AMENDMENTS AND UPDATES TO HUMAN GENE TRANSFER PROTOCOLS RECOMBINANT DNA ADVISORY COMMITTEE MEETING MARCH 8, 2001

ID#	Letter Date	Protocol #	Description
39	01/09/2001	**9506-109**	**Treatment of Patients with Advanced Epithelial Ovarian Cancer using Anti-CD3 Stimulated Peripheral Blood Lymphocytes Transduced with a Gene Encoding a Chimeric T-cell Receptor Reactive with Folate Binding Protein.** *Protocol Change:* To date, six individuals have received the highest dose (3-5 x 10^{10}), with only one toxicity--respiratory distress which resolved after 1-2 days. A clinical response has not been observed. The investigator feels that a lack of a response may be due to the fact that cells are not surviving for a sufficient period of time *in vivo*. In an attempt to correct the insufficient survival time, the investigator is proposing to administer dual reactive peripheral blood lymphocytes followed by vaccination with donor peripheral blood mononuclear cells to an additional 10 individuals. These additional 10 will not receive (to ensure safety) IL-2, due to the fact that these individuals are likely to be highly pre-treated
25	10/16/2000	**9706-196**	**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.** *Other:* Received copy of response to the FDA's request regarding gene therapy monitoring plan.
38	01/05/2001	**9709-210**	**Compassionate Use Protocol for Retreatment with Allovectin-7 Immunotherapy for Metastatic Cancer by Direct Gene Transfer. Sponsor: Vical, Inc.** *PI or Site Change:* Dr. Michael Hawkins, Washington Hospital Center, Washington Cancer Institute, Washington, DC has been added as an investigator.
12	12/15/2000	**9802-234**	**A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma. Sponsor: Vical, Inc.** *PI or Site Change:* Dr. Paul Ritch at the Medical College of Wisconsin and Froedtert Memorial Lutheran Hospital, is now an investigator on this trial.
27	12/22/2000		*Protocol Change:* Eligibility criteria have been amended to allow maximum tumor size has been increased from 25 to 100 cm^2 to be consistent with other studies using Allovectin-7. Minimum tumor size is changed from 1cm x 1cm to $1cm^2$ to allow for tumor asymmetry. Additional HLA subtyping will be performed on individuals that have not yet undergone screening tests for enrollment. No additional blood is required to be drawn. This additional information on HLA subtype

			may help to define the individuals that may benefit from this study medication.
5	02/09/2000	**9804-247**	**A Phase I Safety Study of Autologous Transfected Human Fibroblasts Producing Human Factor VIII in Patients with Severe Hemophilia A. Sponsor: Transkaryotic Therapies, Inc.** *Protocol Change:* Number of autologous cells in group 3 has been increased from 1 x 10^8 to 4 x 10^8. Site of implantation has been changed from the omental bursa to the fibrofatty tissue that forms the anatomical boundaries of the lesser omentum. Investigators state that a dose of 4 x 10^8 has been used in groups 1 and 2 and implantation at a different site in group 3 will allow for a comparison of the same dose at different sites.
4	12/08/2000		*Protocol Change:* Final group of three individuals will receive 8 x 10^8 autologous fibroblasts into either the greater omentum or the tissue next to the lesser omentum.
28	12/12/2000	**9805-254**	**Immunization of Patients with Metastatic Melanoma Using DNA Encoding the GP100 Melanoma Antigen. Sponsor: National Cancer Institute - Cancer Therapy Evaluation Program (NCI-CTEP)** *Protocol Change:* Amendment to increase the dose of plasmid DNA from 1mg to 3mg and subsequently to 9mg. Original clinical protocol allowed for a maximum dose of 1mg. An immunologic response has not been observed in 23 individuals who have received the 1mg dose.
32	01/19/2001	**9809-265**	**Mutant MGMT Gene Transfer Into Human Hematopoietic Progenitors to Protect Hematopoiesis During O6-Benzylguanine (BG, NSC 637037) and BCNU Therapy of Advanced Solid Tumors. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)** *Protocol Change:* Two minor changes have been made. Due to unavailability of MGDF, G-CSF will be used in the cytokine cocktail for transduction of CD34+ cells. The retroviral supernatant will be diluted 1:2 to 1:4.
13	11/27/2000	**9901-279**	**A Phase I Safety Study in Patients with Severe Hemophilia B (Factor IX Deficiency) Using Adeno-Associated Viral Vector to Deliver the Gene for Human Factor IX to Skeletal Muscle.** *Annual Update:* Received notification that sponsorship of this study has been transferred from Dr. Katherine High to Avigen, Inc. Also, received a copy of the latest clinical protocol and informed consent. The clinical protocol and/or informed consent has been: 1) modified to include the fact that only individuals with missense mutations, as opposed to mutations leading to a stop codon, or large deletions, are eligible. 2) modified to include the fact that another muscle may be injected for individuals enrolled into cohorts were the total dose per site exceeds

