AMENDMENTS AND UPDATES TO HUMAN GENE TRANSFER PROTOCOLS RECOMBINANT DNA ADVISORY COMMITTEE DECEMBER 15-16, 1997

8-29-97 (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 Methyltrantransferase** **Amendments:** Minor amendments were made to clarify the timing of certain tests and in some cases to increase the amount of blood drawn for tests. Other additions/alterations were made to clarify portions of the text of the protocol. A co-investigator was added, Dr. Jim Croop. The informed consent document was modified to reflect changes in amount of blood to be drawn.
9-3-97	**9708-198 Venook and Fisher**	**A Phase I/II Study of Autologous CC49-Zeta Gene-Modified T Cells and a-interferon in Patients with Advanced Colorectal Carcinomas Expressing the Tumor-Associated Antigen, TAG-72** **Amendment:** One principal investigator is added to the protocol. The new investigator, at a previously approved site (University of California, San Francisco), is Robert S. Warren, M.D.
9-5-97	**9608-157 Maria, *et.al.***	**Prospective, Open-Label, Parrallel-Group, Radomized, 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, Previosly Untreated Glioblastoma** **Amendments:** Majority of the amendments made are minor and administrative in nature. Patients will be enrolled at up to 50 clinical centers which now include Israel in addition to the US, Canada, and Europe. In addition, the protocol has been updated with respect to the status of previously treated patients. Inclusion criteria have been corrected. A major amendment states that patients in the standard treatment arm with a recurrence of glioblastoma will no longer have the option of being treated under the related protocol 9611-167. This change was implemented to help establish a more reliable secondary endpoint of survival time. This change was made in accordance with suggestions from the FDA. It should be noted that patients in the standard treatment arm that were previously enrolled in this protocol who have had a recurrence of glioblastoma will still be offered the option of re-treatment under protocol 9611-167.

9-5-97	**9611-167 Maria, *et.al.***	**Prospective, Open-Label, Multicenter Extension Trial for the Treatment of Recurrent Glioblastoma Multiforme with Surgery and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir for Patients with Disease Progression Following Standard Treatment on Protocol GTI-0115** **Amendments:** Majority of the amendments made are minor and administrative in nature. The protocol has been updated with respect to the status of previously treated patients. Inclusion criteria have been corrected. The target population of this protocol now has to meet the definition of progression as defined by protocol 9608-157. Only patients enrolled in either the May 28, 1996 or November 20, 1996 versions of protocol 9608-157 are eligible for this study.
9-8-97	**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** **Amendments:** Minor amendments have been made to clarify certain portions of the protocol. In addition, the protocol no longer uses chymopapain as a releasing agent, instead a releasing agent that is part of the Baxter Healthcare Corp., the Isolex 300 System, is being employed. Also, patients now only need to wait for 2 days after chemotherapy, instead of 3, before stem cell infusion. A reduction in the amount of fibronectin from 20 to 8 m g for coating cell culture plates, due to no loss in gene transfer efficiency, is now employed. This modificatio will reduce the possibility of developing antibodies and therefore is likely to be beneficial to the patients.
9-15-97	**9706-191 Gluckman, *et al.***	**Phase II Study of Immunotherapy by Direct Gene Trasnfer with Allovectin-7 for the Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck** **Amendment:** One principal investigator/site is added to the protocol. The PI at the new site; University of California, Los Angeles; is Dan J. Castro, M.D., F.A.C.S.
9-17-97	**9709-210 Gonzales**	**Compassionate Use Protocol for Retreatment with Allovectin-7 Immunotherapy for Metastatic Cancer by Direct Gene Transfer** **Amendment:** One principal investigator/site is added to the protocol. The new PI is Evan M. Hersh, M.D. at the Arizona Cancer Center; Tuscon, Arizona.
9-25-97	**9611-169**	**Phase I/II Trial of Interleukin-2 DNA/DMRIE/DOPE Lipid Complex as an**

