AMENDMENTS AND UPDATES TO HUMAN GENE TRANSFER PROTOCOLS

RECOMBINANT DNA ADVISORY COMMITTEE MEETING
September 2002

ID #	Letter Date	Protocol #	Amendment
		9510-129	**Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes as Therapy for Patients Receiving a Bone Marrow Transplant for Relapsed EBV-Positive Hodgkin Disease.**
503	05/21/2002		*Annual Update:* The PI submitted several annual reports on May 21, 2002 to the files of protocols 129 and 130. Both studies are being conducted under the same IND. The reports discuss both studies. 1. 1997 Annual Report: Report date was 6/10/97. Three research participants total enrolled (all into a long-term follow-up study--the ANGEL study). Two research participants died of progressive disease. No major protocol revisions for either protocol 129 or 130. 2. 1998 Annual Report: Report date was 9/1/98. A total of five research participants (since inception) enrolled and all into the ANGEL study. Of these four died of progressive disease. No major protocol revisions. 3. 1999 Annual Report: Report date was 10/14/99. Since IND initiation, six research participants enrolled, all into the ANGEL study. Of these five died of progressive disease. The PI transferred to Baylor. No major protocol revisions. 4. 2000 Annual Report: Report date 10/9/2000. To date, nine research participants enrolled into the ANGEL study and 2 into the ANGELA study. Two research participants (one from each study) developed cachexia and transient flu-like symptoms post-infusion. One research participant (in the ANGEL study) had erosion of their tumor through the left upper lobe bronchus leading to massive hemoptysis and death. This occurred 2 months post-infusion of the gene transfer product and transduced gene-marked CTLs were not found in that area (as per PCR testing). In a few research participants, persistence of the gene-marked CTLs could be detected up to 10 months post-infusion in specifically reactivated and expanded CTL lines. Replication competent retrovirus (study used a retroviral vector to transduce the CTLs) testing was done on two research participants and all results negative by PCR. Seven of the eleven research participants died due to progression of disease. Multiple AEs occurred but besides the cachexia and flu-like symptoms in two research participants, all others were deemed unrelated to study agent.

In regard to protocol changes, the study site was changed to Texas Children's Hospital and several co-investigators were added. T-cell infusion time restricted to 1-10 minutes and SOPs developed for monitoring post-infusion. In addition, multiple SOPs were developed for the Center for Cell and Gene Therapy GMP cell processing facility, validated, and submitted for FDA review.

5. 2001 Annual Report:
Report date 9/10/2001. One additional research participant added to ANGEL study (thus, bringing total for IND to 12 research participants). One additional research participant (for a total of eight) died during this reporting period due to progression of disease. No new related adverse events, and the only SAE was a central line infection in one of the ANGEL study participants. This infection was deemed unrelated to study agent.

In regard to protocol changes, research participants will now be followed until death. Eligibility criteria for ANGEL study broadened so as to improve enrollment rate. In regard to the IND, a new study was submitted on 7/27/01: “Administration of EBV-specific cytotoxic T-lymphocytes to patients with EBV-positive nasopharyngeal carcinoma.

ID #	Letter Date	Protocol #	Amendment
		9510-130	**Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes to Patients with Relapsed EBV-Positive Hodgkin Disease.**
504	05/21/2002		*Annual Update:* The PI submitted several annual reports on May 21, 2002 to the files of protocols 129 and 130. Both studies are being conducted under the same IND. The reports discuss both studies. 1. 1997 Annual Report: Report date was 6/10/97. Three research participants total enrolled (all into a long-term follow-up study--the ANGEL study). Two research participants died of progressive disease. No major protocol revisions for either protocol 129 or 130. 2. 1998 Annual Report: Report date was 9/1/98. A total of five research participants (since inception) enrolled and all into the ANGEL study. Of these four died of progressive disease. No major protocol revisions. 3. 1999 Annual Report: Report date was 10/14/99. Since IND initiation, six research participants enrolled, all into the ANGEL study. Of these five died of progressive disease. The PI transferred to Baylor. No major protocol revisions. 4. 2000 Annual Report: Report date 10/9/2000. To date, nine research participants enrolled into the ANGEL study and 2 into the ANGELA study. Two research participants (one from each study) developed cachexia and transient flu-like symptoms post-infusion. One research participant (in the ANGEL study) had erosion of their tumor through the left upper lobe bronchus leading to massive hemoptysis and death. This occurred 2 months post-infusion of the gene transfer product and transduced gene-marked CTLs were not found in that area (as per PCR testing). In a few research participants, persistence of the gene-marked CTLs could be detected up to 10 months post-infusion in specifically reactivated and expanded CTL lines. Replication competent retrovirus (study used a retroviral vector to transduce the CTLs) testing was done on two research participants and all results negative by PCR. Seven of the eleven research participants died due to progression of disease. Multiple AEs occurred but besides the cachexia and flu-like symptoms in two research participants, all others were deemed unrelated to study agent. In regard to protocol changes, the study site was changed to Texas Children's Hospital and several co-investigators were added. T-cell infusion time restricted to 1-10 minutes and SOPs developed for monitoring post-infusion. In addition, multiple SOPs were developed for the Center for Cell and Gene Therapy GMP cell processing facility, validated, and submitted for FDA review. 5. 2001 Annual Report: Report date 9/10/2001. One additional research participant added to ANGEL study (thus, bringing

