SAFETY REPORTS, ADVERSE EVENTS AND UPDATES FOR HUMAN GENE TRANSFER PROTOCOLS RECOMBINANT DNA ADVISORY MEETING JUNE 13 AND 14, 1997

2-14-97 **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.

U pdate: The clinical trial is open for enrolled subject follow-up only; it is closed. "Of the six sets of twins enrolled, all continue to be followed in clinic. All six HIV-infected recipient twins received a second infusion of marked cells and rolled over to 94-1-0202 (protease inhibitors plus IL-2). One twin recipient received a third infusion of marked cells in the past year, in an effort to prospectively evaluate for the development of an anti-neo immune response. As previously reported, one patient never received IL-2 because of the development of an opportunistic infection (PCP) and severe hyperbilirubinemia on indinavir, a second patient discontinued IL-2 because of lack of response (but continues on protease inhibitors on 94-1-0202), and a third patient stopped indinavir because of toxicity (lactic acidosis, bronchospasm, and dyspnea). This patient was subsequently rechallenged with indinavir and these symptoms recurred. (The patient) remains eligible to receive further IL-2 on 94-1-0202. "We continue to detect genetically marked lymphocytes in the circulation in all six twin recipients. The major rationale for continuing to follow these patients is to define the survival time of adoptively transferred, genetically modified lymphocytes. In addition, we are obliged (by the FDA) to follow participants of gene transfer studies lifelong where retroviral vectors have been used in order to assess for the appearance of replication-competent retrovirus and other late adverse sequelae."

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 Indentical Twins.

Safety Report/Adverse Events: "Four HIV-infected patients have received one infusion each of genetically modified cells obtained form their respective uninfected identical twin. The total number of cells infused has ranged from 4.9 billion to 9.4 billion. All patients treated thus far have received 2 pooled populations of cells transduced with the neo-resistance control vector (G1Na) and the anti-HIV combination vector (GC-RevTDSN(anti-TAR)DC), containing both a transdominant Rev gene and an anti-sense TAR gene. "Data on persistence of gene-modified cells for the four treated patients is available through 9-18 weeks post-infusion. Gene-modified cells are detectable in the peripheral circulation. A trend appears to favor preferential survival of cells transduced with the anti-HIV vector compared to the control vector, although this is very preliminary. "In terms of adverse events: no grade 4 toxicities have occurred, and the adverse events recorded to date have not been judged to be related to cell infusions. All grade 3 adverse events and all significant ungraded adverse events that occurred during the study period are reported below: "*Summary of Adverse Events to Date:*

Pt.	Event	Grade	Relatedness	Comments
KC	hyperbilirubinemia	3	Unrelated	3 mos. post cells
KC	thrombocytopenia	3	Unrelated	pre-dated cells
AD	chest tightness	Ungraded	Unrelated mild	hx. asthma, developed