			1.5 x 10^{12} vector genomes. This change was made based upon ongoing studies in dog models that have led the investigators to believe that inhibitory antibodies are more likely to develop if the injected dose at any given site exceeds 1.5 x 10^{12}. 3) clinical protocol has been modified to more clearly define follow-up tests that must be performed if a semen sample tests positive, by PCR, for vector sequences. This change was implemented due to a preliminary positive PCR result in one individual. Subsequent testing, further analysis of the PCR products, and retesting of the individual were negative. The original PCR result was therefore determined to be a "false positive."
6	12/21/00	**9901-280**	**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. Sponsor: Schering Corporation** *Status Change:* Received notification on that informed consent had been changed several times at one participating site--the Univ. of Kentucky to include additional risks. Subsequent to these changes, the PI at the U. of Kentucky decided to not enroll any additional participants. Therefore this study is now closed to enrollment at the U. of Kentucky under Dr. Gallion. The one individual who was enrolled in this trial at this will continue to be followed.
1	11/30/2000		*PI or Site Change:* Dr. Kelly Molpus is now the PI at the Univ. of Nebraska site. *Protocol Change:* Also changed inclusion criteria
30	01/18/2001	**9902-292**	**Immunization of Patients with Metastatic Melanoma Using a Recombinant Fowlpox Virus Encoding a GP 100 Peptide Preceded by an Endoplasmic Reticulum Insertion Signal Sequence. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)** *Protocol Change:* The time frame for certain tests performed prior to dosing has been defined as one year for: EKG, chest X-ray, HIV and Hepatitis testing. In addition, the clinical protocol has been modified to include statements that describe the data and safety monitoring plan (as outlined by the NIH Office of Intramural Research) and revisions made to incorporate the NCI Guidelines for Expedited Adverse Event Reporting.
21	12/07/2000	**9903-297**	**Intensive Immunosuppression Followed by Rescue with CD34 Selected, T Cell Depleted, Leukopheresis Products in Patients with Multiple Sclerosis.** *Protocol Change:* Individuals enrolled will, to comply with the current FDA regulations, be followed for life. On a yearly basis, a brief clinical history with emphasis on outcomes that might indicate retroviral disease (cancer, neurologic disorders, or other hematologic disorders) will be taken. Also, antibodies or PCR products specific

