AMENDMENTS AND UPDATES TO HUMAN GENE TRANSFER PROTOCOLS

RECOMBINANT DNA ADVISORY COMMITTEE MEETING
June 2002

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.**	
399			*Annual Update:*	Study has been closed to enrollment since February 1997. There is no new information to report on this study since the last update in 2001.
		9601-143	**Antimetabolite Induction, High-Dose Alkylating Agent Consolidation, and Retroviral Transduction of the MDR1 Gene Into Peripheral Blood Progenitor Cells Followed by Intensification Therapy with Sequential Paclitaxel and Doxorubicin for Stage 4 Breast Cancer.**	
420			*Status Change:*	Notification that trial was closed June 2000.
			Other:	Notification that 27 individuals were accrued, 18 received gene transduced cells. 19 of the 27 individuals are still alive and being followed for disease progression and/or disease-free survival. Of the nine individuals who did not receive transduced cells, two were removed due to secondary comorbid conditions, two were taken off study due to progressive disease prior to mobilization, and five did not mobilize a sufficient number of cells for transduction.
		9701-172	**High Dose Carboplatin and Etoposide Followed by Transplantation with Peripheral Blood Stem Cells Transduced with the Multiple Drug Resistance Gene in the Treatment of Germ Cell Tumors - A Pilot Study.**	
459	02/13/2002		*Annual Update:*	Received a copy of the annual report submitted to the FDA. This study is no longer accruing, follow-up continues. Eight participants are alive and are free of disease. Replication competent virus was not detected in the yearly samples. Viral envelope (by PCR assay) was also not detected in the yearly samples.

ID #	Letter	Protocol #	Amendment	
		9701-173	**A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine(PCV) for Poor Prognosis Pediatric and Adult Brain Tumors Utilizing Fibronectin-Assisted, Retroviral-Mediated Modification of CD34+ Peripheral Blood Cells with O6-Methylguanine DNA Methyltransferase.**	
437	02/20/2002		*Annual Update:*	Trial has enrolled ten individuals, out of a planned 20 (intent was to enroll 10 individuals/year; trial started accrual in June 1998) and is now closed to accrual; investigators stated that they feel their scientific objectives have been met. Participation of seven of the ten individuals enrolled was terminated prior to completion of the study course due to progressive disease. Nine of the ten individuals have died; one individual is in long-term follow-up. Investigators state that there were no toxicities associated with infusion of the transduced autologous CD34+ stem cells.

ID #	Letter	Protocol #	Amendment
		9709-214	**A Phase II Multi-Center, Open Label, Randomized Study to Evaluate Effectiveness and Safety of Two Treatment Regimens of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 78 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN). Sponsor: Aventis (formerly Gencell)**
428	02/14/2002	*Other:*	Received a treatment extension request for protocol 214 submitted by the corporate sponsor (Introgen Therapeutics) on January 18, 2002 on behalf of the Principal Investigator. This submission consists of a modified version of protocol 214 (allowing for the treatment extension for one individual subject) and all of the necessary documentation needed for a new protocol. The sponsor requests that this be treated as a new protocol. Subsequently, the sponsor concurred that this request could be treated as an amendment to protocol 214 and not as a new submission. Background: Protocol 214 enrolled subjects with recurrent SCCHN and subjects were randomized to two different treatment regimens (note, subjects were to receive radiotherapy and/or surgery, as needed): a. Treatment on days 1, 2 and 3, every 28 days b. Treatment on days 1, 3, 5, 8, 10, and 12, every 28 days. This study is presently closed to enrollment with all subjects having completed their courses of injections. However, due to the lack of response to all other treatment modalities (including chemotherapy, radiotherapy, and aggressive surgical resections) the PI would like to continue injections in one of his subjects. The gene transfer product, Ad5CMV-p53, has been administered to over 500 subjects with a total of 2500 doses given, and has been used in the following NIH OBA protocols: 96, 214, 226, 366, 412 (for SCCHN); 79, 217, 250, 278, and 418 (various indications). The subject in question was randomized to treatment arm A and received the first dose on June 8, 1998 and has received $6X10^{10}$ pfu (or $1X10^{12}$ viral particles) per injection on days 1, 2, and 3 of each 28 day cycle since then (total of 40 administration cycles completed). The subject has tolerated the multiple injections well and has met the definition of partial clinical response. The planned duration for extension is estimated to be an additional 25 months including a one-month follow-up period at the end of each cycle. An individualized informed consent form has been developed for this subject and approved by the IRB on November 9, 2001. OBA reviewer's Comments: As written, the modified protocol and individualized informed consent document are adequate. In addition, there is a detailed section with responses to Appendix M, and the CV of the principal investigator. All in all, the package is adequate and the proposal to move forward with extension of therapy appears to be well-founded and reasonable.

