AMENDMENTS AND UPDATES TO
HUMAN GENE TRANSFER PROTOCOLS
RECOMBINANT DNA ADVISORY COMMITTEE MEETING
SEPTEMBER 2-3, 1999

June 1, 1999 (letter date)	**9804-245 Moss and Aitken**	**A Phase I Study of Aerosolized tgAAVCF for the Treatment of Cystic Fibrosis Patients with Mild Lung Disease** **Amendments:** Minor amendments have been made to more clearly define when sputum samples would be collected during both the baseline and study periods. Quantitative assays for bacterial cultures, cell counts, and differentials have also been added. In addition, one or more therapies that aid in the clearance of mucous are allowable prior to administration of the vector.
June 9, 1999	**9902-284 Ragni**	**Phase I Multi-Center, Single Treatment Dose Escalation Study of Factor VIII Vector [HFVIII(V)] for Treatment of Severe Hemophilia A** **Amendment:** Two new investigators/sites are added. The new investigators are (1) Jeanne M.Lusher, M.D. at Children's Hospital of Michigan; Detroit, Michigan; and (2) Jerry S. Powell, M.D. at the University of California, Davis, Medical Center; Sacramento, California.
June 16, 1999	**9812-274 Comerota**	**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** **Amendments:**

		1) Inclusion requirement that restricted enrollment of only sterile patients has been modified t allow patients of childbearing potential. This new patient population must agree to use barrier contraception for six months after initiation of treatment. This change was made following the decision by the Center for Biologics and Evaluation, FDA to lift its ban on fertile patient enrollment in these types of studies. 2) One new investigator/site is added. The new investigator is John R. Laird, M.D. at Washington Hospital Center; Washington, D.C.
June 17, 1999	**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** **Amendments:** Definition of "intent to treat analysis patients" has been modified to include patients regardless of whether they have received prior decarbazine treatment or not. The inclusion criteria have been modified to allow enrollment of patients that have LDH values that are within two times the upper limit of normal. In addition, timing of retreatment, for stable or responding patients, has been reduced from 24 weeks (end of study) to 12 weeks, at the option of the PI. This change is consistent with the standard of care for this patient population.
June 17, 1999	**9805-251 Figlin**	**Phase I/II Trial of Antigen-Specific Immunotherapy in MUC-1 Positive Patients with Adenocarcinoma of the Prostate Using Vaccinia Virus-MUC1-IL-2** **Amendments:** In addition to several minor amendments, two more substantial amendments have been made. The first of these deletes the phase II portion of the trial. Additional cohorts have been added with a slightly altered dosing schedule. The investigator stated that "...this schedule change would provide dosing regimen information that should be explored prior to expanding to a Phase II design." Another amendment excludes patients with a history of eczema or who have

		contact with persons with eczema. This change was made in response to an assessment of vaccinia protocols made by the FDA. In addition, the informed consent has been modified to reflect the fact that there is currently a shortage of vaccinia immune globulin.
June 18, 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** **Amendment:** One new investigator/site is added. The new investigator is Gilbert White, M.D. at the University of North Carolina School of Medicine; Chapel Hill, North Carolina.
June 21, 1999	**9701-173 Croop**	**A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine (PCV) for Poor Prognosis Pediatric and Adult Brian Tumors Utilizing Fibronectin-Assisted, Retroviral-Mediated Modification of CD34+ Peripheral Blood Cells with O^6-Methylguanine DNA Methyltransferase** **Amendments:** Changes have been made that make it clear that a bone marrow aspirate will be performed aft the first and third course of treatment. Radiation will not be administered until after the third course of chemotherapy instead of concurrently. This is to avoid the potential of increased toxicity if chemotherapy and radiation are administered at the same time. The fourth course of chemotherapy will not be administered until completion of radiation therapy. Finally, peripheral blood is requested to be drawn for baseline studies to assess the following: MGMT cDNA, MGMT mRNA, repair activity, progenitor colony assay, nitrosourea resistance, and safety testing."
June 23, 1999	**9801-280 Buller**	**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) Linda F. Carson, M.D. at the University of Minnesota; Minneapolis, Minnesota; (2) Tracey Weisberg, M.D. at the Maine Center for Cancer Medicine; Scarborough, Maine [IBC approval is limited to the