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			total for IND to 12 research participants). One additional research participant (for a total of eight) died during this reporting period due to progression of disease. No new related adverse events, and the only SAE was a central line infection in one of the ANGEL study participants. This infection was deemed unrelated to study agent. In regard to protocol changes, research participants will now be followed until death. Eligibility criteria for ANGEL study broadened so as to improve enrollment rate. In regard to the IND, a new study was submitted on 7/27/01: "Administration of EBV-specific cytotoxic T-lymphocytes to patients with EBV-positive nasopharyngeal carcinoma.
		9512-138	**A Phase I Study of the Safety of Injecting Malignant Glioma Patients with Irradiated TGF-beta-2 Antisense Gene Modified Autologous Tumor Cells.**
526	05/10/2002		*Annual Update:* Received a copy of the May 1, 2000 to April 30, 2002 annual report. To date, six research participants have been enrolled, four of the six have completed the study. Expected enrollment is nine to 12 research participants. Two additional research participants have enrolled in this study under a compassionate exemption.
		9706-196	**Fibronectin-Assisted, Retroviral-Mediated Transduction of CD34+ Peripheral Blood Cells with gp91 phox in Patients with X-Linked Chronic Granulomatous Disease: A Phase I Study.**
477	05/13/2002		*Annual Update:* Received annual reports are for 1998 and 1999 that had been previously submitted to the FDA for this protocol. In the 1998 annual report, there are no major amendments to the protocol and no research participants had been enrolled. In the 1999 annual report, there is reference to the enrollment of the first research participant who tolerated well the apheresis and reinfusion of transduced $CD34^{+}$ cells. No adverse events were seen. Changes in the protocol during the 1999 reporting period included changes in the cytokine cocktail used and time of incubation during the transduction.
488	06/27/2002		*Annual Update:* Received the 2002 annual report for this study. To date, two research participants have been enrolled in this study (study has a target enrollment of five). No changes have been made to the investigational plan.

ID #	Letter Date	Protocol #	Amendment	
		9712-223	**Phase I Study of Chemokine and Cytokine Gene Modified Allogeneic Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using a Retroviral Vector.**	
470	05/24/2002		*PI or Site Change:*	Dr. Gregory Hale has replaced Dr. Laura Bowman as the PI at St. Jude Children's Research
491	07/29/2002		*Annual Update:*	Received an addendum to the December 2001 annual report. This addendum provided information regarding testing for replication competent retrovirus (RCR) in both prepared batches of vector and in samples from research participants who participated in this study. RCR was not found in any of the samples tested.
		9712-224	**Phase I Study of Chemokine and Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using an Adenoviral Vector.**	
471	05/24/2002		*PI or Site Change:*	Dr. Gregory Hale has replaced Dr. Laura Bowman as the PI at St. Jude Children's Research
		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.**	
482	07/08/2002		*PI or Site Change:*	Dr. Jeffrey Giguere, Hematology and Oncology Associates, Greenville, South Carolina has been added as an investigator.

ID #	Letter Date	Protocol #	Amendment
		9802-238	**Phase 1/2 Study of the Effects of Ascending Doses of Adenovirus Mediated Human FGF-4 Gene Transfer in Patients with Stable Exertional Angina. Sponsor: Berlex Laboratories, Inc.**
508	06/27/2002	*Annual Update:*	Specific Protocol Number under the IND: 97166

PI of this Multi-site Trial: Joon S. Lee, MD University of Pittsburgh

Dates of Study: Not provided in this annual report.

Status of Study: Completed. Study results reported in article, "Angiogenic Gene Therapy (AGENT) Trial in Patients with Stable Angina Pectoris" published in the March 19, 2002 edition of the journal Circulation.

Total Number of Research Participants planned for Enrollment: 120
Total Number of Research Participants Entered into the Study: 79
Total Number of Research Participants who have completed the Study (12 months): 74
Total Number of Research Participants who did not complete the 12 months follow-up: 5

Study Population: CCS class 2-4 and NYHA class 1-3 with LVEF > 30%

Study Results in Brief:
Seventy-nine research participants with stable angina were randomized to active treatment (n=60) or matching placebo (n=19) in a double-blind design. There were 5 dose groups each of single doses ranging from 3.2×10^8 vp to 3.2×10^{10} vp in half log increments. Each dose group had at least 12 research participants (at least 3 of whom received placebo).

This study has been completed and all but 5 research participants have completed 12 months of follow-up. The data has been analyzed and a report written, but this report was not included in this annual report. According to the sponsor, the additional follow-up data up to 12 months does not reveal additional findings that would change the overall interpretation of safety as reported in the earlier summary report submitted to the FDA April 19, 2001. The sponsor noted that there is no excess of worsening angina / unstable angina.

During this latest reporting period there were no deaths. During the study in the previous reporting period there were 3 deaths (all in the active group) reported to OBA: one research participant had unstable angina and experienced subsequent cardiac arrest; one research participant with a glioblastoma; and one research participant with metastatic colon cancer and renal cell carcinoma.

The sponsor reported that there is no evidence of undue bleeding, angiomas, or unwanted angiogenesis with any of the subjects enrolled in this study.

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		9805-251	**Phase I/II Trial of Antigen-Specific Immunotherapy in MUC-1 Positive Patients with Adenocarcinoma of the Prostate Using Vaccinia Virus-MUC1-IL2 (TG 1031). Sponsor: Transgene, S.A.**	
478	07/02/2002		*Annual Update:*	This study is complete and a final report is being prepared. A total of 16 research participants were enrolled in this protocol in the U.S.; a total of 56 research participants, worldwide, have received the vector used in protocol 251. Fifteen of the 16 research participants in the US study were withdrawn due to disease progression. The sponsor, does not plan to pursue trials with the vector employed in this study. A new generation vector is being used in NIH OBA protocols 9911-356 and 0109-497; both of these studies are for the same indication (MUC-1 expressing tumors) as protocol 251.
		9809-265	**Mutant MGMT Gene Transfer Into Human Hematopoietic Progenitors to Protect Hematopoiesis During O^6-Benzylguanine (BG, NSC 637037) and BCNU Therapy of Advanced Solid Tumors. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)**	
512	05/23/2002		*Other:*	Laboratory conditions for culturing $CD34^+$ cells after enrichment have been changed. Cells will now be cultured in Lifecell X-fold culture bags instead of 175 cm^2 flasks.
		9902-284	**Phase I Multi-Center, Single Treatment Dose Escalation Study of Factor VIII Vector [HFVIII(V)] for Treatment of Severe Hemophilia A. Sponsor: Chiron Corporation**	
497	07/22/2002		*Other:*	Received a copy of the long-term follow-up protocol (extended safety study) for research participants who participated in protocol 9902-284, which will not be assigned a new NIH OBA protocol number. Adverse events reported on this extended study will reference protocol 284.
		9902-291	**Retroviral-Mediated Gene Transfer of the Fanconi Anemia Group A Gene into Hematopoietic Progenitor Cells of Group A Patients.**	
529	06/26/2002		*Annual Update:*	Received the annual reports for 2001 and 2002. To date four research participants have been enrolled in this study, out of a proposed enrollment of ten. The four research participants have tolerated the G-CSF mobilization; however, the number of $CD34^+$ cells mobilized in all four research participants has been low.

