AMENDMENTS TO HUMAN GENE TRANSFER PROTOCOLS
RECOMBINANT DNA ADVISORY COMMITTEE
JUNE 12 AND 13, 1997

2-24-97	**9503-103 Morgan, Walker**	**Gene Therapy for AIDS using Retroviral Mediated Gene Transfer to deliver HIV-1 Antisense TAR and Transdominant Rev Protein Genes to Syngeneic Lymphocytes in HIV Infected Identical Twins.** **Amendments:** "*Amendments during the past year:* 5/96 expedited amendments: to clarify the use of a single therapeutic vector and plans to submit proposals for new vectors as they become available; to limit the study population to infected patients with CD4 counts above 50 cells/mm^3; to clarify that monitoring for replication-competent retrovirus is a lifelong requirement. 9/96 amendments: to permit the use of a new therapeutic vector (G1RSN3) and a new control vector (G1NS); to permit repeated infusions with cells modified by the same or different vector(s) used for prior infusions; to modify the retreatment period to "approximately every 8 weeks"; and to inform the Institutional Review Board (IRB) that protocol recruitment was extending to patients with CD4 counts above 500 cells/mm^3." Additionally, a revised informed consent document and clinical protocol was submitted to the Office of Recombinant DNA Activities (ORDA).
2-24-97	**9608-157 Maria**	**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 (GTI Protocol 0115).** **Amendment:** *Four new investigators are being added to the study.*

		Mathew Quigley, M.D., is at Allegheny University of Health Sciences, Division of Neurosurgery, Pittsburgh, Pennsylvania. Troy Payner, M.D., is at the Undianapolis Surgical Group, Indianapolis, Indiana. Leena Kivipelto, M.D., is at the Helsinki University Central Hospital, Department of Neurosurgery, Helsinki, Finland. Rolf W. Seiler, M.D., is at the University Hospital, Clinic for Neurosurgery, Bern, Switzerland.
2-26-97	**9212-035 Wilson and Simon**	**Gene Therapy of Cystic Fibrosis Lung Diseases Using E1 Deleted Adenoviruses: A Phase I Trial.** **Amendment:** *One new investigator/new site is added to the study.* Dr. Karen McCoy is the principal investigator (PI) of a new site: the Cystic Fibrosis Center at Ohio State University.
3-11-97	**9601-150 Hersh and Sondak**	**Evaluation of Intratumoral Gene Therapy with HLA-B7/DMRIE/DOPE plus Subcutaneous Low Dose IL-2.** **Removal of Protocol from Consideration:** The sponsor (Vical, Inc.) is putting this project on hold. No patients have been screened or enrolled under this protocol.
3-14-97	**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 O6-Methylguanine DNA Methyltransferase.** **Amendments:** *All amendments are approved by the IRB.* Stephanie Holbrook, RN, is added as Clinical Research Coordinator. Section 5.2: A size appropriate hemodialysis catheter is to be used. Section 5.4.1: Dosing of G-CSF will not be determined by WBC. G-CSF will be administered at a dose of 10mcg/kg/day. Section 5.8.3: The standard irradiation of blood products is 3000cGY. Section 9.5 and Informed Consent: Fever is not considered to be a side effect of G-CSF. Appendix III 4.2.1: Stem cells should be frozen at a final concentration of $0.5x10^6$ nucleated cells (nc)/ml to $1.2x10^8$ nc/nl. Entire cryopreservation SOP revised. Appendix IV: Transduction incubation is for approximately 30-48 hours. Iscove's media now contains IL-6 (100u/ml), SCF (100 ng/ml) and gentamycin sulfate (50 mg/L). After prestimulation, $8\text{-}40x10^6$ prestimulated cells will be resuspended in retroviral supernatant. Cells will be incubated 4-6 hours, then another 4-6 hours, plus an additional 6-12-hours. The CH-296 (recombinant fibronectin fragment used to coat the petri dishes) solution will not be filtered. The reconstitution and coating of petri dishes with CH-296 is described: sterile CH-296 in PBS is added to 10 cm petri dishes at a concentration of 1.6ml/10 cm petri dish + 3.4 ml PBS = 5 mls total/dish (1.6 mg CH-296/10 cm dish). Plates

