AMENDMENTS AND UPDATES TO HUMAN GENE TRANSFER PROTOCOLS

RECOMBINANT DNA ADVISORY COMMITTEE MEETING
March 2002

ID #	Letter	Protocol #		Amendment
		9209-026	**A Study of the Safety and Survival of the Adoptive Transfer of Genetically Marked Syngeneic Lymphocytes in HIV Infected Identical Twins.**	
373	01/17/2002		*Annual Update:*	Received an annual report and termination of study notice for protocol 026 ("A study of the safety and survival of the adoptive transfer of genetically marked syngeneic lymphocytes in HIV infected identical twins") submitted on January 17, 2002 by Dr. Jorge Tavel (the PI) from NIAID. This study enrolled 6 sets of twins of which 4 continue to be followed by NIAID (of note, one set is followed by their local physicians for routine medical care only and one set of twins is no longer followed since the HIV+ twin died of disease progression). No gene altered cells have been infused since 12/2/96 and the subjects that are still followed are currently receiving high-dose IL-2 for maintenance of their transduced T-cell population (as well as for maintenance of their native CD4+ cells). These subjects will be followed long-term under a new study (referred to as the "Gemini protocol". A separate email will be sent which describes this new long-term follow-up protocol). In regard to safety, all studies looking for replication competent retroviruses have been negative. Post-mortem samples on the deceased subject were investigated by NIAID and found to be RCR negative as well. Annual archival specimens are collected from the four subjects still seen by NIAID. Multiple AEs have occurred since the last reporting period, with all of these deemed either complications of HIV infection or of the IL-2 therapy. In regard to efficacy, while the levels detected are low, there continues to be the persistence of the transduced T-lymphocytes (received from the HIV-negative twin) in the subjects followed. OBA Reviewer's Comments: 1. Our database has a total of 12 adverse event reports for this protocol. None of these are deemed as related to the gene transfer product, but due to either disease progression or IL-2 therapy complications. 2. This is one of 4 NIAID studies in which identical twins were studied (transduced cells from

ID #	Letter	Protocol #		Amendment
				the HIV-negative cells were transduced and infused into the HIV+ sibling). All of these studies are officially terminated with long-term follow-up to occur via the "Gemini study". We have received the final annual report for three of these 4 studies. 3. Agree with the investigator that while the levels are low it is encouraging that persistence of the transduced cells is still noted over 5 years out.
385	01/17/2002		*Other:*	Received a new study submitted by Dr. Jorge Tavel (of NIAID) on January 17, 2002. This study, referred to as "The Gemini Study", is entitled "Study of the long-term safety and persistence of cells following cell transfers or gene therapy in identical twins discordant for HIV infection" and is meant as a follow-up study that will enroll subjects from four prior NIAID studies. Background: The NIAID has conducted 4 studies in which lymphocytes have been harvested and then transferred from the HIV-negative twin to the HIV+ one. In three of these studies (our OBA #s are 026, 069, and 103) the T-cells were first transduced with a retroviral vector and then infused into the recipient twin. Study 26 was a marking study so the T-cells were transduced with the neomycin phosphotransferase cDNA. Study 69 transduced the cells with the genes for a CD4-zeta chimeric receptor, while in study 103 the T-lymphocytes were transduced with antisense TAR and transdominant Rev protein genes. The fourth study did not utilize gene-modified cells, but strictly infused purified and expanded pools of CD4+ cells. All 4 studies are closed to enrollment and the final annual report for the three recombinant DNA studies have been recently submitted to us. In order to simplify follow-up, the NIAID is proposing to enroll all subjects from these 4 studies into one long-term study ("The Gemini Study") Details: The objectives of this study are to: * Consolidate previous intramural NIAID HIV discordant twin gene-modified cell infusion/ cell transfer studies into a single long-term monitoring protocol. * To evaluate the long-term safety of gene-modified and unmodified infusions in HIV-infected subjects * To evaluate the long-term safety of multiple aphereses in HIV-negative donors. * To evaluate the long-term survival of gene-altered cells and cell transfer in HIV infected individuals.

ID #	Letter	Protocol #	Amendment	
				This study is strictly observational with no research interventions involved. Due to this, subjects are invited to participate in various other NIAID HIV protocols, such as the long-term high-dose IL-2 study and the continuous-infusion HAART study. Subjects will be monitored at the minimum annually, with appropriate laboratory studies (listed on page 13 of the protocol) and various research studies (such as immune profiling, gene-specific signal, and storage of plasma and serum for potential future RCR studies. These are also described on page 13 and 14 of the protocol). No formal statistical analysis is planned, with this study being viewed strictly as an observational study whose information will potentially lead to future, larger trials. OBA Reviewer's Comments: In regard to participation in other non-gene-transfer studies, how will this impact the interpretation of adverse events in this study population? IL-2 and HAART are both associated with multiple adverse events, which would make it difficult to sort out any potential adverse event impact of the gene-modified cells.
332	01/17/2002		*Status Change:*	This trial is closed to enrollment. Individuals enrolled in this trial and protocol 9503-103 will be followed, long-term, in a single protocol. There will be no administration of any study agent in this follow-up trial. Individuals who enroll are therefore free to co-enroll in other trials of experimental agents.

ID #	Letter	Protocol #	Amendment
		9403-069	**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. Sponsor: NIH/Cell Genesys, Inc.**
374	11/26/2001		*Annual Update:* Received an annual report for study 069 ("A phase I/II study of the safety of the adaptive transfer of syngeneic gene modified cytotoxic T lymphocytes in HIV-infected identical twins) submitted on November 26, 2001 by Dr. Tavel (the PI) of NIAID. This study is being terminated with long-term follow-up of the remaining subjects to be conducted under the "Gemini study" (which will be described in a subsequent email). To date, a total of 43 sets of identical twins have been enrolled, with 32 sets receiving gene-modified cells (i.e., the HIV+ twin received transduced T-lymphocytes from the HIV-negative twin). Of the 32 HIV+ subjects who have received gene-modified cells, 9 are in long-term follow-up, 9 are participating in a IL-2 extension phase of this study (high dose IL-2 is administered on an individualized regimen in an effort to maintain detectable circulating transduced T-lymphocytes as well as to maintain the native CD4+ cell counts), 3 are enrolled in the IL-2 phase of the study but are currently not receiving IL-2 due to medication adverse events, 3 have been co-enrolled into study 103, and one co-enrolled in a NIAID study which does not utilize gene-modified cells. The remaining 7 subjects have either died from disease progression or have been lost to follow-up. In regard to safety, there are several serious adverse events listed in this annual report, but all are deemed to be secondary to the use of high-dose IL-2. RCR testing has been conducted on all subjects who received gene-modified cells and one subject was found to have a positive serum ELISA test. PCR analysis using primer pairs with specificity for the Moloney murine retrovirus was done and found to be negative. Subsequently, this subject has had 14 more samples obtained, all of which are PCR negative. Archiving of annual samples continues for those subjects still followed. Fourteen subjects have died (13 HIV+ and one a HIV-negative twin). Some of these occurred prior to receipt of the gene-modified cells. In all cases but one (see comments below), death was deemed by the PI as unrelated to the gene transfer. In regard to efficacy, as seen in the sister study (protocol 103) low levels of transduced cells have been noted even long-term (greater than 100 weeks). Further analysis will continue under the Gemini study. OBA Reviewer's Comments: 1. As with his other protocols, Dr. Tavel has been diligent in submitting adverse events. There are many adverse events in our database for this protocol. 2. In regard to the AEs in our database, there are several of concern:

