.; University of Kansas School of Medicine, Wesley Medical Center; Wichita, Kansas; and (6) Harriet O. Smith, M.D.; the University of New Mexico School of Medicine; Albuquerque, New Mexico.
September 20, 1999	**9709-210 Gonzales *et al.***	**Compassionate Use Protocol for Retreatment with Allovectin-7 Immunotherapy for Metastatic Cancer by Direct Gene Transfer** **Amendment:** One new site/investigator is added. Paolo A. Paciucci, M.D.; Mt. Sinai Medical Center; New York, New York.
September 20, 1999	**9905-312 Belldegrun**	**Phase II Study Evaluating the Safety and Efficacy of Neoadjuvant Leuvectin Immunotherapy for the Treatment of Prostate Cancer** **Amendment:** One new site/investigator is added. Eric Klein, M.D.; Cleveland Clinic Foundation; Cleveland, Ohio.
September 20, 1999	**9810-268 Antonia**	**Treatment of Patients with Stage IV Renal Cell Carcinoma with B 7-1 Gene-Modified Autologous Tumor Cells and Systemic IL-2** **Update:** From November 1998 to August 1999, 12 patients have been treated under this protocol. Enough cells were not obtained for two of the 12 patients. These two individuals, requested, and received a dose lower (dose not specified in update) than the proposed starting dose. Almost all of the patients experienced toxicities that were expected from IL-2 administration. However, two patients experienced significant progression of their disease. One patient died three weeks after receiving the first vaccine injection. Death was determined to be due to progressive disease. No other information about this event was supplied to ORDA.

September 22, 1999	**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** **Amendment:** The second infusion of cells will now occur at least six months after the initial infusion. At this six month time point, peripheral blood DHR (test for circulating neutrophils) and PCR results have been negative for to consecutive months. In addition, minor amendments (clerical in nature) have been made.
September 29, 1999	**9905-318 Venook *et al.***	**A Phase II Study of SCH 58500 in Combination with Chemotherapy Alone in Patients with Colorectal Cancer Metastatic to the Liver** **Amendment:** Two new investigators/sites are added. The new investigators are: (1) Kelly M. McMasters, M.D., Ph.D.; University of Louisville; Louisville, Kentucky; and (2) Laurence Elias, M.D.; University of New Mexico School of Medicine; Albuquerque, New Mexico.
September 30, 1999	**9902-284 Ragni *et. al*** .	**Phase I Multi-Center, Single Treatment Dose Escalation Study of Factor VIII Vector [hFVIII(V)] for Treatment of Severe Hemophilia A** **Update:** Letter from Dr. Ragni in response to the September RAC review of the above protocol. The informed consent document was modified based on suggestions made at the RAC meeting: (1) mention of female study participants and pregnancy has been deleted; (2) information regarding possible participation in future studies based using the same vecto has been added; (3) explanation of the background science has bee re-worded into more easily understandable language; and (4) minimum age requirement has been lowered to 18 years of age.
October 1, 1999	**9701-173 Croop**	**A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine (PCV) for Poor Prognosis Pediatric and Adult Brian Tumors Utilizing Fibronectin-Mediated Modification of CD34+ Peripheral Blood Cells with** **O^6-Methylguanine DNA Methyltransferase** **Update:** To date, five of a proposed 20 patients have been enrolled. Three of the five did not complete treatment under the study, due to progressive disease. Three patients have died while on this protocol; all due to progressive disease. These deaths have been reported to ORDA on the annual reports (report that was submitted

		closest to the date of the death) submitted for this study. First death occurred back in September 1998.
October 8, 1999	**9701-173 Croop**	**A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine (PCV) for Poor Prognosis Pediatric and Adult Brian Tumors Utilizing Fibronectin-Mediated Modification of CD34+ Peripheral Blood Cells with** **O^6-Methylguanine DNA Methyltransferase** **Update:** According to the clinical protocol, peripheral blood and bone marrow will be tested at defined time points for methylguanine methyltransferase mRNA. However, due to problems with sample storage, mRNA testing was not able to be accomplished. A new storage procedure has been initiated. Hopefully, samples from all future patients will be able to be tested.
October 12, 1999	**9902-287 Schiller and Carbone**	**Phase I Pilot Trial of Adenovirus p53 in Bronchiolalveolar Cell Lung Carcinoma (BAC) Administered by Bronchoalveolar Lavage** **Amendments:** Maximum number of allowable doses has been removed. Also, the definition of dose limiting toxicity has been revised.
October 15, 1999	**9409-083 Zeitlin**	**A Phase I Study of an Adeno-Associated Virus-CFTR Gene Vector in Adult CF Patients with Mild Lung Disease** **Amendments:** 1) One new site/investigator is added. Terence R. Flotte, M.D.; University of Florida; Gainesville, Florida. 2) Large number of amendments have been made. Significant changes are that, based upon rabbit toxicological data, the maximum dose will now be $1x10^9$ RU (replication units) of tgAAVCF administered to the lung. In addition, the lower age has been changed from 18 to 15 years old.
October 20, 1999	**9910-352 Belldegrun**	**Phase II Study Evaluating the Safety and Efficacy of Neoadjuvant Leuvectin Immunotherapy for the Treatment of Prostate Cancer** **Amendment:** One new site/investigator is added. Eric A. Klein, M.D; Cleveland Clinic Foundation; Cleveland, Ohio.
October 20,	**9905-318 Venook *et al.***	**A Phase II Study of SCH 58500 in Combination with Chemotherapy Alone in**