ID #	Letter	Protocol #	Amendment	
		9801-227	**IL-12 Gene Therapy Using Direct Injection of Tumors with Genetically Engineered Autologous Fibroblasts (A Phase II Study).**	
439	02/28/2002		*Other:*	Received a copy of the response to the internal audit by the Univ. of Pittsburgh's Research Conduct and Compliance Office (RCCO). As previously reported, this trial is closed to accrual and since a number of the issues raised by the RCCO were only relevant to a study enrolling new individuals, these issues were not addressed. Five of the 11 individuals who were enrolled in this study are alive. The investigators have indicated that they will continue long-term follow-up per the recommendations of the FDA, which will include testing for retroviral replication.
		9802-237	**Molecular Synovectomy by In Vivo Gene Transfer: A Phase I Trial.**	
429	05/15/2002		*Status Change:*	Since the study has been initiated there has been the enrollment of but one subject, with no new enrollees since 4/1/00. The subject tolerated the gene transfer agent well and continues to be followed by the PI. The Data and Safety Monitoring Committee of the University of Michigan Center for Gene Therapy has decided that due to the extremely slow enrollment and very strong possibility that the target of 8 subjects will not be reached, the study should be formally closed to further enrollment. The one study subject will be followed to 2005 and since this study utilized a plasmid vector, lifelong or long-term follow-up issues are not an issue (as would be, for a retroviral vector study, for example)
		9804-249	**Phase I Study of T Cells Modified with Chimeric AntiCEA Immunoglobulin-T Cell Receptors (IgTCR) in Adenocarcinoma.**	
409	03/05/2002		*Status Change:*	Notification that due to an ongoing review of the site's procedures and facilities, this study has remained on hold for all of 2001.

ID #	Letter	Protocol #	Amendment	
		9809-265	**Mutant MGMT Gene Transfer Into Human Hematopoietic Progenitors to Protect Hematopoiesis During O6-Benzylguanine (BG, NSC 637037) and BCNU Therapy of Advanced Solid Tumors. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)**	
411	03/04/2002		*Protocol Change:*	Due to a difficulty in obtaining cytokines approved by the FDA for *ex vivo* expansion of CD34 cells, the trial has not been opened to accrual.
427	03/19/2002		*Protocol Change:*	Changes in culture conditions for transduction to incorporate fibronectin instead of protamine sulfate and human MSCs. Dosage of G-CSF given for mobilization has been increased to 10μg/kg/day. A resting CD34+ count will be assessed at enrollment and antibody testing against to the fibronectin fragment being used for transduction will be performed at 35, 84, 168 days and at 12 and 24 months
		9810-268	**Treatment of Patients with Stage IV Renal Cell Carcinoma with B7-1 Gene-Modified Autologous Tumor Cells and Systemic IL-2.**	
402	03/25/2002		*Annual Update:*	Received a copy of the annual update for this trial. Regression of metastases have been observed in four of nine individuals with measurable disease.
		9811-269	**A Phase I Trial Testing MART-1 Genetic Immunization in Malignant Melanoma.**	
395	05/08/2002		*Other:*	Received a copy of the response from the PI to the FDA's hold. Many of the changes involved lot release testing of the vector. One of the changes involved the informed consent: the consent has been modified to state that an adenoviral vector is being used; previously, the consent only mentioned that "gene therapy techniques" were being employed. The first research participant was enrolled on March 15, 2002.

ID #	Letter	Protocol #	Amendment	
		9812-274	**A Phase I, Multi-Center, Open Label, Safety and Tolerability Study of Increasing Single Dose of NV1FGF Administered by Intra-Muscular Injection in Patients with Severe Peripheral Artery Occlusive Disease. Sponsor: Aventis (formerly Gencell).**	
407	02/28/2002		*Status Change:*	Study is now closed.
			Annual Update:	A total of 51 individuals were enrolled in this study.
		9902-285	**A Phase I Trial of Intratumoral Antisense EGFR DNA and DC-Chol Liposomes in Advanced Oral Squamous Cell Carcinoma.**	
455	01/16/2002		*Other:*	Received a copy of OHRP's letter to the University of Pittsburgh acknowledging that the institutes response to issues raised under 45 CFR 46.103(b)(5).
406	03/19/2002		*Status Change:*	Notification that this study is closed. Changes to this trial were recommended by the University of Pittsburgh IRB Executive Committee. The trial was suspended while the investigator addressed the issues raised by the IRB. However, a new production site for the liposomes which are part of the study agent complex has not been found at the time of the annual renewal for this study. The IRB informed the PI that the study could not remiain on indefinite suspension, therefore the study was officially terminated. The PI wishes to continue with this study and will apply for permission to do so when the concerns of the Executive Committee are adressed
		9903-297	**Intensive Immunosuppression Followed by Rescue with CD34 Selected, T Cell Depleted, Leukopheresis Products in Patients with Multiple Sclerosis.**	
450	04/09/2002		*Other:*	Clinical protocol has been amended to indicate that 30 cc of blood will be collected for immune reconstitution studies.