ID #	Letter	Protocol #	Amendment
			a. Monoclonal lymphoproliferative disorder. Believed to be unrelated to gene transfer by the PI. b. Rectal area lymphoma, believed to be probably unrelated though RCR testing not reported. c. CNS lymphoma, believed to be probably unrelated but with no RCR test results submitted with the report. d. Hypertension, chest pain and tightness occurring 10 minutes after infusion of the gene-modified cells. Responded to oral NTG and deemed related. No long-term sequelae. e. Pericarditis noted 3 weeks after the last infusion. Believed to be unrelated to the gene-modified cells but possibly related to IL-2. f. Changes in visual acuity 3 days after infusion. Cleared spontaneously. Etiology not clear. g. Death which was believed to be due to HIV disease progression but due to temporal proximity to infusion, possible relationship with gene-modified cell infusion can not be ruled out. 3. Agree with the PI that the persistence of the gene-modified cells is encouraging and warrants further study.
386	01/17/2002	*Other:*	Received a new study submitted by Dr. Jorge Tavel (of NIAID) on January 17, 2002. This study, referred to as "The Gemini Study", is entitled "Study of the long-term safety and persistence of cells following cell transfers or gene therapy in identical twins discordant for HIV infection" and is meant as a follow-up study that will enroll subjects from four prior NIAID studies. Background: The NIAID has conducted 4 studies in which lymphocytes have been harvested and then transferred from the HIV-negative twin to the HIV+ one. In three of these studies (our OBA #s are 026, 069, and 103) the T-cells were first transduced with a retroviral vector and then infused into the recipient twin. Study 26 was a marking study so the T-cells were transduced with the neomycin phosphotransferase cDNA. Study 69 transduced the cells with the genes for a CD4-zeta chimeric receptor, while in study 103 the T-lymphocytes were transduced with antisense TAR and transdominant Rev protein genes. The fourth study did not utilize gene-modified cells, but strictly infused purified and expanded pools of CD4+ cells. All 4 studies are closed to enrollment and the final annual report for the three recombinant DNA

studies have been recently submitted to us. In order to simplify follow-up, the NIAID is proposing to enroll all subjects from these 4 studies into one long-term study ("The Gemini Study")

Details:
The objectives of this study are to:
* Consolidate previous intramural NIAID HIV discordant twin gene-modified cell infusion/ cell transfer studies into a single long-term monitoring protocol.

* To evaluate the long-term safety of gene-modified and unmodified infusions in HIV-infected subjects

* To evaluate the long-term safety of multiple aphereses in HIV-negative donors.

* To evaluate the long-term survival of gene-altered cells and cell transfer in HIV infected individuals.

This study is strictly observational with no research interventions involved. Due to this, subjects are invited to participate in various other NIAID HIV protocols, such as the long-term high-dose IL-2 study and the continuous-infusion HAART study. Subjects will be monitored at the minimum annually, with appropriate laboratory studies (listed on page 13 of the protocol) and various research studies (such as immune profiling, gene-specific signal, and storage of plasma and serum for potential future RCR studies. These are also described on page 13 and 14 of the protocol). No formal statistical analysis is planned, with this study being viewed strictly as an observational study whose information will potentially lead to future, larger trials.

OBA Reviewer's Comments:

In regard to participation in other non-gene-transfer studies, how will this impact the interpretation of adverse events in this study population? IL-2 and HAART are both associated with multiple adverse events, which would make it difficult to sort out any potential adverse event impact of the gene-modified cells.

ID #	Letter	Protocol #	Amendment
		9503-103	**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.**
387	01/17/2002	*Other:*	Received a new study submitted by Dr. Jorge Tavel (of NIAID) on January 17, 2002. This study, referred to as "The Gemini Study", is entitled "Study of the long-term safety and persistence of cells following cell transfers or gene therapy in identical twins discordant for HIV infection" and is meant as a follow-up study that will enroll subjects from four prior NIAID studies. Background: The NIAID has conducted 4 studies in which lymphocytes have been harvested and then transferred from the HIV-negative twin to the HIV+ one. In three of these studies (our OBA #s are 026, 069, and 103) the T-cells were first transduced with a retroviral vector and then infused into the recipient twin. Study 26 was a marking study so the T-cells were transduced with the neomycin phosphotransferase cDNA. Study 69 transduced the cells with the genes for a CD4-zeta chimeric receptor, while in study 103 the T-lymphocytes were transduced with antisense TAR and transdominant Rev protein genes. The fourth study did not utilize gene-modified cells, but strictly infused purified and expanded pools of CD4+ cells. All 4 studies are closed to enrollment and the final annual report for the three recombinant DNA studies have been recently submitted to us. In order to simplify follow-up, the NIAID is proposing to enroll all subjects from these 4 studies into one long-term study ("The Gemini Study") Details: The objectives of this study are to: * Consolidate previous intramural NIAID HIV discordant twin gene-modified cell infusion/ cell transfer studies into a single long-term monitoring protocol. * To evaluate the long-term safety of gene-modified and unmodified infusions in HIV-infected subjects * To evaluate the long-term safety of multiple aphereses in HIV-negative donors. * To evaluate the long-term survival of gene-altered cells and cell transfer in HIV infected individuals. This study is strictly observational with no research interventions involved. Due to this, subjects are invited to participate in various other NIAID HIV protocols, such as the long-term

ID #	Letter	Protocol #		Amendment
				high-dose IL-2 study and the continuous-infusion HAART study. Subjects will be monitored at the minimum annually, with appropriate laboratory studies (listed on page 13 of the protocol) and various research studies (such as immune profiling, gene-specific signal, and storage of plasma and serum for potential future RCR studies. These are also described on page 13 and 14 of the protocol). No formal statistical analysis is planned, with this study being viewed strictly as an observational study whose information will potentially lead to future, larger trials. OBA Reviewer's Comments: In regard to participation in other non-gene-transfer studies, how will this impact the interpretation of adverse events in this study population? IL-2 and HAART are both associated with multiple adverse events, which would make it difficult to sort out any potential adverse event impact of the gene-modified cells.
333	01/17/2002		*Status Change:*	This trial is closed to enrollment. Individuals enrolled in this trial and protocol 9209-026 will be followed, long-term, in a single protocol. There will be no administration of any study agent in this follow-up trial. Individuals who enroll are therefore free to co-enroll in other trials of experimental agents.
375	01/17/2002		*Annual Update:*	Received the final annual report for protocol 103 ("Gene therapy for AIDS using retroviral mediated gene transfer to deliver HIV-1 antisense TAR and Transdominant Rev protein to syngeneic lymphocytes in HIV infected identical twins") submitted on January 17, 2002 by Dr. Tavel (the PI) from NIAID. This is the final annual report since this study is being terminated with long-term follow-up of subjects in a NIAID protocol referred to as the "Gemini Study" (Note: This long-term follow-up study will enroll subjects from the 4 HIV gene transfer studies conducted by NIAID). Ten sets of twins were enrolled into this study, with 2 HIV+ subjects receiving but 1 infusion of gene-modified cells (from their HIV-negative twin), 7 HIV+ subjects receiving 2 infusions, and only 1 HIV+ subject receiving all three infusions. The last infusion was administered on 5/24/99 and all 10 infused subjects continue to be followed by NIAID. In regard to safety, RCR testing has been negative for all subjects. Annual archiving of serum samples continues. In addition, one subject who developed lymphoma had several biopsies sent for analysis and found to be RCR-negative as well. There have been multiple adverse events since the last reporting period, none of which are deemed to be related to gene transfer.

In regard to efficacy, data from 9 out of the 10 subjects demonstrated a preferential survival of CD4+ lymphocytes containing the anit-HIV genes in the immediate weeks after infusion. In 6 subjects where long-term testing was conducted, presence of these transduced lymphocytes have been noted over 100 weeks out.

The subjects will continue to be followed under the auspices of the Gemini Study. As per the PI, the data from this study (and sister studies 026 and 069) support the hypothesis that intracellular immunization with anti-HIV genes affords a survival to T-cells and has potential benefit in the treatment of HIV+ individuals.