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		9903-296	**Phase I Trial of Immunotherapy with Adenovirus-Interferon-Gamma (TG1041) in Patients with Malignant Melanoma. Sponsor: Transgene, Inc.**
485	07/11/2002		*Annual Update:* This study has been closed to further enrollment since June 2001. A new generation vector has been developed to replace the one employed in this study. Eleven out of a planned 12 research participants received the study agent in this dose escalation study. Enrollment at the highest dose cohort was not completed due to the development of the improved vector.

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		9904-304	**Pediatric Phase I Study of AdV/RSV-TK Followed by Ganciclovir for Retinoblastoma**
475	05/21/2002	*Annual Update:*	The following records were submitted to OBA: a. A copy of the notification of protocol violation sent to the FDA on July 20, 2000. b. IND annual report dated 5/23/2000 c. IND annual report dated 6/30/2001 d. IND annual report dated 2/15/2002. a. In regard to the protocol violation, a research participant who received study agent was accidentally dosed with 1/10th of the intended dose. This was due to a labeling error which was subsequently corrected. b. The annual report dated 5/23/2000 acknowledges that both the RAC and FDA were uncomfortable allowing the study agent to be used in research participants without bilateral disease. Stricter criteria were employed in which the first three research participants enrolled into the study had to have bilateral retinoblastoma who have already lost one eye and in whom the standard of care has failed in the second eye. c. The annual report dated 6/30/2001documents an amendment to open enrollment to unilateral retinoblastoma research participants after the second research participant was enrolled. This was done after the first two research participants (with progressive bilateral disease) were dosed and no dose-limiting toxicities were noted. At the time of this annual report, three research participants had been enrolled and dosed. In all three research participants clearance of some vitreal seeds (small foci of tumor in the vitreous humor) was noted though the first two research participants did ultimately require enucleation of the injected eye. In all three research participants, a grade 1/2 anterior uveitis and grade 1 conjunctival response were seen and deemed related to the gene transfer products. However, in all three research participants this was not considered to be a dose-limiting toxicity. d. The annual report dated 2/15/2002 documents the fact that the protocol had not been modified since the prior reporting period. A total of four research participants had been enrolled and dosed, with one of the research participants also experiencing anterior uveitis and conjunctival reaction (grade 2 for both). In addition, corneal edema was noted and steroid drops lead to the resolution of all three of these adverse events. The fourth research participant was specifically notable due to a history of a large vitreal and subretinal hemorrhage (as a complication of radiation therapy) and with prior immunity to adenovirus. The PI noted that despite this, the adverse events seen and their severity were very comparable to those of the first four research subjects.

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501	06/24/2002		*Other:*	As per the protocol, research participants can receive up to four injections. In a recent annual report, summary information about the first four research participants showed that three received more than one injection, with no increase in adverse reactions seen compared to the first dose. In all cases, a grade 1 / 2 anterior uveitis and conjunctival reaction occurred shortly after the injection with clearance after initiating steroid eye drops. A research participant has received all of the allowed injections "...without significant toxicity related to the viral vector itself" (as per the PI). Due to a new tumor focus with overlying vitreal seeds being found, the PI requested FDA permission to give an additional injection. The only other therapeutic option, as per the PI, is enucleation.
498	07/11/2002		*Other:*	Changes have been made to clarify the roles of several affiliated investigators. The protocol has been amended to indicate that research participants will be evaluated (via a clinic visit or contact from the research nurse) at least once a year for 15 years. Eligibility criteria have been amended to indicate that an unambiguous diagnosis of retinoblastoma will be substantiated by either ultrasound and/or enhanced MRI. A statement was added that would allow injections of study agent to be delayed for up to four weeks due to the onset and resolution of adverse events. The protocol was amended to clarify that 3D-Ultrasound of the eyes and/or MR imaging of the brain orbits will be done at four, eight, and twelve weeks, then every three months up to a year post study agent administration.

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		9905-319	**Treatment of High Risk Acute Leukemia with CD40 Ligand and IL-2 Gene Modified Autologous Bone Marrow Fibroblasts and Tumor Cells.**	
516	05/29/2002		*Annual Update:*	Received annual reports for 2000 (dated 5/26/00), 2001 (dated 8/31/01) and 2002 (dated 5/13/02). Of the proposed 12 research participants to be enrolled, eight have been entered. Two research participants have died of progressive disease and these deaths have been reported to the FDA and OBA in the past. One research participant did not receive the sixth vaccine due to a lack of transduced autologous tumor cells. Several research participants have exhibited immune responses to the vaccines based on various parameters. No mention of clinical markers of efficacy being met, however. Multiple changes have been made to the protocol over the three year period. Most of these were done to clarify either investigator roles or manufacturing issues. Several additional laboratory studies were added to allow for long-term follow-up of these research participants.
493	07/15/2002		*Other:*	Clinical protocol has been corrected to remove the requirement for a bone marrow aspirate six months post vector administration. This requirement was inadvertently retained in the final version of the clinical protocol.

