RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

March 10, 1998

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

*** * * TABLE OF CONTENTS * * ***

- - -

I. Call to Order and Opening Remarks/Mickelson 3

II. Minutes of the December 15-16, 1997, Meeting 3

III. Data Management Update/Greenblatt 4

IV. Overview of the March 9, 1998, Gene Therapy Policy Conference Entitled: *Lentiviral Vectors for Gene Delivery*/McIvor 10

V. Amendment to Appendix M-I, *Submission Requirements - Human Gene Transfer Experiments* 15

VI. Chimeraplasty: A Gene Modification Technology Employing Oligonucleotides/Kumar 16

VII. Discussion Regarding Human Gene Transfer Protocol 9802-235 Entitled: *A Dose Escalating Phase I Study of the Treatment of Malignant Glioma with G207, a Genetically Engineered HSV-1*/Markert and Medlock 22

VIII. Discussion Regarding Format for RAC Discussion of Human Gene Transfer Protocols and Related Issues/Skirboll 28

IX. Discussion Regarding Enrollment of Children in Early Phase Gene Transfer Clinical Trials that May Involve Greater than Minimal Risk/Macklin 31

X. Update on the Gene Therapy Advisory Committee (GTAC), United Kingdom/Taylor 40

XI. Chair's Closing Remarks/Mickelson 42

XII. Future Meeting Dates/Mickelson 42

XIII. Adjournment/Mickelson 43

Attachment I: Roster
Attachment II: Human Gene Transfer Protocol List
Attachment III: Amendments to Human Gene Transfer Protocols
Attachment IV: Safety Reports, Adverse Events, and Updates for Human Gene Therapy Protocols
Attachment V: Acronyms

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING[1]
March 10, 1998

The Recombinant DNA Advisory Committee (RAC) was convened for its seventieth meeting at 9:00 a.m. on March 10, 1998, at the National Institutes of Health (NIH), Building 31, Conference Room 10, 9000 Rockville Pike, Bethesda, Maryland 20892. Dr. Claudia Mickelson (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public on March 10 from 9:00 a.m. until 5:30 p.m. The following were present for all or part of the meeting:

Committee Members:

C. Estuardo Aguilar-Cordova, Texas Childrens Hospital
Dale G. Ando, Cell Genesys, Inc.
Jon W. Gordon, Mt. Sinai School of Medicine
Jay J. Greenblatt, National Institutes of Health
Eric T. Juengst, Case Western Reserve University
M. Therese Lysaught, University of Dayton
Ruth Macklin, Albert Einstein College of Medicine
M. Louise Markert, Duke University Medical Center
R. Scott McIvor, University of Minnesota
Claudia A. Mickelson, Massachusetts Institute of Technology
Karen Rothenberg, University of Maryland School of Law
Inder M. Verma, The Salk Institute

Executive Secretary:

Debra W. Knorr, National Institutes of Health
A committee roster is attached (Attachment I).

Non-Voting Representatives:

Melody Lin, Office of Protection from Research Risks
Philip Noguchi, Food and Drug Administration

National Institutes of Health staff:

Thomas Fleisner, CC
Christine Ireland, OD
Julie Kaneshiro, OD
Mikel Miller, OD
Pearl O'Rourke, OD
Julie Rhie, NIGMS
Gene Rosenthal, OD
Thomas Shih, OD
Lana Skirboll, OD

[1] The RAC is advisory to the National Institutes of Health (NIH), and its recommendations should not be considered as final or accepted. The Office of Recombinant DNA Activities should be consulted for NIH policy on specific issues.

Others:

Kerin Ablashi, Magenta Corporation
W. French Anderson, University of Southern California
Bridget Binko, Cell Genesys, Inc.
R. Michael Blaese, Kimeragen
Amy Bosch, Targeted Genetics Corporation
David Brown, Codon Pharmaceuticals, Inc.
Jeff Carey, Genetic Therapy, Inc.
A. Antonio Championsmith, Cell Genesys, Inc.
Yawen Chiang, Rhone-Poulenc Rorer
Kenneth Culver, Codon Pharmaceuticals, Inc.
Boro Dropulic, Johns Hopkins University
Anne Dunne, Strategic Results
Thomas Eggerman, Food and Drug Administration
Dean Engelhardt, Enzo Biochem, Inc.
Suzanne Epstein, Food and Drug Administration
Diane Fleming, Biosafety Consultant
Tina Grasso, GenVec
James Hawkins, Drug and Market Development
Kathy High, University of Pennsylvania
Sunil Iyengar, The Blue Sheet
Dorothy Jessop, Public
Alexander Khorlin, Codon Pharmaceuticals, Inc.
Steven Kradjian, Vical, Inc.
Michael Kulka, AuRx, Inc.
Gary Kurtzman, Avigen
Lisa Malseed, Kimeragen
J. Tyler Martin, SyStemix, Inc.
Gerald Messerschmidt, Kimeragen
Robert Moen, Baxter Healthcare Corporation
J. Michael Morgan, R.O.W. Sciences, Inc.
Tina Moulton, Food and Drug Administration
Sheryl Osborne, NeuroVir, Inc.
Amy Patterson, Food and Drug Administration
Anne Pilaro, Food and Drug Administration
Andrew Quon, Association of American Medical Colleges
Zhong Shaobin, Food and Drug Administration
Tomiko Shimada, Ambiance Awareness International, Inc.
Jonathan Simons, Johns Hopkins University
Cindy Smith, University of Maryland School of Medicine
Gean Starr, Family Health Center
Anthony Taylor, Department of Health, England
Frank Tufaro, NeuroVir, Inc.
Ruth Turner, Genzyme Corporation
Scott Wheelwright, Calydon
Robert Wherry, Rhone-Poulenc Rorer

I. Call to Order and Opening Remarks/Dr. Mickelson

Dr. Claudia A. Mickelson, Chair of the Recombinant DNA Advisory Committee (RAC), called the meeting to order at 9:02 a.m. and stated that due notices of the meeting and the proposed actions under the *Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* were published in the *Federal Register* on February 11, 1998 (63 FR 7054).

Dr. Mickelson welcomed Dr. Melody H. Lin, Deputy Director, Office for Protection from Research Risks, as a non-voting agency representative to the RAC.

Dr. Mickelson noted that the RAC will consider one proposed action to Appendix M-I, *Submission Requirements - Human Gene Transfer Experiments*, under the *NIH Guidelines*. This proposed action would simplify the registration process by allowing optional electronic submission of documentation for human gene transfer protocols to the Office of Recombinant DNA Activities (ORDA).

Dr. Mickelson noted that three actions under the *NIH Guidelines* were published in the *Federal Register* on February 17, 1998 (63 FR 8052). These actions included the following changes to the *NIH Guidelines:* (1) Section III-D-4, *Experiments Involving Whole Animals*, was amended to permit experiments involving the generation of transgenic rodents under Biosafety Level 1 containment (not all animals) simultaneous with Institutional Biosafety Committee (IBC) notification. (2) Section III-D-4, *Experiments Involving Whole Animals*, was amended to exempt the purchase and transfer of transgenic rodents from the *NIH Guidelines*. (3) Appendix K, *Physical Containment for Large Scale Uses of Organisms Containing Recombinant DNA Molecules*, was amended to permit the production and harvest of biologically active viral vectors for volumes larger than 10 liters. (4) Appendix M-I, *Submission Requirements - Human Gene Transfer Experiments*, was amended to include an eight-week deadline for submission of human gene transfer protocols to ORDA. This deadline applies to all human gene transfer protocols recommended for full public discussion by the RAC. Any protocol recommended for full RAC discussion and submitted less than eight weeks before a RAC meeting will be reviewed at the next scheduled quarterly RAC meeting.

Dr. Gordon stated that the 10-liter designation represents an arbitrary standard for establishing additional containment procedures. He suggested that the RAC should reexamine current containment policies as described in Appendix K of the *NIH Guidelines*.

II. Minutes of the December 15-16, 1997, Meeting
Reviewers: Gordon, Markert

Committee Motion 1

The RAC approved a motion made by Dr. Gordon and seconded by Dr. Greenblatt to accept the minutes of the December 15-16, 1997, RAC meeting (with the incorporation of minor editorial changes) by a vote of 8 in favor, 0 opposed, and no abstentions.

III. Data Management Update
Summary: Greenblatt

Protocol Registration

Dr. Greenblatt stated that 232 human gene transfer protocols have been registered with ORDA to date. These protocols are categorized as follows: (1) 30 gene marking protocols, (2) 200 gene therapy protocols, and (3) 2 non-therapeutic protocols. The therapeutic protocols are further categorized as follows: (1) 23 for infectious diseases (all HIV-1), (2) 33 for monogenic diseases, (3) 138 for cancer, and (4) 6 for other disorders or diseases, e.g., rheumatoid arthritis and cardiovascular disease.

Since the December 15-16, 1997, RAC meeting, the following ten protocols were recommended for sole FDA review:

9708-207
Kaufman, Howard L.; Albert Einstein Cancer Center, Bronx, New York; *Phase I Clinical Trial of a Recombinant ALVAC-CEA-B7 Vaccine in the Treatment of Advanced Colorectal Carcinoma.*
Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP).
NIH/ORDA Receipt Date: 8-21-97. Sole FDA Review Recommended by NIH/ORDA: 11-25-97.

9709-215
von Mehren, Margaret; Fox Chase Cancer Center, Philadelphia, Pennsylvania; *Phase I/Pilot Study of ALVAC-CEA-B7.1 Immunization in Patients with Advanced Adenocarcinoma Expressing CEA*
Sponsor: National Cancer Institute - Cancer Therapy Evaluation Program (NCI-CTEP).
NIH/ORDA Receipt Date: 9-24-97. Sole FDA Review Recommended by NIH/ORDA: 10-28-97.

9709-216
von Mehren, Margaret; Fox Chase Cancer Center, Philadelphia, Pennsylvania; *Phase I/Pilot Study of p53 Intralesional Gene Therapy with Chemotherapy in Breast Cancer* Sponsor: National Cancer Institute - Cancer Therapy Evaluation Program (NCI-CTEP).
NIH/ORDA Receipt Date: 9-24-97. Sole FDA Review Recommended by NIH/ORDA: 10-28-97.

9710-220
Dobbs, Tracy W.; East Tennessee Oncology/Hematology, P.C., Knoxville, Tennessee; *A Phase II Gene Therapy Study in Patients with Non-Small Cell Lung Cancer Using SCH 58500 (rAd/p53) in Combination with Chemotherapy for Multiple Cycles* Sponsor: Schering Plough Research Institute.
NIH/ORDA Receipt Date: 10-31-97. Sole FDA Review Recommended by NIH/ORDA: 12-15-97.

9711-222
Freese, Andrew; Thomas Jefferson University, Philadelphia, Pennsylvania; *Gene Therapy of Canavan Disease*
NIH/ORDA Receipt Date: 11-12-97. Sole FDA Review Recommended by NIH/ORDA: 1-26-98.

9712-223
Bowman, Laura; St. Jude Children's Research Hospital, Memphis, Tennessee; *Phase I Study of Chemokine and Cytokine Gene Modified Allogeneic Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using a Retroviral Vector*
NIH/ORDA Receipt Date: 12-3-97. Sole FDA Review Recommended by NIH/ORDA: 12-29-97.

9712-224
Bowman, Laura; St. Jude Children's Research Hospital, Memphis, Tennessee; *Phase I Study of Chemokine and Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using an Adenoviral Vector*
NIH/ORDA Receipt Date: 12-3-97. Sole FDA Review Recommended by NIH/ORDA: 12-29-97.

9712-225
Isola, Luis M.; Mount Sinai Medical Center, New York, New York; *A Phase I Trial of Autologous and Allogeneic Bone Marrow Transplantation with Genetically Marked Cells for the Treatment of HIV Associated Lymphoid Malignancies*
NIH/ORDA Receipt Date: 12-15-97. Sole FDA Review Recommended by NIH/ORDA: 1-7-98.

9712-226
Dreicer, Robert; University of Iowa College of Medicine, Iowa City, Iowa; *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)* Sponsor: Gencell (Division Rhone-Poulenc Rorer Pharmaceuticals, Inc.)
NIH/ORDA Receipt Date: 12-17-97. Sole FDA Review Recommended by NIH/ORDA: 1-9-98.

9801-228
Kieback, Dirk G.; Baylor College of Medicine, Houston, Texas; *Phase I Study of Concomitant Adenovirus-Mediated Transduction of Ovarian Cancer with HSV-tk Gene Followed by Intravenous Administration of Acyclivor and Chemotherapy with Topotecan in Patients after Optimal Debulking Surgery for Recurrent Ovarian Cancer*
NIH/ORDA Receipt Date: 1-14-98. Sole FDA Review Recommended by NIH/ORDA: 2-5-98.

Dr. Greenblatt noted that although the RAC recommended sole FDA review of protocol # 9711-222, *Gene Therapy of Canavan Disease*, the committee agreed that there would be value in holding a generic discussion on a single issue arising from the RAC's consideration of this protocol. Specifically, the RAC recommended that a discussion involving *ad hoc* bioethics experts should be held on the issue of enrolling children in early phase gene transfer clinical trials that may involve greater than minimal risk. This discussion is scheduled for later during today's meeting.

Dr. Greenblatt stated that the following five human gene transfer protocols are currently under review by the RAC: #9801-227, #9801-229, #9801-230, #9802-231, and #9802-232. A preliminary discussion of Protocol #9802-235 (employing a herpesvirus vector) will be discussed later during today's meeting.

Protocol Amendments

Dr. Greenblatt noted that 12 human gene transfer protocol amendments were submitted to ORDA since the December RAC meeting.

Reports of Safety and Adverse Events and Protocol Updates

Dr. Greenblatt noted the submission of seven safety reports since the December RAC meeting. He highlighted the following three adverse reports as follows: (1) Two adverse reactions were reported for Protocol #9512-137. This protocol involves administration of the E1A gene via DNA/liposome complexes to patients with metastatic breast or ovarian cancer. One of these adverse reactions was similar to a previous report in which patients experienced nausea and vomiting following treatment. The breast cancer arm of this protocol has subsequently been closed; the ovarian cancer arm of the study remains open. (2) An adverse event was reported for Protocol #9709-214. This protocol involves administration of the adenovirus vector, Ad5CMV-p53, to patients with squamous cell carcinoma of the head and neck. Fourteen days following the third course of treatment, the patient experienced bleeding from the oral cavity, a drop in hematocrit, decreased blood pressure, and bloody emesis with clots. This event was considered possibly related to the treatment.

Dr. Greenblatt noted that one update was received involving Protocol #9703-183. The single patient proposed for this study was never treated due to the inability to grow out Epstein Barr Virus-specific cytotoxic T lymphocytes. The patient subsequently underwent a course of chemotherapy.

Gonadal Biodistribution of Gene Transfer Vectors

Dr. Greenblatt noted that Drs. Steven Bauer and Anne Pilaro, Center for Biologics Evaluation and Research, FDA, presented an overview related to the FDA's observation that multiple preclinical animal studies designed to assess vector biodistribution have demonstrated unexpected persistence of vector nucleic acid sequences in gonadal tissue. Specifically:

> **Nucleic acid persistence in gonadal tissues is evidenced by positive polymerase chain reaction (PCR) signals in DNA extracted from whole gonads.**
>
> **Evidence of nucleic acid persistence in gonadal tissues has been observed with multiple classes of vectors, formulations, and routes of administration.**

The FDA became aware of these data as part of multiple Investigational New Drug (IND) applications; however, under the limits of confidentiality, they could not discuss the specifics of these observations.

FDA representatives noted several issues that must be resolved before the implications of these observations can be determined:

The source of the gonadal PCR signal has not been determined, i.e., germ cells, blood cells, or stroma. Current PCR methods for detecting vector sequences are highly sensitive (capable of detecting one vector copy per microgram of cellular DNA); however, there is a high incidence of false positives and negatives.

There are limited data about whether these vectors are episomal or integrated.

It is unknown whether the presence of vector nucleic acid sequences in gonadal tissue is associated with any developmental effects.