OBA's Reviewer's Comments:
1. This study has multiple adverse events listed in our database, with the PI being very diligent in submitting events. There are two cases of malignancy occurring in the subjects, with these being:

a. B-cell lymphoma with colonic infiltration. RCR-negative on testing and deemed by the PI to be probably unrelated to gene transfer.

b. Basal cell carcinoma. No note of RCR testing being done. Believed to be unrelated to gene transfer.

The vast majority of AEs in our database have been deemed by the PI as probably unrelated to gene transfer and more likely due to disease progression. There is, however, one case of mild myalgias which occurred in close temporal proximity to an infusion which may be related.

2. Agree with the PI that the persistence of the transduced lymphocytes is encouraging and this warrants further study.

9508-116 Gene Therapy of Malignant Gliomas: A Phase I Study of IL-4 Gene -Modified Autologous Tumor to Elicit an Immune Response.

347 12/11/2001 *Status Change:* Received notification that trial has been amended to include a request for an autopsy per the IBC. Temporary suspension of this trial has been removed by the IRB due to the incorporation of the autopsy request.

ID #	Letter	Protocol #	Amendment
		9705-187	**Phase I Trial of Adenoviral-Mediated Herpes Simplex Thymidine Kinase Gene Transduction in Conjunction with Ganciclovir Therapy as Neo-adjuvant Treatment for Patients with Clinically Localized (Stage T1c and T2b&c) Prostate Cancer Prior to Radical Prostatectomy.**
342	11/12/2001		*Status Change:* Trial is closed to accrual.
			Annual Update: A total of six individuals were enrolled (last individual received study agent in September 1999) in this study. Three received 9 x 10^{10} virus particles and three received 9 x 10^{11}.

ID #	Letter	Protocol #	Amendment	
		9707-202	**A Phase I Study of Vaccination with Autologous, Lethally Irradiated Melanoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor.**	
376	12/27/2001		*Annual Update:*	Received a copy of the annual report for the that IND covers protocols 9707-202, 9707-203, 99008-335, and 0001-369. This report was submitted on December 27, 2001 by the IND holder, Dr. Glenn Dranoff of the Dana-Farber Cancer Institute. The information included regarding toxicity and patient deaths covers the period from 12/30/00 until 12/27/01; otherwise, the information included covers the entire period (which started in October 1997) that clinical testing under this IND has been performed. A brief summary of the four studies that are being conducted under this IND: 1. Study 202: In this study the focus is on the potential use of this construct as a vaccine in subjects with melanoma. 2. Study 203: In this study the focus is on the potential use of this construct as a vaccine in subjects with non-small cell lung cancer. 3. Study 369: In this study the focus is on the potential use of this construct as a vaccine in subjects with either advanced myelodysplasia or acute myelogenous leukemia. 4. Study 335: potential use of this construct as a vaccine in subjects with ovarian cancer. This study differs from the prior three since the vaccination consists of a mixture of non-transduced irradiated autologous tumor cells in addition to the transduced cells. Studies 202 and 203 have completed subject enrollment, with but long-term follow-up being presently conducted. Studies 369 and 335 are enrolling subjects at a slower than anticipated pace due to the small supply of the adenoviral vector currently available to the investigator through Cell Genesys. However, a new lot of vector (using the master lot from Cell Genesys) has been manufactured by Harvard Institute of Medicine and this product is currently being tested for equivalency with the Cell Genesys product. Once tests are completed, a manufacturing amendment will be submitted to verify the new manufacturing site and standards. Study 202: A total of 36 subjects were enrolled into the study. Of these, 26 subjects received a minimum of 6 vaccinations (a protocol specified amount needed so as to be evaluated for efficacy). The 26 subjects were divided into three dose levels depending on the amount of total cell yield obtained at the completion of vaccine production. Eight subjects received the low dose of $1X10^6$ cells per injection, 10 received the middle dose of $4X10^6$ cells per injection, and 8 received the high dose of $1X10^7$ cells per injection. On average, the GM-CSF secretion rate (prior to injection) was 627 ng/10^6 cells/24 hours.

In regard to safety, no serious toxicities attributable to the vaccination were observed in any of the subjects. All subjects did develop grade 1-2 skin reactions at the site of immunization, characterized by substantial erythema and induration (up to 25 cm in some cases), with related moderate pruritus. Several subjects experienced grade 1 fatigue.

In regard to efficacy, biologic activity was demonstrated in all treated subjects by pathologic examination of the vaccination sites. "Impressive" infiltrates of inflammatory cells could be noted in all specimens, as well as tumor necrosis (in some cases, marked) seen in the majority of subjects

OBA's Reviewer's Comments:
The PI has been meticulous in submitting adverse event forms to OBA. Our database contains AEs comparable to those described in this annual report.

ID #	Letter	Protocol #	Amendment	
		9707-203	**A Phase I Study of Vaccination with Autologous, Lethally Irradiated Non-Small Cell Lung Carcinoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor.**	
377	12/27/2001		*Annual Update:*	Received a copy of the annual report for the IND that covers protocols 9707-202, 9707-203, 99008-335, and 0001-369. This report was submitted on December 27, 2001 by the IND holder, Dr. Glenn Dranoff of the Dana-Farber Cancer Institute. The information included regarding toxicity and patient deaths covers the period from 12/30/00 until 12/27/01; otherwise, the information included covers the entire period (which started in October 1997) that clinical testing under this IND has been performed. A brief summary of the four studies that are being conducted under this IND: 1. Study 202: In this study the focus is on the potential use of this construct as a vaccine in subjects with melanoma. 2. Study 203: In this study the focus is on the potential use of this construct as a vaccine in subjects with non-small cell lung cancer. 3. Study 369: In this study the focus is on the potential use of this construct as a vaccine in subjects with either advanced myelodysplasia or acute myelogenous leukemia. 4. Study 335: potential use of this construct as a vaccine in subjects with ovarian cancer. This study differs from the prior three since the vaccination consists of a mixture of non-transduced irradiated autologous tumor cells in addition to the transduced cells. Studies 202 and 203 have completed subject enrollment, with but long-term follow-up being presently conducted. Studies 369 and 335 are enrolling subjects at a slower than anticipated pace due to the small supply of the adenoviral vector currently available to the investigator through Cell Genesys. However, a new lot of vector (using the master lot from Cell Genesys) has been manufactured by Harvard Institute of Medicine and this product is currently being tested for equivalency with the Cell Genesys product. Once tests are completed, a manufacturing amendment will be submitted to verify the new manufacturing site and standards. Study 203: A total of 38 subjects were enrolled into this study, with 25 receiving a minimum of 6 vaccinations. Of these 25, 6 received the low dose (same definitions for dose level as for Study 202), 15 received the middle dose and 4 received the high dose. On average, the GM-CSF secretion rate (prior to injection) was 253 ng/10^6 cells/24 hours. In regard to both safety and efficacy, the results are very comparable to those from Study 202. One difference seen was that several subjects in this study also developed low-grade

ID #	Letter	Protocol #	Amendment	
				fevers associated with the vaccination. The product was examined for sterility and found to be free of bacteria, endotoxin and mycoplasma (as per FDA standards for lower level of detection). Additionally, in regard to efficacy, two subjects had complete clearance of disease and have remained disease-free at 42 and 43 months post-vaccination. Also, one subject is alive with disease but has survived over 36 months. OBA's Reviewer's Comments: The PI has been meticulous in submitting adverse event forms to OBA. Our database contains AEs comparable to those described in this annual report. Considering the disease being studied (with a very poor 1 year survival rate, let alone disease-free rate) it is quite impressive that two subjects are disease free for nearly 3.5 years and one is still alive after 3, though with disease.
		9709-210	**Compassionate Use Protocol for Retreatment with Allovectin-7 Immunotherapy for Metastatic Cancer by Direct Gene Transfer. Sponsor: Vical, Inc.**	
360	12/03/2001		*PI or Site Change:*	Dr. John Richart has replaced Dr. Frank Dunphy as the PI at St. Louis University Health Sciences Center.

