AMENDMENTS AND UPDATES TO HUMAN GENE TRANSFER PROTOCOLS RECOMBINANT DNA ADVISORY COMMITTEE MEETING DECEMBER 9, 1996

Amendment Date	Protocol Number & Principal Investigator	Protocol Title & Amendment
12-18-95	**9508-115 Chang**	**Phase II Study of Immunotherapy of Metastatic Cancer by Direct Gene Transfer.** **Amendment:** *All 3 new Principal Investigators (PIs) have IBC Approval; Rinehart and Doroshow have IRB Approval.* Addition of 3 new investigators and clinical trial sites: John J. Rinehart, M.D., Scot and White Memorial Hospital; James H.Doroshow, M.D., City of Hope Research Center; Hulbert Silver, M.D., Ph.D., British Columbia Cancer Agency.
2-13-96	**9206-020 Deisseroth**	**Use of Two Retroviral Markers to Test Relative Contribution of Marrow and Peripheral Blood Autologous Cells to Recovery After Preparative Therapy.** **Amendment:** Close of trial. Of the 5 patients registered on the protocol, only 2 received their marked cells. 1 patient went into blast crisis immediately after transplant and was never evaluated. 3 patients were never transplanted due to insufficient marking. This double marking study was proposed for advanced phase CML patients, but they were doing so poorly inautologous transplant trials (separate from this marking trial) that the PIs want to close the trial. Additionally,Deisseroth has left the institution.
2-14-96	**9512-140, 9604-151, 9610-163 Rosenberg**	**Phase I Trial In Patients withMetastatic Melanoma of Immunization with a Recombinant Adenovirus Encoding the MART-1 Melanoma Antigen.,** **Phase I Trial In Patients withMetastatic Melanoma of Immunization with a Recombinant Adenovirus Encoding the GP100 Melanoma Antigen.,** **Phase I Trial In Patients WithMetastatic Melanoma of Immunization with a**

		Recombinant Fowlpox Virus Encoding the MART-1 Melanoma Antigen. **Amendment:** ORDA received a copy of 2 letters, 1 dated February 14, 1996. This letter is to Dr. Rosenberg from the NIH Biosafety Committee, stating approval of the amendment to the protocol "...Adenovirus encoding the MART-1 Melanoma Antigen and the GP-100 Melanoma Antigen." (They were submitted as two protocols; ORDA has given the MART-1 protocol the #9512-140, and the GP-100 protocol the #9604-151.) This letter references the second letter, dated December 7 1995, which is addressed to Dr. Michael Blaese, Chairman, NIH Biosafety Committee, from Dr. Rosenberg. It states that they "...received approval to administer recombinant adenoviruses expressing MART-1 and GP100 to humans.." This letter additionally states that "...We would now like to amend our vaccinia and fowlpox virus safety protocols to include in vivo work in humans". This second letter is stamped as an approved amended registration document by the NIH Biosafety Committee on 2-7--96.
2-26-96	**9409-090 Albelda**	**Treatment of Advanced Mesotherlioma with the Recombinant Adenovirus H5.010RSVTK: A Phase I Trial.** **Amendment:** *After discussions with the FDA, the dosing schedule modified as follows:* Dose increase at half log increments instead of log increments, allowing the total number of patients potentially enrolled to increase to 24. The FDA has given approval to use a production lot which has shown to be positive for RCA when tested at 10^{10} pfu. **Update:** Update on 3 patients: Patient #1: Temperature elevation to a maximum of 101.8, GST to a maximum of 63, ALT elevation to a maximum of 61, all declining to normal. Hemoglobin declined from 15.6 to 12.6, returning to 14.6 at last evaluation. Patient #2: Hemoglobin declined from 11.9 to 8.0, at which point he was transfused Albumin declined from 3.5 to 2.7, maximal temperature reached 100. Hemoglobin was 11.4 at first outpatient evaluation.

