AMENDMENTS AND UPDATES TO
HUMAN GENE TRANSFER PROTOCOLS
RECOMBINANT DNA ADVISORY COMMITTEE MEETING
MARCH 11-12, 1999

September 8, 1998(letter date)	**9806-261 Amado**	**A Phase I/II Study of the Safety and Feasibility of RevM10Transduced Hematopoietic Stem Cells (HSC) in HIV-1 Related Non-Hodgkin's Lymphoma Patients Already Being Treated with High Dose Chemotherapy and Peripheral Blood Stem Cell Support** **Amendments:** 1) One new investigator/site has been added. Alan R. Yuen, M.D. at Stanford University Medical Center; Stanford, California 2) Amendment for the use of a slightly different vector that contains both a transdominant Rev (as in the initial submission) and antisense to the HIV-1 polymerase gene. A summary of this amendment was sent to all 15 RAC members. None of the RAC members determined that this amendment should be discussed at a meeting. The title of the protocol has been changed to reflect the addition of the polymerase gene to the construct.
September 21, 1998	**9805-253 Scadden**	**A Phase II Study of Autologous CD4-Zeta Gene-Modified T Cells in HIV Infected Patients with Undetectable Plasma Viremia on Highly Active Anti-Retroviral Drug Therapy** **Amendment:** Two new investigators/sites have been added. 1) Ronald Mitsuyasu, M.D. at the University of California, Los Angeles; Los Angeles, California and 2) Steven Deeks, M.D. at the University of California, San Francisco; San Francisco, California
October 6, 1998	**9712-226 Dreicer *et al.***	**A Phase II, Multi-Center, Open Label, Study to Evaluate Effectiveness and Safety of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 39 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)**

		Amendments: 1) Minor amendments have been made it terms of contact personnel and labeling information of the study drug. 2) One new investigator/site has been added. Scott Wadler, M.D. at Montefiore Medical Center, Albert Einstein College of Medicine; Bronx, New York.
October 8, 1998	**9802-233 Dreicer *et al.***	**Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Imunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives** **Amendment:** One new investigator/site has been added. Rene Gonzalez, M.D. at the University of Colorado Cancer Center; Denver, Colorado.
October 16, 1998	**9802-233 Dreicer *et al.***	**Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Imunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives** **Amendment:** One new investigator/site has been added. Ronald Blum, M.D. at Saint Vincent's Hospital and Medical Center; New York, NY.
October 16, 1998	**9802-234 Thompson *et al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:** One new investigator/site has been added. Ronald Blum, M.D. at Saint Vincent's

		Hospital and Medical Center; New York, NY.
October 19, 1998	**9802-233 Dreicer *et al.***	**Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Imunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives** **Amendment:** One new investigator/site has been added. Laura Hutchins, M.D. at the University of Arkansas for Medical Sciences/Arkansas Cancer Research Center; Little Rock, Arkansas.
October 19, 1998	**9802-234 Thompson *et al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:** One new investigator/site has been added. Laura Hutchins, M.D. at the University of Arkansas for Medical Sciences/Arkansas Cancer Research Center; Little Rock, Arkansas.
October 30, 1998	**9802-233 Dreicer *et al.***	**Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Imunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives** **Amendment:** One new investigator/site has been added. Wolfram E. Samlowski, M.D. at the University of Utah Health Sciences Center; Salt Lake City, Utah.
November 10, 1998	**9701-173 Croop**	**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 O^6-Methylguanine DNA Methyltransferase** **Amendments:** Minor changes have been made, including the source of the cell selection device and the procedure for coating plates with fibronectin for retroviral transduction.
November 13,	**9802-234**	**A Controlled, Randomized Phase III Trial Comparing the Response to**