ID #	Letter	Protocol #	Amendment	
		9802-232	**Gene Therapy for Myocardial Angiogenesis.**	
380	01/14/2002		*Annual Update:*	Received the final annual report for protocol 232 ["Plasmid DNA Vector (phVEGF165) Expressing Vascular Endothelial Growth Factor Gene, Direct Myocardial Injection via Thoracotomy". Note, the title has changed compared to the RAC reviewed protocol], which was sent to OBA on January 14, 2002 by Dr. Douglas Losordo of St. Elizabeth's Medical Center. This study is now officially closed to enrollment, though long-term follow-up continues. Thirty subjects have been enrolled (which was the number designated in the study protocol), with the first subject enrolled and treated on 2-27-98 and the 30th on 5-4-99. Of these 30 subjects, one died and 4 have been either lost to follow-up or refuse to return for follow-up visits. In regard to safety, a comprehensive list with adverse events (both serious and non-serious and with no relationship to study therapy listed) for each subject is included. Details about two concerning reports are provided: a. One subject was diagnosed with a chordoma. The subject is stable post surgical resection. No evidence of progression of residual chordoma seen on follow-up and no evidence of recurrence of chordoma elsewhere in the body. b. A second subject received a heart transplant and had a complicated pre- and post-transplant course. Stable when last seen on June 9, 2000 and subsequently lost to follow-up. In regard to efficacy, when comparing pre-gene transfer and post-gene transfer, the following was noted: * Reduced angina episodes/week (56.2 +/- 4.1 versus 3.8 +/- 0.9. p value of <0.0001) * Reduced use of sublingual nitroglycerin tables ((60.1 +/- 4.4 versus 2.8 +/= 0.8 p value of <0.0001) * Improved exercise tolerance (utilizing the Bruce protocol, increase from 230 seconds to 410 seconds, on average. p value of <0.0001) * Improvements (in most cases significant) seen on mean perfusion-defect scores (on SPECT myocardial imaging studies) at rest and for stress. Also, improvement (though not statistically significant) in left ventricular ejection fraction. Overall, this study was deemed a success by the PI and the results warrant further investigations of VEGF for the treatment of unstable angina. OBA Reviewer's Comments: 1. The safety and efficacy results for this study are encouraging, as noted by Dr. Losordo.

ID #	Letter	Protocol #	Amendment	
				2. Our safety database for this study has 5 reports listed. Of these, the only clinically concerning one is the chordoma case which is elaborated on in this final annual report. The many adverse events listed in this annual report are consistent with the population studied and none appear out of ordinary for this patient group. 3. Of note, this protocol was discussed at the June 1998 RAC meeting, but the first subject was enrolled in February of 1998.
		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.**	
359	12/03/2001		*PI or Site Change:*	Dr. John Richart has replaced Dr. Frank Dunphy as the PI at St. Louis University Health Sciences Center.

ID #	Letter	Protocol #	Amendment	
		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.**	
381	11/29/2001		*Annual Update:*	Received an annual report for protocol 247 ("A phase 1 safety study of autologous transfected human fibroblasts producing human factor VIII") sent on November 29, 2001 by Transkaryotic Therapies Inc., the corporate sponsor. The PI is Dr. David Roth of Harvard Medical School. In this protocol autologous dermal derived fibroblasts are isolated, and via electroporation of a human factor VIII gene expressing plasmid, are transduced. The modified fibroblasts are then cultured and re-implanted in the subject intraperitoneally via a laparoscopic procedure. To date 8 subject have been enrolled. All subjects have experienced adverse events, with several serious in nature. All of the SAEs have been deemed to be unrelated to the gene transfer product by the PI, and the vast majority of the non-serious adverse events have been deemed by the PI to be due to study disease. Several of the related AEs, such as pain at the site of implantation, were expected and documented in the protocol and informed consent form. In regard to efficacy, four of the first 6 subjects demonstrated levels of factor VIII activity above pretreatment, with a concomitant decrease in bleeding episodes and/or reduction in the use of exogenous factor VIII. In three of these 4 subjects, the factor VIII activity levels have remained above those pretreatment for over 6 months. Dr. Roth reported on these findings in the June 7, 2001 edition of the New England Journal of Medicine ("Nonviral Transfer of the Gene Encoding Coagulation Factor VIII in Patients with Severe Hemophilia A", vol. 344:1735-1742). OBA Reviewer's Comments: 1. The PI (via the corporate sponsor) has submitted many AEs to OBA for the protocol file. Those submitted match very closely to those noted in this annual report. The medical officer agrees with the PI that no SAE stands out as being potentially or probably related to the gene transfer product. 2. This protocol was amended on 2-26-01 with the addition of a pharmacokinetic study so as to obtain data on the clearance of exogenous Factor VIII in subjects who do not have this data available. The purpose of this endeavor is to help clarify the actual additive effect of the transfected autologous human fibroblasts that are to be producing human factor VIII.

ID #	Letter	Protocol #	Amendment	
		9902-285	**A Phase I Trial of Intratumoral Antisense EGFR DNA and DC-Chol Liposomes in Advanced Oral Squamous Cell Carcinoma.**	
336	01/11/2002		*Other:*	Received a copy of the response from the Univ. of Pittsburgh to OHRP's letter. Some of the changes made to this study include the following: 1)The gene that is being studied in this trial will be modified, based upon a recommendation of the IBC, to remove a non-essential promoter sequence. This new construct will be sequenced before it is sent to the new site of production of clinical grade material. 2) Clinical grade vector for this trial will no longer be produced at the U. of Pittsburgh. The new source of vector will be the NGVL at the City of Hope Medical Center. 3) After consultation with Drs. Trump (former Deputy Director of the U. of Pitt. Cancer Institute for Clinical Research), Herberman (Director of the U. of Pitt. Cancer Center), and DeLuca (Chair, IBC) it was recommended that Dr. Dong Shin be named as principal investigator of this study. This change in PI will be submitted to the IRB and IBC for review and approval.

ID #	Letter	Protocol #	Amendment	
		9906-324	**Phase I-II Study Evaluating HSV-tk + Valacyclovir Gene Therapy in Combination with Radiotherapy for Prostate Cancer.**	
382	11/14/2001		*Protocol Change:*	The changes instituted included more clearly defining the amount of radiotherapy each subject should receive (that is, subjects in Arm C of this study have node positive disease and, as such, should receive an additional 45 gray of radiation to the pelvic area compared to Arm A and B subjects), and extending the amount of time that Lupron (leuprolide acetate, a long-acting GnRH analog approved for use in prostatic cancer and endometriosis) is used post-radiation out to 2 years. OBA Reviewer's Comments: The changes in the protocol appear reasonable and follow recent literature suggesting that long-term hormonal therapy should be instituted in post-radiotherapy prostate cancer subjects.
			Annual Update:	Received an annual report for protocol 324, submitted on November 14, 2001 by the PI (Dr. Estuardo Aguilar-Cordova). Included in the annual report is a brief summary of changes, a summary of significant adverse events (regardless of relationship to gene transfer product) and a revised clinical protocol. In regard to adverse events, there were three significant ones all of which were determined to be either unrelated to the experimental treatment or expected (of note, this study is looking at a combination of high-dose radiation therapy plus long-term hormonal therapy in addition to the gene transfer product). The events were: a. Allergic reaction to valacyclovir (part of the gene transfer aspect of the study since the gene injected into the prostate utilizing an adenoviral vector is the HSV-tk gene). Subject taken out of this study but continued with radiation therapy as planned. b. Chest pain in a subject with a known history of cardiovascular disease. No evidence of MI. c. Abdominal pain and ruptured appendicitis. Because this event occurred over one year after receiving the gene transfer product it was deemed as unrelated. There was a follow-up on the one SAE filed in the previous year's annual report. In this case a subject was hospitalized for fever to 103 and had a sepsis work-up done with negative cultures. In retrospect, the subject did not take the protocol specified prophylactic antipyretics prior to the injection of the adenoviral vector. OBA Reviewer's Comments: Our database contains but one SAE for this study, namely the high fever case reported in last year's annual report.