FDA representatives welcomed the opportunity to present this information to the RAC and the public as a timely and appropriate mechanism for increasing public awareness of these findings and to stimulate continued public discussion of the implications of these observations.

Under the limits of confidentiality, the FDA could not discuss further specifics of the observations. Therefore, the RAC recommended that ORDA should send a letter to all principal investigators of clinical gene therapy trials and all IBCs requesting submission of all preclinical and clinical data available related to persistence of nucleic acid vectors in gonadal tissue. In a letter dated January 26, 1998, the RAC requested this information as part of its role and responsibility to ensure public awareness of recombinant DNA issues within the context of the *NIH Guidelines*. The *NIH Guidelines* are applicable to all research that is conducted at, or sponsored by, an institution that receives any support from the NIH for recombinant DNA research.

ORDA received approximately 80 responses to this request, and the RAC discussed these responses. Four responses indicated that vector sequences were detected in either the ovaries or testes in preclinical animal studies; however, the number of responses received was not representative of the number of clinical trials currently registered with ORDA.

The four responses indicating that vector sequences were detected in either ovaries or testes in preclinical animal studies are summarized as follows: (1) Peter T. Scardino, M.D., Baylor College of Medicine, Houston, Texas, stated that they published a paper documenting their preclinical data (Timme, T. L., et al., *Cancer Gene Therapy*, Volume 5, No. 1, 1998). Briefly, in murine experiments with adenoviral vectors expressing the Herpes Simplex Virus Thymidine Kinase (HSV-TK) gene, only 1 animal of 28 was found to have evidence of vector DNA present in testicular tissue by PCR analysis. (2) Simon J. Hall, M.D., The Mount Sinai Medical Center, New York, New York, stated that in murine experiments, 1 out of 14 mice had vector sequences in testes after injection of an adenovirus expressing HSV-TK into the prostate. No vector DNA sequences were noted within sperm aspirated from the epididymis. (3) Jeffrey Holt, M.D., Vanderbilt University, Nashville, Tennessee, stated that after intraperitoneal and intraprostate

injection of a retroviral vector in mice and rats, the vector sequences were detected by PCR in ovaries and testes for up to four weeks. (4) Verma Fimbres, Gencell Division of Rhone-Poulenc Rorer, Inc., stated that they have studied the biodistribution of adenovirus-p53 sequences. After intratumoral administration in nude mice, a weak signal was detected in ovaries; after intratracheal administration in mice, the ovaries were positive at day 3 but negative at day 31; after intraperitoneal administration in cotton rats, they reported vector sequences in ovaries but not in testes.

Four responses indicated that no vector sequences were detected in human gonadal tissues in follow-up studies as follows: (1) Genetic Therapy, Inc. (Gaithersburg, Maryland), no vector sequences were detected in gonads in 45 samples from 45 patients treated with retroviral vectors. (2) Steven M. Albelda, M.D., University of Pennsylvania, Philadelphia, Pennsylvania, no gonadal distribution was observed in four testicular samples analyzed from patients with mesothelioma treated with an adenovirus expressing HSV-TK in pleural space. (3) Chiron Corporation (Emeryville, California) reported no evidence of inadvertent germ-line transfer in samples of 118 patients infected with the human immunodeficiency virus (HIV) who received intramuscular injection of a retrovirus encoding the HIV *rev* gene. (4) Introgen Therapeutics, Inc. (Houston, Texas) reported no vector sequences were observed in the testes following administration of an adenovirus vector expressing the p53 tumor suppressor gene to three lung cancer patients, and one patient with head and neck cancer. (In the latter patient, an initial positive finding in testes was subsequently found to be due to surface contamination of the samples during processing.)

The RAC expressed concern about whether the information collected thus far was subject to quality control, and if researchers took any precautions to prevent contamination of the analyzed tissue. Of additional concern was the fact that many clinical investigators were not conducting appropriate assays to determine the presence of nucleic acid vectors in gonadal tissue.

Other Comments

Dr. Mickelson said the ORDA letter to IBCs and investigators was a first step in gathering data that would inform the public and the FDA regarding the issue of vector gonadal biodistribution. She noted that conclusive data demonstrating the risk of inadvertent germ-line alteration would require that potential subjects be informed of such information within the Informed Consent document; however, definitive data documenting such risk have not been submitted. Dr. Noguchi said the FDA was very pleased with this first effort at information gathering, and that there may be additional data that were not submitted to ORDA but that are pertinent to this issue. Dr. Mickelson noted a need to develop assays to assess whether vector integration into host genomes has occurred and, if so, to what cell types.

Dr. Gordon said he believed the RAC should raise a cautionary note regarding the possibility of inadvertent germ-line alteration. He suggested that the RAC should recommend to the NIH Director that NIH issue a Request for Applications (RFA) for proposals to develop animal systems to assess whether certain classes of vectors are capable of integrating their sequences into embryos or gametes.

Dr. McIvor stated that the major issue is whether there is any vector sequence integration in germ cells that will result in vertical transmission. Dr. Gordon explained that the problem of germ-line integration may be studied by direct introduction of the vectors into the embryos, e.g., via ovary follicle cells.

Dr. Ando stated that testing sperm samples for vector sequences is a complex issue. Sperm samples are usually contaminated with cells from tissue fluids, e.g., mononuclear cells. It is extremely difficult to determine whether the detected vector sequences are within the sperm cells. Dr. Gordon noted another layer of complexity, i.e., there are many sperm in the sample, and only one of those will fertilize the egg. Dr. Gordon suggested an experiment involving direct exposure of vectors to sperm cells at high vector to sperm cell ratios, and then *in vitro* fertilization to look for reporter gene expression in newborn animals for evidence of DNA transmission.

Dr. Markert agreed that a RFA to study DNA integration in the embryo is an excellent idea. Dr. Verma expressed a note of caution regarding interpretation of data if extremely small numbers of sperm cells are found to contain vector sequences. He asked how the significance of such findings would be recommended to the gene therapy community in general, and to the research subjects in particular. Dr. Gordon said that such findings should not hold up gene therapy research. The patients, however, should be provided with more definitive information than simply stating in the Informed Consent that the risk is unknown.

As a point of clarification, Dr. Noguchi said that the FDA did not bring this issue to the RAC to call a moratorium to gene therapy research, but, rather, to disclose this information publicly and to stimulate public discussion of the issue. Dr. Lysaught agreed that potential research subjects should be apprised of definitive information within the Informed Consent about the need for contraception.

Dr. Verma agreed that there is a need to gather more definitive research information regarding gonadal biodistribution to assess the level of positive findings that would pose significant risk to potential subjects and to determine whether these findings are related to specific classes of vectors.

Dr. Gordon made a motion to send a letter to the NIH Director recommending that an RFA be issued to study gonadal biodistribution of gene transfer vectors. Dr. Verma seconded the motion.

Dr. Mickelson stated that the objective of the RFA is to seek development of assays to study potential germ-line alteration. The RAC will continue to gather data from IBCs, Institutional Review Boards (IRBs), and investigators related to this issue. The objective of the RAC's recommendation is to advance the scientific state of the art and the knowledge about germ-line alteration as part of its public responsibility.

Committee Motion 2

A motion was made by Dr. Gordon and seconded by Dr. Verma to send a letter to the NIH Director recommending that NIH issue a Request for Applications (RFA) for proposals to develop assay systems for the study of inadvertent germ-line alteration by gene transfer vectors. The motion passed by a vote of 9 in favor, 0 opposed, and no abstentions.

Additional Comments

Ms. Knorr said that she would prepare a draft of the RAC's recommendation to circulate among the committee members. Dr. Mickelson suggested that Dr. Gordon work with ORDA on the proper language of the recommendation. Dr. Gordon agreed.

Dr. Lysaught stated that the RAC should demand more rigorous data from the investigators about the question of gonadal biodistribution of vectors, and should strengthen relevant statements in the Informed Consent documents. Ms. Knorr noted that Appendix M, *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects (Points to Consider)*, of the *NIH Guidelines*, should be revised to provide more specific instruction regarding reproductive consideration and patient follow-up. Dr. Mickelson agreed that the *Points to Consider* needs to be amended to stress the importance of reproductive considerations.

Dr. Gordon said that the proper assay systems may be technically too demanding for individual investigators to perform in their own laboratories. He suggested that the National Gene Vector Laboratories be entrusted with the task of assessing the germ-line risk of current and future vectors for human gene transfer. Dr. Gordon noted that in terms of the present state of the art, testing for gonadal biodistribution of vector sequences in human tissues is of limited value, and the statements in the Informed Consents about the need of contraception should be cautious. Dr. Mickelson emphasized the need for preclinical studies to develop definitive information.

Ms. Knorr noted a long overdue need to revise the *Points to Consider*. Dr. Mickelson charged the *Points to Consider* Subcommittee to develop specific recommendations to revise this document, and she encouraged ORDA to continue gathering information from IBCs and investigators. Ms. Knorr suggested including representatives from the FDA on the Subcommittee, and Dr. Mickelson agreed. Dr. Noguchi agreed to participate on the Subcommittee, and stated that the FDA recently revised its own guidance document.

Dr. Verma said that IBCs and investigators need to be reminded about the need to respond urgently to RAC requests for information. Dr. Gordon noted that the quality of data submitted by the investigators in response to this specific request lacks scientific rigor. Dr. Greenblatt said the letters did not show if any precautions were taken to prevent contamination of the analyzed tissue.

IV. Overview of the March 9, 1998, Gene Therapy Policy Conference (GTPC) Entitled: *Lentiviral Vectors for Gene Delivery*

Summary: McIvor

Dr. McIvor summarized the highlights of the second GTPC entitled: *Lentiviral Vectors for Gene Delivery,* held on March 9, 1998, at the Bethesda Marriott Hotel, Bethesda, Maryland. The GTPC was sponsored by the NIH ORDA and the RAC. The co-chairs were Peter K. Vogt, Ph.D., The Scripps Research Institute, La Jolla, California; and R. Scott McIvor, Ph.D., a RAC member, who is Director of the Gene Therapy Program at the University of Minnesota, Minneapolis, Minnesota.

The GTPC covered two major topics. The morning session chaired by Dr. Vogt focused on the biology of lentiviral vectors. The speakers were: (1) Malcolm Martin, M.D., NIH, Bethesda, Maryland, on *The Biology of Primate Lentiviral Infections*; (2) Inder Verma, Ph.D., The Salk Institute, La Jolla, California, on *Lentiviral Vectors for Gene Delivery*; (3) Didier Trono, M.D., University of Geneva, Geneva, Switzerland, on *Multiple Attenuated Lentiviral Vectors: Safety and Performance*; (4) Garry P. Nolan, Ph.D., Stanford University School of Medicine, Palo Alto, California, on *Regulated Determinants of Lentiviral Entry*; (5) Alan Kingsman, Ph.D., Oxford Biomedica, Ltd., Oxford, England, on *Human and Non-Human Lentiviral Vectors for Gene Delivery*; (6) John C. Olsen, Ph.D., University of North Carolina, Chapel Hill, North Carolina, on *Equine Lentivirus Vectors*; (7) Jakob Reiser, Ph.D., NIH, Bethesda, Maryland, on *High Titer HIV-1 Based Vector Systems*; and (8) James M. Wilson, M.D., Ph.D., University of Pennsylvania, Philadelphia, Pennsylvania, on *Delivery of Lentivirus CFTR into the Lungs*.

The afternoon session chaired by Dr. McIvor focused on manufacturing, safety, and testing issues related to lentiviral vector development. The speakers were: (1) Michael S. Wyand, D.V.M., Ph.D., GTC Mason Laboratories, Worcester, Massachusetts, on *Lessons from HIV Vaccine Development*; (2) Luigi Naldini, M.D., Ph.D., Cell Genesys, Inc., Foster City, California, on *Development of Safe and Effective Lentiviral Vectors*; (3) R. Paul Johnson, M.D., New England Primate Research Center, Southborough, Massachusetts, on *Biology of Lentivirus Infection in Non-Human Primates*; (4) Anne Pilaro, Ph.D., FDA, Rockville, Maryland, on *Preclinical Safety Evaluation of Lentivirus Vectors: FDA Regulatory Expectations*; (5) Dale Ando, M.D., Cell Genesys, Inc., Foster City, California, on *Biosafety Issues in the Clinical Applications of Lentiviral Vectors*; and (6) Douglas J. Jolly, Ph.D., Chiron Technologies, San Diego, California, on *First Steps Toward Commercial Use of Lentivirus Vectors*.

Both sessions ended with roundtable discussions with speakers. Special panelists in the afternoon session included Estuardo Aguilar-Cordova, Ph.D., a RAC member from Texas Childrens Hospital, Houston, Texas; and Carolyn Wilson, Ph.D., FDA, Rockville, Maryland.

Dr. McIvor presented the *Consensus Summary of the March 9, 1998, GTPC*. The final consensus document of the GTPC will be prepared after review by RAC members.

Dr. McIvor stated that the overall conclusion of this GTPC indicated a rapidly-developing technology over the last two to three years in the field of lentiviral vectors. The results indicate remarkable gene transfer efficiency and gene expression in a variety of dividing and non-dividing cell types. The advance makes a compelling argument for potential clinical use of these viral vectors. Dr. McIvor summarized the highlights of the presentations as follows:

Dr. Malcolm Martin presented an overview of lentivirus biology and replication using HIV as an example. He provided an extensive review of the functions of various HIV genes. Similar to the murine retroviruses, HIV has *gag, pol,* and *env* genes plus the long terminal repeat (LTR) controlling viral RNA transcription. In addition, HIV has several accessory genes, e.g., *tat, rev, vif, vpr, vpu,* and *nef*. He discussed receptors that mediate cell entry of the virus.

Dr. Verma presented an overview of his work on the development of vectors using HIV sequences. The early vectors contained most of the accessory viral genes, but the *env* gene has been replaced

with the amphotropic *env* gene of Moloney murine retrovirus or the G protein gene of vesicular stomatitis virus (VSV). Most of the accessory genes have been deleted from the second generation vectors, and questions regarding inclusion and exclusion of these accessory genes for optimized efficiency of transgene expression were discussed. He presented data on gene transfer and expression in differentiated tissues such as brain and retina.

Dr. Trono presented an assessment of the molecular components responsible for the attractive feature of lentivirus vectors, i.e., their capability to integrate into the genome of non-dividing cells. At least three components of the pre-integration complex of the cell nuclear transport machinery contribute to the karyophilic character, i.e., matrix, Vpr, and integrase.

Dr. Nolan presented data demonstrating a relationship between NFκB signaling pathway and activation of T cells to overcome the block of first strand jump during reverse transcription. (Dr. McIvor noted that the block may be relevant to Dr. Wilson's data on the lack of proviral DNA integration in his lung cell system.) In his presentation of feline immunodeficiency virus vectors, Dr. Nolan also discussed the advantage and disadvantage of using non-human lentiviruses.

Dr. Kingsman discussed the development of vectors based on equine infectious anemia virus (EIAV). These vectors are similar to HIV vectors in structure but differ in two genes, dUTPase and S2. These vectors exhibit expression in brain, but the tropism and toxicity are not yet well characterized.

Dr. Olsen presented data on the development of EIAV vectors. These vectors can transduce a transgene into cultured human fibroblasts at a transduction efficiency of 50 percent. The transduction efficiency was increased in equine and canine cells when treated with aphidocolin, an inhibitor of cell division.

Dr. Reiser presented HIV vector data indicating a very high titer (10^7 colony forming units/ml); the titer was reduced upon deletion of the *tat* gene. The accessory proteins, however, are not needed for transduction of non-dividing cells.

Dr. Wilson presented data related to an HIV vector in a lung xenograft model. Transduction of poorly differentiated cells *in vivo* was observed; however, no transduction of well differentiated cells *in vivo* was observed. There are issues that need to be resolved regarding an entry block of HIV vectors into lung cells involving the formation of a pre-integration complex.