ID #	Letter	Protocol #	Amendment
		9904-310	**Stromal Therapy of Osteodysplasia After Allogeneic Bone Marrow Transplantation: A Phase I Study.**
432	05/03/2002		

Annual Update:

Received an annual report for protocol 310 ("Stromal Therapy of Osteodysplasia after Allogeneic Bone Marrow Transplantation") submitted on May 3, 2002.

Study dates: Not provided in the annual report. The time period covered by the annual report is not specified either, though the last annual report was submitted on 4/26/01.

Number of subjects enrolled: Six subjects and the study is now closed to accrual but remains open for follow-up.

Number of subjects completed: All six and one of these reported to have died since last annual report.

Efficacy Results: All six subjects received bone marrow stromal cell infusions. In 5 subjects engraftment of transduced cells was noted in bone, skin, and/or marrow strata, but only the G1PLII (nonexpressing vector) transduced cells were identified. The LNc8 transduced cells (expressing neomycin phosphotransferase gene) were not found in any of the subjects. One subject demonstrated a cytotoxic T-cell response against the LNc8 transduced marrow stromal cells. One subject showed an increase in total body bone mineral content (the ultimate efficacy parameter in this protocol) at 3 months after the infusions.

Safety Results: Since the last annual report, one subject died following head trauma suffered after falling out of bed at home. The subject was rushed to the local hospital and found to have a significant subdural hematoma that was drained. He required blood transfusions, but ultimately suffered a DIC-like picture, arrested and died due to the complications from the large bleed. The event was deemed as not related to the gene transfer agent. Another subject was hospitalized for 30 hours for constipation, dehydration, and hyperglycemia, was treated with IV fluids and discharged home completely recovered. The etiology of this incident is not clear but the PI believes that it was not related to the gene transfer product.

Conclusions: The study is closed to accrual but the remaining subjects continue to be followed. The plan is to follow them annually for life, with RCR testing being done as per FDA guidances.

OBA has 4 adverse events in our system for this protocol. One describes the 30 hour hospitalization described above. The other 3 all report details regarding the one death described above.

ID #	Letter	Protocol #	Amendment	
		9905-314	**A Phase I Trial of Intralesional RV-B7.1 Vaccine in the Treatment of Malignant Melanoma. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)**	
416	05/13/2002		*PI or Site Change:*	PI, Dr. Kaufman, has moved from Albert Einstein to Columbia University.
			Status Change:	Trial is closed to new enrollment. Follow-up is continuing.
		9905-319	**Treatment of High Risk Acute Leukemia with CD40 Ligand and IL-2 Gene Modified Autologous Bone Marrow Fibroblasts and Tumor Cells.**	
405	03/14/2002		*Other:*	Informed consent was amended to include information that the skin biopsy test is performed, in part, to ensure that leukemia cells are not growing at the injection site.
433	05/13/2002		*Other:*	Received a proposed single subject exemption submitted by Dr. Malcolm Brenner (the PI for this study). Details about this exemption follow: a. This study proposes to inject tumor vaccines to subjects in remission from leukemia, but based on clinical parameters (such as response to first course of therapy, age, tumor type, etc) at high risk for remission. b. As part of the exclusion criteria, subjects on any antimicrobials other than those for prophylaxis are to be excluded from enrollment. This criterion was added so as avoid treating acutely ill subjects. c. To date, 7 subjects have been enrolled. While adverse events have occurred (we have 10 in our database) none of them were serious and no subject has developed any liver dysfunction attributable to the vaccine (have reviewed the AEs in our database and agree with this assessment). In regard to activity, four of the seven subjects have demonstrated specific cellular and/or humoral immune responses against their autologous blasts (as measured by *in vitro* testing). d. The subject of note is in complete remission since February 2001 after a matched unrelated BMT. In March 2001 he developed mucosal and liver GVHD and started receiving cyclosporin and corticosteroids. After nearly a year of treatment, the liver GVHD appears to be resolved. The subject did have elevated transaminases, but they have decreased since the GVHD has been resolved. However, they are still approximately 2-3 times above upper limit of normal.

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			e. The suspected cause for the continued elevated transaminases is believed to be due to chronic use of clarithromycin. The subject was diagnosed with atypical mycobacterial infection and is being treated with the above noted macrolide until 8/2002. In addition, the subject is on cyclosporin (tapering dose, with complete stoppage planned for 6/02), acyclovir (for HSV prophylaxis), itraconazole (for fungal prophylaxis) and monthly pooled IVIG and pentamidine (for CMV prophylaxis). f. The PI would like to enroll this subject into study 319 and administer the vaccine starting in June. However, due to the chronic use of a non-prophylactic antimicrobial (clarithromycin) this subject violates the exclusion criterion noted before. It is argued that he is not acutely ill and his mycobacterial infection is well controlled. g. The proposal is to: Obtain both FDA and IRB approval (from Baylor College of Medicine) for this single subject exemption Recheck liver transaminases prior to enrollment. If less than 200 for both ALT and AST then proceed Recheck subject immediately prior to vaccination to again check LFTs and clinical status.
436	05/21/2002	*Other:*	Clinical protocol has been amended to state that long-term follow-up will be done, in accordance with the FDA's current recommendation, for 15 years. Peripheral blood will be obtained on a yearly basis to assess for an immune response.