			for replication competent virus will be looked for.
35	01/09/2001	**9904-304**	**Pediatric Phase I Study of AdV/RSV-TK Followed by Ganciclovir for Retinoblastoma** *Protocol Change:* Clinical protocol has been modified to permit intra-individual dose escalation of study agent (ADV/RSV-TK).
22	12/05/2000	**9905-315**	**A Phase I/II Study of a Prime-Boost Schedule of Human GM- CSF Gene Transduced Irradiated Prostate Allogeneic Cancer Vaccine (Allogeneic Prostate GVAX TM) in Hormone-Refractory Prostate Cancer (G9803). Sponsor: Cell Genesys, Inc.** *Other:* Received notification of re-administration for one individual previously enrolled in this study. This one individual was previously administered a mixture of two allogeneic prostate cancer cell lines that, under this protocol, were modified to secrete GM- CSF. Individual has demonstrated a complete response, judged by PSA criteria.
14	11/28/2000	**9907-327**	**A Phase I Double-Blind, Placebo Controlled, Escalating Dose, Multi-Center Study of Ad2/Hypoxia Inducible Factor (HIF)-1?/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization. Sponsor: Genzyme Corporation** *PI or Site Change:* Dr. Sanjay Rajagopalan at the University of Michigan is a new investigator.
44	01/25/2001		*Status Change:* For this and protocols 9907-328/329, received notification from the sponsor (Genzyme) that Dr. Isner has been reinstated as an investigator. Notification was sent toOBA on May 26, 2000 indicating that Dr.Isner had been suspended, by Genzyme, from further enrolling individuals on these trials.
15	11/28/2000	**9907-328**	**A Phase I, Open-Label, Multi-Center Extension Study of Ad2/Hypoxia Inducible Factor (HIF)-1?/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization. Sponsor: Genzyme Corporation** *PI or Site Change:* Dr. Sanjay Rajagopalan at the University of Michigan is a new investigator.
16	11/28/2000	**9907-329**	**A Phase I, Open-Label, Single Dose, Roll-Over, Multi-Center Study of Ad2/Hypoxia Inducible Factor (HIF)-1?/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization. Sponsor: Genzyme Corporation** *PI or Site Change:* Dr. Sanjay Rajagopalan at the University of Michigan is a new investigator.
24	10/16/2000	**9908-336**	**Post-Transplant Infusion of Fibronectin-Assisted, Retroviral-Mediated Gene-Marked and Ex Vivo Expanded CD34+**

			Placental and Umbilical Cord Blood Cells *Other:* Received copy of response to the FDA's request regarding gene therapy monitoring plan.
23	10/16/2000		*Other:* Received copy of letter from the investigator in response to the FDA's August 23 letter placing trial on clinical hold.
26	11/20/2000		*Status Change:* Received copy of response from FDA indicating that study is off clinical hold.
9	11/21/2000	**9910-346**	**A Phase II, Randomized, Multicenter, 26-Week Study to Assess the Efficacy and Safety of CI-1023 Delivered Through Minimally Invasive Surgery Versus Maximum Medical Treatment in Patients with Severe Angina, Advanced Coronary Artery Disease, and No Options for Revascularization. Sponsor: Parke-Davis Pharmaceutical Research** *PI or Site Change:* Dr. J. Malcolm Arnold at the University of Western Ontario is now an investigator on this trial.
43	01/18/2001	**9911-357**	**Protocol for Retreatment with Leuvectin Immunotherapy for Cancer. Sponsor: Vical Inc.** *PI or Site Change:* Dr. Michael Hawkins, Washington Hospital Center, Washington Cancer Institute, Washington, DC has been added as an investigator.
11	12/19/2000	**9912-366**	**A Phase III Multi-Center, Open-Label, Randomized Study to Compare the Overall Survival and Safety off Bi-Weekly Intratumoral Administration of RPR/INGN 201 Versus Weekly Methotrexate in 240 Patients with Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN). Sponsor: Aventis Pharmaceuticals - Gencell Division (formerly Rhone-Poulenc Rorer)** *PI or Site Change:* Dr. Bruce Brockstein at Evanston Northwestern Healthcare is now an investigator.
41	01/19/2001	**0001-387**	**A Randomized, Double-Blind, Placebo-Controlled, Multicenter, 12-Week Follow-up, Pilot Study of the Tolerability and Feasibility of Administering ADGVVEGF121.10 (CI-1023) Via the Biosense Intramyocardial Injection Device to Patients with Advanced Coronary Artery Disease. Sponsor: Parke-Davis Pharmaceutical Research** *PI or Site Change:* Dr. Nabil Dib at the Arizona Heart Institute & Foundation, Phoenix, AZ has been added as an investigator.
2	11/27/2000	**0002-388**	**A Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, 26-Week Study to Assess the Safety and Efficacy of CI-1023 (ADGVVEGF121.10) in Peripheral Arterial Disease Patients with Severe, Disabling Intermittent Claudication. Sponsor: Parke-Davis Pharmaceutical Research** *PI or Site Change:* Dr. Rhee is now the PI at the Univ. of Pittsburgh