ID #	Letter	Protocol #	Amendment
		9908-335	**A Phase I Study of Vaccination with Lethally Irradiated, Autologous Ovarian Carcinoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor**
378	12/27/2001		*Annual Update:* Received a copy of the annual report for the IND that covers protocols 9707-202, 9707-203, 99008-335, and 0001-369. This report was submitted on December 27, 2001 by the IND holder, Dr. Glenn Dranoff of the Dana-Farber Cancer Institute. The information included regarding toxicity and patient deaths covers the period from 12/30/00 until 12/27/01; otherwise, the information included covers the entire period (which started in October 1997) that clinical testing under this IND has been performed. A brief summary of the four studies that are being conducted under this IND: 1. Study 202: In this study the focus is on the potential use of this construct as a vaccine in subjects with melanoma. 2. Study 203: In this study the focus is on the potential use of this construct as a vaccine in subjects with non-small cell lung cancer. 3. Study 369: In this study the focus is on the potential use of this construct as a vaccine in subjects with either advanced myelodysplasia or acute myelogenous leukemia. 4. Study 335: potential use of this construct as a vaccine in subjects with ovarian cancer. This study differs from the prior three since the vaccination consists of a mixture of non-transduced irradiated autologous tumor cells in addition to the transduced cells. Study 335: This study seeks to obtain safety data on 25 subjects who have received a minimum of 6 vaccinations. To date 15 subjects have been enrolled with 13 completing the minimum number of vaccinations needed. Two subjects received the low dose (in this study it is 2X10x6 cells per injection), three received the middle dose ($2X10^7$ cells per injection) and eight the high dose ($6X10^7$ cells per injection). On average, the GM-CSF secretion rate (prior to injection) was 4000 ng/10^6 cells/24 hours. As with the other studies, skin reactions were the most common adverse event, with all subjects developing grade 1-2 reactions consisting of erythema, induration (in one case it was 30 cm) and mild pruritis. Several subjects developed low-grade fever and grade 1 fatigue as well. One subject developed syncope which was previously reported to the FDA and OBA as possibly attributable to the vaccination. However, this subject has received several additional vaccinations without toxicity, so the attribution is now unclear. To date, all subjects have shown biologic activity on pathologic specimen examinations, with findings comparable to those seen in the other studies.

ID #	Letter	Protocol #	Amendment
			OBA's Reviewer's Comments: In our database there are actually three separate subjects reported who have had adverse events related to the cardiovascular system. These subjects had: [1] exertional angina, [2] dyspnea on exertion with coronary-artery disease-like symptoms, and [3] palpitations leading to syncope. Besides the third case, the other two were called unrelated to vaccine administration, though there was no mention of cardiac abnormalities noted in the subjects' past medical history.
		9908-337	**Transduction of CD34+ Cells from the Umbilical Cord Blood of Infants or the Bone Marrow of Children with Adenosine Deaminase (ADA)-Deficient Severe Combined Immunodeficiency (SCID)**
384	11/21/2001		*Other:* This is a summary of a request for a single subject exemption submitted on November 21, 2001 by Drs. Kohn, Podsakoff and Candotti (Dr. Kohn is the PI for this study). Study 337 is investigating the safety and efficacy of ex vivo transduced CD34+ cells (by retroviral vectors with the gene for adenosine deaminase) obtained from either umbilical cord blood or from the bone marrow of children with ADA-SCID. This study is similar in design to earlier ADA studies, including Dr. Blaese's first study, but instead of using an amphotropic retroviral vector this study is using a GALV-pseudotype. The subject in question did not violate specifically any of the inclusion or exclusion criteria in this protocol, however the subject had been enrolled in two prior ADA gene transfer studies. The investigators believed that this subject should be allowed to proceed with entry into this study since the response to the two prior attempts at gene transfer was minimal, and the retroviral vectors used by the prior studies differ from that used in protocol 337. Additionally, the PI has been able to differentiate between the retroviral vectors by PCR. The request was forwarded to Drs. Mickelson (former RAC Chair) and Friedmann (current RAC Chair), as well as reviewed by OBA staff. Multiple questions were raised and sent to the PIs for review, to which responses were sent. Of concern were not only issues specific to this request and protocol (such as the issue of increasing the potential for the production of a replication competent retrovirus, to which the investigators responded in very detailed fashion) but the more global issue of enrolling subjects into two or more gene transfer studies and the potential difficulties in discerning what role, if any, a specific gene transfer agent had in regard to both safety and efficacy. The IRBs at NIH (NHGRI) and at the Children's Hospital of Los Angeles, and the FDA/CBER approved this single subject exemption and the subject underwent bone marrow harvest on January 4th and received gene-corrected CD34+ cells on January 9th. The subject is to return for follow-up evaluation on February 5th.

ID #	Letter	Protocol #	Amendment	
		9912-365	**A Phase I/II Study of the Safety, Survival, and Trafficking of Autologous CD4-zeta Gene-Modified T Cells With and Without Exogenous Interleukin-2 in HIV-Infected Patients. Sponsors: University of Pennsylvania and Cell Genesys, Inc.**	
338	11/06/2001		*Status Change:*	Notification from the IRB that due to inconsistencies (not specified) between the study agent as described in the clinical protocol/informed consent and the material provided by the sponsor (U. of Pennsylvania), this trial has been suspended. To date, four individuals have received the study agent, two additional individuals have enrolled in the study (but have not received study agent). The IRB has requested guidance from the FDA. No additional individuals will be accrued on this study until this issue is resolved.
		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)**	
339	12/13/2001		*PI or Site Change:*	Dr. William Solomon at SUNY Health Science Center at Brooklyn is now an investigator.
328	01/09/2002		*PI or Site Change:*	Dr. Troy H. Guthrie Jr., at the University of Florida, Jacksonville, FL is now an investigator.

ID #	Letter	Protocol #	Amendment
		0001-369	**A Phase I Study of Vaccination with Lethally Irradiated, Autologous Acute Myeloblastic Leukemia Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor in Patients with Advanced Myelodysplasia or Acute Myelogenous Leukemia.**
379	12/27/2001	*Annual Update:*	Received a copy of the annual report for the IND that covers protocols 9707-202, 9707-203, 99008-335, and 0001-369. This report was submitted on December 27, 2001 by the IND holder, Dr. Glenn Dranoff of the Dana-Farber Cancer Institute. The information included regarding toxicity and patient deaths covers the period from 12/30/00 until 12/27/01; otherwise, the information included covers the entire period (which started in October 1997) that clinical testing under this IND has been performed. A brief summary of the four studies that are being conducted under this IND: 1. Study 202: In this study the focus is on the potential use of this construct as a vaccine in subjects with melanoma. 2. Study 203: In this study the focus is on the potential use of this construct as a vaccine in subjects with non-small cell lung cancer. 3. Study 369: In this study the focus is on the potential use of this construct as a vaccine in subjects with either advanced myelodysplasia or acute myelogenous leukemia. 4. Study 335: potential use of this construct as a vaccine in subjects with ovarian cancer. This study differs from the prior three since the vaccination consists of a mixture of non-transduced irradiated autologous tumor cells in addition to the transduced cells. Study 369: This study seeks to obtain safety data on 25 subjects who have received a minimum of 6 vaccinations. To date 5 subjects have been enrolled and have received at least the minimum amount of vaccinations. One subject received the middle dose (as described before) and 4 the high dose. On average, the GM-CSF secretion rate (prior to injection) was 11 ng/10^6 cells/24 hours. In regard to safety, all five subjects developed skin reactions at the site of vaccination, consisting of erythema, induration, and mild pruritus. Several subjects developed grade 1 fatigue and low-grade fever associated with the vaccinations as well. In regard to efficacy, biologic activity was demonstrated in all five subjects with moderate infiltration of inflammatory and immune cells at the sites of vaccination. OBA's Reviewer's Comments: The PI for this study is Dr. Daniel DeAngelo, from Dana-Farber. In our database there are several reports of fever (usually developing within 4-5 days after vaccination) which is called “unrelated" by the PI. It is interesting to note that in this annual report the relationship has been changed to related.