ID #	Letter	Protocol #	Amendment	
		9906-322	**A Phase I Study of NGF Ex Vivo Gene Therapy for Alzheimer's Disease**	
393	05/09/2002		*Protocol Change:*	Due to an unexpected adverse event, unrelated to the study agent, the following changes have been made to the clinical protocol: 1) All medications that may affect platelet function (including aspirin) must be discontinued at least two weeks prior to surgery 2) Fibrin glue will not be used at the site of needle entry 3) An MRI, that is sensitive for detecting hemorrhage, will be performed during the cell implantation procedure 4) A modified informed consent that describes this adverse event will be provided to individuals who have received the study agent 5) A non-trial associated neurosurgeon will be contacted for an opinion as to the advisability of continuing with cell implants in a given individual if another unexpected intra-operative event occurs during the surgical procedure
		9908-336	**Post-Transplant Infusion of Fibronectin-Assisted, Retroviral-Mediated Gene-Marked and Ex Vivo Expanded CD34+ Placental and Umbilical Cord Blood Cells**	
412	03/04/2002		*Annual Update:*	Study has not been opened. Investigators are waiting for certification of a different retroviral construct that appears to have a much higher transduction efficiency.
		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.**	
413	03/04/2002		*PI or Site Change:*	Dr. Farrell O. Mendelsohn at Cardiology, P.C., Birmingham, Alabama is now an investigator.

ID #	Letter	Protocol #	Amendment	
		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.**	
457	02/19/2002		*Annual Update:*	Received a copy of the annual report as submitted to the FDA. To date, no individuals have been enrolled in this study. Additional preclinical studies have been performed to assess if toxicities from intratumoral injection observed in the investigator's previous animal studies were due to the adenoviral vector or expression of the IL12 transgene. Mice bearing MCA26 colon cancer metastases in the liver were injected with either an adenoviral vector (dl 312), at a particle dose equivalent to the toxic dose observed in the preclinical studies with the IL12 adeno vector, not expressing a transgene or buffer. No organ toxicities were observed in the mice injected with dl 312, suggesting that the toxicities previously observed with the adeno-IL 12 vector were due to the IL 12 transgene.
		9911-359	**Phase I Trial of Adenoviral Vector Delivery of the Human Interleukin-12 cDNA by Intratumoral Injection in Patients with Primary or Metastatic Malignant Tumors in the Liver.**	
458	02/19/2002		*Annual Update:*	Received a copy of the annual report as submitted to the FDA. To date, no individuals have been enrolled in this study. Additional preclinical studies have been performed to assess if toxicities from intratumoral injection observed in the investigator's previous animal studies were due to the adenoviral vector or expression of the IL12 transgene. Mice bearing MCA26 colon cancer metastases in the liver were injected with either an adenoviral vector (dl 312), at a particle dose equivalent to the toxic dose observed in the preclinical studies with the IL12 adeno vector, not expressing a transgene or buffer. No organ toxicities were observed in the mice injected with dl 312, suggesting that the toxicities previously observed with the
		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)**	
445	10/09/2001		*PI or Site Change:*	Dr. Douglas Trask, University of Iowa Health Care, Iowa City, Iowa has been added.
452	02/19/2002		*PI or Site Change:*	Dr. Douglas Villaret, University of Florida, Gainesville, Florida has been added.
447	04/30/2002		*PI or Site Change:*	Dr. Andrew Nemechek, Tulane University School of Medicine, New Orleans, Louisiana has been added as an investigator.
434	05/13/2002		*PI or Site Change:*	Dr. Amy Law, Geisinger Medical Center, Danville, Pennsylvania has been added.