		bronchospasm 1 hr. after cell infusion, resolved with beta-agonist MDI "*Subject Accrual:* A total of five sets of twins (ten patients) have been enrolled: All are male; 8 are white and 2 are Hispanic; the age range is 28 to 46 years. "*FDA IND Report:* The annual report to the FDA has not yet been assembled. This will be forwarded to the IRB when it has been prepared...."
3-10-97	**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 Indentical Twins.** **Adverse Event:** One patient was hospitalized on 2-24-97 for pulmonary infiltrates and azotemia, which is approximately 4 months after receiving the last cell infusion. The patient had been receiving genetically-modified syngeneic CD8 cells on this protocol. The patient had a pre-study history of cutaneous Kaposi's sarcoma. The principal investigator (PI) states that no specific diagnosis is available at present.
3-4-97	**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 Indentical Twins.** **Safety Report:** ***Report of testing for RCR.*** The assays employed for RCR detection include a serum ELISA for anti-gp70 antibodies (developed by investigators at Cell Genesys) and a DNA-PCR on peripheral blood mononuclear cell pellets that specifically amplifies vector-derived DNA. The PI states: "All samples analyzed to date are negative, with the exception of samples from (one patient). In this case, serum from 11/19/96 tested positive at 1:10 and 1:40 dilutions (serum from 10/21/96, 11/19/96. 12/16/96, and 1/13/97 tested positive only at a 1:10 dilution). For this assay, a sample is considered negative if it has an O.D. less than or equal to 2X the O.D. of the negative control. Based on extensive prior testing, a 1:10 serum dilution results in many false positives. Therefore, we routinely screen serum at a 1:10 dilution, and repeat those samples with O.D.'s greater than 2X the negative control by further dilution to a 1:40 dilution. Only those samples testing positive at a 1:40 dilution are considered true positives in this assay. "Using our standard criteria for assigning a positive value to a test result, the serum obtained on (the same patient) on 11/19/96 tested positive by anti-gp70 ELISA, but serum obtained on the other dates tested negative. DNA-PCR analysis of PBMC obtained on the other dates gave negative results, including the sample obtained on 11/19/96. "Of note, this patient has a history of chronic hepatitis C virus infection. Because of elevated hepatic transaminase and the concern of drug-related toxicity, (the patient) stopped all anti-retroviral drugs beginning 9/27/96. A liver biopsy performed on 11/18/96 confirmed the diagnosis of HCV hepatitis. During the period in question, off anti-HIV therapies, the patient's plasma HIV-RNA levels increased from less than 500 copies/ml to nearly 400,000 copies/ml. Thus, the possibility of a cross-reacting antibody directed against HIV-1 or HCV that resulted in a false positive anti-gp70 ELISA seems a possible explanation for these results. With the exception of elevated hepatic enzymes (for which this patient is now undergoing treatment with interferon alpha), the patient's health status is no different from the pre-study baseline. "To summarize, we have identified one patient in whom anti-gp70 antibody testing on serum from a single date was positive. The cell pellet from the corresponding date tested negative for RCR using a DNA-PCR assay. All other samples tested, including one and two months after the positive ELISA, were negative. We believe the positive ELISA represented a false positive that might be related to cross-reacting anti-HIV-1 and/or anti-HCV antibody. No changes to the protocol are planned, and this patient's participation will continue. All patients will continue to have serum and PBMC pellets analyzed for RCR according to the timetable outlined in the FDA recommendations."

3-17-97	**9406-074 Evans and Robbins**	**Clinical Trial to Assess the Safety, Feasibility, and Efficacy of Transferring a Potentially Anti-arthritic Cytokine Gene to Human Joints with Rheumatoid Arthritis.** **Adverse Event:** One of the patients enrolled in the trial felt unwell on 2-5-97. It was initially thought that (the patient) might have had a heart attack, but subsequent examination reveals that (the patient) did not. At the time of this report, the PI states: "The patient is presently well and asymptomatic."
3-17-97 (letter date)	**9503-103 Morgan and 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.** **Adverse Event:** This adverse event involves the development of grade 3 thrombocytopenia judged by the investigators unlikely to be related to the gene-modified cell infusions. The date of onset was 3/10/97, with no resolution as of the date of the report (3-17-97), although the patient condition is stable. The event was judged severe, and unlikely to be related to the study product, with suspected etiology listed as "ITP vs. medication reaction vs. HIV related". The event is described as "Patient with history of grade I thrombocytopenia since 7/1/96 presented for second infusion with platelet count of 47K (Grade III toxicity). Cells administered without problems on 3/10/97. Repeat platelet count Day 1 post cells continued to decline - was 35K. Patient denies bleeding, bruising, petechiae." Infusion A of twin donor CD4 lymphocytes was administered on 9/3/96. 8.4×10^9 cells were administered intravenously, the vectors were LATRSN and G1NA. Infusion B of the same cell type was administered on 3/10/97 (as mentioned above), containing 12.2×10^9 cells. The vectors that transduced the Infusion B cells were G1NS and G1RSN3. The patients relevant medical history/pre-existing conditions are listed as: primary dx: HIV/AIDS; opportunistic infections: Cryptococcal Meningitis (dx: 7/26/96), CMV retinitis (dx: 10/1/95), MAC infection (dx: 1/1/96); Thrombocytopenia - Grade I, dx: 7/1/96; Anemia - Grade I, dx: 10/30/96 - now on Epogen; Neutropenia - Grade I, dx: 10/30/96 - 11/13/96 - now on Neupogen.
3-21-97	**9412-095 Hersh and Rinehart**	**Phase I Trial of Interleukin-2 Plasmid DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Solid Malignant Tumors or Lymphomas by Direct Gene Transfer.** **Update:** *This update was enclosed in the submission of protocol #9703-184.* This protocol has been conducted in 23 patients with metastatic neoplastic disease, who received six doses of 10, 30, 100, or 300 ug of Leuvectin. The protocol sponsor (Vical, Inc.) states that an analysis of the data showed Leuvectin to be safe and non-toxic when administered intratumorally.
3-21-97	**9611-169 Hersh, Rinehart, Rubin and Sondak**	**Phase I Trial of Interleukin-2 DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Cancer by Direct Gene Transfer.** **Update:** *This update was enclosed in the submission of protocol #9703-184.* This study is currently being conducted in patients with metastatic melanoma, renal cell carcinoma and sarcoma, who will receive six doses of 300, 750, or 1500 ug Leuvectin directly into the tumor. 19 patients have been treated, 7 of which have received doses of 750 ug. The sponsor (Vical, Inc.) states that "To date, no significant safety concerns have resulted from this study."
3-25-97	**9409-083 Flotte**	**A Phase I Study of an Adeno-associated Virus-CFTR Gene Vector in Adult CF Patients with Mild Lung Disease.** **Update:** Total enrollment is 13 patients, 8 at Johns Hopkins and 5 at the University of Florida.
4-2-97	**9503-101 Economou**	**A Phase I Testing of Genetically Engineered Interleukin-7 Melanoma Vaccines.** **Update:** The protocol was closed effective March 1997, with 5 patients entered. The PI