Dr. McIvor reported that, at the roundtable discussion, there was much discussion about the details of specific molecular components of the lentiviral vector systems and experiments used to discern their relevant importance. There was discussion of integration, specificity, insertional mutagenesis, and relative effectiveness of HIV vectors versus non-human lentivirus vectors. The benefits and disadvantages of non-human lentiviruses were discussed. As non-human pathogens, lentivirus vectors may pose fewer safety concerns; however, the potential benefits must be carefully weighed against any unknown risks.

Dr. Wyand presented his experience with the development of lentivirus vaccines using the simian immunodeficiency virus (SIV) system. He noted that the greater the number of deletions

engineered into the virus, the less pathogenic the virus becomes. Pathogenicity is absent in viruses with three or more deletions in accessory proteins. The issue of recombination following co-administration of two viruses with different types of deletions should be addressed.

Dr. Naldini presented his studies on development of first, second, and third generation HIV vectors. Increased safety was achieved by splitting different packaging functions into separate plasmids and using a self inactivating vector. In one construct, there was an overlap of only 40 base pairs of DNA sequence between the vector and the packaging function; therefore, the likelihood of homologous recombination leading to generation of replication-competent viruses (RCV) is very unlikely.

Dr. Johnson provided a perspective from studies of non-human primate lentivirus biology for better understanding of potential safety issues regarding the usage of lentiviral vectors in humans. Primate lentiviruses are non-pathogenic in their natural hosts; cross species transmission is primarily responsible for primate lentivirus pathogenicity. Non-human primates are not good models for the study of HIV pathogenesis due to low level of virus replication and lack of acquired immunodeficiency syndrome development. The chimeric HIV-2/SIV based lentivirus vectors in macaques may provide an animal model for analyzing immunogenicity and pathogenicity.

Dr. Pilaro presented the FDA's perspective on preclinical safety evaluation of lentivirus vectors. Many of the FDA's concerns are similar to those originally faced with murine retrovirus vectors, i.e., RCV, germ-line transmission, and insertional mutagenesis. Important questions that should be addressed include the relationship between dosage and biological activity, relationship between dosage and toxicity, and effective routes of administration. Lentiviruses are novel agents. Supporting preclinical data should include thorough pharmacological and toxicological analyses; such analyses will be critical to the development of these vectors.

Dr. Ando addressed several concerns about the development of lentiviruses as gene transfer vectors, e.g., potential for mobilization of lentiviral vectors in HIV-infected patients, and the necessity to discontinue antiviral therapies in these patients (most of the antiviral agents would block the effectiveness against lentivirus vectors). The need to stop antiviral therapies presents a disadvantage for the use of lentiviral vectors; on the other hand, it provides an advantage as a therapy if adverse effects were observed in the use of these vectors. Dr. Ando presented several scenarios by which RCV might arise during the use of lentiviral vectors.

Dr. Jolly presented clinical trial results in which a murine retroviral vector was used to promote immunity against HIV envelope proteins. The results of these clinical trials indicate that administration of the vector is safe and induced cytotoxic T lymphocyte responses.

Dr. McIvor stated that, in the roundtable discussion after the afternoon session, there was a discussion addressing the possibility of recombination between different molecular components of the vectors and packaging cells that might result in the generation of RCV. He noted that there is no indication that a greater stringency for RCV tests will be required for lentiviruses than for murine retroviruses; the tests may just be different between these two virus systems. Specific tests include HIV Gag p24 immunocapture, HIV-1 *gag* RNA PCR, and a test for VSV-G protein; the

release criteria of these test results have not been established. A question was raised about appropriate animal models to assess the risk of mobilization in HIV-infected patients.

Several people asked about the appropriate biosafety level needed to conduct experiments with lentiviral vectors in the laboratory; these inquiries reflected a wide range of interest in using these vectors.

Other Comments

Dr. Verma clarified several points regarding HIV vectors. First, vectors with deletion of all six accessory genes perform just as well as vectors retaining all the accessory genes in terms of their ability to introduce genes into non-dividing cells (variation may occur if different target cells are used). The deletion of all the pathogenic proteins is an important step in the development of a safer and more acceptable vector. Second, the issue of viral DNA integration of lentiviral vectors is the same as for murine retroviral vectors, i.e., how efficient, how productive (entire or partial proviral DNA), and the extent of target cells having integration. Third, the vectors are designed to have very limited possibility of recombination (retaining only 22 percent of the viral genome). The relative short term of two years in the development of lentiviral vectors is made possible by building on the long term experience gained over 15 years of developing murine retroviruses. Dr. Verma emphasized that the field of lentiviral vectors research is still evolving.

Dr. Aguilar-Cordova commended Dr. McIvor for organizing this informative conference. He noted that the release criteria of lentiviral vectors, particularly with replication-competent retrovirus (RCR) assays, were not addressed in the conference. The development of these criteria for the murine retroviral vectors has been an evolving experience. In terms of refinement, the first generation lentiviral vectors are equivalent to third generation murine retroviral vectors, so there is much less likelihood of generating RCR. Dr. Aguilar-Cordova, however, saw the need for collaborative efforts involving NIH, the FDA, and industry to develop RCR assay systems that can be standardized and extended in the future.

Dr. Ando noted that the early NIH/FDA Gene Therapy Conferences have been very successful in coordinating FDA officials and industry representatives to develop standards and endpoints for sensitivity and types of assays relevant to the release criteria. Such collaborative assessment has been very successful for developing murine retroviral and other gene delivery systems; a similar effort should be made to develop lentiviral vectors.

Dr. Mickelson agreed that this kind of concerted effort of all the parties is important to assuage any kind of heightened public concern about safety issues with HIV-based vectors. The public should be assured that NIH, the FDA, and industry are developing safety criteria for the use of these vectors.

Dr. McIvor credited Drs. Verma and Ando for their initial efforts in assembling the speaker list for the GTPC, which he and Dr. Vogt co-chaired. Dr. McIvor emphasized that the GTPC provided the groundwork for evaluating gene transfer protocols using these novel vectors, if they are submitted to ORDA. Only then can the actual criteria be established about the proposed vector

and the safety testing to be performed. These criteria should be established on a case-by-case basis.

Dr. Noguchi stated that the FDA is ready to evaluate any lentiviral protocols on a case-by-case basis. He encouraged any investigators intending to use these vectors to contact Dr. Pilaro at the FDA for a pre-IND discussion.

Dr. Mickelson noted that the observation of no HIV integration in HIV-infected adults or newborns is not completely relevant to the situation where lentiviral vectors are used. Administration of a vector with an extensive deletion of several viral genes is not equivalent to the natural course of infection with HIV in humans.

Dr. Verma stated that it is difficult to address Dr. Mickelson's concern in any definitive way because there are not enough data about the use of these vectors. From the knowledge of lentivirus life cycle, however, the accessory proteins do not contribute to the mechanism of integration. In addition, as opposed to the situation in HIV-infected patients, there is no reintegration of the vectors within the subjects administered with the vectors because the vectors are replication incompetent.

Dr. Gordon said that, based on the experience with experiments of infecting mice or embryos with Moloney murine leukemia virus and vectors derived from it, virus integration depends more on the titer of the virus used in the infection than on whether the virus is intact or has some viral genes deleted.

Dr. McIvor asked for RAC volunteers to help him in developing the final report on the GTPC proceedings. Drs. Verma, Lysaught, and Mickelson volunteered to help him.

A summary of the March 9, 1998, GTPC entitled: *Lentiviral Vectors for Gene Delivery*, can be found at the following web site: http://www.nih.gov/od/orda/.

V. Amendment to Appendix M-1, *Submission Requirements - Human Gene Transfer Experiments*

Summary: Aguilar-Cordova

Dr. Aguilar-Cordova noted the February 11, 1998, *Federal Register* notice of the proposed action regarding an optional electronic format for submission of human gene transfer protocols to ORDA.

Appendix M-I, *Submission Requirements -- Human Gene Transfer Experiments*, of the *NIH Guidelines*, stipulates requirements for submission of documents to ORDA. In January 1998, Dr. Aguilar-Cordova participated in a pilot test with ORDA staff regarding electronic submission of documents. In this test, the documents submitted electronically included a human gene transfer protocol; responses to Appendices M-II through M-V, *Points to Consider*; and the ORDA registration document. The 82-page electronic submission, including tables, satisfactorily proved the efficiency and effectiveness of using this method for submission of protocols.

ORDA recognizes that electronic submission of documents is an accepted standard of practice within the scientific community; therefore, this practice is not novel. The practice of using this medium to submit protocols to ORDA, however, is novel and therefore requires amendments to the *NIH Guidelines*. As a result, ORDA proposed to amend Appendix M-I of the *NIH Guidelines* to provide guidance to investigators regarding optional electronic submission procedures.

Electronic submission of human gene transfer protocols to ORDA offers several distinct advantages over the current practice of submitting protocols by printed matter, including: (1) ORDA can review protocols more expeditiously because they are received immediately; (2) electronic submission allows ORDA to search protocols electronically for keywords or phrases; (3) the time needed for ORDA to prepare summary registration documents would be reduced substantially because the investigator would be required to complete most of the registration information as part of the electronic submission; and (4) the RAC review of individual protocols would be expedited.

Other Comments

Dr. Mickelson asked if the documents submitted by the electronic format required point-by-point responses to Appendix M-II through V. Dr. Aguilar-Cordova responded no; however, recent amendments to the *NIH Guidelines* require that all of the issues addressed in these appendices must be included within the clinical protocol if point-by-point responses are not submitted. Dr. Aguilar-Cordova explained that he entered the information directly onto the ORDA summary sheet. This summary information was forwarded to RAC members for their preliminary review of the protocol. The other documents were sent to ORDA by E-mail with attachments. No additional documents were required in the electronic submission. Documents such as IRB and IBC approvals, which require signature, were sent to ORDA by facsimile.

Ms. Knorr explained that ORDA would like the electronic format to remain flexible. The objective is to provide investigators with a variety of options for protocol submission. If electronic submission is preferred by some investigators, ORDA will provide this option. She noted that ORDA plans to work with the FDA, perhaps toward developing a unified submission format.

Dr. Gordon noted the additional advantage of the electronic format is that this process should also facilitate the transmission of protocol amendments.

Committee Motion 3

A motion was made by Dr. Aguilar-Cordova and seconded by Dr. McIvor to accept the proposed action published in the *Federal Register* of February 11, 1998 (63 FR 7054) to permit submission of human gene transfer protocols to ORDA for registration in an optional electronic format. The motion passed by a vote of 9 in favor, 0 opposed, and 1 abstention

VI. Chimeraplasty: A Gene Modification Technology Employing Oligonucleotides
Speaker: Kumar

Presentation--Dr. Kumar

Dr. Ramesh Kumar, Kimeragen, Newtown, Pennsylvania, presented an emerging new technology termed "chimeraplasty" that has the potential to treat human diseases, as suggested by recent animal studies. There are many approaches to gene-based therapeutics: antisense, ribozyme, gene therapy, homologous recombination, and gene activation. Chimeraplasty, which uses chimeric molecules to induce gene repair, is distinct from all these approaches. This technology is similar to an antisense or a ribozyme approach because it uses synthetic oligonucleotides; however, rather than a RNA-based approach, chimeraplasty involves gene repair at the DNA level.

In the last 25 years, the tools of molecular biology have provided methods for actually inserting DNA into the genome. Until recently, such integration has been mostly random and homologous recombination is rare in most organisms. The limiting step to homologous recombination is the precise pairing of vector sequences with the target DNA. The problem facing the pairing efficiency is twofold: to find and repair the target efficiently, and to overcome the problem of mismatches. If the vector has a mismatch sequence, the question is how to make the DNA mismatch stable.

A solution to the stability problem is to devise a chimeric, or a hybrid, molecule of RNA and DNA that results in the more stable DNA/RNA hybridization rather than the less stable DNA/DNA hybridization. This concept led to the design of the chimeric molecule, termed a "chimeraplast." A chimeraplast is a synthetic oligonucleotide that has the ability to fold into a duplex due to its self-complementary sequences. The folding is aided by the hairpin "T-loops" formed by a stretch of thymidine residues at both ends of the chimeric molecule. The function of the single-stranded T-loops is to prevent random insertion. One strand of the duplex is a chimeric sequence consisting of the DNA-like "mutator region" flanked by RNA-like sequences at both sides. The key properties of this molecule are: (1) chimeric in nature, (2) double-stranded, and (3) the single stranded T-loops.

The fate of this double-stranded chimeric molecule when given to the cell is different from a double-stranded plasmid DNA. Dr. Kumar showed a slide to illustrate the molecular pairing of the chimeraplast with a target DNA sequence. The intermediate complex is a four-strand structure with classical double D-loops. Two important features of the complex are: (1) the chimera is involved in hybridization, and (2) as a result of hybridization and the design of the chimera two mismatched pairs are created, i.e., one involving the DNA/DNA loop and another the RNA/DNA hybrid loop. One critical feature of this new technology is that the more stable RNA/DNA hybrid loop activates a naturally occurring gene-correction mechanism, which modifies precisely the DNA at the target site.

Dr. Kumar noted several advantages of chimeraplasty over the conventional homologous recombination technology: (1) complex targeting vectors are not required because synthetically designed oligonucleotides are used, (2) drug selection is not required, (3) the frequency of repair is greater than 1 in 1,000, and is higher than homologous recombination, (4) gene correction experiments can be performed in less than one week (as opposed to more than one month using homologous recombination), and (5) licenses are not required (in contrast to technology that involves genes that may be patentable).

Dr. Kumar presented gel electrophoresis data showing that a chimeraplast has properties similar to double-stranded DNA molecules. On high performance liquid chromatography, chimeric molecules are clearly separated from the DNA molecules. The chimeric molecules have enhanced thermal stability over DNA molecules. Distinctive fragments are formed upon digestion with S1 nuclease. The chimera is stable to DNAase digestion and is completely resistant to RNAase A and RNAase H. Resistance to nuclease digestion is a property compatible with *in vivo* delivery.

Dr. Kumar presented data to demonstrate that chimeraplasts can work in cell culture systems *in vitro*, and in animal systems *in vivo*. The test system involved a vector carrying the green flourescent protein (GFP) and a new vector constructed by site-directed mutagenesis to introduce a stop codon mutation (GAG to TAG) of GFP to render it non-flourescent (NFP). Vectors containing GFP and NFP were used to transfect monkey CV1 cells, human 293 cells, and porcine PK15 cells. Stably transfected cells were isolated. Dr. Kumar showed data to demonstrate *in vivo* correction of the mutation with specially designed chimeraplasts in this cell system. One of the chimeraplasts restored the fluorescent property of the protein by converting the TAG sequence back to GAG, and another converted TAG to a new codon (TCG), making a new protein. Dr. Kumar showed slides illustrating the flourescent properties of the cells in tissue culture dishes.

In summary, Dr. Kumar noted that the reason for the high efficiency gene repair was partly due to the small size of chimeraplast molecules permitting efficient entry into the cell nucleus. In contrast, most transfected large-plasmid DNA molecules are trapped in the cytoplasm and fail to enter the nucleus.

He described an experiment conducted at Cornell University, Ithaca, New York, in which a chimeraplast was introduced into tobacco plant cells causing a mutation encoding herbicide resistance. The gene-corrected plant cells were grown to mature tobacco plants. The same technique has been successfully applied to corn.

Dr. Kumar described a study published in *Science* (September 1996) involving the β hemoglobin gene. A form of sickle cell anemia results when the β globin gene contains a single point mutation. (A control experiment was performed with the δ globin gene to rule out any experimental artifact of non-specific action of the chimeraplast on a non-target gene.) The cells were transfected *in vitro*, and the DNA of the corrected cells was analyzed. The data demonstrated that 6 out of 23 cell clones converted the sickle mutation to the normal genotype, an unexpected high frequency. Other control experiments ruled out that the observed effect was the result of a PCR artifact in the presence of excess chimeraplast molecules. Importantly, chimeraplasts with one mismatch corrected the mutation much more efficiently than chimeric molecules with two or three mismatches.