ID #	Letter	Protocol #	Amendment	
		0001-386	**Phase II Study of a B-7.1 Gene Modified Autologous Tumor Cell Vaccine and Systemic IL-2 for Patients with Stage IV Renal Cell Carcinoma.**	
403	03/25/2002		*Annual Update:*	Five individuals were enrolled in this phase II study using the adenoviral construct (see UAI 131). Four of the five individuals died from progressive disease, one from a pulmonary embolus that occurred after the individual suffered a hip fracture.
		0004-393	**Phase II Study of a TGF-b2 Antisense Gene Modified Allogeneic Tumor Cell Vaccine in Patients with Non-Curable Non-Small Cell Lung Cancer. Sponsor: NovaRx**	
389	04/12/2002		*PI or Site Change:*	Dr. Raj K. Batra at the University of California, Los Angeles and the West Los Angeles Veteran's Administration Medical Center and Dr. Robert O. Dillman at the Hoag Cancer Center, Newport Beach, CA, have been added as new investigators.
		0005-396	**A Phase I, Open-Label, Dose-Escalating Study of the Safety, Tolerability, and Anti-Tumor Activity of a Single Intrahepatic Injection of a Genetically Modified Herpes Simplex Virus NV1020, in Subjects with Adenocarcinoma of the Colon with Metastasis to the Liver and the associated, long-term follow-up protocol: Long-Term Follow-Up of the Safety and Survival of subjects with Adenocarcinoma of the Colon with Metastasis to the Liver Who Enrolled in a Phase I Dose-Escalating Study Evaluating a Genetically Engineered Herpes Simplex Virus, NV 1020. Sponsor: NeuroVir Therapeutics, Inc.**	
404	05/01/2002		*Protocol Change:*	Inclusion criteria have been modified to state that individuals may undergo the liver biopsy, that is part of the study, either at the time of intrahepatic artertial infusion pump placement or as a an image-guided procedure. This change was made to allow the participation of other clinical sites. Exclusion criteria have been clarified to indicate that: 1) Individuals with a documented history of extrahepatic metastasis, except for those individuals with previously resected lymph nodes, are excluded 2) Individuals with a history of any other malignancy, except skin or cervical cancer, are excluded

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		0005-399	**An Open-Label, Phase I, Dose-Escalation Study of Tumor Necrosis Factor-alpha (TNFeradeTM Biologic) Gene Therapy with Radiation Therapy for Locally Advanced, Recurrent, or Metastatic Solid Tumors.**	
461	02/13/2002		*Protocol Change:*	Two lower doses (4×10^8 and 4×10^7 particle units) with 3 to 6 individuals at each dose have been added. Purpose is to obtain additional information on the safety of doses below 4×10^9.
414	03/05/2002		*PI or Site Change:*	Dr. Barry S. Berman, Cancer Care Centers of Florida, Orlando, Florida is now an investigator.
		0005-401	**Open-Label, Multicenter, Phase II Study of Autologous Ad-CD154 Expressing Transduced CLL Cells in B Cell Chronic Lymphocytic Leukemia Patients Enrolled in Three Strata. Sponsor: F. Hoffmann-La Roche**	
394	04/22/2002		*PI or Site Change:*	Drs. John Gribben (at Dana-Farber Cancer Institute) and M. Wayne Saville (at Univ. of California-San Diego Medical Center) are now the two PIs for this trial.
			Protocol Change:	The trial design has been changed so that only two cohorts will be studied. The cohort comprised of individuals with "poor prognostic markers" has been eliminated. The total number of individuals now planned for this trial has been reduced from 60 to 40 (still 20 per arm).
		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**	
408	03/01/2002		*PI or Site Change:*	Dr. Carlos Milla at the University of Minnesota has been added as an investigator.
397	04/05/2002		*Annual Update:*	The submission contains a letter from the Cystic Fibrosis Foundation (CFF) (dated 3-14-02) which details their review of the safety and tolerability data from all subjects enrolled to date. Based on their review of the information (on the eight subjects enrolled in the first two study cohorts), the CFF Data Monitoring Committee recommends that the protocol may continue as currently written.
423	05/17/2002		*Annual Update:*	The submission contains a letter from the Cystic Fibrosis Foundation (CFF) (dated 5-13-02) which details their review of the safety and tolerability data from all subjects (33) enrolled to date. Based on their review of this information and the safety information on the eight subjects enrolled in the first two study cohorts (UAI 397), the CFF Data Monitoring Committee recommended that the protocol may continue as currently written.

ID #	Letter	Protocol #	Amendment	
		0007-407	**A Phase I Double-blind, Placebo-Controlled, Escalating Dose, Multi-center Study of Ad2/Hypoxia Inducible Factor (HIF)-1-alpha/VP16 Gene Transfer Administration by Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Areas of Viable and Underperfused Myocardium not Amenable to Bypass Grafting or Percutaneous Intervention. Sponsor: Genzyme Corporation**	
451	03/14/2002		*PI or Site Change:*	Dr. Timothy Henry, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota has been added as an investigator.
424	05/14/2002		*PI or Site Change:*	Dr. Nicolas Chronos, Atlanta Cardiology Research Institute, Atlanta, Georgia is a new investigator.
		0009-411	**Restenosis Gene Therapy Trial - Phase I Study (Regent I). Sponsor: Cardiogene Genetherapeutische**	
419	04/05/2002		*Status Change:*	Notification that trial has been closed (without enrolling any individuals) in the US. A very similar trial, not conducted under the IND for protocol 0009-411, was completed in Europe.
		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**	
446	10/09/2001		*PI or Site Change:*	Dr. Douglas Trask, University of Iowa Health Care, Iowa City, Iowa has been added as an investigator.
448	03/18/2002		*PI or Site Change:*	Dr. Matthew Arquette, Washington University School of Medicine, St. Louis, Missouri has been added as an investigator.