ID #	Letter Date	Protocol #	Amendment
		9906-321	**A Phase I Study of E1B-Attenuated Replication Competent Adenovirus Vector-Mediated Intratumoral Administration of the E. coli Cytosine Deaminase/HSV-1 Thymidine Kinase Fusion Gene in Conjunction with Two Prodrugs, 5-Fluorocytosine and Ganciclovir for Patients with Local Recurrence of Prostate Cancer after**
531	07/03/2002		*Status Change:* Trial is completed.
			Annual Update: This is a single-site trial. PI is Dr. Jae Ho Kim at the Henry Ford Health System, Detroit, Michigan Dates of Study: January 2000 - December 2001 Status of Study: Completed. Total number of research participants planned for enrollment: 16 Total number of research participants entered into the study: 16 Total number of research participants who dropped out of the study: 0 Study results in brief: Sixteen research participants with local recurrence of prostate cancer after radiation therapy were divided into four cohorts. This was a dose escalation study (10^{10}, 10^{11}, and 10^{12} virus particles) followed by one (cohorts 1-3) or two (cohort 4) weeks of 5-flurocytosine and ganciclovir administration. The investigators report that seven of the 16 research participants exhibited a 25% or greater reduction in serum PSA levels; three of the 16 research participants exhibited a 50% or greater reduction in serum PSA levels. Vector DNA was detected in the blood up to Day 76 and infectious adenovirus was not detected at any time point in either blood or urine. One research participant died approximately four months post vector administration; as reported to OBA in this annual report the death was ascribed to the underlying COPD and not related to gene transfer study product.

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		9906-322	**A Phase I Study of NGF Ex Vivo Gene Therapy for Alzheimer's Disease**	
474	06/18/2002		*Status Change:*	Notification from the principal investigator that this trial is now closed to enrollment, due to a second research participant (out of six enrolled) in this trial experiencing an intracranial hemorrhage. The investigator plans to discuss this trial with the DSMB and IRB to determine if any unforeseen risk factors could explain these events. The trial will not be reopened to enrollment unless the continuation is approved by the FDA, IRB, and DSMB. The report of the first intracranial bleed and changes to the clinical protocol were discussed at the June 2002 RAC meeting.
		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)**	
507	04/22/2002		*Protocol Change:*	Trial has been amended to allow inclusion of delayed/late onset ADA-deficient research participants who are not being treated with PEG-ADA enzyme replacement therapy. The investigators would like to include research participants who have declined both bone marrow transplantation (BMT) and PEG-ADA. Initiation of PEG-ADA enzyme replacement therapy will not affect participation is this trial. In addition, trial has been amended to allow enrollment of research participants who are diagnosed as ADA-deficient based upon molecular diagnostic testing (sequence analysis) in conjunction with clinical evidence of combined immunodeficiency based upon lymphopenia and
469	05/31/2002		*PI or Site Change:*	Dr. Joel Brochstein, Hackensack University Medical Center, Hackensack, New Jersey has been added as an investigator.

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		9910-345	**A Phase I/II Dose Finding Trial of the Intravenous Injection of Calydon CV787, a Prostate-Specific Antigen Cytolytic Adenovirus, in Patients with Hormone Refractory Metastatic Prostate Cancer. Sponsor: Cell**	
517	05/24/2002		*Other:*	Cell Genesys is now the sponsor and Dr. Kirn (VP, Clinical Research at Cell Genesys) is the medical monitor for this study.
		9910-346	**A Phase II, Randomized, Multicenter, 26-Week Study to Assess the Efficacy and Safety of CI-1023 Delivered Through Minimally Invasive Surgery Versus Maximum Medical Treatment in Patients with Severe Angina, Advanced Coronary Artery Disease, and No Options for Revascularization. Sponsor: GenVec.**	
494	06/25/2002		*Other:*	Sponsorship of this study has been transferred to GenVec, Inc.
		9911-356	**Phase I Bridging Trial of TG4010 as Antigen-Specific Immunotherapy in Patients with MUC-1 Positive Advanced Cancer. Sponsor: Transgene, Inc.**	
525	06/13/2002		*Status Change:*	Trial was completed on September 11, 2000. Three research participants were enrolled in this study, a total of six to ten were proposed for enrollment. This study was terminated early due to the completion of a parallel trial in Europe and the finding that the product had genetic instability. Frameshift mutations in the MUC1 transgene were found and the sponsor is working on a more stable product at this time. The research participants enrolled in the US trial received between four and ten injections of the study agent at a dose of 5×10^6 pfu.

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		9911-358	**Phase I Trial of Adenoviral Vector Delivery of the Human Interleukin-12 cDNA by Intratumoral Injection in Patients with Metastatic Breast Cancer to the Liver.**
513	06/04/2002		*Protocol Change:* Elevated serum levels (determined from prior clinical trials) for four cytokines, above the following thresholds, will be considered to be dose-limiting toxicities. Serum levels greater than or equal to (in pg/ml) for IL-12 (11,000) or IFN-γ (6,000) or IL-6 (4,000) or TNF-α (12,000) will be considered as dose-limiting toxicities. Levels of these four cytokines will be measured on three separate occasions prior to administration of study agent and on days 2, 3, 4, 5, 6, 8, 11, and 15 post-administration. The mean of the three pre-administration determinations will be considered as the baseline. A Data and Safety Monitoring Board will be established for this study. This DSMB will be composed of at least three clinician-investigators from Mount Sinai, who are not associated with this trial, and a clinician-investigator not associated with either the trial or Mount Sinai. The DSMB will meet prior to activation of the study; at the completion of each cohort, prior to dose escalation to the next cohort; and at study termination. The DSMB will be approved by the IRB and DSMB meeting minutes will be provided to the IRB.
			Other: The adeno-IL-12 vector will now be supplied by the production facility at Mount Sinai; previously, the vector was supplied by the gene vector lab at the Univ. of Pennsylvania. A statement has been added to the "Research Participant Information Sheet" that indicates that two of the co-investigators are co-inventors of the gene transfer vector technology that is being employed in this study. A patent application has been filed by Mount Sinai. Both the Mount Sinai School of Medicine and the two co-investigators could gain financial and other benefits from the results of this trial.