Dr. Kumar then turned to studies of simple bacterial systems in order to understand the genetics of the process and the enzymology behind the process of gene repair. The experiments were to convert the tetracycline resistance gene of plasmid pBR322, or the kanamycin resistance gene of plasmid AB15, to non-functioning forms sensitive to antibiotics. Dr. Kumar showed DNA sequencing data of successful conversion of the kanamycin gene from a resistant to an antibiotic sensitive phenotype. Similar successful results were obtained in the tetracycline gene conversion system. Analysis of the genetic mechanism of the bacterial gene correction system indicated that

RecA was essential for this correction process; correction was not observed in RecA$^-$ bacteria. The second enzyme required for this repair pathway was Mut S.

Dr. Kumar concluded that the genetic analysis revealed two important steps involved in the gene correction pathway in bacteria: (1) the "pairing" activity requiring the presence of RecA, and (2) the "mismatch repair" activity requiring the presence of Mut S.

To address whether the same process found in bacteria occurs in mammalian cells, two experimental systems were used. First, mammalian cell lines lacking Rec A- and Mut S-like activities were studied. Second, a cell-free system was used to study this problem. A liver cell mitochondria extract was incubated with the tetracycline resistance plasmid (described above) in the presence of gene-correction chimeraplast. The incubation mixture was then put into a cell deficient in RecA- and Mut S-like activities to determine if the activities present in the mitochondria extract would complement the RecA$^-$/Mut S$^-$ phenotype of the cell. These experiments, performed in Dr. Clifford J. Steer's laboratory at University of Minnesota, confirmed the expected complementation of the enzyme activities by the mitochondria extract. A similar experiment was performed with a nuclear extract. These experiments established a cell-free system of gene repair assay to investigate which chimera is superior and what is the biochemical mechanism of gene repair.

Dr. Kumar noted several issues for *in vivo* delivery of chimeraplasts: (1) stability in biological fluids, (2) efficient uptake by desired cells, (3) nuclear translocation, (4) optimal stoichiometry, and (5) lack of toxicity. Dr. Kumar referred to the *in vivo* animal experiments performed by Dr. Clifford J. Steer and his colleagues at University of Minnesota to provide answers to several of these questions.

Dr. Kumar described the hepatocyte experiments published in *Hepatology* in 1997 by Dr. Steer and his colleagues. The chimeric oligonucleotide was delivered as a complex with a protecting polycation, polyethylenimine, that in turn was modified with a ligand, lactose. This allowed targeting to a specific receptor, in this case the asialoglycoprotein receptor (ASGPR), of hepatocytes. Dr. Kumar showed the fluorescence data obtained from experiments using the human hepatoma cells, HUA7. The first experiment showed that, without the ASGPR ligand, the fluorescence-labeled chimeraplast entered some liver cells but not all cells. An improved experiment was performed in primary rat liver cells using the ASGPR ligand that activated ligand-mediated endocytosis. The data showed that almost all treated cells had green fluorescence in the nuclei. This experiment demonstrated a highly efficient nuclear translocation of the chimeraplast in the liver cells.

To address the question of site-specific correction of a genetic defect in an animal systems, Dr. Steer and his colleagues performed experiments in the rat factor IX gene (B. T. Kren et al., *Nature Medicine* 4: 285-290, 1998). In this study, a chimeric RNA/DNA oligonucleotide was constructed to induce a sequence mutation in the rat factor IX gene, resulting in prolonged coagulation. Oligonucleotides were targeted to hepatocytes in cell culture or *in vivo* by intravenous injection. Nucleotide conversion was both site specific and dose dependent. The mutated gene was associated *in vivo* with significantly reduced factor IX coagulant activity and a marked prolongation of the activated partial thromboplastin time. The results demonstrated that

single-base-pair alterations can be introduced in hepatocytes *in situ* by RNA/DNA oligonucleotides, suggesting a powerful strategy for hepatic gene repair without the use of viral vectors. Dr. Kumar noted the high frequency of gene conversion in this rat factor IX model. The gene conversion was confirmed by analyses at the DNA, RNA, and protein levels.

Dr. Kumar stated that the *in vivo* experiments have been extended to another rat model of gene deficiency for an enzyme involved in conjugating bilirubin in serum. Without this enzyme, bilirubin builds up in the blood stream. This animal model is useful to perform preclinical studies for a potential gene transfer study of a similar gene deficiency in humans. Dr. Kumar said that the study performed at Albert Einstein College of Medicine, New York, New York, is ongoing and the data have not been published. The preliminary results suggested gene correction by an appropriately designed chimeraplast.

In conclusion, Dr. Kumar summarized the rationale for high efficiency targeting by chimeraplasty: (1) a favorable high stoichiometry of chimeras to the targeting sequences (up to 10^8 : 1), (2) favorable stability of chimeric molecules (indicated by high melting temperature of the duplex and resistant to nucleases), (3) a unique structure of a "A form" duplex with no free ends to reduce the chance of random insertion, and (4) an integration-independent biochemical mechanism involving RecA and Mut S enzyme activities of the gene repair pathway.

Other Comments

Dr. Gordon asked about the average size of the T-loop duplexes and whether using a chimera of longer sequences will be able to repair a DNA sequence containing more than one mismatch. Dr. Kumar responded that the average size of the chimeraplasts is 25 nucleotides in the homology region. The length is chosen based on the literature data showing that a sequence of 19 bases is expected to represent a unique sequence in the human genome. Increasing the duplex length might improve its ability to correct genes with more than one mismatch. The T-loop size, however, is not important for this function; it needs a minimum of three thymidine bases.

Dr. Gordon asked if gene correction by the chimera is dependent on the cell cycle. Dr. Kumar responded that, to the extent of his knowledge, the process is independent of the cell cycle; the non-dividing hepatocytes in G_0 phase are receptive to chimeraplasts. He noted that this repair pathway is distinct from DNA replication.

Dr. Noguchi asked if all gene mutations are equally susceptible to correction by chimeraplasts. Dr. Kumar responded that the question involves two parts. First, is the sequence context important? From the samples of DNA sequences he and other scientists have studied, there is no decipherable context effect. Second, is there any difference between transition and transversion mutations? He said from all the studies performed to date, there is no difference between these two types of point mutations; however, deletion mutations appear to be less efficiently corrected than point mutations.

Dr. Verma noted that there are 10^8 hepatocytes in a rat liver, and to produce 5 µg/ml of factor IX in the serum, the gene correction efficiency must be at least 80 to 90 percent. He asked what is the serum factor IX level before gene correction. Dr. Kumar did not answer that question directly, but

he said that they are collaborating with the investigators at the University of North Carolina on a dog hemophilia model in which there is no factor IX activity.

Dr. Verma noted that in the tetracycline resistance experiments, there are only 50 transformed colonies on each culture plate. Dr. Kumar explained that the small number of colonies is due to poor efficiency of plasmid entry into the bacterial cells. They are working on receptor-mediated endocytosis to improve the uptake of chimeraplasts into cells, particularly when applied to animal systems.

Dr. McIvor was impressed with the efficiency of gene correction, and he asked if these genetic changes are passed along to daughter cells. Dr. Kumar responded that there are unpublished data showing permanent changes. Dr. Steer's group (rat liver experiments) saved liver biopsy samples taken from different time points after gene correction, and analysis of these samples indicated persistent gene correction. In another study, they found that corrected cells were present in the regenerated liver after partial hepatectomy. In the bacterial systems, the corrected genes persisted after propagation of the bacterial colonies for many generations. A similar observation was made in the sickle cell system. Dr. Kumar noted that the evidence from all different systems suggests that the genetic changes are permanent and inheritable. Dr. McIvor noted that all the experiments pertaining to his question are still unpublished; it has not been demonstrated that any such genetic correction is passed on to the offspring. Dr. Kumar agreed.

Dr. Aguilar-Cordova asked if there was any chimera sequence integrated into the genome; he noted there were 10^8 chimeric molecules per nucleus. As a point of clarification, Dr. Kumar said that 10^8 is the upper limit of the uptake; typically, there are 10^4 to 10^5 molecules per nucleus. Dr. Kumar said that the experiment to rigorously rule out integration is difficult. Evidence from Southern blot and PCR analyses has, indirectly, ruled out integration of cells treated with chimeraplasts containing no correcting mismatches. The background mutation rate was not increased following treatment of animal cells with chimeric molecules.

Dr. Aguilar-Cordova noted that these assays are not rigorous enough to rule out integration. Dr. Kumar agreed, and stated that they are trying to develop assays to detect the low frequency integration. He noted that the technology is very new, and much more work remains to be done. Dr. Aguilar-Cordova commended Dr. Kumar for bringing this new technology to the attention of the RAC well before submission of any clinical trial protocol.

Dr. Kathleen High (University of Pennsylvania) noted that for hemophilia patients with factor IX deficiency the efficiency of gene correction in the liver must be very high to have any clinical benefit. She asked if a mixing experiment has been performed with sera obtained from treated and untreated animals to see whether the treated serum can neutralize the inhibitory effect exhibited by the factor IX with serine residue mutation. Dr. Kumar responded that Dr. Steer's group is conducting a study in another animal model in which there is no background activity of the mutated factor IX.

Dr. Robert Moen (Baxter Healthcare Corporation, Round Lake, Illinois), asked if chimeraplasty can be applied to germ-line alteration. Dr. Kumar responded that the technology is very new, and such applications have not been investigated.

Dr. Verma noted a "News and Views" item (*Nature Medicine, 4* 274-275, 1998) by Dr. Michael Strauss (Berlin, Germany) stating, "Many researchers (including our group) have since applied this technology to their gene of interest and most of them have failed so far." Dr. Verma asked Dr. Kumar to comment on this statement.

Dr. Kumar responded that his company is trying to solve the technical problems for its potential customers. He explained that many factors may contribute to the failure of such experiments. The synthesis of the chimeric oligonucleotides could be deficient; most of the commercially prepared oligonucleotides did not pass his company's quality control tests. Another problem is efficient nuclear delivery of the chimeric molecules; most of the failed experiments did not use proper tests to show that the chimera was indeed delivered to nuclei of cells. Another potential problem involves the selection of the target and the chimera; some target genes may not be amenable to correction by this technique. Dr. Kumar stated that his company is striving to provide high quality reagents for investigators in their experiments. He emphasized that the technique is very new, and it will take time and experience to make such a technology a routine practice.

Dr. Mickelson thanked Dr. Kumar for the very interesting presentation about this novel technology for gene correction.

VII. Discussion Regarding Human Gene Transfer Protocol 9802-235 entitled: *A Dose Escalating Phase I Study of the Treatment of Malignant Glioma with G207, a Genetically Engineered HSV-1*

Investigators: James Markert, M.D., University of Alabama at Birmingham, and Michael Medlock, M.D., Georgetown University Medical Center
Sponsor: NeuroVir, Inc.

Dr. Mickelson stated that NeuroVir, Inc. has proposed a human gene transfer protocol for the treatment of malignant glioma with G207, a genetically engineered Herpes Simplex Virus Type 1 (HSV-1). This protocol represents the first use of a replication-competent HSV-1 vector for human gene transfer research. Dr. Mickelson welcomed the representatives from NeuroVir, Inc. to the RAC to make an informal presentation about the novel application of an HSV-1 vector for the treatment of a human disease. She noted that the RAC had invited several *ad hoc* herpes virus experts to the December 15, 1997, RAC meeting, in anticipation of this first herpesvirus protocol. During that meeting, Dr. Stephen Straus, NIH, Bethesda, Maryland, raised nine safety issues that the RAC should consider when reviewing herpesvirus proposals: (1) replication, (2) stability, (3) virulence, (4) latency, (5) shedding, (6) reactivation, (7) recombination, (8) effectiveness of antiviral therapy, and (9) seroconversion.

Presentation and Discussion--Dr. Tufaro and Ms. Osborne

Frank Tufaro, Ph.D., Chief Scientific Officer, and Sheryl Osborne, Vice President for Regulatory and Clinical Affairs, NeuroVir, Inc. (Vancouver, British Columbia, Canada), were present to respond to the RAC members' comments and questions.

Dr. Mickelson said that the proposal is to treat patients with malignant glioma by direct intracranial injection of a HSV vector. The vector was derived from a parental laboratory strain

HSV-1(F) by deletions in both copies of the $\gamma_1$34.5 neurovirulence gene and a disabling insertion of the *E. coli LacZ* gene into the ICP6 region. This insertion inactivates the viral ribonucleotide reductase gene, and serves as a marker for monitoring the spread or potential shedding of the vector.

Dr. Mickelson asked if inactivation of the ribonucleotide reductase adds a safety factor to render the virus replication incompetent in non-dividing normal brain cells. Dr. Tufaro responded yes, that inactivation of the viral enzyme activity is useful for differentiating between dividing and non-dividing cells. *LacZ* insertion simultaneously serves both purposes of ICP6 inactivation and as a marker for the vector.

Dr. Mickelson noted that the range of dose escalation is from 1×10^6 to 1×10^9 plaque forming units (pfu) of G207 in half log increases, and a total of 24 patients will be enrolled.

Dr. Mickelson asked about the relative replication-competence of the vector in dividing versus non-dividing brain cells *in vivo*; the situation is different from the tissue culture cells *in vitro*, which are generally actively dividing. Dr. Tufaro explained that tissue culture is not a relevant model for HSV, and said an animal model is needed for the study of this virus, e.g., latency is impossible to establish in tissue culture. The "gold standard" for HSV replication and toxicity is the Aotus monkey. Fewer than 1,000 virus particles injected intracranially will cause serious encephalitis within several days. Dr. Tufaro said the G207 vector caused no disease in Aotus monkey in doses as high as five times of the highest proposed human dose (1×10^9 pfu). In mice, no encephalitis and virus replication was noted after intracranial injection of 10^7 pfu of G207. There are four orders of magnitude of therapeutic index (therapeutic doses vs. toxic doses) for brain tumors in these animal models. Dr. Tufaro said that G207 is a safe vector that kills tumor cells selectively.

Dr. Mickelson asked about the issue of latency. Dr. Tufaro said that G207 can establish a latent infection. The viral genome is present in Aotus monkey brain two years after injection of the vector. In rodent experiments, there is latency but no virus reactivation; apparently, reactivation of G207 in rodents is compromised by inactivation of ribonucleotide reductase and $\gamma_1$34.5 neurovirulence gene.

Dr. Mickelson asked how the vector preparations are characterized in terms of the stability of the virus genome. Dr. Tufaro said that they have set up stringent assays for vector characterization. The $\gamma_1$34.5 neurovirulence gene is assayed by a PCR technique that assesses junction sequences. The vector preparations for clinical use were injected into the highly sensitive Aotus monkey to assure that no wild type virus was present. Sensitivity to acyclovir, the antiviral agent against the thymidine kinase (TK), is a useful parameter. Dr. Tufaro said many biochemical and functional assays have been developed to characterize the vector products for human application. These include Southern blot analysis, PCR analysis, and a sensitive functional assay for suppression for the lack of $\gamma_1$34.5 gene.

Dr. Mickelson inquired if tumor biopsy and HSV antibody status were part of the eligibility criteria. Ms. Osborne said that HSV antibody status is not an exclusion criterion because HSV infection is very prevalent among the general population. The antiviral antibody titer, however,

will be monitored as part of the study plan. Dr. Tufaro said that multiple injections of vectors have been performed in the Aotus monkey and no serious toxic effect was noted. Regarding the question of biopsy, Ms. Osborne said that a pathologically-proven brain tumor is a part of the eligibility criteria; additional brain biopsy to monitor the treatment is not a part of the protocol unless there is a serious adverse effect, e.g., encephalitis.

Dr. Mickelson inquired about the prevalence of HSV in the brain of individuals who have HSV antibodies in the blood. Dr. Tufaro said more than 80 percent of the general population has been infected with HSV, and most of the infected population has HSV latent infection in the brain or in neural tissue; however, serious encephalitis is very rare.

Dr. Verma asked if a replication-competent virus could emerge if a vector with the $\gamma_1$34.5 gene deletion is co-infected with a virus deleted in another gene, e.g., the TK gene. Dr. Tufaro said that there is the possibility of generating a replication-competent virus, including a neurovirulent virus, if a high number of virus particles are co-infected together. Dr. Verma asked if there is any probability of generating neurotropic virus following injection of G207 into a patient who has a latent HSV infection. Dr. Tufaro responded that they have performed animal experiments in which the animals were injected with wild type virus to establish latency prior to G207 administration. Results indicated that recombinant viruses were not detected. If recombinant viruses are generated, the effect would be no greater than with wild type virus.

