AMENDMENTS TO HUMAN GENE TRANSFER PROTOCOLS
RECOMBINANT DNA ADVISORY COMMITTEE
SEPTEMBER 12, 1997

5-15-97(letter date)	**9611-169 Hersh, et.al.**	**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 investigator/site is added to the trial; the amendment is IRB and IBC approved, the cv enclosed.* Dr. Robert E. Sobol is added as a principal investigator at Sharp Healthcare in San Diego, California.
5-19-97	**9306-047 Karlsson, Dunbar and Kohn**	**Retroviral Mediated Transfer of the cDNA for Human Glucocerebrosidase into Hematopoietic Stem Cells of Patients with Gaucher Disease.** **Amendment:** The sponsor (Genetic Therapies, Inc./Novartis) has withdrawn the IND from the FDA, effective April 30, 1997. The protocol is now registered as closed.
5-19-97	**9303-041 Wilmott, Whitsett and Trapnell**	**A Phase I Study of Gene Therapy of Cystic Fibrosis Utilizing a Replication Deficient Recombinant Adenovirus Vector to Deliver the Human Cystic Fibrosis Transmembrane Conductance Regulator cDNA to the Airways.** **Amendment:** The sponsor (Genetic Therapies, Inc./Novartis) has withdrawn the IND from the FDA, effective April 28, 1997. The protocol is now registered as closed.
5-23-97	**9611-169 Hersh et.al.**	**Phase I/II Trial of Interleukin-2 DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Cancer by Direct Gene Transfer.** **Amendment:** *One principal investigator/clinical trial site is added to the protocol. IRB and IBC Approvals are submitted, along with informed consent and curricula vitae for Dr.Sondak.* Vernon K. Sondak, M.D., is added as a principal investigator at the University of Michigan Medical Center in Ann Arbor, Michigan.
5-29-97	**9608-157**	**Prospective, Open-Label, Parallel-Group, Randomized Multicenter Trial**

	Maria, et.al.	**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, Previoulsy Untreated Glioblastoma.** **Amendment:** *One principal investigator/clinical trial site is added to the protocol, replacing Dr. Thomas Campbell.* Dr. Ivor Royston, M.D., is now the principal investigator at Sharp Healthcare, Sidney Kimmel Cancer Center, in San Diego, California.
5-29-97	**9306-050 Raffel, Villablanca and** Packer	**Gene Therapy for the Treatment of Recurrent Pediatric Malignant Astrocytomas with In Vivo Tumor Transduction with the Herpes Simplex Thymidine Kinase Gene.** **Amendment:** *One principal investigator/clinical trial site is added to the protocol.* Jorg-Christian Tonn, M.D., is the principal investigator at the Neurochirurgische Klinik und Polyklinik, Universitats-Klinikin, Wurzburg, Germany.
6-4-97	**9702-177 Verfaillie, McIvor, McCullough and McGlave**	**Autologous Marrow Transplantation for Chronic Myelogenous Leukemia Using Retrovirally Marked Peripheral Blood Progenitor Cells Obtained after In Vivo Cyclophosphamide/G-CSF Priming.** **Amendment:** The vector to be used in the trial is changed from LNL-6 to LN.
6-17-97	**9611-168 Hersh, et al.**	**Phase II Study of Immunotherapy of Metastatic Melanoma by Direct Gene Transfer.** **Amendment:** One principal investigator/clinical trial site is added to the protocol. John A. Thompson, M.D., is the principal investigator at the University of Washington Medical Center, Seattle, Washington.
6-17-97	**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 O^6-Methylguanine DNA Methyltransferase.**