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		0010-427	**Effect of AdGVCFTR.10 on the Cystic Fibrosis Phenotype.**	
464	02/14/2002		*Protocol Change:*	Changes have been made to the inclusion criteria. Individuals must have an FEV1 > 1.0 L/sec. Previously, the protocol required an FEV1 > 1.2 L/sec. This higher FEV1 level was based upon a previous clinical trial that had a bronchoscopy requirement. Individuals enrolled in protocol 0010-427 will not undergo bronchoscopy. In addition the sweat rate test will no longer be used as a criterion for inclusion. However, a sweat chloride concentration of greater than 60 mmol/L is still part of the inclusion criteria. The informed consent has been modified to include the fact that individuals will now be compensated for sweat chloride tests ($50 per test), sweat rate tests ($50 per test), and skin biopsies ($50 per biopsy).
		0011-431	**A Phase II Study of High-Dose Allovectin-7 in Patients with Advanced Metastatic Melanoma. Sponsor: Vical**	
449	02/22/2002		*PI or Site Change:*	Dr. Evan M. Hersh, Arizona Cancer Center, Tucson, Arizona has been added as an investigator
443	03/13/2002		*Protocol Change:*	This amendment removes the maximum number (previously four) of allowable cycles of administration of the study agent. Individuals may continue to receive study agent as long as they demonstrate stable or responding disease. In addition, this amendment allows the sponsor, Vical Incorporated, the right to discontinue participant enrollment in this study. Reasons for discontinuation include, but are not limited to, safety concerns and availability of the study material.
396	03/22/2002		*PI or Site Change:*	Dr. Barbara Klencke at the University of California, San Francisco Comprehensive Cancer Center at Mount Zion, has been added as an investigator.
454	04/17/2002		*Protocol Change:*	The first portion of this study is designed to examine the safety of elevated repeat doses of Allovectin-7. This portion of this study has been completed. The second portion is designed to examine the systemic rate of response to intratumoral injection of the maximum tolerated dose (2000 μg) into one versus multiple lesions. This amendment increases the number of individuals to be enrolled in the second phase of this study from 62 to 124. This increase is designed to increase the power to detect any difference between individuals with multiple tumors who only receive an injection of Allectin-7 in one lesion versus those individuals who receive an injection into multiple lesions.

ID #	Letter	Protocol #	Amendment	
		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.**	
441	03/14/2002		*PI or Site Change:*	Dr. Paul Friedlander, Louisiana State University Health Sciences Center, New Orleans, Louisiana is now an investigator.
		0101-440	**Phase I Study of gp75 DNA Vaccine in Patients with AJCC Stage III and IV Melanoma. Sponsor: ImClone Systems, Inc.**	
400	04/02/2002		*Protocol Change:*	Changes to the inclusion criteria: Individuals who have had surgery for their melanoma at least 6 months prior to study entry, or have had prior interferon therapy, or developed unacceptable toxicities to interferon therapy, or have a pre-existing condition(s) that precludes the individual for receiving interferon treatment are eligible. Exclusion criteria have been amended to include individuals with stage III disease who are otherwise eligible to receive standard of care melanoma therapy. Dose limiting toxicity has been amended to include a grade 2 or greater allergic and/or immunologic reaction to the treatment.
		0101-441	**A Phase I Trial of Intralesional rV-TRICOM Vaccine in the Treatment of Malignant Melanoma.**	
417	05/13/2002		*PI or Site Change:*	PI, Dr. Kaufman, has moved from Albert Einstein to Columbia University.

ID #	Letter	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.**
430	02/20/2002	*Other:*	Received a protocol change to enroll a subject who did not meet inclusion criteria to protocol 446 ("Transplantation of gene corrected autologous CD34+ hematopoietic stem cells in previously transplanted patients with JAK3 deficiency and persistent humoral immune defects"). This change involves the enrollment of a child who had failed two prior bone-marrow transplantation attempts which did not utilize full immunosuppression prior to the transplantation, with little to no T-cell activity noted after each attempt. This subject is also afflicted with several infectious complications common with JAK3 SCIDS (such as disseminated herpes simplex infection and candidal esophagitis) and, thus, not capable of tolerating another BMT attempt with full pre-transplantation immunosuppression. Due to a lack of viable clinical options, the PIs (Dr. Buckley at Duke and Dr. Sorrentino at St. Jude's) formally petitioned and received approval from the relevant institution's IRB and from CBER/FDA to proceed with the enrollment with this child. As per the study protocol, the first inclusion criterion (section 5.1.1) states: "Patients with a genotypically confirmed diagnosis of JAK3 mutations in both alleles, who have received an allogeneic bone marrow transplantation with successful allogeneic T-cell reconstitution (peripheral blood CD3 cells >250/µl)". This subject did not meet this criteria, which was waived for this one subject. The subject has already undergone apheresis, transduction of autologous CD34+ cells, and re-infusion. Further details about this subject's response to the gene transfer will be submitted by the PIs in the future.