Dr. Verma expressed concern that a new neurotropic virus could possibly emerge in a setting where a patient is taking a drug (for example, glucocorticoids). Under such conditions, a latent virus could potentially be reactivated in the brain when G207 is introduced. Dr. Tufaro said that HSV reactivation had never been observed in a clinical setting where a patient with latent HSV infection was treated with glucocorticoids. In addition, there is no direct route of transmission of a virus in the brain to another individual; the virus is transmitted horizontally through peripheral nerve infection. Dr. Verma explained that his concern was related to a scenario in which a patient could become infected with a more pathogenic recombinant virus. Dr. Tufaro responded that, in his opinion, it is highly unlikely a recombinant virus would be more pathogenic than the wild type virus.

Dr. Noguchi noted that, in discussions with NeuroVir, Inc. scientists, the FDA had asked a question similar to Dr. Verma's. He said the FDA concluded that the scenario for reactivation and recombination is very difficult to simulate in animal models; he acknowledged that the FDA would closely monitor the progress of the clinical trial to obtain such information.

Dr. Gordon asked if a recombinant virus would emerge by co-infection in cells in tissue culture that are actively dividing. Any such recombination would similarly occur in brain tumor cells, which are also mitotically more active than normal brain cells. Dr. Tufaro responded that reactivation and recombination of viruses are not simply dependent on the cell cycles; neuronal tissue is well suited for latency. Dr. Tufaro pointed out that when G207 is injected directly into the brain of Aotus monkeys, very little virus replication occurs that could lead to any recombinational event. He said this situation is similar to injection of G207 directly into a patient's brain tumor.

Dr. Verma asked if the approach of using a replication-competent HSV for brain tumor treatment was chosen because such viruses are capable of infecting larger numbers of brain tumor cells. The other approach used in many brain tumor protocols employing the HSV-TK/ganciclovir strategy depends on the "bystander" effect for tumor killing. Dr. Tufaro responded that the major advantage of G207 is its ability to differentiate between brain tumor cells and normal cells in its cell lysis effect; cell lysis does not depend on the "bystander" effect.

Dr. Verma asked how injection of 10^7 pfu of G207 would be expected to kill 10^{12} tumor cells within a tumor mass. Dr. Tufaro said that the brain tumor would be debulked before G207 injection; after the surgical procedure to reduce the tumor mass, the ratio of virus-to-tumor cells would be favorable. In addition, higher doses of virus will be injected at multiple sites to favor infection of a larger number of tumor cells. Ms. Osborne noted that in this dose escalation study the first dose level is very low. Dr. Tufaro said within the therapeutic window there are enough virus particles to be delivered to most tumor cells that remain after debulking.

Dr. Aguilar-Cordova asked if any inflammatory response to the vector was observed following injection of large doses of G207 in Aotus monkey brains. Ms. Osborne responded that after injection of 10^7 to 10^9 pfu of the virus in monkeys, no significant inflammatory response was observed between 28 days and 2 years post-injection; only mild inflammation was noted along the needle tracts immediately after injection. Dr. Aguilar-Cordova asked if these were preimmunized animals. Dr. Tufaro said that several animals were injected more than once and demonstrated seroconversion; no inflammation was observed following repeat dosages.

Dr. Aguilar-Cordova asked if in any remaining virus was detected after the tumor was eradicated in animals. Dr. Tufaro responded that in rodent experiments, such vector sequences can be detected around the tumor site for more than two years following tumor eradication. Persistence of vector DNA was also observed in various parts of the brain in Aotus monkeys. Ms. Osborne clarified that in Aotus monkeys, vector DNA sequences were detected by PCR only in the brain and not in any peripheral nervous tissue; no virus shedding was noted in tear, saliva, or vaginal swabs.

Dr. Aguilar-Cordova expressed concern that virus shedding could occur in brain tumor patients whose blood-brain barrier had been compromised by tumor invasion or other surgical procedure. He asked if the patients would be tested for viral shedding before release. Ms. Osborne answered that there is no need to test patients for viral shedding based on the preclinical studies. Dr. Tufaro said that virus shedding would be monitored by simple PCR analysis or by virus culture.

Dr. Mickelson asked if there are any second generation vectors under development that include deletion of additional neurovirulence genes; such deletions could further abate any chances of reactivation, recombination, or latency. Ms. Osborne responded that G207 has all the appropriate safety features; further attenuation of the virus would compromise its efficacy. She believed that G207 is the best virus to gain safety information from in human studies. Dr. Tufaro said the safety profile of G207 suggested that it is the best virus to establish the safety of HSV vectors. In the future, the virus platform might be extended to increase its capacity for tumor killing. Methods of achieving this are: (1) using low dose irradiation to enhance virus spreading within the tumor

mass, (2) including the interleukin-12 gene to enhance immune response, and (3) inserting a stronger promoter for TK gene expression to be used in tandem with ganciclovir.

Dr. Mickelson asked whether such potent treatment procedures would pose additional safety concerns, i.e., if the virus caused rapid tumor cell lysis that made toxic cellular products. Dr. Tufaro said that the situation would be similar to massive cell dying following extensive X-ray therapy.

Dr. Verma asked if the protocol would come back for a full review. Dr. Mickelson responded that this protocol represents the first use of a replication-competent HSV vector for gene therapy research, and it is important to hear from the sponsor before the RAC reviews the protocol. Dr. Verma stated that he would prefer to invite a HSV expert as a consultant to review this protocol; he suggested deferring the full RAC discussion of the protocol until the June 18-19, 1998, meeting.

Dr. Noguchi stated that this particular protocol has undergone extensive review by many virologists at the FDA, including herpesvirus experts. The sponsor has been consulting with the FDA for almost three years in trying to answer questions in both animal models and *in vitro* studies. Most of the FDA concerns have been addressed. Dr. Noguchi stated that the RAC no longer has approval authority; therefore, there is no benefit in holding a full discussion of the protocol in June.

Dr. Verma disagreed with Dr. Noguchi. Dr. Verma stated that the RAC is a public forum to conduct public discussion of human gene transfer protocols, particularly novel protocols such as this one. Therefore, there is justification for discussing a new viral vector in public and with the inclusion of ad hoc herpesvirus experts. Dr. Verma noted that the FDA review is considered confidential and that there is value in holding such a discussion in the public domain. Dr. Aguilar-Cordova agreed with Dr. Verma about the need for a public review. In particular, he stressed the importance of providing safety data demonstrating the absence of viral shedding. Such data would provide reasonable assurance that there would not be any horizontal transmission of this replication-competent vector. It is important to allay any fears that such a virus could be passed to health care workers or other family members. Dr. Noguchi responded that there are ample viral vaccine studies employing replication-competent viruses that should allay such concerns.

Dr. McIvor stated that it is inappropriate to have full discussion of this protocol at the current RAC meeting. The protocol was recommended for full RAC discussion by 11 RAC members during their preliminary review of the summary information of the protocol. (According to the *NIH Guidelines*, full RAC review of an individual human gene transfer experiment can be initiated by the NIH Director or recommended to the NIH Director by three or more RAC members.) The required documentation for this protocol was not received by ORDA until February 10, 1998 (less than the eight-week deadline for receipt of all materials concerning protocols that will be publicly discussed in a RAC meeting). Therefore, full review of the protocol cannot occur until the June 18-19, 1998, RAC meeting.

As a point of clarification, Ms. Osborne stated that she approached ORDA as early as July 1997 regarding submission of the protocol. Since she was waiting for IRB approval, the required

documentation of this protocol was not submitted to ORDA until February 10, 1998. Dr. McIvor said that since the protocol was submitted after the eight-week submission deadline for the current meeting, the RAC should not continue to discuss this protocol.

Dr. Mickelson stated that the RAC appreciates the sponsor and the investigators bringing new human applications of emerging gene transfer technologies to the attention of the RAC as soon as possible, e.g., the presentation of chimeraplasty at today's meeting; however, the RAC should not give full discussion of a protocol until all required documentation has been submitted. She invited the sponsor and the investigators to attend the June RAC meeting to explain publicly the preclinical safety studies relevant to the protocol. Dr. Tufaro said many preclinical studies have been performed for this protocol, and he said that NeuroVir, Inc. would be agreeable to discussing these issues at the June RAC meeting.

Dr. Gordon noted that this protocol is a Phase I safety study, and does not have a therapeutic endpoint as the primary objective. He was concerned whether an immune reaction to the vector would be an obstacle for future therapeutic applications to treat a large tumor mass requiring multiple administration. Dr. Tufaro said that the virus had evolved empirically to survive in the face of immune responses; the virus could evade immune surveillance by transmission via direct cell-to-cell contact without involving an extracellular transmission route.

Dr. Melody Lin made a comment on the Informed Consent document approved by the University of Alabama and Georgetown University IRBs. She expressed concern about the use of the terms "treatment" and "therapeutic procedure." The Informed Consent document should be very clear that this study involves no therapeutic intent. Ms. Rothenberg agreed with the concerns raised by Dr. Lin.

Ms. Osborne explained that "treatment" is a neutral term used to describe administration of a test article. She said that the Informed Consent document as written is appropriate for a protocol studying safety as well as the potential therapeutic utility of a gene transfer procedure. As a point of clarification, Ms. Knorr explained that the RAC has deliberated this issue in the past. The term "treatment" refers to a neutral intervention procedure and the RAC has deemed the term to be an appropriate description; however, the RAC has repeatedly cautioned investigators against using the term "therapy".

Dr. Markert noted that if the NIH implements the RAC recommendation to eliminate the prior IRB/IBC approvals at the time of protocol submission to ORDA, the RAC would have been able to review this protocol at an earlier stage.

Dr. Mickelson thanked Ms. Osborne and Dr. Tufaro for bringing the protocol to the attention of the RAC, and she invited both of them to participate in a full RAC discussion of the protocol at the June 18-19, 1998, meeting.

Protocol Summary

Dr. James Markert, University of Alabama at Birmingham, Birmingham, Alabama; and Dr. Michael Medlock, Georgetown University, Washington, D.C.; proposed to conduct gene transfer

experiments on 24 patients with malignant glioma. The vector, G207, was derived from the laboratory HSV-1(F) strain by deletions in both copies of the $\gamma_1$34.5 neurovirulence gene and a disabling insertion of the *E. coli LacZ* gene into the ICP6 (viral ribonucleotide reductase) region for use as an easily detectable marker, which allows for differentiation from HSV-1(F). The clinical strategy takes advantage of the virus' ability to infect and lyse neuronal cells. Treatment will consist of a single stereotactic injection of approximately 0.1 ml of G207 into a region of the tumor defined by magnetic resonance imaging (MRI). Higher doses will be achieved by multiple 0.1 ml injections. The escalating doses range from 1×10^6 to 1×10^9 focus forming units of G207. The primary purpose of the study is to obtain safety information in a small number of individuals (three patients per group), with successive groups receiving escalating doses of G207 after appropriate intervals for evaluation of safety. As a secondary objective, patients will be followed serially by MRI for potential clinical response to G207.

VIII. Discussion Regarding Format for RAC Discussion of Human Gene Transfer Protocols and Related Issues

Introduction: Skirboll

Presentation–Dr. Skirboll

Dr. Skirboll, NIH Associate Director for Science Policy, addressed the RAC regarding the future role of the RAC in the absence of NIH approval authority over individual human gene transfer protocols. She noted that the final action to promulgate the amendments to the *NIH Guidelines* relinquishing NIH approval authority of human gene transfer protocols was published in the *Federal Register* on October 31, 1997 (62 FR 59032). The purpose of these changes to the RAC's authority regarding human gene transfer research is to allow the RAC to focus on new issues raised by the emerging technologies, without duplicating the regulatory authority of the FDA. She asked the RAC to formulate an action plan regarding how the RAC will function in the next period of evolution and how to provide oversight over human gene transfer protocols.

Dr. Skirboll emphasized that the RAC will continue to provide oversight of research involving recombinant DNA molecules. She said that Dr. Harold Varmus, the NIH Director, and officials at the Department of Health and Human Services (DHHS) consider the functions provided by the RAC to be vital to the nation. The RAC's authority to provide oversight of human gene transfer research has been affirmed by the NIH Office of the General Counsel.

Dr. Skirboll stated that Dr. Varmus expects the RAC to conduct adequate and complete public discussion of novel human gene transfer protocols and develop broad policy recommendations, when appropriate. Dr. Skirboll noted the two successful GTPCs held on September 11, 1997, on *Human Gene Transfer - Beyond Life-Threatening Disease*, and on March 9, 1998, on *Lentiviral Vectors for Gene Therapy*. GTPCs serve the purpose of focusing on broad legal, ethical, social, as well as scientific issues of modern gene therapy research. GTPCs are to complement the RAC's role of discussion of individual novel human gene transfer protocols.

Dr. Skirboll emphasized that the RAC's primary responsibility is to recommend national standards for gene therapy research. The RAC should develop public policy based on the recommendations made at GTPCs and discussion of individual novel human gene transfer protocols. Such public

policy should be incorporated into the *NIH Guidelines* as guidance to IBCs and IRBs, and investigators. Specific recommendations regarding a particular protocol may be transmitted to the NIH Director, the FDA Commissioner or the FDA officials in charge of human gene transfer protocols, Chairs of IBCs and IRBs, and -- when NIH funding is involved -- to the appropriate NIH Institute Director and Program Officer.

Dr. Skirboll emphasized that in the absence of approval authority, the RAC now has the flexibility to conduct public discussion of protocol issues at anytime, and can transmit its recommendations to appropriate institutional and regulatory bodies. She noted that the RAC is not intended to be a national IRB; however, the RAC can provide IRBs with appropriate recommendations. The RAC can broaden its approach to protocol review. For example, the RAC has traditionally focused on aspects of protocols that need improvement; perhaps the RAC can begin to conduct comparative analyses as well. Highlighting the positive as well as negative aspects of certain protocols or techniques may increase public awareness about a variety of issues. Dr. Skirboll reiterated that the primary RAC responsibility is to recommend public policy and not to duplicate the FDA's responsibility of reviewing details of individual protocols.

Dr. Skirboll asked the RAC to develop an action plan that will clearly define its roles and responsibilities as it moves into the twenty-first century. She suggested that this plan, once developed, should be published in the *Federal Register* for public comment and RAC deliberation.

Other Comments

Dr. Gordon inquired how the RAC would deal with protocols that do not involve NIH funding. Dr. Skirboll responded that the *NIH Guidelines* apply not only to protocols funded directly by NIH but also to protocols conducted in collaboration with investigators or institutions that receive NIH funding for research involving recombinant DNA molecules. For protocols that do not involve any NIH funding, the investigators or sponsors are not obligated to register their protocols with ORDA; however, they are encouraged to submit such protocols on a voluntary basis. Dr. Skirboll noted that it is still a rarity that a protocol does not involve any NIH funding. She speculated that once gene therapy is proven to be efficacious, more protocols might fall outside the jurisdiction of the RAC. Dr. Noguchi stated that the FDA would bring novel protocols for public discussion at the RAC meeting even if they are entirely funded by private sources. Dr. Gordon noted that public discussion of novel issues will benefit the field of gene therapy research.

Dr. McIvor said the RAC should develop a procedure that, at the end of the discussion of a particular protocol, would allow the RAC to bring the review to closure. A summation of the discussion should be brought to closure and subsequently transmitted to all concerned parties.

Dr. Gordon suggested that following a protocol discussion, a RAC subgroup could draw up recommendations to transmit any concerns to relevant parties to ensure that the investigators respond to the RAC's concerns.

Dr. Verma volunteered to participate on a subcommittee to explore this issue further.