		Patient #3: Temperature rose to 101, hemoglobin fell to 9.0, calcium 7.7.
3-04-96	**9209-030 Deisseroth**	**Use of Retroviral Markers to Identidy Efficacy of Purging and Origin of Relapse Following Autologous Bone Marrow and Peripheral Blood Cell Transplantation in Indolent B Cell Neoplasms (Follicular Non-Hodgkin's Lymphoma or Chronic Lymphocytic Leukemia) Patients.** **Amendment:** Change in protocol necessitated by the unavailability of vector. Patients will receive only G1Na vector, not LNL6 in this double marking trial. **Update:** As per the original protocol, 2 patients have received both vectors. 2 additional patients received G1Na in their marrow, but their peripheral blood was nc marked.
3-13-96	**9409-090 Albelda**	**Treatment of Advanced Mesothelioma with the Recombinant Adenovirus H5.010RSVTK.** **Amendment:** *Following recommendations by FDA reviewers the protocol is amended:* The number of patients in a cohort is reduced from 3 to 2, the interval between cohorts is changed to 21 days, thus the next cohort can begin one week after cessation of ganciclovir treatment.
4-10-96	**9512-140 Rosenberg**	**Phase I Trial in Patients with Metastatic Melanoma of Immunization with a Recombinant Adenovirus Encoding the MART-1 Melanoma Antigen.** **Update:** Adverse reaction reported: 4 patients developed transient urticaria, welts and pruritus after receiving immunization with AdenoMART-1 followed by high dose bolus IL2. The rashes occurred at the end of IL2 administration or within 1-2 days of completing IL2, and lasted less than 24 hours. Some patients have been re-challenged, without recurrence of the rash.
4-16-96	**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 Identicle Twins.** **Amendment:** *NAIAD-IRB Approval of the amendment and the Informed Consent Document enclosed in submission of documents to ORDA on May 29, 1996.*

		Some of the patients who are scheduled to receive genetically modified cells will receive interleukin-2 (IL2). Received additional informed consent document for thos patients eligible for the IL2 portion. Period II, the multiple dosing part of the study, amended as follows: (1) Those patients scheduled to receive genetically modified cells and whose CD4 counts are greater than 200 (or who are taking protease inhibitors with CD4 counts above 50) may receive genetically modified cells plus IL2 administered intravenously by continuous 5 day infusion. CIV-IL2 will begin 4-5 hours before receiving the cells, at 12 million I.U./day, the dose to be adjusted downward as needed in increments of 1 to 6 million units depending on tolerance. (2) Those patients receiving IL2 must take concurrent anti-retroviral drugs (licenced or expanded access) at least during the IL2 infusion and for 1 week following. The choice of drugs will be based on discussions with the patient and the primary physician. (3) IL2 will be infused for the first cycle on an inpatient basis, and thereafter on an outpatient basis by portable infusion pump. (4) Patients will be excluded from the IL2 portion of the study if they have any of the following conditions: malignancy other than mucocutaneous Kaposi's sarcoma, active substance abuse, active psychiatric disturbance or illness which may affect safety or compliance as determined by the protocol team, significant cardiac, pulmonary, rheumatologic, gastrointestinal, thyroid, kidney, or CNS disease, hypertension requiring continuous anti-hypertensive therapy. (5) Patients receiving IL2 will require thyroid function studies every 4 weeks, electrocardiograms every 8 weeks, and echocardiograms every 6 months. (6) A Grade 3 toxicity will be managed by either a decrease in IL2 dose or an interruption in the IL2 schedule. A Grade 4 toxicity will result in stopping IL2. If the abnormal parameter resolves within 48 hours, the IL2 may be restarted. (7) IL2 will be permanently discontinued: (a) development of a malignancy other than Kaposi's sarcoma or non-melanoma skin cancer , (b) progressive Kaposi's sarcoma requiring systemic therapy, (c) noncompliance or inability to tolerate anti-retroviral therapy, (d) grade 4 toxicity attributable to IL2 that does not resolve within 4 weeks duration off IL2, (e) judgement of the protocol team, even if the patient disagrees, (f) patient desire, (g) decline in CD4 count below 50 (patients taking protease inhibitor) or below 200 on two consecutive measurements after the second round of cells plus IL2. (8) Patients who discontinue IL2 may continue to receive cells alone at the discretion of the protocol team.
4-30-96	**9510-131 Connick**	**A Randomized, Controlled, Phase II Study of the Activiey and Safety of Autologous CD4-Zeta Gene-Modified T Cells in HIV-Infected Patients.** **Amendment:** *IRB Approval for the amendment and the approved informed consent documents enclosed in submission of materials to ORDA. Additionally, the changes have been approved by the FDA under the IND.* (1) Dosing schedule changes to 2-3 x 109 cells each day for 3 days, (2) The addition of a non-randomized, open-label cohort of up to 10 patients to precede the randomized portion of the study, (3) The vector is changed to *kat*4SVGF3e- (the