ID #	Letter	Protocol #	Amendment	
		0001-381	**Gene Therapy of Canavan Disease using AAV for Brain Gene Transfer.**	
383	11/13/2001		*Annual Update:*	Received a periodic safety summary (for November, 2001) for protocol 381, which was submitted by the PI (Dr. Andrew Freese, Thomas Jefferson University Medical College) on November 13, 2001. This study is investigating the intracranial infusion of an AAV/ASPA product into subjects afflicted with Canavan's Disease. To date, three subjects have been treated. The first subject experienced an adverse event (fever) which had been described by an earlier submission (and summarized in an earlier email that can be found in the protocol's email file). This subject is presently stable with complete resolution of this adverse event. The second and third subject experienced no SAEs during their treatment phase and are presently stable as well. Three month follow-up visits for all three children reveal essentially unchanged safety laboratory results (compared to baseline) and MRIs, with some "possible" improvement in a few of the neurologic markers followed. Repeat examinations for all of the subjects is scheduled in late December/early January.
		0002-388	**A Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, 26-Week Study to Assess the Safety and Efficacy of CI-1023 ($AD_{GV}VEGF_{121.10}$) in Peripheral Arterial Disease Patients with Severe, Disabling Intermittent Claudication. Sponsor: Parke-Davis Pharmaceutical Research**	
357	12/18/2001		*PI or Site Change:*	Dr. Mark G. Davies at the University of Rochester Medical Center, Rochester, New York is now an investigator.
356	12/18/2001		*PI or Site Change:*	Dr. R. David Anderson at Sarasota Memorial Healthcare System, Sarasota, Florida is now an investigator.
		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**	
337	11/28/2001		*Protocol Change:*	Lot release criteria for replication adenovirus have been modified to be less than one replication competent virus in 1 x 10^9 international units. Previously, release criteria were based upon dose.
330	01/15/2002		*PI or Site Change:*	Dr. Jon M. Richards at Oncology Specialists, S.C., Chicago, Illinois has been added as an investigator.

ID #	Letter	Protocol #	Amendment	
		0005-399	**An Open-Label, Phase I, Dose-Escalation Study of Tumor Necrosis Factor-alpha (TNFerade™ Biologic) Gene Therapy with Radiation Therapy for Locally Advanced, Recurrent, or Metastatic Solid Tumors. Sponsor: GenVec**	
344	12/12/2001		*PI or Site Change:*	Dr. Chandan Guha has replaced Dr. Anand Sharma at Albert Einstein College of Medicine/Montefiore Medical Center as a co-PI.
350	01/16/2002		*PI or Site Change:*	Dr. Donald A. Richards at the Tyler Cancer Center, Tyler, Texas is now an investigator.
371	02/08/2002		*PI or Site Change:*	Dr. Alexander Rosemurgy at the University of South Florida, Tampa, Florida is now an investigator.

ID #	Letter	Protocol #	Amendment	
		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**	
352	11/27/2001		*Protocol Change:*	Received a copy of the notification from the Cystic Fibrosis Foundation Data Monitoring Committee (DMC) regarding reducing the minimal age for enrollment to 12. This decision to allow individuals 12 and older to participate was based upon a review of the study data for the 30 day period following administration of the three doses to the first 8 individuals enrolled in addition to the safety and tolerability data from all individuals to date that have received the study agent.
354	12/06/2001		*PI or Site Change:*	Drs. Pamela Zeitlin at Johns Hopkins University, Baltimore, Maryland; and Moira Aitken at University of Washington, Seattle, Washington have been added as investigators.
353	12/06/2001		*PI or Site Change:*	Drs. Isabel Virella-Lowell, Mark Brantly, and Terry Flotte have been added as co-principal investigators at the University of Florida site.
372	01/24/2002		*Protocol Change:*	A submission dated January 24, 2002 from the corporate sponsor of protocol 404 (Targeted Genetics Corporation) has been received. In this submission, the following are included: * A copy of the results of the Cystic Fibrosis Foundation DMC data review decision, dated 1-15-02. * A summary of protocol changes (this is the fourth time that this protocol has been amended) * A complete copy of the revised protocol. In regard to the CFF DMC review, safety and tolerability data from the first 8 enrolled subjects was analyzed. All of these subjects were in the first two study cohorts and all had underwent their scheduled day 90/day 120 bronchoscopy. The CFF DMC recommended that the protocol may continue as written, but did recommend that long term monitoring of shedding of the AAVCF vector should be considered. Taking this consideration into mind, the sponsor amended the study on January 17, 2002 in the following manner: a. At two of the late follow-up visits (days 90 and 150) collection of expectorated sputum for the determination of viral shedding is now necessary. b. While receiving study medication via nebulizer, the subject must be in a hospital room with either neutral or negative pressure and with the door closed. This was not previously specified.

ID #	Letter	Protocol #		Amendment
				c. The timing of DMSB review (being done by the CFF DMC) was more clearly specified. d. Documentation to increase the number of investigators from 6 currently registered to 9 will be submitted later this year. This increase is to complete enrollment in a more expedited manner.
		0009-412	**A Phase III, Multi-Center, Open-Label, Randomized Study to Compare the Effectiveness and Safety of Intratumoral Administration of RPR/INGN 201 in Combination with Chemotherapy Versus Chemotherapy Alone in 288 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN). Sponsor: Aventis Pharmaceuticals - Gencell Division**	
329	01/09/2002		*PI or Site Change:*	Dr. Troy H. Guthrie Jr., at the University of Florida, Jacksonville, FL is now an investigator.
327	01/10/2002		*PI or Site Change:*	Dr. Andrew Nemechek at Tulane Cancer Center, New Orleans, LA has been added as an investigator.

ID #	Letter	Protocol #	Amendment
		0010-420	**Phase I, Prospective, Placebo Controlled, Randomized Assessment of Direct Administration of a Replication Deficient Adenovirus Vector ($Ad_{CU}VEGF_{121.1}$) Containing the VEGF121 cDNA to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease as an Adjunct to Coronary Bypass Surgery**
326	01/07/2002		*Protocol Change:* Changes have been made for safety monitoring. An ophthalmology exam will now be performed prior to administration of study agent and 180 days post-administration. Exclusion criteria have been modified to exclude individuals who might be at high risk for adverse events: 1) recent (less than 6 weeks) coronary artery bypass grafting, transmyocardial revascularization, or percutaneous transluminal coronary angioplasty; 2) any pre-study evaluation test/symptom which, in the investigator's opinion, could be the result of an underlying malignant condition (e.g., unexplained chest x-ray observations consistent with a possible tumor, hemoptysis, hematuria, PSA greater than 4 ng/ml or a positive stool guaiac test; and 3) individuals with moderate or severe proliferative retinopathy or severe non-proliferative retinopathy. Individuals with both Q and non-Q wave myocardial infarction within six weeks of enrollment are now excluded. Acute arrhythmia has been added as a potential risk of the direct myocardial injection procedure. Statements regarding the potential that VEGF administration may increase the risk of progressive atherosclerosis and stimulate pathological angiogenesis have been added. Information has been added to the risk section of the protocol and the informed consent concerning the subject death in another study at another institution following the myocardial injection of VEGF 121. Due to VEGF 121 having the potential to increase the size of occult tumors, a stool guaiac and PSA level determination have been added to the procedures performed prior to study agent/placebo administration. The title of this protocol has been changed to reflect the fact that possible efficacy will be determined; therefore, this is a phase I/II study. Due to the potential of VEGF increasing occult tumor size, screening according to the American Cancer Society Guidelines will be offered to individuals prior to enrollment. This option has been added to the informed consent and is considered to be part of a routine medical care and the cost of the screening is the responsibility of the research participant. A listing of all adverse events (regardless of causality) reported in the investigator's prior VEGF 121 studies has been added to both the clinical protocol and informed consent.