1998	**Thompson *et al.***	**Dacarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:** One new investigator/site has been added. Wolfram E. Samlowski, M.D. at the University of Utah Health Sciences Center; Salt Lake City, Utah.
November 13, 1998	**9712-226 Dreicer *et al.***	**A Phase II, Multi-Center, Open Label, Study to Evaluate Effectiveness and Safety of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 39 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)** **Amendment:** One new investigator/site has been added. Glenwood D. Goss, M.D. at Ottawa Regional Cancer Center; Ottawa, Ontario.
November 16, 1998	**9709-214 Breau *et al.***	**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)** **Amendment:** One new investigator/site has been added. William A. Flood, M.D. at the Milton S. Hershey Medical Center, Hershey, Pennsylvania.
November 17, 1998	**9709-212 Gonzalez *et al.***	**Phase I Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Leuvectin) as an Immunotherapeutic Regimen in Patients with Metastatic Melanoma** **Amendment:** Protocol has been amended to allow for more than one additional course of treatment fo those patients that have stable disease or experience a partial response or shrinkage of th injected nodule or distant nodules.

November 17, 1998	**9701-172 Cornetta and Abonour**	**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** **Update:** To date, 14 patients have been enrolled in the study. Three of the patients did not mobilize a sufficient number of cells and were not evaluated farther. Of the 11 patients that received transduced cells, nine have received three cycles, the prescribed number, of etoposide. Two of the three patients that did not receive treatment under this study are still alive with disease. Another patient who died received two cycles of etoposide. All of the patients that received three cycles of etoposide are without active disease and are well. Two patients have, to date, only received two of the three etoposide cycles; both are alive with disease.
November 19, 1998	**9802-233 Dreicer *et al.***	**Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Imunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives** **Amendment:** One new investigator/site has been added. James D. Bearden, M.D. at Spartanburg Regional Medical Center, Spartanburg, South Carolina.
November 19, 1998	**9802-234 Thompson *et al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:** One new investigator/site has been added. James D. Bearden, M.D. at Spartanburg Regional Medical Center, Spartanburg, South Carolina.
November 23, 1998	**9709-214 Breau *et al.***	**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)**

		Amendments: Two amendments have been made. The first is to increase the maximum number of patients enrolled to ensure that 70 evaluable patients are participants. The second amendment is to change, slightly, the criteria of long-term follow-up. Patients, regardless of whether they have progressive disease, will be followed for up to 18 months.
November 23, 1998	**9712-226 Dreicer *et al.***	**A Phase II, Multi-Center, Open Label, Study to Evaluate Effectiveness and Safety of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 39 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)** **Amendments:** Two amendments have been made. The first is to increase the long-term follow-up from 12 to 18 months. The second amendment is to allow for the continued treatment of a subset of patients. These are patients who have exhibited either a partial response to the study medication o have exhibited stable disease. This subpopulation will, on a case-by-case basis, be eligible for additional treatment up to a maximum of 12 cycles. This additional treatment may only continue as long as progressive disease does not occur.
November 25, 1998	**9802-233** **Dreicer *et al.***	**Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Imunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives** **Amendment:** One new investigator/site has been added. Michael B. Atkins, M.D. at the Beth Israel Medical Center, Boston, Massachusetts.
November 25, 1998	**9802-234 Thompson *et al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:**

		One new investigator/site has been added. Michael B. Atkins, M.D. at the Beth Israel Medical Center, Boston, Massachusetts.
December 10, 1998	**9701-173 Croop**	**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 O^6-Methylguanine DNA Methyltransferase** **Amendments and Update:** Minor amendments have been made that include clarification that toxicity from infusion of transduced cells is the equivalent to the development of RCR. Another amendment was made to state specifically that prior treatment with nitrosourea or procarbazine are part of the exclusion criteria. As of this date, three patients have been enrolled out of a total of 20 over a two year period. None of the three enrolled patients completed the study due to disease progression.
December 11, 1998	**9703-184 Belldegrun**	**A Phase I Study of Evaluating the Safety and Efficacy of Interleukin-2 Gene Therapy Delivered by Lipid Mediated Gene Transfer (Leuvectin) in Prostate Cancer Patients** **Amendments:** The first amendment is to allow re-treatment of patients who initially responded to this treatment by exhibiting stable or decreased PSA levels; and subsequently experienced a rise in PSA. The second amendment is to allow two additional patients at the highest dose level "... to obtain additional histological information on the immune response and its time course."
December 16, 1998	**9706-196 Smith and Dinauer**	**Fibronectin-Assisted, Retrovirus-Mediated Transduction of CD34+ Peripheral Blood Cells with $gp91^{phox}$ in Patients with X-linked Chronic Granulomatous Disease: A Phase I Study** **Amendments:**