		volunteers the information that they have not seen any immunological or clinical benefit to this IL-7 based vaccine.
4-10-97	**9312-059 Oldfield and Ram**	**Intrathecal Gene Therapy for the Treatment of Leptomeningeal Carcinomatosis**. **Update:** A telephone conversation with personnel from Genetic Therapies, Inc., revealed that this trial was closed effective January 1995.
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.* The PI notified this office of amendments to the protocol following the adverse event reported in January 1997. Those amendments are outlined in the "Amendments to Gene Therapy Protocols..." document. The patient has had no subsequent symptoms or laboratory abnormalities that can be related to the possible drug reaction. The PI states: "Several experts at the National Institutes of Health have indicated that some patients receiving similar cell preparations have encountered possible infusion-related reactions in protocols for: (1) lymphocyte gene therapy for adenosine deaminase deficiency (Drs. Michael Blaese and Linda Muul) and (2) lymphocyte administration to patients with AIDS (T.A. Selvaggi, R.E. Walker, T.A. Fleisher, 'Development of antibodies to fetal calf serum with arthus-like reactions in human immunodeficiency virus-infected patients given syngeneic lymphocyte infusions', Blood 89:776-779, 1997). Although information is limited to a small series of 14 patients, retrospective studies indicated that the 9 patients who did have adverse reactions associated with cell infusions did have antibodies to fetal bovine serum (FBS) as assayed in Ouchterlony diffusion plates. In contrast, those patients who did not have such antibodies did not have such adverse reactions. "The sole patient currently enrolled in our study of lymphocyte gene therapy for Hunter syndrome was recently tested for the presence of antibodies to FBS by Linda Muul, Ph.D. and Michael Blaese, M.D. (NIH) and by Miriam Segall, Ph.D. (University of Minnesota). Both series of tests found no antibodies against FBS by Ouchterlony diffusion tests in patient serum including specimens obtained: (a) immediately prior to the possible ADR; and (b) two weeks after this infusion. "Among the possible interpretations are that: (a) the patient has developed antibodies against FBS but at levels too low to detect by the Ouchterlony method; (b) the patient reaction is mediated by a cellular response against FBS; (c) the possible adverse reaction is mediated by an immune response to other neoantigens (e.g., immune response to Neo^r or IDS retrovirus transgene products); (d) the reaction is due to another characteristic of the activated T-cells (e.g. cytokine release); (e) the possible reaction was actually an unrelated "viral flu" or other coincident infectious disease. We are continuing to investigate these other possibilities to whatever extent possible." The amendments submitted to ORDA are a result of discussions with the Food and Drug Administration (FDA) and the University of Minnesota Institutional Biosafety Committee. The plan for the continued treatment of the sole patient follows: "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 (the patient) used for relief of symptoms following the last cell infusion."
4-25-97	**9507-114 Gardner**	**A Phase I/II Study of tgAAV-CF for the Treatment of Chronic Sinusitis in Patients with Cystic Fibrosis.** **Update:** The sponsor (Targeted Genetic, Inc.) submitted the following: "In response to Dr. Jude Samulski's comment regarding evidence of CFTR expression in our cystic fibrosis trials...we refer back to our submission of November 27, 1997 where we presented summary