ID #	Letter Date	Protocol #	Amendment
		9911-359	**Phase I Trial of Adenoviral Vector Delivery of the Human Interleukin-12 cDNA by Intratumoral Injection in Patients with Primary or Metastatic Colorectal Cancer to the Liver.**
514	06/04/2002		*Protocol Change:* This trial will now be performed on research participants with metastatic colorectal cancer rather than metastatic cancer from any nonhematologic origin. The title of the trial has been changed to reflect this. Elevated serum levels (determined from prior clinical trials) for four cytokines, above the following thresholds, will be considered to be dose-limiting toxicities. Serum levels greater than or equal to (in pg/ml) for IL-12 (11,000) or IFN-γ (6,000) or IL-6 (4,000) or TNF-α (12,000) will be considered as dose-limiting toxicities. Levels of these four cytokines will be measured on three separate occasions prior to administration of study agent and on days 2, 3, 4, 5, 6, 8, 11, and 15 post-administration. The mean of the three pre-administration determinations will be considered as the baseline. A Data and Safety Monitoring Board will be established for this study. This DSMB will be composed of at least three clinician-investigators from Mount Sinai, who are not associated with this trial. In addition a clinician-investigator not associated with either the trial or Mount Sinai, will be a member of the DSMB. The DSMB will meet prior to activation of the study; at the completion of each cohort, prior to dose escalation to the next cohort; and at study termination. The DSMB will be approved by the IRB and DSMB meeting minutes will be provided to the IRB. *Other:* The adeno-IL-12 vector will now be supplied by the production facility at Mount Sinai; previously, the vector was supplied by the gene vector lab at the Univ. of Pennsylvania. A statement has been added to the "Research Participant Information Sheet" that indicates that two of the co-investigators are co-inventors of the gene transfer vector technology that is being employed in this study. A patent application has been filed by Mount Sinai. Both the Mount Sinai School of Medicine and the two co-investigators could gain financial and other benefits from the results of this trial.

ID #	Letter Date	Protocol #	Amendment	
		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)**	
521	04/09/2002		*PI or Site Change:*	Dr. Thomas McCaffrey, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida has been added as an investigator.
520	06/10/2002		*PI or Site Change:*	Dr. Richard Wheeler, Huntsman Cancer Institute, Salt Lake City, Utah has been added as an investigator.
522	06/10/2002		*PI or Site Change:*	Dr. Missak Haigentz has replaced Dr. Scott Wadler as the PI at Montefiore Medical Center.
490	07/22/2002		*PI or Site Change:*	Dr. David Van Echo, University of Maryland School of Medicine, Baltimore, Maryland has been added as an investigator.
		0001-381	**Gene Therapy of Canavan Disease using AAV for Brain Gene Transfer.**	
502	06/11/2002		*PI or Site Change:*	Dr. Leone has transferred from Thomas Jefferson Medical Center to the Cooper Health System, the core teaching facility for the University of Medicine and Dentistry of New Jersey (UMDNJ). A list of new co-investigators from both Cooper and the Children's Hospital of Philadelphia (CHOP) was also submitted.
			Annual Update:	Annual summary of the first cohort of research participants. Three research participants have been enrolled and treated to date. All were treated in either June or July of 2001. The first research participant experienced post-operative fever and emesis that resolved quickly. This SAE was submitted to OBA previously. No other serious adverse events were seen. All three research participants have been seen at seven to nine month post-op visits and appear to have tolerated the gene transfer procedure well. As per the PI, there have been some minor improvements clinically.
			Other:	A list of independent data monitoring committee members for this study was provided.

ID #	Letter Date	Protocol #	Amendment	
		0001-387	**A Randomized, Double-Blind, Placebo-Controlled, Multicenter, 12-Week Follow-up, Pilot Study of the Tolerability and Feasibility of Administering AD_{GV}VEGF121.10 (CI-1023) Via the Biosense Intramyocardial Injection Device to Patients with Advanced Coronary Artery Disease. Sponsor: Parke-Davis Pharmaceutical**	
495	06/25/2002		*Other:*	Sponsorship of this study has been transferred to GenVec, Inc.
		0002-388	**A Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, 26-Week Study to Assess the Safety and Efficacy of CI-1023 (AD_{GV}VEGF121.10) in Peripheral Arterial Disease Patients with Severe, Disabling Intermittent Claudication. Sponsor: Parke-Davis Pharmaceutical Research**	
496	06/25/2002		*Other:*	Sponsorship of this study has been transferred to GenVec, Inc.
		0004-393	**Phase II Study of a TGF-ß2 Antisense Gene Modified Allogeneic Tumor Cell Vaccine in Patients with Stages II-IV Non-Small Cell Lung Cancer.**	
527	07/02/2002		*Other:*	A number of modifications have been made. 1) Injection sites for the vaccine will be rotated between the right and left upper arms; injections will no longer be made to the lower extremities. Injections in the upper arms are less painful. 2) Inclusion criteria have been amended to indicate that eligible research participants must have completed or refused conventional therapy. And the estimated tumor burden may be 125 cc or less; previously, the criterion was less than 125 cc. 3) Exclusion criteria have been amended to indicate that research participants who have undergone surgery that involved general anesthesia within four weeks of study entry are not eligible. The previous criterion did not specify surgery with general anesthesia. This change was made to clarify that the risk involved is general anesthesia, which may be immunosuppressive, not the surgery itself. 4) Changes have been made to ensure that adverse event reporting is consistent with
528	07/03/2002		*Annual Update:*	Received a copy of the April 24, 2001 to April 23, 2002 annual report. One research participant, out of 27-75 planned, has been enrolled.
			Other:	Received copies of previous versions of the clinical protocol that were not submitted to OBA due to an administrative oversight. Changes documented in these versions include: 1) presence of non-small cell lung cancer may be determined by histology; 2) modification to title to indicate that trial involves stage II-IV non-small cell lung cancer; 3) microarray technology may be employed in an attempt to evaluate genetic differences between tumors that responded to the study agent and those that did not; and 4) other administrative changes, including incorporation of the names of additional investigators/trial sites.