	Hersh, *et al.*	**Immunotherapeutic Agent in Cancer by Direct Gene Transfer** **Amendment:** One principal investigator/site is added to the protocol. The new PI is Charles A. Forscher, M.D. at Cedars-Sinai Comprehensive Cancer Center; Los Angeles, California.
10-6-97	**9706-191 Gluckman, *et al.***	**Phase II Study of Immunotherapy by Direct Gene Trasnfer with Allovectin-7 for the Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck** **Amendment:** One principal investigator/site is added to the protocol. The PI at the new site; Veterans Affairs Medical Center; Minneapolis, Minnesota; is Marku Gapany, M.D., F.A.C.S.
10-9-97	**9709-212 Gonzales**	**Phase I Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovctin-7) with IL-2 Plasmid DNA/DMRIE/DOPE Lipid Complex (Leuvectin) as an Immunotherapeutic Regimen in Patients with Metastatic Melanoma** **Amendment:** One principal investigator/site is added to the protocol. The new PI is Evan M. Hersh, M.D. at the Arizona Cancer Center; Tuscon, Arizona.
10-13-97	**9707-200 Levy**	**A Phase I/II Study of Vaccine Therapy for B-Cell Lymphoma Utilizing Plasmid DNA Coding for Tumor Idiotype** **Amendments** 1) Study design was changed from 4 different dose levels (50, 150, 450, and 1350 mg) with 3 patients at each level to 3 dose levels (200, 600, and 1800 mg) with 4 patients at each dose Change was made to better evaluate safety. And change was made based on preclinical data. 2) Two baseline immune assessments were added. General immune competence will be assessed by a quantative lymphocyte subset analysis. In addition, delayed-type hypersensitivity responses will be analyzed by skin testing to recall antigens. These amendments have been approved by the FDA.
10-14-97	**9706-191 Gluckman, *et al.***	**Phase II Study of Immunotherapy by Direct Gene Transfer with Allovectin-7 for the Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck** **Amendments**

		Amendments were made to the protocol to explain more clearly human experience with gene transfer involving alteration of MHC class I. This change documents that the majority of adverse events experienced were due to the underlying disease, injection of drugs, or to biopsy procedures but not to the study drug itself. Patient enrollment was changed to advanced or recurrent instead of metastatic head and neck squamous cell carcinoma. In addition, inclusion criteria were changed to require that patient have at least one injectable lesion from one injectable metastatic lesion. Exclusion criteria were also changed to prohibit indomethacin therapy within the past four weeks. In addition, uncontrolled brain metastases are no longer an exclusion criterium. These changes have been approved by the U. of Cincinnati Medical Center IRB. IRB approvals for the other clinical sites will be forwarded to ORDA when received by the trial sponsor (Vical, Inc.).
10-16-97	**9508-117 Rosenblatt**	**A Phase I Trial of Autologous CD34+ Hemaptopoietic Progenitor Cells Transduced with an Anti-HIV-1 Ribozyme** **Amendments** *Even though this protocol was exempted from full RAC review (sole FDA review recommended by NIH/ORDA) on 8-7-95, it was never initiated; an IND submission for this protocol was not made until Sept. 1997*. Dr. Mitsuyasu is now the chief investigator, replacing Dr. Rosenblatt. Changes include a switch to PG13 from PA317 as the packaging cell line. The cytokine mixture used to induce cell division of CD34+ cells has been changed from SCF (Stem Cell Factor)/IL-3/IL-6 to SCF and MGDF (Megakaryocyte Growth and Development Factor). The non-nucleoside RT inhibitor employed to suppress HIV replication in transduced CD34+ cultures has been changed from delavirdine to nevirapine. Other changes include: 1) An additional secondary objective of the trial is to determine the efficiency and safety of G-CSF mobilization of peripheral blood progenitor cells in HIV-1 infected patients. 2) 7 instead of 10 patients will be recruited. 3) Changes to the inclusion criteria: a) CD4 counts must be 300 to 700/mm^3, instead of 200-500 b) HIV-1 RNA plasma levels less than 10,000 copies/ml (if on anti-retroviral therapy) or