		vector currently being used in protocol #9403-069).
5-28-96	**9503-103 Morgan**	**Gene Therapy for AIDS using Retroviral Mediated Gene Transfer to Deliver HIV-1 Antisense TAR and Transdominant Rev Proten Genes to Syngeneic Lymphocytes in HIV Infected Identicle Twins.** **Amendment:** *NAIAD-IRB approved the following amendment:* (1) Inclusion criteria added: Recipients CD4 count greater than 50 cells/mm3. (2) Informed Consent Document B changed to read '...monitored for the presence of RCR periodically during the study, and at least yearly thereafter for the rest of your life.' (3) In order to minimize potential risk to patients with asymptomatic and early infection, the FDA requested that the first 3 recipients have screening CD4 counts below 500 cells/mm3. If no significant toxicity occurs, subsequent patients may be recruited with CD4 counts above 500 cells/mm3 at the discretion of the PI. (4) In order to clarify that the current protocol will use only two vectors, the Section 1.0 Precis language will be changed to read '...individually transduced with either a control(NeoR containing) retroviral vector or a retroviral vector containing two potentially therapeutic genes (antisense TAR and transdominant Rev).' (5) Protocol revisions will be submitted to the FDA regarding any new vectors that become available.
5-31-96	**9409-083 Flotte**	**A Phase I Study of an Adeno-associated Virus-CFTR Gene Vector in Adult CF Patients with Mild Lung Disease.** **Amendment:** *University of Florida IRB and IBC Approved the following amendment:* It is anticipated that Patients 9,10,11,and 12 will be enrolled at the University of Florida (the PI has accepted a position at the University of Florida). The trial will continue jointly at Johns Hopkins and the University of Florida. Dr. Pamela Zeitlin agreed to take over as the responsible investigator to follow-up the patients at Johns Hopkins.
7-26-96	**9508-115 Chang**	**Phase II Study of Immunotherapy of Metastatic Cancer by Direct Gene Transfer.** **Amendment:** *This information has been submitted to the FDA:*

		Change in Principal Investigator at the British Columbia Cancer Agency to: Richard Klasa, M.D., and the addition of one sub-investigator: David Klaassen, M.D. At Mayo Clinic, six sub-investigators are being added: Joseph P. Colgan, M.D., Thomas M. Habermann, M.D., David J. Inwards, M.D., William Louis White, M.D., Scott H. Okuno, M.D. , and Thomas E. Witzig, M.D. Additionally, one sub-investigator is being deleted: David Lawrence Ahmann, M.D.
7-30-96	**9503-104 Malech**	**Gene Therapy Approach for Chromic Granulomatous Disease.** **Update:** *First annual report for the protocol submitted to ORDA:* 5 patients have entered the study with the p47phox deficient form of chronic granulomatosis disease (CGD), and have received gene corrected autologous CD34+ cells. Patient 1 suffered relapse of her pneumonia 3 weeks after receiving her cells (she had recovered from pneumonia 6 weeks prior to the study) - she has fully recovered. Patient 3 has recently gotten married and become pregnant; this occurre between 7 and 8 months after the gene therapy procedure. It was not planned or expected at the time of enrollment. Peripheral blood cells and serum continues to b collected. RCR testing by PCR is negative. No antibodies directed at either human p47phox or mouse IgG are present. The CD34+ cells were transduced with an efficiency of 10% to over 30%. The total number of transduced, autologous CD34+ cells infused into each of Patients 1-5 was respectively, 4.7, 0.9, 4.3, 2.5, and 0.1 million cells per kg body weight. For the first 3 weeks after infusion of transduced CD34+ cells, no corrected neutrophils were detected. Beginning at 3 weeks post gene therapy very small numbers of functionally corrected neutrophils were detected in all 5 patients. Over the next 7 to 10 days the number of oxidase positive neutrophils in the peripheral blood rose to a peak frequency ranging from 1 in 1,500 to 1 in 30,000 neutrophils in different patients. The level of oxidant production in corrected cells was not distinguishable from that of normal neutrophils in the DHR FACS assay. Thereafter, the frequency of corrected cells declined over several months to undetectable levels. Patient 1 and 3 had detectable corrected neutrophils for over 4 months. PCR analysis of the cells paralleled the DHR functional studies. Because Patient 1 had empyema complicating her pneumonia, the pus from thoracentesis was analyzed, and was found to contain corrected neutrophils. A mouse knock out model of the p47phox form of CGD developed to assure that a high level of expression of the gene in marrow was not detrimental to blood cell