		data for the two trials conducted thus far. We now have evidence suggestive of expression based on electrophysiological measurements and are in the process of preparing this data for publication."
4-25-97	**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, Previoulsy Untreated Glioblastoma.** **Adverse Event:** *The report was faxed to all RAC members.* A patient death is reported. The event is described as follows: "On April 9, the patient underwent surgery with tumor resection and received injection of GLI-328 therapy (vector producing cells -7 mls) into the tumor bed. Post-operatively the patient exhibited obtundation and an increased right pupil. A CT scan showed severe edema of the tumor bed and a small epidural hematoma. (The patient) was diagnosed as demonstrating an epidural hematoma and complications of increased intracranial pressure (ICP), was admitted to the ICU and was re-intubated. An SAE was reported by the investigator on April 9 because of the post-operative complications of edema and hemorrhage. The investigator characterized the hematoma as a post-operative complication, the edema as a complication of total resection of glioblastoma and assessed the causal relationship of these complications to the experimental therapy as unlikely. On April 10, the patient underwent surgical evacuation of the hematoma and over the next few days demonstrated clinical improvement. However, problems with increased ICP and intracerebral hemorrhage recurred and the patient underwent a repeat surgical evacuation of the hemorrhage into the tumor bed on April 15 and a ventriculostomy and evacuation of an intraparenchymal hematoma on April 17. The patient also demonstrated: 1) a deep venous thrombosis (shown by Doppler) in the left iliac vein and extension into the lower inferior vena cava and was treated with a Greenfield filter placement; 2) hyperglycemia treated with insulin; 3) hypernatremia and hypersomolality; 4) progressive azotemia and mild hyperkalemia; and a 5) marked decrease in hematocrit from 60 to 29. Because of the recurring/persistent complications of increased ICP and hemorrhage, many other complications which have been outlined, progressive coma, and overall poor prognosis the family decided to withdraw supportive measures and the patient died on April 20.... "The increased ICP/cerebral edema and hemorrhage are recognized as potential complications of surgical resection of glioblastoma and the hemorrhagic complications may have been exacerbated by the patient's polycythermia with possibly platelet dysfunction and coagulopathy demonstrated by the prolonged PT. However, increased ICP/cerebral edema and corresponding clinical complications are also associated with GLI-328 therapy after intracerbral injection of vector producing cells. Considering the simultaneous administration of surgical therapy and gene therapy, the close temporal sequence of the increased ICP/cerebral edema and corresponding clinical complications after these therapies, it is not possible to distinguish the degree that either therapy comtributed to this continuing serious adverse event (SEA) which ultimately resulted in death. Thus the sponsor (Genetic Therapy, Inc.) views this SAE/death as possibly related to the experimental therapy with GLI-328. Although the SAE initially was not unexpected, the death resulting from the SAE may be viewed as unexpected. Conclusion: SAE ultimately resulting in death is unexpected and possibly related to the study medication/experimental therapy."
4-29-97	**9312-061 Schuening**	**Retrovirus-Mediated Transfer of the cDNA for Human Glucocerebrosidase into Peripheral Blood Repopulating Cells of Patients with Gaucher's Disease.** **Update:** The PI has requested the FDA to inactivate the protocol. The protocol is closed.
4-29-97	**9209-027 Schuening**	**Study on Contribution of Genetically Marked Peripheral Blood Repopulating Cells to Hematopoietic Reconstitution after Transplantation.** **Update:** The PI has requested the FDA to inactivate the protocol. The protocol is closed.