		less than 30,000 copies/ml (if off therapy) c) Patients no longer must have tolerance to AZT 4) Changes to exclusion criteria include patients with hemoglobin levels less than 10 g/dl. Also patients previously treated with nevirapine are ineligible, as are patients with known hypersensitivity to *E. coli*- derived proteins. 5) For the five day period of G-CSF mobilization and apheresis, patients will be requested to discontinue treatment with all nucleoside RT inhibitors to circumvent any potential inhibition of retroviral integration of transduced CD34+ stem cells. Non-nucleoside RT inhibitors, during this time, may be used either alone or in combination with a protease inhibitor. After the five days, patients may resume their anti-retroviral therapy. 6) For patients not on anti-retroviral therapy, approved anti-retroviral agents will be allowed if: i) CD4 counts are less than 300/mm^3 on two monthly determinations (instead of less than 200/mm^3) or ii) a decrease in CD4 counts to less than 50% of baseline or iii) an increase in plasma RNA to greater than 30,000 copies/ml.
10-21-97	**9306-050 Raffel, *et al.***	**Gene Transfer for the Treatment of Recurrent Pediatric Malignant Astrocytomas with *In Vivo* Tumor Transduction with the *Herpes Simplex* Thymidine Kinase Gene** **Amendment:** One principal investigator is added to the protocol. The new investigator is Stefan Burdach, M.D.; at the University Center for Paediatrics; Dusseldorf, Germany.
10-21-97	**9608-157 Maria, *et al.***	**Prospective, Open-Label, Parrallel-Group, Radomized, 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, Previosly Untreated Glioblastoma** **Amendments:** Five principal investigators/sites are added to the protocol. 1) Robert J. Maciunas, M.D.; Vanderbilt University Medical Cente;, Nashville, Tennessee; 2) Roger Henriksson, M.D.; at University Hospital; Umea, Sweden; 3) Zvi Ram, M.D.; The Chaim Sheba Medical Center; Tel-Hashomer, Israel; 4) David Andrews, M.D.; Thomas Jefferson University Hospital; Philadephia, Pennsylvania; and 5) Jan Verlooy, M.D.; University Hospital Antwerp; Antwerp, Belgium.
10-21-97	**9611-167 Maria, *et al.***	**Prospective, Open-Label, Multicenter Extension Trial for the Treatment of Recurrent Glioblastoma Multiforme with Surgery and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir for Patients with Disease Progression Following Standard Treatment on Protocol GTI-0115** **Amendments:** Six principal investigators/sites are added to the protocol. 1) Anthony Asher,

		M.D.; at the PresbyterianHospial; Charlotte, North Carolina; 2) TroyPayner, M.D.; Indianapolis Neurosurgical Group; Indianapolis, Indiana; and 3) Friedrich Weber, M.D.; Heinrich Heine Universitat; Dusseldorf, Germany; 4) John Van Gilder, M.D.; University of Iowa College of Medicine; Iowa City, Iowa; 5) JohnGutheil, M.D.; Sharp HealthCare, Sidney Kimmel Cancer Center; San Diego, California; and 6) ManfredWestphal, M.D.; University Klinikum Eppendorf; Hamburg, Germany.
10-15-97	**9709-214 Breau and Clayman**	**A Phase II Multi-Center, Open Label, Randomized Study to Evaluate Effectiveness and Safety of Two Treatment Regimens of Ad5CMV-p53 Aministered by Intra-Tumoral Injections in 78 Patients with RecurrentSquamous Cell Carcinoma of the Head and Neck (SCCHN)** **Amendment:** One pricipal investigator/site is added to the protocol. The new investigator is George H. Yoo, M.D.; at Wayne State University/Barbara AnnKarmanos Cancer Center; Detroit, Michigan.
10-27-97	**9706-191 Gluckman, *et al.***	**Phase II Study of Immunotherapy by Direct GeneTrasnfer with Allovectin-7 for the Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck** **Amendment:** One principal investigator/site is added to the protocol. The PI at the new site; University of Alabama, Birmingham; is William R. Carroll, M.D.
11-6-97	**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 RecurrentSquamous Cell Carcinoma of the Head and Neck (SCCHN)** **Amendments** Made to the clinical protocol include optional monitoring of fecal and nasopharyngeal samples for adenoviral vectorbiodistributionand surveillance. These changes made due to potential difficulty in obtaining these samples. Urine and blood plasma, however, will still be checked for biodistribution In addition, the stopping rule has been revised. "Based on discussions with clinical investigators, it was felt that a more careful evaluation of response should be made before deciding to terminate the study if one or two responses are seen in the first 18 patients treate taking into consideration the extent and clinical importance of those responses". Under the previous rule, in stage-one of the trial, the treatment regimen would be stopped if less than three patients responded after a total of 18evaluable patients are treated and followed for a time period sufficiently long for an evaluation of efficacy.

11-13-97	**9706-191 Gluckman, *et al.***	**Phase II Study of Immunotherapy by Direct Gene Trasnfer with Allovectin-7 for the Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck** **Amendment:** One principal investigator/site is added to the protocol. The PI at the new site; University of Washington Medical Center; Seattle, Washington; is Marc D. Coltrera, M.D.
11-14-97	**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** : Four principal investigators/sites are added to the protocol. 1) Jesus E. Medina, M.D.; University of Oklahoma, Health Sciences Center; Oklahoma City, Oklahoma 2) Barbara S. Murphy, M.D.; Vanderbilty University Medical Center; Nashville, Tennessee; 3) W. Jarrard Goodwin, M.D.; University of Miami Hospitals and Clinics; Miami, Florida; and 4) Jeffery S. Weber, M.D.; University of Southern California; Los Angeles, California.