		Amendments: 1) Children under 5 years of age are excluded due to a concern about exposing young children to a new agent (fibronectin) that could lead to an immune response. 2) Infusion of transduced cells will occur after the first and after the second course of PCV. Radiation therapy, if necessary, will be administered after recovery from the second infusion of transduced cells; in the original protocol radiation therapy was scheduled after the fourth course of PCV. 3) The vector to be used in the trial is changed from PGK-MGMT to MSCV-MGMT~1.67, due to positive RCR. This vector expresses the same cDNA as PGK-MGMT via the MSCV LTR. The packaging cell line for this new vector is the same as in the original protocol.
7-7-97	**9706-191 Gluckman, Gleich, and Swinehart**	**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** **Amendment**: One principle investigator/clinical trial site is added to the protocol. James M. Swinehart, M.D., is the principal investigator at Colorado Medical Research Center; Denver, Colorado.
7-8-97	**9409-087 Whitley**	**Retroviral-Mediated Transfer of the Iduronate-2-Sulfatase Gene into Lymphocytes for Treatment of Mild Hunter Syndrome (Mucopolysaccharidosis Type II)** **Amendment:** To the clinical protocol. Experience with the clinical trial has shown a lymphocyte transduction frequency of less than 5%. Change in the transduction schedule from one 100 ml aliquot of L2SN vector on days 2, 3, and 4 of culture to one aliquot on day 1 and two aliquots on day 2.
7-11-97	**9406-079 Roth**	**Clinical Protocol for Modification of Tumor Suppressor Gene Expression and Induction of Apoptosis in Non-Small Cell Lung Cancer (NSCLC) with an Adenovirus Vector Expressing Wildtype p53 and Cisplatin** **Amendments:** To the clinical protocol. Amendments have been made to the exclusion/inclusion criteria to: (1) allow patients who have recovered from any toxicity of prior cheomtherapy (less than or equal to a grade 2 toxicity) to participate in this study, (2) allow prior experimental therapy directly involving the indicator lesion within the previous three months, and (3) eliminate the exclusion criteria of radiation therapy within six weeks. In addition, stable cardiac condition (New York Heart classification < III) is moved from the inclusion to exclusion criteria. Other minor changes have been made to the timing of serveral tests in the screen/baseline evaluation section, to the post-study follow-up evaluation section, on-study evaluations by timepoint section,

		efficacy evaluation section, and records retention section. In addition, the Informed Consent document has been modified to allow patients to be treated on an outpatient basis.
8-6-97	**9510-131 Connick and Deeks**	**A Randomized, Controlled, Phase II Study of the Activity and Safety of Autologous CD34-zeta Gene-modified T Cells in HIV-Infected Patients** **Amendment**: The protocol is no longer enrolling patients.
8-12-97	**9306-050 Raffel, Packer, Villablanca, and Tonn**	**Gene Therapy for the Treatment of Recurrent Pediatric Malignant Astrocytomas with In Vivo Tumor Transduction with the Herpes Simplex Thymidine Kinase Gene** **Amedments:** One principal investigator/clinical site is added to the protocol. Stefan Burdach, M.D., Ph.D. is the pricipal investigator at Heinrich-Heine Universitat; Dussseldorf, Germany. In addition, changes have been made to the clinical protocol. The clincial summary has been updated to incorporate results from an earlier trial (9206-019, closed 12-94). The source of ganciclovir has been changed from Syntex Corporation to Roche BioSciences. A semipermanent venous access line may now be used for ganciclovir administration. Minor changes have been made to the preparation and growth sections for the vector producing cell line. Alterations to the surgical procedures have been made to define more precisely the proper administration of the vector producing cells. Potential surgical complications have been elaborated. Exclusion criteria now include: "patients in whom ventricular entry has occurred during resection of their tumor". The section on adverse experiences has been expanded. All adverse experiences must be recorded and serious adverse experiences (defined as fatal or life-threatening, which require hopitalization, cause permanent disability, cancer, congenital anomaly, or overdose) reported within 24 hours. A section on the handling of the biologic has been added. This section states that, where feasible, the vector producer cells and ganciclovir will be supplied to the PI by the Sponsor. The PI will maintain accurrate records concerning the shipment, dispersal, and disposal of the biologic. Correct storage and labeling of the vector producer cells is also detailed. As is the correct method of disposing the vector producer cells.
8-13-97	**9610-164 Sung and**	**Phase I Trial of Adenoviral Vector Delivery of the Herpes Simplex Thymidine Kinase Gene by Intratumoral Injection Followed by Intravenous Ganciclovir in**

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Patients with Hepatic Metastases.