ID #	Letter Date	Protocol #	Amendment
		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**
484	06/26/2002		*Protocol Change:* A previous melanoma study sponsored by Genzyme was not able to enroll all research participants. Therefore, enrollment has been increased (following FDA approval) to 44 for this study. Extended ophthalmologic follow-up will be conducted on any research participant who experiences retinal changes. Research participants who are identified as having retinal changes on routine ophthalmologic exams during the course of this study will under a follow-up ophthalmologic exams every four months for the first year after completion of the study, every six months in the second year, and once a year for years three through five. After the first year of follow-up, if the retinal changes have not progressed or have resolved, then further follow-up, contingent upon agreement by Genzyme, the study PI, and the FDA, may be discontinued.

ID #	Letter Date	Protocol #	Amendment
		0006-403	**A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Effect of Ad5FGF-4 on Myocardial Perfusion Defect Size and Safety in Patients with Stable Angina. Sponsor: Berlex Laboratories**
509	06/27/2002	*Annual Update:*	Specific Protocol Number under the IND: 303800A PI: Multi-site Trial Dates of Study: Status of Study: Ongoing Design/Dosage: Randomized 2:1 ratio (active:placebo), parallel group, placebo control, double-blind Objectives of the Study: To determine whether the 1.0 x 10^10 dose of [Ad5FGF-4] will significantly decrease the area of an adenosine 99mTc-sestamibi perfusion defect, when the myocardial underperfusion represented by the defect has been previously shown to be reversible in whole or in part. Study Population: Research participants with stable angina, Canadian Cardiovascular Society (CCS) Classes 2 to 4. Total Number of Research Participants planned for Enrollment: up to 50 Total Number of Research Participants Entered into the Study: 52 Total Number of Research Participants who have completed the Study (12 months): 40 Total Number of Research Participants who Dropped out of the Study to Date: 1 Study Results: The twelve-month follow up is ongoing and as such is still blinded. Adverse Events: In this report the sponsor submitted 13 reports of adverse events. OBA had previously received and reviewed twelve of these thirteen reports. The new report is of a research participant who required coronary artery bypass surgery 128 days post-injection of the study agent. The research participant also experienced atrial fibrillation, wide complex tachycardia, and had a defibrillator implanted. The research participant recovered after a 10-day hospitalization and the events were were considered unrelated to the study agent.

ID #	Letter Date	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**	
467	06/03/2002		*PI or Site Change:*	Dr. John Clancy, University of Alabama at Birmingham has been added as an investigator.
		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**	
523	06/10/2002		*PI or Site Change:*	Dr. Missak Haigentz has replaced Dr. Scott Wadler as the PI at Montefiore Medical Center.
492	07/10/2002		*PI or Site Change:*	Dr. Douglas Villaret, University of Florida, Gainesville, Florida has been added as an investigator.
		0010-421	**A Dose Escalating Phase I Study of AdPDGF-B/GAM in the Treatment of Diabetic Ulcers of the Lower Extremity. Sponsor: Selective Genetics, Inc.**	
500	05/31/2002		*PI or Site Change:*	Dr. David Mozingo, University of Florida College of Medicine, Gainesville, Florida has replaced Dr. Steed at the University of Pittsburgh as the PI. No research participants were enrolled in this study at the Univ. of Pittsburgh.
			Protocol Change:	The dose escalation scheme has been amended. Single doses will be administered at 1 x 10^{10}, 3 x 10^{10}, and 1 x 10^{11} viral particles/cm^2 of wound bed. Another cohort will receive multiple doses at 3 x 10^{10}. The cell line employed for vector production has been changed from 293 to PerC6 and modifications have been made to the vector to reduce the potential for the generation of replication competent adenovirus.
			Other:	A long-term follow-up protocol has been submitted which will follow research participants who received the adenoviral construct employed in this and other studies.

ID #	Letter Date	Protocol #	Amendment
		0101-446	**Transplantation of Gene-Corrected Autologous CD34+ Hematopoietic Stem Cells in Previously Transplanted Patients with JAK3 Deficiency and Persistent Humoral Immune Defects.**
476	05/16/2002		*Other:* Submission of a single research participant protocol exemption for a participant who was also a participant in a prior study exemption in March 2002. The research participant is a JAK3 deficient patient who had failed two prior allogeneic bone-marrow transplantations, with little to no T-cell activity noted after each attempt. A study exemption was granted which allowed this participant to receive the transduced $CD34^+$ hematopoietic stem cells (HSC) despite the lack of a successful BMT. At 90 days post-gene transfer product infusion, there have been no adverse events deemed as related to this product. There is also no evidence of gene correction. The investigators believe that one probable cause for the poor response was the low number of $CD34^+$ HSCs obtained from the research participant prior to transduction. The PIs have identified a more effective $CD34^+$ selection technique, utilizing the AmCell CliniMACS device, and have referenced an article in which this device was used clinically. The PIs are proposing to re-treat the research participant with transduced $CD34^+$ HSCs isolated by using the new device. The FDA has already approved this study exemption. An OBA medical officer contacted the PI to ask about any potential immune response to the second infusion. The PI responded that such a response would be very difficult to mount due to this research participant's immune deficiency.

ID #	Letter Date	Protocol #	Amendment
		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.**
510	06/27/2002	*Annual Update:*	Specific Protocol Number under the IND: 304386

PI: Multi-site Trial

Dates of Study:

Status of Study: Ongoing

Design/Dosage: Randomized 2:1 ratio (active:placebo), parallel group, placebo control, double-blind. The two doses studied will be 1.0×10^9 viral particles (2.87×10^8 total particles) and 1.0×10^{10} viral particles (2.87×10^9 total particles).