ID #	Letter	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.**	
444	03/06/2002		*PI or Site Change:*	Dr. Abel E. Moreyra, Robert Wood Johnson Medical School, New Brunswick, New Jersey is now an investigator.
390	04/03/2002		*PI or Site Change:*	The following investigators have been added: Dr. Theresa Brennan, University of Iowa Healthcare, Iowa City, Iowa; Dr. Kevin F. Browne, Jr., Watson Clinic LLP, Lakeland, Florida; Dr. Nabil Dib, Arizona Heart Institute, Phoenix, Arizona; Dr. Stephen Ellis, Cleveland Clinic Foundation, Cleveland, Ohio; Dr. Kevin Hart, Stucky Research Center, Fort Wayne, Indiana; Dr. Ami E. Iskandrian, University of Alabama at Birmingham, Birmingham, Alabama; Dr. Neal S. Kleiman, Baylor College of Medicine, Houston, Texas; Dr. Jonathan Marmur, Mount Sinai Hospital, New York, New York; Dr. J. Jeffrey Marshall, Crawford Long Hospital, Atlanta, Georgia; Dr. William F. Penny, San Diego VA Medical Center, San Diego, California; Dr. Carl J. Pepine, University of Florida, Gainesville, Florida; Dr. Carlos Saenz and Dr, Andrew Taussig, Florida Hospital, Orlando, Florida; Dr. Gary L. Schaer, Rush-Presbyterian St. Luke's Medical Center, Chicago, Illinois; and Dr. Rafael F. Sequeira, University of Miami-Jackson Memorial Hospital, Miami, Florida.
391	05/07/2002		*PI or Site Change:*	The following new investigators have been added: Dr. Kenneth W. Baran, United's John Nasseff Heart Hospital, Saint Paul, Minnesota; Dr. Gregory A. Helmer, Minnesota Heart Clinic, P.A., Edina, Minnesota; Dr. Farrell O. Mendelsohn, Cardiology, P.C., Birmingham, Alabama; Dr. John F. Moran, Loyola University Medical Center, Maywood, Illinois; Dr. Timothy Sanborn, Evanston Northwestern Healthcare, Evanston, Illinois; and Dr. Barry L. Sharaf, Rhode Island Hospital, Providence, Rhode Island.
		0101-457	**An Open-Label, Phase I, Dose-Escalation Study of TNFeradeTM Biologic with Radiation Therapy as an Adjunct to Surgery or for Palliation of Soft Tissue Sarcoma of the Extremities. Sponsor: GenVec.**	
415	03/05/2002		*PI or Site Change:*	Dr. Barry S. Berman, Cancer Care Centers of Florida, Orlando, Florida is now an investigator.

ID #	Letter	Protocol #	Amendment	
		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.**	
418	05/16/2002		*PI or Site Change:*	The following investigators have been added: Dr. Robert M. Conry at The University of Alabama at Birmingham, Birmingham, Alabama; Dr. John Marshall at Georgetown University Medical Center, Washington D.C.; Dr. William J. Heim at Hematology & Oncology Associates of Northeastern PA, Dunmore, Pennsylvania; and Dr. Heinz-Josef Lenz at the University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California.
		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.**	
388	05/01/2002		*Protocol Change:*	Study has been changed to now exclude individuals with aggressive non-Hodgkin's lymphoma. Individuals are eligible if they present with B cell chronic lymphocytic leukemia; either with or without measurable disease. No individuals were or are planned to be enrolled under the previous criteria.
		0104-467	**VEGF Gene Transfer for Diabetic Neuropathy.**	
465	03/15/2002		*Other:*	This submission follows the request of the FDA for the Sponsor (Dr. Losordo) to submit protocol 467 (BB-IND-9785) with a new IND. This submission includes the protocol as reviewed in the February 5, 2002 submission (UAI 368).

ID #	Letter	Protocol #	Amendment
		0104-468	**VEGF Gene Transfer to Promote Angiogenesis in Patients with Advanced Heart Failure.**
466	03/28/2002	*Other:*	Submissions: March 28, 2002 (Patrick McCarthy, M.D. -Principal Investigator) and April 17, 2002 (Douglas Lorsordo, M.D.-Sponsor) OBA Receipt Date: May 9, 2002 Submission Type: New IND with Dr. Losordo as Sponsor; Amended Protocol; and Investigators' Brochure (Appendix 25) Description of Materials Submitted: This submission includes the new IND application, the Investigator's Brochure (Appendix 25), and also the amended protocol. The cover letter delineates the changes made to the protocol which were prompted by questions from the FDA. The changes incorporated into the protocol were summarized in the cover letter. These include: 1.) Additional information provided regarding previous human subjects 2.) Clarification of criteria for LVAD implantation 3.) Addition of 12 patient pilot study to precede randomized study 4.) Changes in randomization and blinding 5.) Addition of baseline phase assessments to include: a. PSA (males only) if PSA is >4.0ng/ml patients will be further examined for latent prostate cancer. 6.) Post treatment assessments to include: a. Fundoscopic exam for IDDM patients at 3 months instead of 12 months b. Mammogram (females only) at 12 months c. 1 red top tube to be collected and frozen for 1 year 7.) Additional information provided regarding identification and description of test agent 8.) Clarification of dosing instructions, schedule, preparation and dispensing of drug 9.) Changes in study termination and patient discontinuation 10.) Change in CRO and monitoring plan 11.) Clarification of plasmid preparation protocol 12.) Addition of shipping protocol 13.) Additional information provided regarding QA/QC of DNA production 14.) Several appendices regarding information provided above.