		are later blocked using 2% human serum albumin (protease free). The amendments change the informed consent document. A revised, approved informed consent document was submitted along with a current IRB approved protocol.
3-17-97	**9701-172 Cornetta and Abonour**	**High Dose Carboplatin and Etoposide Followed by Transplantation with Peripheral Blood Stem Cells Transduced with the Multiple Drug Resistence Gene in the Treatment of Germ Cell Tumors - A Pilot Study.** **Amendment:** *Two amendments were submitted by the investigator to the IRB.* Some minor rearrangements are made to the protocol. Section 9.4: Test Article Name A12M1 Vector: a sentence is added at the request of the FDA: "5% of the supernate from the final collection day will be tested prior to release of the product." Section 5.3: Gentamycin sulfate (50 mg/L) is added to the media. After selection, at least $2x10^6$ CD 34+ cells must be obtained for transduction. Section 5.3.3: Prestimulation is approximately 30-48 hours. Petri dishes pretreated at a final concentration of 1.6 ml/10 cm dish + 3.4 ml PBS. Section 7.1.4 and 7.5: PCR for MDR and Flow data for MDR expression added to bone marrow testing. Section 7.6: Fibronectin antibody screen and MDR expression by RT-PCR and by flow added to blood testing. Testing to be performed monthly x3, every three months x3, then yearly. Section 9.3: Fever is not considered to be a side effect of G-CSF. Section 12.0: The CH-296 (recombinant fibronectin fragment used to coat the petri dishes) solution will not be filtered. Section 13: IRB correspondence to be kept on file by Dr. Abonour. Informed consent: 1-3 tablespoons of blood will be collected monthly x3, every three months x3, then yearly. Patient may call Dr. Abonour with questions and concerns. A revised informed consent document was submitted. A response from the investigator to the Food and Drug Administration's (FDA) request for additional information was enclosed.
3-18-97	**9611-168 Hersh, Klasa, and Gonzales**	**Phase II Study of Immunotherapy of Metastatic Melanoma by Direct Gene Transfer.** **Amendment:** *A new site/investigators added. This amendment is IRB and Institutional Biosafety Committee (IBC) approved.* The new site added to this protocol is the Northern California Melanoma Clinic in San

		Francisco, California. The new principal investigator is Gary Silver, M.D., with three subinvestigators: Lynn Spitler, M.D., Mark Jacobs, PharmD., and James Good, M.D.
3-28-97	**9611-169 Hersh, Rinehart, Rubin and Sondak**	**Phase I/II Trial of Interleukin-2 DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Cancer by Direct Gene Transfer.** **Amendment:** *A new site/new investigator is added. This amendment is IRB and IBC approved.* Rene Gonzales, M.D., is added as a new principal investigator on the protocol. The clinical trial site is the University of Colorado Cancer Center, Denver, Colorado.
4-10-97	**9409-087 Whitley**	**Retroviral Mediated Transfer of the Iduronate-2-Sulfatase Gene into Lymphocytes for Treatment of Mild Hunter Syndrome (Mucopolysaccharidosis Type II).** **Adverse Event:** *This notice and the January adverse event were faxed out to the RAC members on April 17, 1997 for their comment.* **Amendment:** The amendments submitted to ORDA are a result of discussions with the FDA and the University of Minnesota Institutional Biosafety Committee. "The current plan for the next infusion of cells...is to administer standard doses of Tylenol and Benadryl prior to infusion of cells, and to administer hydrocortisone if there is any adverse reaction. As before, an IV would remain in place after the infusion to administer medications or fluids if indicated. Also, ibuprofen will be available to the patient which (the patient) uses frequently for chronic joint pains and which he used for relief of symptoms following the last cell infusion." The following amendments to the protocol pertain to cell transduction and expansion and were discussed and approved by telephone with FDA personnel. (1) Reduction of FBS in medium. (2) Additional "in process" cell wash. By this reduced FBS procedure, cell exposure to FBS occured only in the early steps of lymphocyte culture. This reduced FBS procedure will be used to provide cells for the next patient treatment (#4) and is expected to yield the 5×10^9 cells for infusion as specified in the original clinical protocol.