			site.
42	01/09/2001		*PI or Site Change:* Dr. John Blebea at Penn State College of Medicine has been added as an investigator.
19	11/28/2000	**0005-395**	**A Phase I/II Trial Investigating the Safety and Immunotherapy of Adenovirus Encoding the Melan-A/MART-1 and gp100 Melanoma Antigens Administered Intradermally to Patients with Stage II-IV Melanoma. Sponsor: Genzyme Corporation** *PI or Site Change:* Dr. John Nemunaitis at US Oncology is now an investigator. *Protocol Change:* Protocol is now restricted to individuals who are HLA-A2+ in order to assess both gp100 and MART-1 reactivity. Melanoma antigen DTH testing has been eliminated due to potential interference of pre-treatment with a peptide that may cross react with antibodies against gp100 and MART-1. Additional tests have been added to ensure that eligibility criteria of no evidence of disease is met. These tests include: 1) Chest X-ray 2) CT scans of chest and abdomen 3) MRI of the brain 4) Additional radiologic tests as deemed appropriate by the PI based on any signs/symptoms
36	01/15/2001	**0006-404**	**A Multicenter, Double-Blind, Placebo-Controlled, Phase II Study of Aerosolized AAVCF in Cystic Fibrosis Patients with Mild Lung Disease. Sponsor: Targeted Genetics** *PI or Site Change:* Dr. David Waltz at Children's Hospital, Boston, MA is has been added as an investigator. *Protocol Change:* A decision monitoring plan has been incorporated.
40	01/26/2001		*Other:* Received a copy of an updated version of the informed consent document that incorporates additional language regarding the recent pre-clinical finding of liver tumors.This document has been submitted to the FDA (on January 18) and is under review at the IRBs of all participating trial sites.
46	01/31/2001		*PI or Site Change:* Dr. David Rodman, University of Colorado Health Sciences Center, Denver, Colorado, has been added as an investigator. Minor administrative changes have been made to clarify the description of the hospital room for study drug administration and to correct formatting and spelling errors.
18	11/28/2000	**0007-407**	**A Phase I Double-blind, Placebo-Controlled, Escalating Dose, Multi-center Study of Ad2/Hypoxia Inducible Factor (HIF)-1-alpha/VP16 Gene Transfer Administration by**

			Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Areas of Viable and Underperfused Myocardium not Amenable to Bypass Grafting or Percutaneous Intervention. Sponsor: Genzyme Corporation *Other:* Received copies of the latest IBC and IRB approvals and informed consent.
37	01/15/2001		*Protocol Change:* Exercise treadmill testing has been eliminated as a requirement. The sponsor, Genzyme Corporation, has indicated that in response to comments of the RAC, additional Holter-Monitoring studies have been added to aid in the detection of new cardiac arrhythmias. Monitoring is now planned for days 21 and 180 in addition to at screening, discharge and day 60. Individuals will now be excluded if creatinine levels are greater than or equal to 2.0mg/dL (previously 2.5mg/dL) to preclude individuals who may have marginal renal function reserve.
33	01/22/2001		*PI or Site Change:* Dr. Kenneth McCurry at the University of Pittsburgh Medical Center is a new investigator.
29	12/28/2000	**0009-413**	**A Phase I Dose Ranging Safety Study Using Intra-Nodal Delivery of a Plasmid DNA (Syncrotope TA2M) in Adult Stage IV Melanoma Patients.** *PI or Site Change:* Two new sites/PIs have been added. Dr. John W. Smith at the Earl A. Chiles Research Institute Providence Portland Medical Center and Dr. Denise Johnson at Stanford University are now investigators.