ID #	Letter	Protocol #	Amendment	
		0105-473	**Administration of Neomycin Resistance Gene Marked LMP2A-Specific Cytotoxic T Lymphocytes to Patients with Relapsed EBV-Positive Hodgkin's Lymphoma.**	
435	05/14/2002		*Other:*	Clinical protocol has been amended to state that long-term follow-up will be done, in accordance with the FDA's current recommendation, for 15 years. Blood will be obtained on a yearly basis, and cells and serum archived.
		0106-478	**A Phase I Study of Active Immunotherapy with Autologous Dendritic Cells Infected with CEA-6D Expressing Fowlpox-TRICOM in Patients with Advanced or Metastatic Malignancies Expressing CEA.**	
442	02/26/2002		*Other:*	In a protocol deviation letter dated January 22, 2002, OBA was informed a that subject received twice the protocol-defined dosage for the first three treatments. The subject had no adverse experiences per se as a result of this dosing. However, these incorrect dosages were captured as adverse events in the OBA database. It was recognized that there was a lack of congruence between the SOP for manufacturing the DC (dendritic cells) and the protocol procedures for administering the investigational agents that led to the subject receiving the incorrect dose. Therefore, there were changes made to the protocol, consent form, case report form, manufacturing procedures, and SOP's, to make all of the supporting documentation congruent with the protocol, and to clarify the final product descriptions in the protocol. These were included in this submission, along with the IRB amendment form listing the changes as submitted to the IRB. A copy of the IRB approval was to follow.
		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**	
462	02/13/2002		*Other:*	Notification that the first individual at the University of Chicago Medical Center site was enrolled on January 22, 2002. Other information for this site was submitted on January 29, 2002.
		0107-484	**A Phase I Open-Label Study of the Safety and Feasibility of Vaccinating Cancer Patients with Repeated Doses of ZYC300. Sponsor: ZYCOS, Inc.**	
392	04/11/2002		*PI or Site Change:*	Notification of a change in the principal investigator at Dana-Farber. PI is now Dr. John Gribben.

ID #	Letter	Protocol #	Amendment	
		0107-488	**A Phase I Open-Label Clinical Trial of the Safety and Tolerability of Single Escalating Doses of Autologous CD4 T Cells Transduced with VRX496 in HIV Positive Subjects. Sponsor: VIRxSYS Corporation.**	
431	04/02/2002		*Other:*	Received, via electronic mail, a final draft of the informed consent document for protocol 488. This protocol was discussed at the September 2001 RAC meeting and it was stated on several occasions that the RAC would be willing to help with development of this document. The letter to the PI makes note of this as well. This final draft was sent to the RAC members on 4-04-02.
		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.**	
410	04/19/2002		*PI or Site Change:*	Dr. Evan M. Hersh at the Arizona Cancer Center, Tucson, Arizona and Dr. John W. Smith II at the Providence Portland Medical Center, Portland, Oregon have been added as investigators.
		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.**	
463	02/13/2002		*PI or Site Change:*	Dr. Eric Small, University of California, San Francisco, has been added as an investigator.
453	03/13/2002		*Protocol Change:*	The phase II portion of this study has been amended. The number of individuals who will receive the anticipated maximum tolerated dose has been reduced from 40 to 30. This new group, termed group A will receive the aniticipated maximum tolerated dose every four weeks for six months. A second group of research participants, gropu B, has been added to the phase II portion. This group will receive the same dose as in group A; however this group will receive a dose every two weeks for six months. The rationale for this change is based on a previous study with the study agent that suggested that there was a trend toward longer median time to disease progression with booster doses of cells administered at two week intervals for six months (Proc Am Soc Clin Onc 20 (Pt 1):269a).
398	04/17/2002		*Other:*	The clinical protocol has been updated to reflect the fact that 11individuals have now received the GVAX prostate cancer vaccine. As of April 5, 2002 no dose limiting toxicities have been observed. Inclusion criteria have been altered to define adequate bone marrow function as a WBC >3,000 cells/mm^3 (previously the definition was >3,500). The exclusion criteria have been modified to clarify that clinical evidence of brain metastases or a history of brain metastases would dictate the need for diagnostic tests. Tests would not be required to rule out brain metastases in the absence of clinical evidence.