ID #	Letter	Protocol #	Amendment	
		0010-427	**Effect of Ad_{GV}CFTR.10 on the Cystic Fibrosis Phenotype.**	
363	01/08/2002		*Protocol Change:*	Modifications have been made to indicate more clearly that this is a blinded study and certain injection sites will receive study agent or vehicle solution. To aid in identification, several days post-injection, sites of injection will be photographed at the time of study agent administration. The clinical protocol and informed consent have been
			Status Change:	As of this date, this study has not been initiated.
		0011-431	**A Phase II Study of High-Dose Allovectin-7 in Patients with Advanced Metastatic Melanoma. Sponsor: Vical**	
343	12/13/2001		*PI or Site Change:*	Dr. Marc Ernstoff at the Dartmouth-Hitchcock Medical Center, Lebanon, NH is now an
340	12/18/2001		*PI or Site Change:*	Dr. Evanthia Galanis at the Mayo Clinic, Rochester, MN has been added as an investigator.
370	02/08/2002		*PI or Site Change:*	Dr. Jon Richards at Oncology Specialities, S. C., Park Ridge, Illinois is now an investigator.
		0011-432	**A Phase II Study of Safety and Efficacy of Allovectin-7 Immunotherapy for the Treatment of Primary Resectable Squamous Cell Carcinoma of the Oral Cavity or Oropharynx. Sponsor: Vical Inc.**	
345	12/13/2001		*PI or Site Change:*	Dr. Thomas McCaffrey at the H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL is now an investigator.

ID #	Letter	Protocol #	Amendment
		0012-436	**Gene Therapy of Malignant Gliomas: A Pilot Study of Vaccination with Irradiated Autologous Glioma and Dendritic Cells Admixed with IL-4 Transduced Fibroblasts to Elicit an Immune Response.**
365	01/25/2002		*Protocol Change:* Changes have been made to the procedures used to generate dendritic cells. The title of the study has been modified to reflect these changes. Title of study changed from: Gene Therapy of Malignant Gliomas: A Pilot Study of Vaccination with Irradiated Autologous Glioma and Dendritic Cells Admixed with IL-4 Transduced Fibroblasts to Elicit an Immune Response, to: Gene Therapy of Malignant Gliomas: A Pilot Study of Vaccination with Autologous Glioma-Lysate and Dendritic Cells Admixed with IL-4 Transduced Fibroblasts to Elicit an Immune Response. The eligible population for this trial has been changed from "recurrent" cases to "newly diagnosed." In addition, individuals, at the time of study agent administration, must be off all treatment. However, prior to study agent administration, individuals are now permitted to receive radiation therapy. The possibility that a biopsy of the tumor site may be performed to aid in the assessment of brain-swelling following study agent administration has been added. The cause of the swelling: an inflammatory response to the study agent, or tumor progression will influence the management of the swelling. A biopsy may be necessary if other diagnostic tests (PET or MR spectroscopy) are not definitive for the cause of the swelling. A data safety monitoring plan has been established for this trial. On a weekly basis, the investigators and the clinical research coordinator will meet to discuss and review study data. On a least a yearly basis, more often if necessary, the Univ. of Pittsburgh Cancer Institute Data Monitoring Committee (independent reviewers from the Univ. of Pittsburgh not associated with this trial) will review this study. This Data Monitoring Committee will review all toxicities observed, compare toxicities to early stopping rules for the study, and review the study with respect to the current literature to determine if the trial should continue. A request for an autopsy has been added to determine whether there has been any transgene expression at the vaccine site or anywhere else.

ID #	Letter	Protocol #	Amendment
		0012-439	**Gene Therapy in Conjunction with Operative Bypass Grafting for Severe Peripheral Vascular Ischemia in Individuals with Insulin-Dependent Diabetes.**
362	12/17/2001	*Protocol Change:*	Changes have been made to the clinical protocol and informed consent: 1) An ophthalmologic examination will be performed prior to study agent administration and 180 days after administration to look for any post-administration retinopathy. 2) Cancer screening following the American Cancer Society Guidelines (sigmoidoscopy, mammogram, and pap smear, as appropriate) will be recommended. This testing will be considered to be part of standard medical care and the cost will not be covered by the study. In addition, a stool guaiac test and for men a PSA level will be performed as part of the study. 3) Information regarding progressive atherosclerosis and pathological angiogenesis as potential side effects from VEGF administration, observed in animal studies, has been added. 4) Information regarding the death of a participant at another trial site enrolled in a study involving myocardial injection of a VEGF-containing vector has been added. 5) A list of the adverse events experienced in this investigator's other cardiac and peripheral vascular disease VEGF studies has been added. Changes have been made to the inclusion/exclusion criteria: 1) Several negative inclusion criteria have been re-written as exclusion criteria. 2) New criteria to exclude individuals who are lactating, individuals who have moderate or severe proliferative retinopathy or severe non-proliferative retinopathy, or the results from any pre-study test/symptom which could, in the investigator's opinion, be the result of an underlying malignant condition. 3) Individuals with both Q and non Q wave myocardial infarction within six weeks prior to enrollment are not eligible. 4) Individuals who have a had basal cell skin carcinoma that has been resolved for at least two years are eligible. Leukocytosis has replaced leukopenia as a more appropriate toxicity parameter. Myositis has also been added as a toxicity parameter. Creatine phosphokinase has replaced creatine phosphokinase-MB (a serum marker specific to cardiac muscle damage) for this study involving injection of the study agent into the leg. Trial design changes:

ID #	Letter	Protocol #	Amendment	
				1) Initial design called for two control arms: placebo and plasmid. In the interest of time, the plasmid arm has been eliminated. Individuals, 60 total, will now be randomized into either a placebo or AdVEGF arm. 2) A primary clinical endpoint for this study has been defined as graft failure at two years. Secondary endpoints include limb preservation and rate of wound healing, for individuals with non-healing wounds. Limb preservation and wound healing were previously primary clinical endpoint variables.
		0101-442	**Phase I/II, Prospective Placebo Controlled, Randomized Assessment of Adenoviral Mediated VEGF121 cDNA Myocardial Angiogenesis Therapy as an Adjunct to Individuals with Diffuse Coronary Artery Disease Undergoing Off-Pump Coronary Artery Bypass Surgery.**	
361	01/02/2002		*PI or Site Change:*	Dr. Todd K. Rosengart at Evanston Northwestern Healthcare, Evanston, Illinois is now an
			Protocol Change:	Due to a request from the NHLBI Data Safety Monitoring Board, the clinical protocol and informed consent have been modified to include a requirement for sigmoid colonoscopy and for women a pap smear and mammography in the eligibility screening procedures. In addition, a statements regarding the potential of progressive atherosclerosis observed in some animal studies employing VEGF and the death of a participant in the OTC trial have been added to both the clinical protocol and informed consent.
		0101-452	**A Multicenter, Randomized, Double-Blind, Placebo Controlled, Dose-Response Study to Evaluate the Efficacy and Safety of Ad5.1FGF-4 in Patients with Stable Angina. Sponsor: Berlex Laboratories.**	
349	12/12/2001		*PI or Site Change:*	The following investigators have been added: Dr. Samuel Butman at University Medical Center, University of Arizona, Tucson, Arizona; Dr. David A. Churchill, at Washington Regional Medical Center, Fayetteville, Arkansas; Dr. Eric H. Conn at The Chattanooga Heart Institute, Chattanooga, Tennessee; Dr. John T. Coppola at Saint Vincent Catholic Medical Centers of New York, New York, New York; Dr. Shmuel Fuchs at Washington Hospital Center, Washington, D.C.; Dr. Jalal K. Ghali at Cardiac Centers of Louisiana, Shreveport, Louisiana; Dr. Zachary I. Hodes at The Care Group, LLC, Indianapolis, Indiana; Dr. Venkatesh K. Nadar at Heritage Cardiology Associates, Camp Hill, Pennsylvania; and Dr. Steven K. Rowe at Heartland Regional Medical Center, St. Joseph, Missouri.