Amendments to the clinical protocol:

1) Patient eligibility: patients no longer have to have an absence of neutralizing antibodies to wild-type adenovirus.

2) Study design is changed

	ADV-tk dose (pfu)
Cohort level 1	1×10^8 changed to 1×10^9
Cohort level 2	5×10^8 changed to 1×10^{10}
Cohort level 3	2.5×10^9 changed to 1×10^{11}
Cohort level 4	new level 1×10^{12}

Changes in cohort levels made due to mice studies showing that highest tolerated, without irreversible toxicity, dose of ADVtk injected directly into metastatic liver tumors was 2.5×10^8 pfu (for a 20 gram mouse). Therefore the originial cohort level 1 dose of 1×10^8 is extremly low for a 70,000 gram human. Also, preliminary results from a Phase I trial of direct injection of ADVtk into prostate cancer showed that patients treated with up to 1×10^{10} pfu did not experience grade 1 or higher toxicities.

3) Protocol may be further amended if no toxicity observed at cohort level 4.

		4) Minimum number of patients to be treated is raised from 9 to 12 to add cohort level 4. (No change in maximum number of patients proposed for treatment.) 5) Minor changes to the timing of certain tests in the study parameters section. Also, deletion of the requirement of nasal swabs to test for adenovirus following intratumoral injection of hepatic metastases. 6) Follow-up will be life-long. Addition requested by ORDA. 7) Information added to inform potential participants that adenoviruses may cause changes in normal cells resulting in cancer. This phenomenon has not been observed in animal studies. (Requested by ORDA) 8) Males must also practice effective birth control (requested by ORDA). 9) Expansion of autopsy section to request for tumor tissue sample in the event that patient is undergoing surgery. Regardless if surgery is related to protocol. Revisions made to Informed Consent document (exact revisions made not specified).
8-25-97	**9706-191 Gluckman, Gleich, and Swinehart**	**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** **Amendment:** A new investigator/site is added to the trial; the amendment is IBC and IRB approved. Dr. Ehab Hanna is added as the principal investigator at University of Arkansas for Medical Sciences/Arkansas Cancer Research Center (UAMS)
8-28-97	**9701-171 * Harvey and**	**Immune Response to Intradermal Administration of an Adenovirus Type 5 Gene Transfer Vector (AD_{GV}CD.10)**

	Crystal	**Amendment:** Requests that an additional 12 healthy volunteers are allowed to be treated with $AD_{GV}CD.10$. These additional 12 individuals are to be treated with an anti-inflammatory agent, prednisone. Prednisone will be administered orally at days 1 (4 hours before vetor administration), 2, 3, 4, 5, 6, and 7. The 12 individuals will be divided into two groups. One group of 6 will receive a single dose (2×10^6 pfu, n=2; 2×10^7 pfu, n=2; and 2×10^8 pfu, n=2) of $AD_{GV}CD.10$, equivalent to Part A of the original protocol. The other group of 6 individuals will receive repeated doses, as liste above of $AD_{GV}CD.10$, equivalent to Part B of the oringinal protocol (three administrations of the vector at two week intervals).In addition, the number of bronchoscopies for each part of the trial has been reduced from 5 to 2 for the single administration phase and from 5 to 3 for the repeat administration phase. Dr. Crystal states that the purpose of this amendment is: "Based on the knowledge that administration of the $AD_{GV}CD.10$ vector to normals elicits local inflammation and systemic neutralizing anti-adenoviral immunity, this amedment seeks to determine if oral cortocosteroids will suppress this immune response. This hypothesis is based on studies in immunocompetent experimental animals showing that a variety of immunosuppressants, including corticosteroids, will suppress host responses induced by adenovirus vectors."