		production/function (as requested by NIH Biosafety Committee) - hematopoiesis did not appear to be affected by continued functional expression of the transduced gene in progenitors.
8-13-96	**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 Identicle Twins.** **Amendment:** *The IRB has approved the Continuing Review Application:* Dr. Karl Czaky from NEI was added as an associate investigator. **Update:** Of the 43 sets of twins enrolled on study, 32 remain active. The 11 withdrawals include: 6 deaths - 3 after receiving modified cells. The IRB judged all deaths to be related to advanced HIV infection. 2 patients were withdrawn because of issues with cell expansion and/or transduction. 2 patients voluntarily withdrew, and there was 1 premature termination for noncompliance with clinic visits. Evidence of persistence of the transduced cells in peripheral blood cells shown by DNA PCR, up to 36 weeks post-infusion in most patients who received 10^{10} cells. In recipients of 10^{10} modified cells, transduced cells continue to circulate through 11-20 weeks post infusion. On two occasions, gene modified cell yields were below the target of 10^{10} cells, and lower (9.3×10^9 and 5.4×10^9) numbers of cells were infused. On one occasion cells were infused into a patient that failed to meet the cut-off (70% of cells transduced must express the transduced gene, as assessed by flow cytometry); after speaking with the FDA clinical reviewer by phone, that lot of 67.3% positive cells were infused into the patient.
9-03-96	**9409-087 Whitley**	**Retroviral -Mediated Transfer of the Iduronate-2-Sulfatase Gene into Lymphocytes for Treatment of Mild Hunter Syndrome (Mucopolysaccharidosis Type II).** **Update:** *Annual Report submitted to ORDA:* No patients have been entered into this clinical trial. Potential candidates are

		currently being evaluated. Pending ongoing approval, the trial is scheduled to begin approximately September 15, 1996.
9-10-96	**9409-087 Whitley**	**Retroviral-Mediated Transfer of the Iduronate-2-Sulfatase Gene into Lymphocytes for Treatment of Mild Hunter Syndrome (Mucopolysaccharidosis Type II).** **Amendment:** *This information has been submitted to the IBC and the FDA:* (1) Production Issues: (a) Since initial FDA approval a facility has been established to manufacture and manipulate experimental therapeutic agents - the Minnesota Molecular and Cellular Therapeutics Facility. Intended to operate under cGMP guidelines, it will manufacture the vector, and it is where the cell transduction will be done. (b) The definition of a 'lot' will be changed. (c) Due to the fact that patient lymphocytes are readily frozen, fewer apheresis procedures will need to be done. The patient will undergo apheresis only 2 times at the beginning of the trial, rather than 12 times spread throughout the trial. (d) Cells will be transduced by exposure to vector once per day for 4 (previously 3) consecutive days. (e) For patient treatments #2-#12, cells from the "medium size" ACS will be transferred to a "large size" ACS hollow- fiber bioreactor, to grow for an additional 7 days in culture. (f) the series of tests and Lot Release Criteria has been revised. The lot release criteria are: (1) bacterial cultures performed 48 hours prior to harvest show no growth after at least 24 hours of incubation, (2) endotoxin testing is negative, (3) gram stain is negative for bacteria. (g) Elimination of PCR test for RCR (in lymphocytes). (2) Clinical Issues: (a) increase in maximal feasible dose 2-fold, to 1 x 100 cell, (b) IQ test deferred, (c) serial eye examinations, electroretinogram, and audiograms will not be done on patients, (d) testing adult subjects will be done at the Adult Pulmonary Function Laboratory, (e) an overnight, 12-hour urine collection will be substituted for the 24-hour collections previously specified.
9-11-96	**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 Identicle Twins.** **Amendment:** Reduction of patient's routine clinic visits from once every other week to monthly.
9-19-96	**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.**