		treatment of two patients]; and (3) Wayne A. Christopherson, M.D. at Mercy Hospital of Pittsburgh; Pittsburgh, Pennsylvania.
June 24, 1999	**9602-147 Kohn**	**Transduction of CD34+ Cells from the Bone Marrow of HIV-1 Infected Children: Comparative Marking by an RRE Decoy and a Neutral Gene** **Update:** No patients were treated during the past year. Follow-up has continued for the four treated patients. In three of the four patients neither the RRE nor neutral genes were detected in peripheral blood leukocytes. In the fourth patient, only the neutral (neo) gene was detected at very low level (less than one cell in 100,000).
June 25, 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: A Phase I Study** **Update:** One, out of five proposed, patient has been treated. Patient did not experience any complications from either the placement of a catheter for apheresis or from the vector transduced blood progenitor cell infusion. Vector transduced cells were detected for 5 ½ weeks in the blood and for 24 days in bone marrow.
June 27, 1999	**9512-142 Gluckman**	**Allovectin-7 in the Treatment of Squamous Cell Carcinoma of the Head and Neck** **Amendment:** Dose of Allovectin-7 has been increased from 10 to 100 mg. This increase is based on experience in other ongoing Allovectin-7 trials.
June 28, 1999	**9701-172 Cornetta and Abonour**	**High Dose Carboplatin and Etoposide Followed by Transplantation with Peripheral Blood Stem Cells Transduced with the Multiple Drug Resistance Gene in the Treatment of Germ Cell Tumors - A Pilot Study**

		Update: Trial has reached number of patients proposed to be enrolled and is closed to new patients.
July 6, 1999	**9709-210 Gonzales and Hersh**	**Compassionate Use Protocol for Retreatment with Allovectin-7 Immunotherapy for Metastatic Cancer by Direct Gene Transfer** **Amendment:** Patients are now eligible for enrollment if they have been on a previous Allovectin-7 protocol and have responded to the treatment and subsequently progressed or were on a Vical-sponsored protocol and did not receive Allovectin-7 due to randomization. Patients who previously received Allovectin-7 will receive the same dose under the same treatment schedul as on the previous protocol Patients who did not receive Allovectin-7 or received Allovectin-7 in combination with other medication will, if appropriate, receive 10 mg of Allovectin-7. It is at the discretion of the PI as to whether a patient will continue to receive Allovectin-7 in combination with another medication.
July 14, 1999	**9905-313 Topalian**	**Immunization of Patients with Metastatic Melanoma Using Recombinant Fowlpox and Vaccinia Viruses Encoding the Tyrosinase Antigen** **Amendment:** Revisions were made to the clinical protocol, as requested by the FDA and CTEP, to reflect the fact that vaccinia immune globulin is currently not available.
July 26, 1999	**9906-323 Zarrabi**	**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:** Two new investigators/sites are added. The new investigators are (1) Merrill A. Biel, M.D.,

		Ph.D. at Ear, Nose & Throat SpecialtyCare of Minnesota, P.A.; Minneapolis, Minnesota and (2) Steven Krasnow, M.D. at Veterans Affairs Medical Center; Washington, D.C.
July 27, 1999	**9403-069 Walker**	**A Phase I/II Pilot Study of the Safety of the Adoptive Transfer ofSyngeneic Gene Modified Cytotoxic T-Lymphocytes in HIV-Infected Identical Twins** **Update:** Yearly update was provided. Trial has been closed to new patient enrollment since February 1997. Of the 43 patients enrolled (43 sets of twins), 32 received gene-modified cells, eight never received any cells, and three received non-modified, culture expanded cells.Of the 32 patients who received gene-modified cells, 13 are in long-term follow-up, three are enrolled in protocol # 9503-103, nine are participating in the Il-2 extension phase of this protocol, five have died, and two patients have been lost to follow-up.
August 6, 1999	**9812-274 Comerota and Laird**	**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** **Amendment:** Two new investigators/sites are added. The new investigators are (1) Rafael F.Sequeira, M.D. at the University of Miami, School of Medicine; Miami, Florida and (2) Timothy Henry M.D. at the Hennepin County Medical Center; Minneapolis, Minnesota.
August 9, 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 investigator/site is added. The new investigator is Patricia Cornett, M.D. at the University of California, San Francisco/Veterans Affairs Medical Center; San Francisco, California.