1999		**Patients with Colorectal Cancer Metastatic to the Liver** **Amendment:** One new investigators/site is added. Rafael G. Amado, M.D.; University of California, Los Angeles; Los Angeles, California.
October 20, 1999	**9901-280** **Buller *et al.***	**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** **Amendment:** Three new investigators/sites are added. The new investigators are: (1) Robert E. Bristow, M.D.; The Johns Hopkins School of Medicine; Baltimore, Maryland; (2) Fouad Abbas, M.D.; Sinai Hospital of Baltimore; Baltimore, Maryland; and (3) Giles Fort, M.D.; Woman's Hospital; Baton Rouge, Louisiana.
October 25, 1999	**9906-323** **Zarrabi *et al.***	**A Multi-Center, Open-Label, Randomized Study of the Safety and Efficacy of Multiple Intratumoral Injections of hIL-2 Plasmid (1.8 mg) Formulated with DOTMA/Cholesterol [Ratio 1:0.5 (-/+)] Liposomes in Patients with Unresectable or Recurrent/Refractory Squamous Cell Carcinoma of the Head and Neck** **Amendment:** One new site/investigator is added. Thomas McCaffery, M.D., Ph.D.; University of South Florida; Tampa, Florida.
November 4, 1999	**9701-173 Croop**	**A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine (PCV) for Poor Prognosis Pediatric and Adult Brian Tumors Utilizing Fibronectin-Mediated Modification of CD34+ Peripheral Blood Cells with** **O^6-Methylguanine DNA Methyltransferase** **Amendment:** Minor amendment to clarify that chemotherapy may not begin until at least four after the completion of radiation therapy.
November 4, 1999	**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** **Amendments:** Exclusion criteria have been modified to include any bacterial or fungal infection that

		requires surgical intervention or antibiotic treatment. Minor changes to the informed consent indicating that some injections may be given by the patient or by a local health care professional. Also, some of the tests mayve performed by the patient's physician or a physician that the patient is referred to by the investigators.
November 5, 1999	**9909-339 Holt and Tait**	**Ovarian Cancer Gene Therapy with BRCA1** **Amendments:** Changes, in response to the FDA's review, have been made to the inclusion, exclusion criteria of the clinical protocol. In addition, two new sections dealing with discontinuatic of the study and adverse events have been added. The informed consent has been modified to exclude pregnant women and to require notification of pregnancy during the trial. (Even though, according to the investigators, a of the patients who are likely to participate in this trial are sterile from previous therapie These changes were made to help to convey"... the possible seriousness and unknown nature of gene therapy [to the patient]."
November 8, 1999	**9905-312 Belldegrun**	**Phase II Study Evaluating the Safety and Efficacy ofNeoadjuvant Leuvectin Immunotherapy for the Treatment of Prostate Cancer** **Amendment:** One new site/investigator is added. JohnCorman, M.D.; VA Puget Sound Health Care System; Seattle, Washington.
November 8, 1999	**9802-233 Dreicer *et. al.***	**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 Treatments Alternatives** **Amendment:** One new site/investigator isadded.Ronald H. Blum, M.D.; Beth Israel Medical Center; New York, New York.
November 8, 1999	**9802-234 Thompson *et. al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine with and without Allovectin-7 in Patients withMetastatic Melanoma** **Amendment:** One new site/investigator is added. Ronald H. Blum, M.D.; Beth Israel Medical Center; New York, New York.
November 8, 1999 (received by ORDA; update dated July 16, 1999)	**9804-249 Junghans**	**Phase I Study of T Cells Modified withChimeric AntiCEA Immunoglobulin-T Cell Receptors (IgTCR) in Adenocarcinoma** **Update:**

		This report was not submitted to ORDA until November 1999. As of July 1999, seven patients have been enrolled. Post infusion studies have indicated that, at most, 25% of the activated T cells (observed in one individual; usual range was 1-10%) were transduced with IgTCR. Results from multiple infusions suggested that the transduced cells are rapidly cleared, within 24 hours. Changes have been made to the manufacturing and microbiological testing portions of the protocol. These changes have been made to increase the transduction efficiency and to aid in insuring sterility throughout the production process. Finally, a second arm was introduced into the study to allow for the continuous infusion of interleukin 12 to aid in the survival and activity of the transduced T cells. In addition, the highest dose of transduced cells ($1x10^{11}$) will now be administered as a single infusion, as opposed to four doses.
November 11, 1999	**9906-323 Zarrabi *et al.***	**A Multi-Center, Open-Label, Randomized Study of the Safety and Efficacy of Multiple Intratumoral Injections of hIL-2 Plasmid (1.8 mg) Formulated with DOTMA/Cholesterol [Ratio 1:0.5 (-/+)]Liposomes in Patients with Unresectable or Recurrent/Refractory Squamous Cell Carcinoma of the Head and Neck** **Amendment:** One new site/investigator is added. Joehassin Cordero, M.D.; Texas Tech University; Lubbock, Texas.