		Amendment: Addition of 4 new investigators and multiple clinical trial sites: John Nemunaitis, M.D., Texas Oncology, and the University of Texas Southwestern, Dallas, Texas; Thomas Origitano, M.D., Ph.D., Loyola University Medical Center, Maywood, Illinois; Ronald Warnick, M.D., University of Cincinnati Medical Center, The Christ Hospital, Good Samaritan Hospital, Jewish Hospital of Cincinnati, Veterans Affairs Medical Center, Cincinnati, Ohio; Dr. med. Friederich Weber, Heinrich Heine Universitat, Dusseldorf, Germany; PD Dr. med. Nikolai Rainov, Martin Luther Universitat, Halle, Germany.
10-03-96	**9503-103 Morgan**	**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 Identicle Twins.** **Amendment:** *These amendments have been submitted to the IRB and the NIH Biosafety Committee. Included in this submission to ORDA was the new consent form, a detailed restriction map, and complete vector sequence.* 1) Addition of a new retroviral vector G1RSN3. The new vector contains only the transdominant Rev gene and not the antisense TAR gene. Additionally, the new vector is packaged by PG13 cells. 2) Some lymphocytes will be transduced with either GC-RevTdSN(anti-TAR)DC or G1RSN3. There will be 3 additional cell infusions at approximate 8 week intervals. The choice of vector infused will be determined by the PI. 3) A new neoR vector will be used in conjunction with G1RSN3. It is G1Ns, produced by Genetic Therapy, Inc. 4) In reference to the the first infusion of cells, the protocol will be changed from "*Once the fraction of engineered cells circulating either falls 2 logs from immediatley post-infusion or falls to the limits of detection, whichever occurs first, the patients will be eligible to receive subsequent infusions of engineered cells*". to "*Retreatment with subsequent infusions of engineered cells will occur at intervals of approximately every 8 weeks.*" **Update:** 3 patients have been treated with a single infusion of GC-RecTdSN(anti-TAR)DC-containing cells.

10-10-96	**9512-137 Hortobagyi**	**Phase I Study of E1A Gene Therapy for Patients with Metastatic Breast or Ovarian Cancer that Overexpresses HER-2/neu.** **Amendment:** (1) Addition of a new investigator, new site: Dr. Robert Kilbourn, at Rush-Presbyterian/St Luke's Medical Center, Chicago, Illinois. (2) Change in vector backbone: the new construct, pE1A-K2 retains the unaltered gene insert, including the enhancer, promoter, and coding sequences, in a higher copy pUK21 plasmid backbone.
10-30-96	**9609-161 Antonia**	**Treatment of Small Cell Lung Cancer Patients in Partial Remission Or At Relapse With B7-1 Gene Modified Autologous Tumor Cells As A Vaccine With Systemic Interferon Gamma.** **Amendment:** *The protocol was amended after a phone conversation with the FDA, and some points addressed:* (1) Prior to administration to patients, the final cell vaccine will be tested for sterility, endotoxin, and mycoplasma. (2) The interferon gamma that will be used is commercially available from Genentech, Inc. (3) A small quantity of the plasmid containing the B7-1 cDNA was obtained directly from Dr. Robert Fenton, amplified, and the amplified DNA was tested. A B7-1 negative human SCLC cell line was transfected with the amplified DNA and the cell line demonstrated expression of B7-1 by FACS analysis.
11-04-96	**9610-162 Kilbourn**	**A Phase I Multicenter Study of Intratumoral E1A Gene Therapy for Patients with Unresectable or Metastatic Solid Tumors that Overexpress HER-2/neu.** **Amendment:** One of the PIs of the study has been replaced: Suzanne LaFollette, M.D., replaces Robert Kilbourn, M.D., Ph.D., at Rush Presbyterian/St. Luke's Medical Center.