ID #	Letter	Protocol #	Amendment	
		0101-453	**A Multi-Center, Open Label, Two Part, Dose Escalation Study to Determine the Tolerability of Interferon-beta Gene Transfer in the Treatment of Recurrent or Progressive Glioblastoma Multiforme. Sponsor: Biogen.**	
358	12/17/2001		*PI or Site Change:*	Dr. Steven S. Rosenfeld at the University of Alabama at Birmingham is now an investigator.
			Other:	Cover letter states that the sponsor, Biogen, Inc., will be responsible for all safety reporting to the NIH. Serious adverse events will be reported by either 7 or 15 days, depending upon the event. All adverse events will be reported in the annual report. Study participants will be followed, via telephone contact, after conclusion of participation, every six months for life for the occurrence of serious adverse events.
		0101-457	**An Open-Label, Phase I, Dose-Escalation Study of TNFerade™ Biologic with Radiation Therapy as an Adjunct to Surgery or for Palliation of Soft Tissue Sarcoma of the Extremities. Sponsor: GenVec.**	
351	01/16/2002		*PI or Site Change:*	Dr. Donald A. Richards at the Tyler Cancer Center, Tyler, Texas is now an investigator.
		0102-458	**Pilot Phase II Study of Safety and Immunogenicity of a ALVAC-CEA/B7.1 Vaccine Administered with Chemotherapy, Alone or in Combination with Tetanus Toxoid, as Compared to Chemotherapy Alone, in Patients with Metastatic Colorectal Adenocarcinoma. Sponsor: Aventis Pasteur Limited.**	
341	12/17/2001		*PI or Site Change:*	Dr. Margaret von Mehren at the Fox Chase Cancer Center, Philadelphia, Pennsylvania has been added as an investigator.
		0104-463	**Phase I Double Blind, Parallel-Group, Multi-Center, Gene Expression (Synthesis of FGF-1 mRNA), Safety and Tolerability Study of Increasing Single Doses of NV1FGF Administered by Intra-Muscular Injection in Patients with Severe Peripheral Artery Occlusive Disease (PAOD) Planned to Undergo Amputation Above the Ankle. Sponsor: Aventis Pharma Recherche-Development.**	
367	01/31/2002		*Protocol Change:*	To help to ensure that individuals with hepatocarcinoma are not entered in this study: 1) Individuals with alpha-fetoprotein levels in serum greater than 15 μg/ml are not eligible; and 2) Individuals with positive serology for hepatitis B & C are not eligible. Unless an ultrasound rules out any malignant disease. In addition, the exclusion criteria regarding the nature of the injection site has been further described. Injection into anterior muscles requires a length of at least 4 cm.

ID #	Letter	Protocol #	Amendment	
		0104-467	**VEGF Gene Transfer for Diabetic Neuropathy.**	
368	02/05/2002		*Other:*	Received a complete response to the FDA's "clinical hold" from the sponsor.
		0105-472	**Phase I/II Study of Vaccination with Irradiated Autologous Lung Tumor Cells Mixed with a GM-CSF Secreting Bystander Cell Line (Lung Bystander GVAX^{R}) in Advanced Non-Small Cell Lung Cancer. Sponsor: Cell Genesys, Inc.**	
334	01/10/2002		*PI or Site Change:*	Dr. David M. Jablons at the University of California, San Francisco is now an investigator.
		0106-479	**Vaccination in Peripheral Stem Cell Transplant Setting for Acute Myelogenous Leukemia: The Use of Autologous Tumor Cells with an Allogeneic GM-CSF Producing Bystander Cell Line. Sponsor: Cell Genesys, Inc.**	
364	01/29/2002		*PI or Site Change:*	Dr. Wendy Stock, University of Chicago, Chicago, Illinois is now an investigator.
		0107-482	**Long-Term Follow-Up of the Safety and Survival of Subjects with Recurrent Malignant Glioma Who Enrolled in a Phase Ib/II Study (protocol 0107-481) of the Safety, Tolerability and Efficacy of G207, a Genetically Engineered Herpes Simplex Type-1 Virus, Administered Intracerebrally. Sponsor: MediGene, Inc.**	
324	01/10/2002		*Annual Update:*	Received a copy of the IRB approval and informed consent for this study; 482 is the long-term follow-up study associated with the phase Ib portion of protocol 0107-481. A number of editorial corrections and minor clarifications have been made. As for protocol 0107-481, selection criteria have been amended to state that individuals who go on to receive cancer therapy after administration of the study agent will still be permitted to continue in the long-term follow-up aspects of this trial and will not be considered a premature terminations. Clarification that tests for Herpes Simplex Virus detection will be performed in serum and tests for virus shedding will be performed in urine, saliva, and conjunctival secretions.
		0107-483	**Long-Term Follow-Up of the Safety and Survival of Subjects with Recurrent Malignant Glioma Who Enrolled in a Phase Ib/II Study (protocol 0107-481) of the Safety, Tolerability and Efficacy of G207, a Genetically Engineered Herpes Simplex Type-1 Virus, Administered Intracerebrally. Sponsor: MediGene, Inc.**	
325	01/10/2002		*Annual Update:*	Received a copy of the IRB approval and informed consent for this study; 483 is the long-term follow-up study associated with the phase II portion of protocol 0107-481. The changes made are in line with the changes made for protocols 481 and 482.

ID #	Letter	Protocol #	Amendment	
		0107-490	**A Pilot Phase I/II Study of Intranodal Delivery of a Plasmid DNA (Synchrotope MA2M) in Stage IV Melanoma Patients. Sponsor: CTL ImmunoTherapies Corp.**	
348	11/30/2001		*Other:*	Notification that changes have been made to the study agent based upon research showing an increase in expression of the incorporated epitopes. Title of study has been change from: A Pilot Phase I/II Study of Intranodal Delivery of a Plasmid DNA (Synchrotope MA2M) in Stage IV Melanoma Patients to A Pilot Phase I/II Study of Intranodal Delivery of a Plasmid DNA (Synchrovax SE M Vaccine) in Stage IV Melanoma
366	01/09/2002		*Protocol Change:*	Based upon ongoing review by the Center for Biologics Evaluation and Research, grade IV toxicities have been removed from the definition of dose limiting toxicity. Exclusion criteria have been clarified to exclude those that who have received chemotherapy, radiotherapy, or immunotherapy within the preceding four weeks of enrollment. In addition, those individuals who have taken drugs that affect immune function, or any investigational study agent within four weeks of enrollment are excluded.
		0107-493	**A Phase I/II Dose Escalation and Efficacy Trial of GVAX^{R} Prostate Cancer Vaccine in Patients with Metastatic Hormone-Refractory Prostate Cancer. Sponsor: Cell Genesys, Inc.**	
335	12/03/2001		*PI or Site Change:*	Dr. Jonathan Simons at Emory University, Atlanta, Georgia is now an investigator.