Objectives of the Study: To evaluate the effect of Ad5FGF-4 on exercise tolerance and other angina parameters quality of life, and to evaluate the short-term, medium-term and long-term safety of Ad5FGF-4. In addition, dose response relationship will be evaluated as well as the effects of Ad5FGF-4 on all-cause mortality and coronary events up to 1 year.

Study Population: Research participants with stable angina, Canadian Cardiovascular Society (CCS) Classes 2 to 4.

Total Number of Research Participants planned for Enrollment: 450
Total Number of Research Participants Entered into the Study to Date: 46
Total Number of Research Participants who have completed the Study (12 months): 0
Total Number of Research Participants who Dropped out of the Study to Date: 0

Study Results:
This study is ongoing so there are no results to report.

Adverse Events:
In this report the sponsor submitted 14 reports of adverse events that occurred during this reporting period, 13 of which had been reported previously. The new event being reported is of a research participant who experienced a lower gastrointestinal bleed in the pretreatment phase of the study and recovered from this event. Another event for the same research participant that occurred 18 days post injection of the study agent had been previously reported to OBA.

ID #	Letter Date	Protocol #		Amendment
486	07/12/2002		*PI or Site Change:*	The following individuals have been added as investigators: Dr. Eric Cohen, Cardiovascular Associates, P.C., Birmingham, Alabama; Dr. Joon Lee, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Dr. Glenn Levine, Houston VA Medical Center, Houston, Texas; Dr. John Lopez, University of Chicago Medical Center, Chicago, Illinois; Dr. Frank McGrew III, The Stern Cardiovascular Center, Memphis, Tennessee; Dr. Hoang Thai, Southern Arizona Veterans Affairs Health Care System, Tucson, Arizona; and Dr. Miguel Zabalgotia, The University of Texas Health Science Center at San Antonio; San Antonio, Texas.
		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.**
487	06/19/2002		*PI or Site Change:*	Dr. E. Antonio Chiocca, Massachusetts General Hospital, Boston, Massachusetts; Dr. Allan Hamilton, University of Arizona, Tucson, Arizona; and Dr. Kevin Lillehei, University of Colorado Health Sciences Center, Denver, Colorado have been added as investigators. Submission of the IRB-approved informed consent and IBC and IRB approvals for the first investigator (Dr. Eck) on this trial.
		0101-454		**Phase II Trial of Surgery with Perioperative RPR/INGN 201 (Ad5CMV-p53) Gene Therapy Followed by Chemoradiotherapy for Advanced Resectable Squamous Cell Carcinoma of the Oral Cavity and Oropharynx. Sponsor: Southwest Oncology Group.**
489	06/25/2002		*Annual Update:*	Notification that this study has not been opened.
		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.**
519	06/18/2002		*PI or Site Change:*	Received a copy of the IRB approval and IRB-approved informed consent for the Columbia Univ. site (PI, Dr. Kaufman, moved from Albert Einsten to Columbia).

ID #	Letter Date	Protocol #	Amendment	
		0103-460	**Treatment of High Risk Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin's Lymphoma (NHL) with IL-2 Gene Modified and CD40 Stimulated Autologous Tumor Cells.**	
480	07/29/2002		*Protocol Change:*	Number of years that individuals will be followed has been increased from 10 to 15. Modifications have been made to the vector lot release criteria, vector potency testing, and to standard operating procedures.
		0104-464	**Phase I Study of Combined Suicide Gene Therapy and Radiation Therapy for Locally Advanced Carcinoma of the Prostate.**	
532	07/03/2002		*Annual Update:*	In a submission dated July 3, 2002 (received in OBA on July 9, 2002), the Co-PI Svend O. Freytag, Ph.D. submitted updated information for the Henry Ford Health System Site and the PI, Jae Ho Kim. The new IRB approval period for the updated protocol is 6/26/02-6/25/03. Updated information includes: 1.) A copy of the revised informed consent document. The informed consent now contains a paragraph describing the death of a research participant at another site in this trial and the word "therapy" has been changed to "investigational treatment." The original IRB-approved IC document was submitted to OBA with the original protocol on 4/16/01. 2.) The IRB-approved updated version of the protocol is dated 6/19/02 3.) The final IBC approval letter from the site is dated 5/22/2001 4.) A copy of the IRB approval letter for continuation of the study is dated June 25, 2002. 5.) Delineation of modifications: a.) Individual RAC members had no recommendations for protocol modification. b.) The protocol had been placed on clinical hold by the FDA from 6/27/01-10/17/01 until three issues were addressed: 1) the need to include greater than or equal to grade 2 (NCI CTC) allergic toxicity to the dose-limiting toxicity definition; 2) the IC document revisions as above; and 3) the submission of a data and safety monitoring plan. This report said that a copy of the letter from the FDA lifting the clinical old was included, but OBA staff did not find such an attachment. The data and safety monitoring plan was not included in this submission.