Ms. Rothenberg proposed two protocol discussion models. The first model involves a continuing dialogue between the RAC and the investigators. The RAC asks questions and requests more information. The investigators come back to the RAC to present additional data and respond to any additional RAC questions. An example is the discussion of the herpesvirus protocol at the current RAC meeting. The second model is to conclude the RAC discussion with a closure statement, leaving it up to investigators and the appropriate regulatory bodies to act on the RAC's recommendation. Ms. Rothenberg asked how the RAC would function without approval authority in either of the above-mentioned models.

Dr. Skirboll responded that the authority to approve a protocol rests with the FDA at the national level, and with IRBs and IBCs at the local level. The RAC's function is to keep the FDA, IRBs, IBCs, and the investigators aware of its concerns, if any. It is up to the regulatory authorities to take the RAC's concerns into their consideration of the protocol. The RAC is entitled to forward its concerns to the oversight bodies and the investigators. Dr. Skirboll emphasized that the important point is to have a public discussion of a novel protocol with the consultation of experts. The protocol may be initiated upon obtaining approvals from the FDA, IRB, and IBC either before or after RAC discussion.

Dr. Verma noted that the interaction of the RAC with the regulatory authorities is evolving. He drew an example from the discussion of the herpesvirus protocol. The RAC expressed its uneasiness about discussing this protocol without a herpesvirus expert being present, and the FDA assured the RAC that such safety issues have been addressed in its review. Despite this assurance from the FDA, the RAC can still insist on further public discussion with consultation of *ad hoc* experts at a future meeting.

Dr. Juengst volunteered to participate on the proposed subcommittee. Dr. Noguchi said that Dr. Andra Miller of the FDA will participate on the subcommittee as an agency representative. Dr. Lysaught also volunteered to participate on the subcommittee. Dr. Noguchi said that the FDA would invite members of the subcommittee to an IND review meeting to familiarize the RAC with the FDA approval process.

Mr. Steven Kradjian (Vical Inc., San Diego, California) asked how the RAC could provide the IRB and IBC with its concerns if a protocol can only be submitted to ORDA after IRB and IBC approvals. He asked if NIH has implemented a previous RAC recommendation to eliminate the requirements of prior IRB and IBC approvals from the submission requirements. Dr. Skirboll responded that the RAC recommendation regarding prior IRB and IBC approval is under consideration within the NIH. The NIH is concerned that RAC discussion of a protocol before IBC and IRB review would effectively make the RAC a national IRB, and impinge upon local approval authority. The investigators, however, are encouraged to bring forward any novel protocols, such as *in utero* gene transfer, to the RAC for a general discussion of novel issues. RAC discussions of this type will give advance guidance for future preparation of formal submissions.

Dr. Markert noted that at her institution the IRB meets once or even twice a month and, therefore, IRB review will occur before any RAC discussion even if the protocol is submitted to ORDA at

the same time it is submitted to the IRB. Dr. Skirboll stated that NIH will consider Dr. Markert's comment.

Dr. Aguilar-Cordova noted that, under current *NIH Guidelines*, the RAC can discuss the novel issues of an impending protocol, such as *in utero* gene transfer studies, before any submission to the IBC, IRB, or the FDA. This type of discussion will not focus on the details of the protocol that will be submitted to the RAC in the future.

Dr. Gordon suggested that the subcommittee should discuss further the issue of IRB and IBC approval. He noted that the present process of RAC discussion after IRB/IBC approvals does not hinder initiation of protocols recommended for full RAC discussion.

Dr. Mickelson noted that due to time constraints, the agenda item surrounding Dr. Michael Oxman's letter to Dr. Varmus about development of guidance on the use of viral vectors will not be discussed at the current meeting. The issue will be addressed at the June RAC meeting. Ms. Knorr noted that Dr. Oxman's letter raised the IBC oversight issue of gene transfer vectors to be used not only for human studies, but for laboratory use.

IX. Discussion Regarding Enrollment of Children in Early Phase Gene Transfer Clinical Trials that May Involve Greater Than Minimal Risk

Summary: Macklin

***Ad hoc* Consultants: Fost, Lantos**

During the preliminary review of the summary information of Protocol #9711-222 entitled: *Gene Therapy of Canavan Disease*, several RAC members recommended that a general discussion should be held on the topic of enrollment of children in early-phase gene transfer clinical trials that may involve greater than minimal risk. The RAC invited two *ad hoc* consultants to participate in the discussion: (1) Norman Fost, M.D., IRB Chair, Professor, Department of Pediatrics, University of Wisconsin, Madison, Wisconsin; (2) John Lantos, M.D., Associate Director, MacLean Center for Clinical Medical Ethics, University of Chicago, Chicago, Illinois.

Presentation–Dr. Macklin

Dr. Macklin noted the Federal regulations for protection of children as research subjects: 45 CFR 46 - *Protection of Human Subjects* and 45 CFR 46 (Subpart D) - *Additional Protection for Children Involved as Research Subjects*. The ethical issues beyond the Federal regulations are discussed in the following reference articles: (1) Benjamin Freedman, Abraham Fuks, and Charles Weijer, *In Loco Parentis - Minimal Risk as an Ethical Threshold for Research upon Children* (Hastings Center Report, Vol. 23, No. 2, March-April, 1993); (2) Esther H. Wender, *Assessment of Risk to Children* (in Michael A. Grodin and Leonard H. Glantz, eds., *Children as Research Subjects: Science, Ethics & Law*, pages 181-192. New York: Oxford University Press, 1994); (3) Robert J. Levine, *Children as Research Subjects* (in Loretta M. Kopelman and John C. Moskop, eds., *Children and Health Care: Moral and Social Issues*, pages 73-87. Kluwer Academic Publishers, 1989).

Dr. Macklin provided an overview of the requirements that afford additional protection for children; these ethical considerations are pertinent to Protocol #9711-222 on Canavan disease. The first threshold is that, before involving children, adequate studies must first be conducted on animals and adults. The IRB is required to determine that, where appropriate, studies have been conducted first on animals and adult humans, then on older children. Robert Levine stated in his article that investigators who propose to do research on children without first performing such research on animals, adults, or both, are obligated to persuade the IRB that the disorder or function to be studied has no parallel in animals or adults. In addition, a new procedure or a new route of administration should be studied first in animals or adults.

The second consideration is the level of risk. The Federal regulations categorize the proposed research according to the degree of risk and whether the research has the prospect of benefitting the individual. The first level of minimal risk is that the probability and magnitude of harm or discomfort anticipated in the research is not greater "in and of themselves", i.e., the risk ordinarily encountered in daily life or routine medical examinations. The second level of risk is a minor increase above the minimal risk. The third level of risk is more than a minor increase above the minimal risk.

Dr. Macklin noted the difficulty of quantitative definition of risk levels. Freedman *et al.* in their article attempted to define the risk from a non-quantitative perspective. Discomfort as well as harm understood in a biomedical sense are all important to children since they are unable to provide their own informed consent. Wender in her article noted that children of different ages can be expected to react differently to the experiences associated with various research procedures. For infants and very young children, the greatest stress is abandonment and separation from their care givers. Long-term hospitalization is a psychological risk to infants that is beyond the minimal risk.

Dr. Macklin gave three examples of how reasonable people can disagree in their determination of levels of risks. One example was from a study of chairpersons of pediatric departments and directors of pediatric clinical research units, cited by Freedman *et al* in the article *In Loco Parentis*. The study asked these clinicians to classify the risks associated with common research procedures administered to pediatric subjects of different ages. For one specific research procedure, Freedman observed that:

> "The results demonstrated serious disagreements among respondents: 14 percent thought tympanocentesis (puncturing of the ear drum) posed minimal risk or less, 46 percent classified this as a minor increment over minimal risk, and 40 percent thought it more than a minor increase. Expressed in practical terms, 40 percent thought research requiring tympanocentesis was impermissible, despite the importance of the research, without the approval of a federally authorized panel of ethics experts in addition to the approval of parents."

From this study, and from researching the medical literature, Freedman concluded that there is no uniform understanding of the phrase "minimal risk," at least in the context of pediatric research.

Dr. Macklin mentioned two other examples, from her experience as a member of a New York State Department of Health committee charged with investigating clinical trials involving incapacitated subjects. The committee members rated the risk levels of several different procedures. Their ratings of risk levels for the lumbar puncture procedure produced responses in all three risk levels. Their ratings of risk levels for indwelling catheters (long-term catheter placement in a subject's urinary bladder) were divided between a minor increase above minimal risk and more than a minor increase. From these three examples, Dr. Macklin concluded that one might expect IRBs to vary in their determination of risk levels for studies involving children.

Dr. Macklin said the third step is to determine whether there is a prospect of direct benefit to individual subjects. In a Phase I study, the primary objectives are to measure safety and assess toxicity. One cannot rule out that there might be some benefit if the procedure or drug eventually will be studied for efficacy. But one cannot automatically assume that prolonging life is a direct benefit to individual subjects if it involves great suffering and no prospect of cure.

Dr. Macklin noted that when the research does not involve greater than minimal risk, Federal regulations provide no additional conditions to protect children; additional protection is provided when research involves more than minimal risk. If the research involves greater than minimal risk, and the question is whether it provides the prospect of direct benefit, the IRB must determine that: (1) the risk is justified by the anticipated benefit, and (2) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative therapies.

It is critical to determine whether the research does provide the prospect of benefit, because if it does provide benefit there is no need to make the further distinction involving the level of risk. If it does not provide direct benefit (even if it is likely to yield generalizable knowledge), the risk levels must be determined and several conditions must be met. For research involving a minor increase over minimal risk, the procedures in the research have to be commensurate with what that child would undergo if the child were not in research. If the research has no prospect of direct benefit, and it represents more than a minor increase above minimal risk, the research is not within the scope of approval by the IRB. In this case, the IRB has to make a special appeal to the Secretary of DHHS to allow such experiments to be initiated. Dr. Macklin was aware of two occasions of appeals to the DHHS in the last 15 years.

The final point is the parental permission to enroll a child in research. The parents are the best decision makers for their children, but can hardly be objective. The National Commission for Protection of Human Subjects concluded that children, being vulnerable subjects and incapable of deciding for themselves, require more protection than adults, who can consent for themselves.

Dr. Macklin noted that her analysis of the research involving children is related to the issues raised by the Canavan protocol.

Presentation–Dr. Fost

Dr. Fost agreed with Dr. Macklin's statement that most reasonable people will disagree on the determination of the levels of the acceptable risk. Dr. Fost offered his analysis from the

perspective of a pediatrician. Dr. Fost has been the chair of the IRB at the University of Wisconsin for about 25 years, and he is the focal point at the University Hospital for questions about medical ethics.

Dr. Fost's comments were divided into two categories: regulatory issues, and his own ethical view on the Canavan protocol. The Federal regulations are very ambiguous about the levels of risks, and it is up to any IRB to make their own judgments.

Dr. Fost said that Phase I studies may offer some hope, expectations, and prospect for direct benefit to the subjects. A good Phase I study is conducted with an objective to find out the proper dose and correct route of administration of a new therapeutic approach. One should be candid about the prospect of benefit; only 5 to 10 percent of Phase I drug studies eventually lead to clinically useful drugs.

Dr. Fost said that the Canavan protocol provides a reasonable prospect of benefit to the children, i.e., improving the quality of their life. The data from the first child treated under this protocol provide plausible evidence that there might have been some brief, although minimal, improvement. Dr. Fost said he believes that the Canavan protocol meets the notion of prospect of direct benefit; therefore, there is no need to consider the levels of minimal risk. Even if the risk level needs to be determined, the Canavan protocol may be defined to be in the first level category of minimal risk. Dr. Fost noted that the Federal regulations allow for a clinical trial of no conceivable benefit up to the second level of minor increase over the minimal risk.

The second question is whether the experiences for participating children are reasonably commensurate with what that child would undergo if the child were not in research. Dr. Fost noted the Federal regulations are not quite appropriate for this protocol. For example, he questioned whether a lumbar puncture performed on an individual with no experience is more traumatic than it is when performed on a patient who has had 10 previous lumbar punctures. It is not accurate to assume automatically that experience with a procedure makes one less vulnerable to the potential pain and misery. For children more than seven years of age who are able to assent to a protocol, such experience is more meaningful; it is less significant for Canavan children who are only two to three years of age.

Dr. Fost said he believed that for the Canavan children, the suffering and anxiety associated with multiple lumbar punctures are more significant than the risk of placing an intracranial reservoir used for the gene transfer procedure. He said that the risk of placing the reservoir is quite minimal; it is a painless procedure performed under anesthesia. According to Federal regulations, the protocol is permitted under the category of a minor increase over minimal risk. In addition, the protocol offers the prospect of potential benefits to the subjects.

Dr. Fost commented on several ethical considerations of the Canavan protocol. First, one should not conduct non-therapeutic research on children without their consent even if generalizable knowledge will be obtained and will benefit a class of children. Second, there are two compelling moral theories about including children in clinical studies: the principle of substituted judgment and the principle of best interest.

Under the principle of substituted judgment, one tries to determine what would be best for the individual if he or she could consent. This would be equivalent to asking whether the Canavan children would be likely to volunteer for this protocol if they could understand the situation as adults.

The principle of best interest is trying to make some reasonable external quasi-objective judgment about whether it would be in the interest of these children to enter the trial. According to these principles, Dr. Fost said, it is plausible to conclude that the Canavan children would consent if they could, and it is in their best interest to participate in this research.

These are desperately-ill children and the intervention, which Dr. Fost does not consider particularly risky or harmful by itself, might improve the experience of the pleasures of the infant and childhood existence. Dr. Fost noted that desperately-ill persons of all ages generally are willing to take quite amazing risks for any kind of chance of a benefit. Most of them would undergo an intervention to give them a few more days of existence even if they are told that the intervention offers almost no prospect.

Dr. Fost speculated that a child with Canavan disease would agree to enter onto the protocol if there is some prospect of benefit. He doubted, however, that children of this young age would agree to a procedure without any prospect of benefit to them. He noted that Dr. During claimed that the two children previously treated under a similar protocol experienced a short period of improvement in their life.

Dr. Fost agreed with Dr. Macklin that simply prolonging life is not clearly a benefit. He said that it would be wrong to treat children with end-stage Tay Sachs disease in a manner that would not improve the quality of life.

Dr. Fost agreed with Dr. Macklin that parents have a serious conflict of interest regarding this protocol. The parents' consent is necessary, but not sufficient, because any normal parents would be desperate for any intervention that might help their children. The IRB has the duty to make paternalistic judgments on behalf of the children to determine if the intervention is in the interest of these children.

Dr. Fost commented on several concerns raised by the RAC during the review of Canavan Protocol #9708-211 at the December 1997 RAC meeting. Regarding the question of gene expression, Dr. Fost said that gene expression by this technique has been shown in preclinical studies in tissue culture cells and in primates. In the clinical studies performed on two children in New Zealand, there appeared to have been some biochemical evidence of gene expression as shown by the nuclear magnetic resonance (NMR) data. Dr. Fost agreed it is crucial to ask whether the veracity of the NMR data is adequate to assess gene expression.

Dr. Fost noted that Dr. Matalon raised relevant questions of the proper diagnosis of Canavan disease, the variable natural history of the disease, the variable levels of N-acetylaspartate (NAA), and the need for a control group in a conclusive study. Dr. Fost agreed it is better to have a control group, or use the patients as their own control; he was concerned that using placebos in children raises another ethical issue.

With regard to the question of costs, Dr. Fost said if the parents have to bear any costs related to the study, the Informed Consent should be clear so it does not raise false hopes. An autopsy, if required, should not be a condition for enrollment in the protocol.

Dr. Fost said that preclinical studies to test the basic methodology for gene expression and toxicity in animals are needed. Conducting the clinical study first on adults is not appropriate, in this case, since children with severe Canavan disease do not survive to adulthood. For serious diseases, such as cancer, usually parents are likely to volunteer their children for protocols of new chemotherapeutic agents based on the principle of substituted judgments.

Dr. Fost stated that based on his analysis of the protocol, as a pediatrician, he would agree to have children enrolled on this study and not to wait for a study on adults. For children who are unable to give informed consent, Dr. Fost drew an analogy to the situation of brain-damaged patients in the emergency room. He favored waiving the Informed Consent for such patients and allowing them to have experimental treatments if such interventions have been proven safe and effective in preclinical studies. He noted a survey that found that 95 percent of adults would agree to such interventions if they were comatose.