4-13-97	**9409-087 Whitley**	**Retroviral Mediated Transfer of the Iduronate-2-Sulfatase Gene into Lymphocytes for Treatment of Mild Hunter Syndrome (Mucopolysaccharidosis Type II).** **Adverse Event:** *This notice and the January adverse event were faxed out to the RAC members on April 18, 1997 for their comment.* **Amendment:** The following minor deviations from the original protocol were discussed with FDA personnel and the University of Minnesota Institional Review Board immediatly prior to the most recent treatment of the sole patient enrolled in the protocol. (1) Hydrocortisone was administered to the patient as a pre-infusion medication (2) As a result of modifying the cell culture method to reduce exposure of the cells to FBS, the amount left for infusion was 158 mls of product containing 9.4 x 10^9 viable cells. (3) Because of concern regarding the possibility of an Arthus reaction, the following medications were administered to the patient prior to the fourth infusion of cells: acetaminophen (Tylenol) 650 mg po, diphenydramine (Benadryl) 25 mg IV, and hydrocortisone 100 mg IV. Thirty minutes after administration of the pre-medications, the patient received 5x10^9 viable cells over one hour. In the immediate post-infusion the patient was "somewhat drowsy (presumably related to Benadryl), but had no adverse reactions, i.e., had no physical complaints, no orthostatic hypotension, and (the patients) vital signs remained entirely normal....Blood counts showed minimal changes, the increase in total leukocyte count presumably resulting from demargination of cells following administration of hydrocortisone. The slight decrease in platelet count was observed after the previous infusion and could be a specific phenomenon related to treatment. Alternatively, this may be a result of the minor upper respiratory tract infection beginnning during this hospitalization....In addition, Demerol will be used to treat any future adverse reactions.
4-9-97	**9511-134 Gilbert**	**Phase I Study to Evaluate the Safety and In Vivo Persistence of Adoptively Transfered Autologous CD4+ T Cells Genetically Modified to Resist HIV Replication.** **Amendment:** *This amendment is IRB and FDA approved*. Mark J. Gilbert will no longer be the PI at Fred Hutchinson Cancer Research Center. A co-investigator on the IND, Philip D. Greenberg, M.D., will be the PI.
4-14-97	**9608-157 Maria, et.al.**	**Prospectve, 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 **Amendment:** *Six new investigators are being added to the trial.* Martin Harvey Weiss, M.D., The University of Southern California, Department of Neurosurgery, Los Angeles, California; James R.Fick, M.D., Medical College of Georgia, Department of Surgery, Augusta, Georgia;Richand Leblanc, M.D., Montreal Neurological Institute, Montreal, Quebec, Canada; MichaelBuchfelder, M.D., Neurochirurgische Klinik mit Poliklinik der Universtat Erlangen-Nurnberg, Erlangen, Germany; Jacques Bortchi, M.D., Ph.D., Hopital Erasme, Neruosergery, Cliniques Universiaites de Bruxelles, Bruxelles, Belgium; Jens Astrup, M.D., Arhus Kommunehospital, Arhus C, Denmark.
4-25-97	**9409-083** Flotte	**A Phase I Study of an Adeno-associated Virus-CFTR Gene Vector in Adult CF Patients with Mild Lung Disease.** **Amendment:** *The following amendment is IRB and IBC approved.* The sponsor (Targeted Genetics, Inc.) submitted documentation indicating the transfer of investigator responsibilities from TerrenceFlotte, M.D., to Pam Zeitlin, M.D., at Johns Hopkins University in Baltimore, Maryland.
4-28-97	**9610-162 LaFollette and Murray**	**A Phase I Multicenter Study of Intratumoral E1A Gene Therapy for Patients with Unresectable or Metastatic Solid Tumors that Overexpress HER-2/neu.** **Amendment:** *The following amendment is IRB and IBC approved.* George Yoo, M.D. is added as a principal investigator at a new clinical trial site.The new site is Wayne State University in Detroit, Michigan.
4-28-97	**9512-137 Hortobagyi, et.al.**	**Phase I Study of E1A Gene Therapy for Patients with Metastatic Breast or Ovarian Cancer that Overexpresses HER-2/neu.** **Amendment:** *The following amendment is IRB and IBC approved.*

		Paul Weiden, M.D., is added as a PI at a new clinical trial site. The new site is Virginia Mason Medical Center in Seattle, Washington.
4-28-97	**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.** **Amendment:** *The following amendment is IRB approved.* An extension phase of the trial is proposed, however, no new patients will be enrolled. This amendment to the protocol is restricted to patients currently enrolled in the trial. Currently CD8+ T cells are transduced and administered to the patient; this amendment proposes to transduce both CD8+ T cells and CD4+ T cells, in a "new cell process" developed at Cell Genesys, Inc. The PI states: "The purpose of the proposed extension to the twin study is to evaluate the safety, immunologic and antiviral activity, and *in vivo* persistence of gene-modified cells using the "new cell process" in a well-characterized cohort of patients. All patients who are participating on the current study are eligible if they choose to enroll in the extension. In order to control for repeated infusions of modified CD8+ T cells alone, those patients who elect to enroll in the extension and who have enough frozen, gene-modified CD8+ T cells remaining to support 3 additional infusions will be randomized in a 1:1 distribution to either continue receiving gene-modified CD8+ T cells (i.e., "old process") or to begin receiving treatment with gene-modified CD4+ and CD8+ T cells. (i.e., "new process"). Those patients who elect to enroll in the extension and who either: 1) do not have enough frozen cell stocks to support 3 additional infusions; 2) are participating in the unmodified (i.e., control) arm of the study; or 3) are participating in the IL-2 arm of the study; will be assigned to treatment with the new process (i.e., these individuals will not be randomized). The target cell number for both old process and new process cells will remain $1x10^{10}$ cells per infusion, and the treatment plan will be a total of 2-3 infusions given at 2-4 week intervals (as opposed to 8 week intervals used in the current study). Every attempt will be made to give a set of 3 infusions at regular 2 week intervals, but some flexibility will be needed to accommodate insufficient cell growth and patient scheduling needs. Patients will return to the NIH Clinical Center OP8 biweekly until 4 weeks after the last cell infusion. Subsequent follow up will be according to the RCR monitering schedule. At the monitoring visits, the following tests will be performed: lymphocyte subsets; plasma viral load

		(bDNA); serum p24 antigen;PCR for CD4-zeta gene; safety bloods and urinalysis; cells, serum, and plasma storage. Additionally, an IRB approved informed consent document was submitted to ORDA.