ID #	Letter Date	Protocol #		Amendment
		0104-467	**VEGF Gene Transfer for Diabetic Neuropathy.**	
534			*Other:*	Amendment 1 (Sponsor/FDA sequence number): Letter dated April 9, 2002, addressed to the FDA. This letter is a copy of the response to questions posed to the sponsor by the FDA in a teleconference on April 5, 2002. The following are the issues / actions as clarified: 1.) The Sponsor Investigator clarified when the lot testing will be done with respect to the pooling of plasmid batches. 2.) The upper limit of endotoxin units/mg DNA for lot release will be reduced from 300 Eu/mg DNA to 80 Eu/mg DNA. 3.) The Sponsor Investigator clarified who will be responsible for reviewing and approving the test results and releasing the lot for use in subjects. The individual designated is not involved in the manufacturing or testing of the plasmid DNA, nor is this person a supervisor for any of the manufacturing personnel. Amendment 2 (Sponsor/FDA sequence number): Letter dated April 22, 2002, addressed to the FDA. This letter is a copy of the response to questions posed to the sponsor by the FDA in a teleconference on April 11, 2002. The following are the issues/actions as clarified: 1.) The Sponsor Investigator clarified that after all testing is complete, the DNA is aliquoted into separate tubes for dosing. 2.) The FDA noted that aliquoting the DNA into tubes AFTER testing introduces a handling step after testing which could possibly result in contamination and suggested aliquoting the DNA into tubes for dosing immediately after reconstituting, and using one of the tubes for lot testing aliquots. This is in accordance with the law. The Sponsor Investigator submitted a reworked paragraph of the section "Plasmid preparation protocol" which incorporated this suggestion.
		0106-475	**A Safety and Efficacy Trial of Lethally Irradiated Allogeneic Pancreatic Tumor Cells Transfected with the GM-CSF Gene in Combination with Adjuvant Chemotherapy for the Treatment of Adenocarcinoma of the**	
506	05/29/2002		*Annual Update:*	Received a copy of the annual report for this study. To date, five research participants have received the study agent and 10 research participants have been enrolled (out of 60 planned). None of the five research participants who have received the study agent have experienced a serious adverse event.

ID #	Letter Date	Protocol #	Amendment	
		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,**	
483	06/24/2002		*PI or Site Change:*	Dr. Lloyd Damon, University of California, San Francisco has been added as an investigator.
		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.**	
505	06/20/2002		*PI or Site Change:*	Dr. Adam Lerner, Boston University School of Medicine, Boston, Massachusetts has been added as an investigator.
		0108-496	**Pilot Feasibility and Safety Study of Cellular Immunotherapy for Recurrent/Refractory Malignant Glioma using Genetically Modified Autologous CD8+ T Cell Clones.**	
515	06/25/2002		*Protocol Change:*	An amended protocol was submitted to OBA prior to enrollment in this study. (Required material within 20 days of enrollment was submitted previously--see UAI 426.) A brain FDG-PET scan will now be performed within seven days of the first T cell infusion. Several other changes were made based upon requests from the FDA. These changes include: a) modifications to the inclusion criteria to indicate that females of child-bearing age must not be pregnant; b) exclusion criteria have been modified to state that individuals who have undergone a prior re-resection for recurrent / progressive disease are not eligible; c) a maximum of six cell infusion cycles are permitted if tumor regression is observed in conjunction with residual disease observed by MRI; and d) changes have been made to the escalation / de-escalation scheme to include, in some instances, the attribution of relatedness of the event.
		0109-497	**Randomized Multicenter Phase II Study Evaluating Two Dosing Schedules ofTG4010 (MVA-MUC1-IL2) in Patients with Adenocarcinoma of the Prostate. Sponsor: Transgene, Inc.**	
468	05/30/2002		*PI or Site Change:*	Dr. Robert Dreicer, Cleveland Clinic Foundation, Cleveland, Ohio has been added as an
481	07/30/2002		*PI or Site Change:*	Dr. Kevin Conlon, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois; and Dr. Deepak Sahasrabudhe, University of Rochester Medical Center, Rochester, New York have been added as investigators.

ID #	Letter Date	Protocol #	Amendment	
		0110-502	**A Phase II, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Efficacy and Safety Study of Different Doses and Schedules of Administration of NV1FGF in Patients with Severe Peripheral Artery Occlusive Disease. Sponsor: Aventis Pharma.**	
472	05/29/2002		*PI or Site Change:*	Dr. Farrell O. Mendelsohn, Cardiology, P.C., Birmingham, Alabama has been added as an
473	06/04/2002		*PI or Site Change:*	Dr. Jorge F. Saucedo, University of Arkansas for Medical Sciences, Little Rock, Arkansas has been added as an investigator.
518	06/11/2002		*PI or Site Change:*	Dr. Corey Goldman, Watson Clinic LLP, Lakeland, Florida; Dr. Adam Greenbaum, Henry Ford Hospital, Detroit, Michigan; Dr. Rafael Sequeira, Jackson Memorial Hospital, Miami, Florida; and Dr. Timothy Henry, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota have been added as investigators.
479	07/02/2002		*PI or Site Change:*	Dr. Julie Miller at The Johns Hopkins University has been added as an investigator.
511	07/17/2002		*PI or Site Change:*	Dr. James Hermiller and Dr. Randy Irwin, St. Vincent Hospital and Health Care Center, Indianapolis, Indiana have been added as investigators.
499	07/24/2002		*PI or Site Change:*	Dr. John Gray, Durham VA Medical Center, Durham, North Carolina has been added as an investigator.
		0110-503	**Single Dose Escalation Study to Evaluate Safety of Nasal Administration of CFTR001 Gene Transfer Vector to Subjects with Cystic Fibrosis.**	
524	06/11/2002		*PI or Site Change:*	Dr. Jeffrey Wagener, University of Colorado School of Medicine, Denver, Colorado has been added as an investigator.

ID #	Letter Date	Protocol #	Amendment
		0205-538	**A phase I-II trial using dendritic cells transduced with an adenoviral vector containing the p53 gene to immunize patients with extensive stage small cell lung cancer after standard chemotherapy.**
533	07/15/2002		*Other:* The following changes to the protocol and informed consent have been made: 1) The inclusion requirement that a tumor biopsy sample be positive for over expression of p53 as measured by immunohistochemistry has been removed. The rationale for removing this requirement is that it is unusual to have a sufficient quantity of biopsy material available for staining and 90% of individuals with small cell lung cancer over express p53. 2) A positive immune response to a panel of recall antigens has been removed as an inclusion criterion. False negatives are frequently obtained; therefore retention of this test would unnecessarily exclude research participants. 3) In response to individual RAC member's comments, a request for an autopsy has been added to the informed consent in the event of a research participant's death. 4) Also in response to individual RAC member's comments, two separate informed consent documents (copies were provided), one for the phase I portion of the study and the other for the phase II portion of the study, will be employed.