Other Comments

Dr. Noguchi asked if the data from the two children treated previously demonstrated any improvement. Dr. Fost said that he would defer to experts regarding the interpretation of the data. If the data are inconclusive, a better study design with a proper placebo control is needed.

Dr. Gordon said that he was concerned about the ambiguity of most Phase I gene transfer studies, i.e., whether they are safety studies or studies intended to demonstrate any potential benefit. He noted most study designs (small cohorts, etc.) preclude any conclusion about efficacy. Dr. Fost said that the Canavan protocol is more appropriately regarded as a Phase II study to show some preliminary efficacy. Since it involves more than a minimal risk, he agreed that it is reasonable to demand some potential benefit.

Dr. Lysaught said she saw some ambiguity in Dr. Fost's analysis of the Canavan protocol in terms of what is considered as potential benefits and the levels of criteria used to make a reasonable judgment. Dr. Fost responded that, based on the preclinical and clinical studies, he noted a reasonable possibility of benefit. He did not think it was unreasonable for the Yale IRB to find there was sufficient prospect of benefit to justify the risks of the protocol.

Ms. Rothenberg asked if any special consideration should be given to this protocol because it uses a gene transfer procedure rather than ordinary pharmaceutical agents. Dr. Fost said he believes gene transfer protocols do not differ significantly from other types of protocols, except for the technical issues related to the gene transfer. As a point of clarification, Ms. Rothenberg said her question was related to the fact that there has not been any evidence of success for any gene transfer protocol to date. Dr. Fost agreed that parents should not be misled with statements that raise false hopes.

Dr. Ando asked if it is reasonable to proceed to a placebo-controlled Phase II study if a Phase I study has been found completely safe but the NMR data, for example, are too variable to be conclusive. Dr. Fost responded that if the study is completely safe without the discomfort of six lumbar punctures, it would justify a placebo controlled trial. Dr. Lantos noted there is no need for six lumbar punctures, since the samples may be obtained from the brain reservoir.

Dr. Pearl O'Rourke, NIH Office of Science Policy, Bethesda, Maryland, noted that the advantage of samples from lumbar punctures is that they are free from any local reactions around the reservoir. She raised two cautionary concerns. First, the situation facing the parents is that their children have a fatal condition that needs to be addressed. Second, there should be a minimum requirement of adequate clinical procedures (e.g., lumbar punctures), and a valid study design to justify a clinical protocol.

Presentation–Dr. Lantos

Dr. Lantos pointed out that the key issue in this discussion of enrollment of children in clinical trials is the role of parents. He noted that with the Canavan protocol there is a group of highly motivated, well-informed parents who are actively involved in the development of the protocol. Dr. Lantos was concerned about the idea of being paternalistic to protect children from their parents.

Dr. Lantos noted a study showing that bioethicists and IRBs are much more protective of children than parents are. Parents are willing to allow their children to take a much higher risk, or to take a higher risk themselves for the sake of their children, than an IRB would allow.

Dr. Lantos noted that his main concern about the Informed Consent is that it does not clearly inform the parents whether the protocol is a Phase I safety study or a Phase II study with certain efficacy endpoints. The Informed Consent should be much more honest and state that the protocol requires brain surgery, and the only possible anticipated benefit is to slow the progression of the disease. It should warn the parents that slowing the progressive neurologic degeneration might prolong the pain and suffering of both the child and the parents.

Dr. Lantos noted that in this protocol the potential benefit to others with similar disease, i.e., community benefit, is important because families with the same disease are well known to each other and constitute a small group. There is a sense of altruism in participating in the trial.

Dr. Lantos agreed that the study design of the protocol needs to include a proper control group to assess efficacy endpoints. He suggested that the non-treatment control group might include children whose parents have declined the treatment after reading the Informed Consent.

Other Comments

Ms. Rothenberg noted that no placebo-controlled study has ever been proposed for protocols for monogenic diseases. Dr. Aguilar-Cordova said that most protocols are Phase I safety studies not primarily directed at assessing efficacy endpoints. Dr. Fost responded that he does not consider the present protocol to be a strict Phase I study. Dr. Aguilar-Cordova noted that the RAC

discussion of the gene transfer protocols may help IRBs in their review of gene transfer protocols; such protocols are considered a relative novelty at most institutions. Dr. Fost agreed that the expertise of the RAC on gene transfer research is invaluable to IRBs.

Responding to comments by Drs. Fost and Lantos, Dr. Macklin noted that a distinction of this protocol is the uncertain benefit to the patients. The argument that these children will benefit from the study is too strong and too broad, and this argument is not appropriate for informed consent decisions by the parents.

Dr. Noguchi noted that the New Zealand study involving two children was funded entirely by parents and their advocacy organization. He said he would like to hear a discussion regarding parents' responsibility to determine the quality of the science that they are funding.

Dr. Markert made two comments. First, in her review of the previous protocol (#9708-211), she suggested including a biostatistician in the study design of the protocol to evaluate any potential efficacy. Second, speaking as a pediatrician, Dr. Markert said she is reluctant to tell parents how much risk they should take to enroll their children. She noted a huge variability in willingness to take risks. In addition, the funding and costs should be clearly stated in the Informed Consent.

Dr. Gordon stated that he was deeply concerned whether or not therapeutic benefit is part of Phase I gene transfer studies. He said the RAC has the responsibility to evaluate the scientific merit of a proposal, and to inform the investigators and the IRB if the study design is deficient in generating any useful information. Dr. Fost noted that the protocol really is a Phase II study since the investigators are very explicit about trying to assess benefit, both biochemically and clinically. It is relevant to ask if the study is scientifically valid. Dr. Lantos agreed the protocol is a Phase II study involving desperate children and parents.

Dr. McIvor noted that for rare diseases there are usually not enough patients to have a control group. Phase I/II studies should strive to determine if there is any gene expression and amelioration of clinical symptoms. Dr. Mickelson noted lack of a rigorous clinical diagnosis for the disease.

Dr. Gordon reiterated his dissatisfaction that, in general, investigators frequently evade the question of whether the study is designed to obtain an interpretable outcome by stating that Phase I studies are just safety studies, with no need to evaluate efficacy.

Ms. Rothenberg commented on the need for an autopsy as part of the study to obtain safety and efficacy information about gene transfer protocols. She noted that the RAC insists on a statement in the Informed Consent regarding the request for autopsy. Dr. Lantos agreed the Informed Consent should adequately state all the risks and the requirements for entering a gene transfer protocol. Dr. Fost agreed that parents should be asked to grant an autopsy, but that they could decline later if they change their minds.

Dr. Lysaught said that Federal regulations for protection of children in research protocols were derived from the concern of a historical experience of either inadvertent or intentional exploitation of vulnerable populations, and that society felt the need to protect children as research subjects.

She stated that it is unethical to put a vulnerable person, who cannot speak for himself or herself, through a procedure that will not produce any useful knowledge due to inadequate study design.

Ms. Knorr noted that in the past several RAC members have insisted on a statement about a requirement in every Informed Consent to request an autopsy. Such a requirement is stated in the *NIH Guidelines* in Appendix M-III-B-2-c, *Request for Autopsy.*

Dr. Noguchi noted that the FDA guidance documents defining the phases of clinical trials are primarily intended for the study of drugs. A typical Phase I study involves 50 to 100 individuals, a Phase II study for up to 200 subjects, and a Phase III study may include thousands of subjects. These studies are mostly for healthy volunteers. Most genetic diseases affect a very small number of individuals, and the criteria for each phase are not strictly applicable. Whether it is a Phase I or Phase II study, an acceptable risk-to-benefit ratio should be considered. RAC recommendations of the study design to obtain useful knowledge are very helpful to the FDA in its evaluation of the protocols.

Dr. Gordon stated that the RAC has the responsibility to inform the investigators or parents of the patients about whether the protocol has any chance of successful transfer of the gene to the target cells, whether the function of the gene can be measured, and what are the side effects related to gene transfer. As for the financial costs related to the protocol, the parents need to be informed whether participation in the study is worth the costs they have to bear.

Dr. Macklin was concerned that it is not proper for an IRB or the RAC to tell the parents how to spend their money on their children; the RAC should insist on making adequate disclosure of the protocol in the Informed Consent. She noted that different families have different views on how best to provide for their children.

Dr. Ando noted that there are far fewer protocols for monogenic disease than for more prevalent diseases such as cancer. Research on diseases such as cancer are more favorably supported by the commercial sector, and such a funding mechanism is not available for rare disorders. He noted that funding for the Canavan protocol is provided by the Canavan Foundation and the involved parents. Dr. Mickelson noted that the RAC may advise the NIH regarding allocation of resources to make sure that research on monogenic diseases is adequately funded.

Dr. Lantos said that the Informed Consent of the Canavan protocol should clearly state what is expected of parents in terms of financial costs. Dr. Fost commented from his experience as the chair of an ethics committee at the University of Wisconsin that some parents demand a highly invasive treatment for their hopelessly-ill infants despite full disclosure of the lack of benefit. Dr. Mickelson observed that perhaps there should be a third party involved in the consent process.

Ms. Rothenberg noted a proliferation of genetic testing for a variety of genetic diseases that have no available cure. She was concerned that some parents may opt for selective abortion as a choice. She said the RAC should send a message to the genetic disease community that one should not give false hope to the patients and their families. On the other hand, the RAC should in a positive way encourage the gene therapy community to develop the field in order to find a therapy for genetic diseases.

Dr. Gordon stated his view that, for genetic disease such as Tay Sachs disease, prenatal diagnosis and selective abortion is a reasonable prevention for the disease. Ms. Rothenberg said that a preferable prevention strategy would to prevent conception of a fetus with a genetic disease.

Dr. Lysaught was concerned that the second Canavan protocol (RAC #9711-222) will enroll an additional 15 patients at the Thomas Jefferson University beyond the 15 patients of the Yale protocol (RAC #9708-211) reviewed at the December 1997 RAC meeting. As a point of clarification, Dr. Mickelson explained that the same population of 15 patients will be enrolled in the same protocol to be performed at two sites, Yale University and Thomas Jefferson University.

As a follow up to Ms. Rothenberg's statement, Dr. Markert remarked that it is a laudable goal to cure a baby with a fatal genetic disorder, even *in utero*.

Dr. O'Rourke said that, after hearing the discussion, she believes that the RAC should deliberate the issues of using a "control" or "placebo" group in the study design of gene transfer protocols.

Dr. Macklin summarized the RAC discussion of the issues related to protocols #9708-211 and #9711-222. She noted the remaining issues of an unfavorable risk-to-benefit ratio in the Canavan protocol due to the variability of the disease manifestation. The issues of parental authority to enroll children in the study, and the prospect of potential benefits to subjects, have been discussed. The classic distinction between Phase I and Phase II clinical trials does not apply to the Canavan protocol because it involves assessment of safety and, to some extent, of efficacy. Questions remain about what can be learned from the outcome of the study based on its inadequate study design, and how to convey such questions of scientific merit to the IRB. The need for a control group or a placebo group in the study design to assess efficacy was raised. These questions should help IRBs in their evaluation of the risk-to-benefit ratio.

Protocol Summary (Protocol 9711-222 entitled: *Gene Therapy of Canavan Disease*)

Dr. Andrew Freese, Thomas Jefferson University, Philadelphia, Pennsylvania, proposed to conduct gene transfer experiments on 15 patients with Canavan disease. Canavan disease is an autosomal recessive leukodystrophy caused by mutations of the aspartoacylase (ASPA) gene. The loss of ASPA activity leads to an elevation in the brain concentration of NAA and spongiform degeneration of oligodendrocytes leading to neurodevelopmental retardation and childhood death. The children will undergo a surgical procedure for the implantation of a Medtronic injection port or similar access with an intraventricular catheter, and intracranial administration of a plasmid vector, pAAVaspa. Plasmid pAAVaspa contains the 145 base inverted terminal repeat from the adeno-associated virus, and expresses the human ASPA cDNA under the control of the cytomegalovirus promoter/enhancer. The plasmid DNA is condensed using protamine then encapsulated in a liposome-polymer-DNA complex with the lipids, 3β[N-(N', N'-dimethylaminoethane)carbamyl]cholesterol and dioleoylphosphatidylethanolamine. The study is to evaluate the safety and efficacy of the gene transfer procedure.

X. Update on the Gene Therapy Advisory Committee (GTAC), United Kingdom
Speaker: Antony Taylor

Mr. Antony Taylor, GTAC Secretariat, gave the RAC an update of the GTAC activities in the United Kingdom (UK). The GTAC was formed in 1993 to consider and advise on the acceptability of proposals for gene therapy research on human subjects. The GTAC reports directly to the Secretary of State for Health on developments in gene therapy research and their implications. In its role, the GTAC functions as the equivalent of a national IRB in the United States. It reviews and approves all human gene transfer protocols in the UK, because 99 percent of the UK population is covered directly or indirectly by the National Health Service.

The GTAC works closely with the Medicines Control Agency, an equivalent of the U.S. FDA, and two of its specialists are agency representatives to the GTAC. All protocols are also reviewed by local committees equivalent to a U.S. IRB, and there are interactions between the GTAC and the local committees. The GTAC has 16 members plus its Chair; half the members are scientists and the other half are public members. It meets five times a year to consider gene transfer protocols. The GTAC has approved 26 human gene transfer protocols to date, most of which are Phase I cancer trials. Mr. Taylor noted that since 1996 there have been a number of protocols in collaboration with U.S. biotechnology companies.

The definition that the GTAC uses for human gene transfer research includes vaccine experiments with genetically modified organisms, which are excluded from Appendix M of the *NIH Guidelines* (see Appendix M-VIII-A). The GTAC meetings are closed to the public as opposed to the public forum of the RAC; however, the GTAC is proactive in ensuring continued public awareness of the GTAC activities and the status of human gene therapy research. The GTAC has held public workshops to review the experience and the future prospect of gene therapy research. The GTAC issues annual reports on human gene transfer research, and it conducts subgroup meetings on new vectors (herpesvirus) and new emerging applications (for example, *in utero* gene therapy).

Mr. Taylor stated that further information related to the GTAC activities can be accessed through the Internet at http://www.open.gov.uk/doh/genetics.htm on the World Wide Web.

Other Comments

Dr. Mickelson inquired whether the GTAC has reviewed a herpesvirus protocol. Mr. Taylor responded that the GTAC has received a protocol using a vector similar to that used in RAC protocol #9802-235.

Dr. Lysaught inquired about the public funding for UK gene therapy research. Mr. Taylor said that the initial funding started in 1995 by the Medical Research Council, and it had a five-year target date to get the research from the bench to the bedside; the second wave of public funding is expected to increase from this year onward.

Dr. Macklin inquired about the interactions between the GTAC and local ethics committees. Mr. Taylor explained that under the Department of Health rules any protocol involving patient records and clinical materials from the National Health Service needs to be reviewed and approved by a local research ethics committee. Since the establishment of the GTAC, the local committees frequently defer to the GTAC for review of scientific merit as well as ethical acceptability; Mr. Taylor noted a very close working relationship between the GTAC and the local committees.

Ms. Rothenberg asked about the GTAC's relationship with the Medicines Control Agency. Mr. Taylor noted that the review by the Medicines Control Agency is product oriented, i.e., quality, efficacy, safety, and manufacturing issues. The GTAC review is protocol driven and includes consideration of issues of patient protection. Mr. Taylor emphasized the close working relationship between these two bodies.

Dr. Lin inquired if the GTAC would have to review an international collaboration if such a protocol has been reviewed and approved by the regulatory bodies of the collaborator's country. Mr. Taylor stated that the GTAC takes into consideration the review by the RAC and the FDA, but that it reserves the right to reach a separate conclusion. Dr. Lin asked if the GTAC requires annual reporting of the approved protocols. Mr. Taylor responded that annual reporting is required.

Dr. Lysaught asked how the collaborators outside the UK reacted to the GTAC system of protocol review. Mr. Taylor responded that from the feedback he received from the collaborators the response has been positive. The vast majority of protocols have been approved within 90 days of receipt. At present all protocols are reviewed by the GTAC including privately funded studies.