		Minor amendments have been made that include clarification that toxicity from infusion of transduced cells is the equivalent to the development of RCR.
December 18, 1998	**9802-234 Thompson *et. al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:** Two new investigators have been added. John Gibbs, M.D. and Leslie Oleksowicz, M.D. both at Roswell Park Cancer Institute, Buffalo, New York.
December 23, 1998	**9802-234 Thompson *et. al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:** One new investigator/site has been added. Paul O. Schwarzenberger, M.D. at Louisiana State University Medical Center, New Orleans, Louisiana.
December 23, 1998	**9802-233 Dreicer *et al.***	**Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Imunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives** **Amendment:** One new investigator/site has been added. Paul O. Schwarzenberger, M.D. at Louisiana State University Medical Center, New Orleans, Louisiana.
January 7, 1999	**9802-234 Thompson *et. al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:** One new investigator/site has been added. Marc Ernstoff, M. D. at the Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire.
January 8,	**9703-184**	**A Phase I Study of Evaluating the Safety and Efficacy of Interleukin-2 Gene**

1999	**Belldegrun**	**Therapy Delivered by Lipid Mediated Gene Transfer (Leuvectin) in Prostate Cancer Patients** **Amendments:** Amendment made to define the maximum number of re-treatments (see amendment of December 11, 1998 that an eligible patient may undergo to five.Rationale is to balance a reasonable number of re-treatment cycles with the length of time that the trial would remain open.
January 13, 1999	**9503-103 Morgan and Walker**	**Gene Therapy for AIDS Using Retroviral Mediated Gene Transfer to Deliver HIV-1 Antisense TAR and Transdominant Rev Protein Genes to Syngeneic Lymphocytes in HIV Infected Twins** **Update and amendment:** To date, nine sets of twins have been treated under this protocol.The investigators have analyzed data on the persistence oftransduced cells; the range is < 0.01% to 2.0%. One set of twins was enrolled in 1998. The other sets of twins are 43 to 94 weeks from the last cell infusion. All recipients are monitored at least yearly for the presence of replication competent retrovirus. None of the patients have experienced any significant clinical events. The investigators would like to increase enrollment to 24 sets (up from 12) of twins in order to study other newly developed gene vectors that lack the gene for neomycin resistance.
January 14, 1999	**9802-234 Thompson *et. al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:** Two new investigators/sites have been added. 1) Laura Campbell, M.D. at Louisiana State University Medical Center, Shreveport, Louisiana and 2) Edward Levine, M.D. at Wake Forest University Medical Center, Winston-Salem, North Carolina.
January 27,	**9811-270**	**Phase II Study of the Safety, Efficacy, and Effect on Quality of Life of Allovectin-7**

1999 and February 1, 1999	**Hanna**	**Immunotherapy for the Treatment of Recurrent or PersistentSquamous Cell Carcinoma of the Head and Neck** **Amendments:** Two new investigators/sites have been added. 1) Lawrence Wagman , M.D. at the City of Hope National Medical Center, Duarte, California and 2) JackGluckman, M.D. at the University of Cincinnati Medical Center, Cincinnati, Ohio.
February 2, 1999	**9712-226 Dreicer *et al.***	**A Phase II, Multi-Center, Open Label, Study to Evaluate Effectiveness and Safety of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 39 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)** **Amendment:** Three new investigators/sites have been added. 1) Kauko Saarilahti, M.D. at Helsinki University Central Hospital, Helsinki Finland; 2) RajaMudad, M.D. at Tulane University Medical Center, New Orleans, Louisiana and 3) Jeffrey Spiro, M.D. at University of Connecticut Health Center, Farmington, Connecticut.