Dr. Robert Moen (Baxter Healthcare Corporation) inquired if there is any prospect for a Pan European GTAC. Mr. Taylor responded that there is a draft European directive on clinical trials, which for the first time would bring a Pan European approach to the review of multi-center trials in Europe. There is no plan for establishing a Pan European GTAC; equivalents of the GTAC exist in separate countries, e.g., France and the Netherlands.

XI. Chair's Closing Remarks/Mickelson

Dr. Mickelson noted that several issues will be discussed at the next RAC meeting: (1) the format for RAC discussion of human gene transfer protocols; (2) an update on the *Points to Consider* working group, particularly regarding development of guidance on the use of viral vectors; and (3) any additional data submitted in response to ORDA's request for data regarding gonadal distribution of vector sequences.

XII. Future Meeting Dates/Mickelson

The next meeting of the RAC will be June 18-19, 1998, at NIH Building 31C, Conference Room 10.

XIII. Adjournment/Mickelson

Dr. Mickelson adjourned the meeting at 5:30 p.m. on March 10, 1998.

Debra W. Knorr
Executive Secretary

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and Attachments are accurate and complete.

Date: 6/18/98

Claudia A. Mickelson, Ph.D.
Chair
Recombinant DNA Advisory Committee
National Institutes of Health

RECOMBINANT DNA ADVISORY COMMITTEE

CHAIR

MICKELSON, Claudia A., Ph.D. (99)
Biosafety Officer
Environmental Medical Service, 56-255
Massachusetts Institute of Technology
77 Massachusetts Avenue
Cambridge, Massachusetts 02139-4307
617 253-1740

AGUILAR-CORDOVA, C. Estuardo, Ph.D. (00)
Director, Gene Therapy Laboratories
Texas Childrens Hospital, Suite 1170
Baylor College of Medicine
1102 Bates Street, MC 3-2374
Houston, Texas 77030
713 770-3917

ANDO, Dale G., M.D. (01)
Vice President
Clinical Department
Cell Genesys, Inc.
342 Lakeside Drive
Foster City, California 94404
650 425-4576

GORDON, Jon W., M.D., Ph.D. (00)
Professor
Departments of Neurobiology and OB/GYN
Mt. Sinai School of Medicine
1 Gustave L. Levy Place
New York, New York 10029
212 241-8942

GREENBLATT, Jay J., Ph.D. (01)
Head, Drug Regulatory Affairs Section
Division of Cancer Treatment, Diagnosis, and Centers
National Cancer Institute, EPN, Suite 718
National Institutes of Health, 6130 Executive Boulevard
Bethesda, Maryland 20892-7428
301 496-7912

JUENGST, Eric T., Ph.D. (01)
Associate Professor, Center for Biomedical Ethics
Case Western Reserve University
Rammelkamp Center, Room R239A
2500 MetroHealth Drive
Cleveland, Ohio 44109-1998
216 778-8497

LAI, Michael M.C., M.D., Ph.D. (98)
Professor, Departments of Microbiology
and Neurology, Univ. of Southern California
Howard Hughes Medical Institute
2011 Zonal Avenue, 503 HMR
Los Angeles, California 90033-1054
213 342-1748

LEINWAND, Leslie A, Ph.D. (00)
Professor and Chair
Department of Molecular, Cellular, and
Developmental Biology, CB# 347
University of Colorado, Porter Biosciences A418
Boulder, Colorado 80309-0347
303 492-7606

LYSAUGHT, M. Therese, Ph.D. (98)
Assistant Professor
Department of Religious Studies
University of Dayton
300 College Park
Dayton, Ohio 45469-1530
937 229-2079

MACKLIN, Ruth, Ph.D. (01)
Professor of Bioethics
Department of Epidemiology and Social Medicine
Albert Einstein College of Medicine
1300 Morris Park Avenue
Bronx, New York 10461
718 430-3574

MARKERT, M. Louise, M.D., Ph.D. (99)
Associate Professor
Department of Pediatrics
Duke University Medical Center
368 Jones Building, Box 3068
Durham, North Carolina 27710
919 684-6263

McIVOR, R. Scott, Ph.D. (00)
Director, Gene Therapy Program
Institute of Human Genetics
University of Minnesota, 4-140 Moos Tower
515 Delaware St., S.E.
Minneapolis, Minnesota 55455
612 626-1497

ROTHENBERG, Karen, J.D., M.P.A. (98)
Director, Law and Health Care Program
Marjorie Cook Professor of Law
University of Maryland School of Law
500 W. Baltimore Street
Baltimore, Maryland 21201
410 706-2429

VERMA, Inder M., Ph.D. (98)
Professor
Laboratory of Genetics
The Salk Institute
10010 North Torrey Pines Road
La Jolla, California 92037
619 453-4100 Extension 1398

WOLFF, Jon A., M.D. (99)
Professor
Department of Pediatrics and Genetics
University of Wisconsin Medical School
Waisman Center, Room 607
1500 Highland Avenue
Madison, Wisconsin 53705
608 263-5993

EXECUTIVE SECRETARY

KNORR, Debra W.
Acting Director
Office of Recombinant DNA Activities
National Institutes of Health, MSC 7010
6000 Executive Boulevard, Suite 302
Bethesda, Maryland 20892-7010
301 496-9838

AD HOC CONSULTANTS

FOST, Norman, M.D.
Professor, Department of Pediatrics
University of Wisconsin Hospital
600 Highland Avenue
Madison, Wisconsin 53792
608 263-8562

LANTOS, John, M.D.
Associate Director
MacLean Center for Clinical Medical Ethics
University of Chicago
5841 S. Maryland Avenue, Room W700
Chicago, Illinois 60637
773 702-9107

SPEAKER

KUMAR, Ramish, Ph.D.
President
Zoology/Animal Health Division
Kimeragen, Inc.
300 Pheasant Run
Newtown, Pennsylvania 18940
215 504-4444

NON-VOTING AGENCY REPRESENTATIVES

DEPARTMENT OF AGRICULTURE

JONES, Daniel D., Ph.D.
National Program Leader/Biotechnology
USDA/CSREES, Aerospace Center, Room 843
1400 Independence Avenue, S.W.
Washington, D.C. 20250-2220
202 401-6854

DEPARTMENT OF COMMERCE

LEVIN, Barbara, Ph.D.
Biotechnology Division
National Institute of Standards and Technology
Building 222, Room A353
Gaithersburg, Maryland 20899
301 975-6682

DEPARTMENT OF ENERGY

DRELL, Daniel W., Ph.D.
Office of Health and Environmental Research
Department of Energy, ER-72
Washington, D.C. 20545
301 903-4742

DEPARTMENT OF LABOR

YODAIKEN, Ralph E., M.D.
Senior Medical Advisor
USDOL/OSHA, Room N-3653
200 Constitution Avenue, N.W.
Washington, D.C. 20210
202 219-5003

ENVIRONMENTAL PROTECTION AGENCY

MILEWSKI, Elizabeth, Ph.D.
Office of Prevention, Pesticides & Toxic Substances
Environmental Protection Agency
401 M Street, S.W., ML Code 7101
Washington, D.C. 20460
202 260-6900

FREDERICK, Robert, Ph.D.
ORD/NCEA
Environmental Protection Agency
401 M Street, S.W., ML Code 8601
Washington, D.C. 20460
202 260-0689

NATIONAL SCIENCE FOUNDATION

HARRIMAN, Philip, Ph.D.
Division of Molecular Biosciences
National Science Foundation, Room 325
4201 Wilson Boulevard
Arlington, Virginia 22230
703 306-1441

DEPARTMENT OF HEALTH AND HUMAN SERVICES (DHHS)

FOOD AND DRUG ADMINISTRATION

NOGUCHI, Philip, M.D.
Division of Cellular and Gene Therapies
Center for Biologics Evaluation & Research
FDA, HFM 515, Bldg. 29, Room B24
1401 Rockville Pike
Rockville, Maryland 20852-1448
301 496-4709

OFFICE OF PROTECTION FROM RESEARCH RISKS

ELLIS, Gary, Ph.D.
Director
Office of Protection from Research Risks
6100 Executive Boulevard
Suite 3B01
Bethesda, Maryland 20892
301 496-7005

LIN, Melody H., Ph.D. (ALT)
Deputy Director
Office of Protection from Research Risks
6100 Executive Boulevard
Suite 3B01
Bethesda, Maryland 20892
301 435-5647

LIAISON REPRESENTATIVES

FAYL, Gilbert
Counselor, Science & Technology Section
Delegation of the Commission of the
European Communities
2300 M Street, N.W., 3rd Floor
Washington, D.C. 20037
202 862-9575

JONES, Daniel P., Ph.D.
Humanities, Science and Technology
Division of Research Programs
National Endowment for the Humanities
Washington, D.C. 20506
202 786-0207

HUMAN GENE THERAPY PROTOCOLS
Last updated: 2-11-98

8810-001 (Open) Gene Marking/Cancer
In Vitro/Tumor Infiltrating Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *The Treatment of Patients with Advanced Cancer Using Cyclophosphamide, Interleukin-2 and Tumor Infiltrating Lymphocytes.*

RAC Approval: 10-3-88/NIH Approval: 3-2-89

9007-002 (Open) Gene Therapy/Phase I/Monogenic Disease/Severe Combined Immune Deficiency due to Adenosine Deaminase Deficiency
In Vitro/Autologous Peripheral Blood Cells/CD34+ Autologous Peripheral Blood Cells/Cord Blood/Placenta Cells/Retrovirus/Adenosine Deaminase cDNA/Neomycin Phosphotransferase cDNA/Intravenous

Blaese, R. Michael; National Institutes of Health, Bethesda, Maryland; *Treatment of Severe Combined Immune Deficiency (SCID) due to Adenosine Deaminase (ADA) Deficiency with Autologous Lymphocytes Transduced with the Human ADA Gene: An Experimental Study.*

RAC Approval: 7-31-90/NIH Approval: 9-6-90

9007-003 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Tumor Infiltrating Lymphocytes/Retrovirus/Cytokine/Tumor Necrosis Factor cDNA/Neomycin Phosphotransferase cDNA/Intravenous

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Gene Therapy of Patients with Advanced Cancer Using Tumor Infiltrating Lymphocytes Transduced with the Gene Coding for Tumor Necrosis Factor.*

RAC Approval: 7-31-90/NIH Approval: 9-6-90

9102-004 (Closed) Gene Marking/Cancer/Acute Myelogenous Leukemia
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; Mirro, Joseph; Hurwitz, Craig; Santana, Victor; and Ihle, James; St. Jude Children's Research Hospital, Memphis, Tennessee; *Autologous Bone Marrow Transplant for Children with Acute Myelogenous Leukemia in First Complete Remission: Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and the Mechanism of Relapse.*

RAC Approval: 2-4-91/NIH Approval: 7-12-91
Closed: 1-21-93

9105-005 (Closed) Gene Marking/Cancer/Neuroblastoma
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; Mirro, Joseph; Santana, Victor; and Ihle, James; St. Jude Children's Research Hospital, Memphis, Tennessee; *A Phase I/II Trial of High Dose Carboplatin and Etoposide with Autologous Marrow Support for Treatment of Stage D Neuroblastoma in First Remission: Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and the Mechanism of Relapse.*

RAC Approval: 5-31-91/NIH Approval: 7-12-91
Closed: 9-1-92

9105-006 (Closed) Gene Marking/Cancer/Neuroblastoma
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; Mirro, Joseph; Santana, Victor; and Ihle, James; St. Jude Children's Research Hospital, Memphis, Tennessee; *A Phase II Trial of High-Dose Carboplatin and Etoposide with Autologous Marrow Support for Treatment of Relapse/Refractory Neuroblastoma Without Apparent Bone Marrow Involvement.*

RAC Approval: 5-31-91/NIH Approval: 7-12-91
Closed: 4-9-93

9105-007 (Closed) Gene Marking/Cancer/Chronic Myelogenous Leukemia
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Deisseroth, Albert B.; M.D. Anderson Cancer Research Center, Houston, Texas; *Autologous Bone Marrow Transplantation for Chronic Myelogenous Leukemia in which Retroviral Markers are Used to Discriminate between Relapse which Arises from Systemic Disease Remaining after Preparative*

Therapy Versus Relapse due to Residual Leukemic Cells in Autologous Marrow: A Pilot Trial.

RAC Approval: 5-31-91/NIH Approval: 7-12-91
Closed: 6-1-93
Closed: 4-9-93

9105-008 (Closed) Gene Marking/Acute Hepatic Failure
In Vitro/Autologous Hepatocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intrahepatic

Ledley, Fred D.; Woo, Savio; Ferry, George; and Hartwell, Whisennand; Baylor College of Medicine, Houston, Texas; *Hepatocellular Transplantation in Acute Hepatic Failure and Targeting Genetic Markers to Hepatic Cells.*

RAC Approval: 5-30-91/NIH Approval: 7-12-91
Closed: Protocol Never Initiated

9105-009 (Closed) Gene Marking/Cancer/Melanoma
In Vitro/Tumor Infiltrating Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Lotze, Michael T.; University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; *The Administration of Interleukin-2 and Tumor Infiltrating Lymphocytes to Patients with Melanoma.*

RAC Approval: 5-30-91/NIH Approval: 1-17-92
Closed: 4-95

9110-010 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Renal Cell/Colon/Breast/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Tumor Necrosis Factor cDNA/Neomycin Phosphotransferase cDNA/Subcutaneous Injection

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Immunization of Cancer Patients Using Autologous Cancer Cells Modified by Insertion of the Gene for Tumor Necrosis Factor (TNF).*

RAC Approval: 10-7-91/NIH Approval: 10-15-91

9110-011 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Renal Cell/Colon/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Immunization of Cancer Patients Using Autologous Cancer Cells Modified by Insertion of the Gene for Interleukin-2 (IL-2).*

RAC Approval: 10-7-91/NIH Approval: 10-15-91

9110-012 (Closed) Gene Therapy/Phase I/Monogenic Disease/Familial Hypercholesterolemia
In Vitro/Low Density Lipoprotein Receptor cDNA/Intrahepatic/Portal Vein Catheter

Wilson, James M.; University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *Ex Vivo Gene Therapy of Familial Hypercholesterolemia.*

RAC Approval: 10-8-91/NIH Approval: 11-14-91
Closed: 3-11-94

9202-013 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Adenocarcinoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DC-Chol/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Direct Injection/Catheter Delivery to Pulmonary Nodules

Nabel, Gary J.; University of Michigan, Ann Arbor, Michigan; *Immunotherapy of Malignancy by In Vivo Gene Transfer into Tumors.*

RAC Approval: 2-10-92/NIH Approval: 4-17-92
Closed: 11-19-92 (Replaced by Protocol #9306-045)

9202-014 (Closed) Gene Marking/Cancer/Acute Myelogenous Leukemia/Acute Lymphocytic Leukemia
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Cornetta, Kenneth; Indiana University, Indianapolis, Indiana; *Retroviral-Mediated Gene Transfer of Bone Marrow Cells during Autologous Bone Marrow Transplantation for Acute Leukemia.*

RAC Approval: 2-11-92/NIH Approval: 4-17-92

Closed 5-1-95

9202-015 (Closed) Gene Marking/Cancer/Melanoma/Renal Cell
In Vitro/CD4+ Autologous Peripheral Blood Lymphocytes/CD8+ Autologous Peripheral Blood Lymphocytes/CD4+ Autologous Tumor Infiltrating Lymphocytes/CD8+ Autologous Tumor Infiltrating Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Economou, James S. and Belldegrun, Arie; University of California at Los Angeles, Los Angeles, California; *The Treatment of Patients with Metastatic Melanoma and Renal Cell Cancer Using In Vitro Expanded and Genetically-Engineered (Neomycin Phosphotransferase) Bulk, CD8 (+) and/or CD4(+) Tumor Infiltrating Lymphocytes and Bulk, CD8(+) and/or CD4(+) Peripheral Blood Leukocytes in Combination with Recombinant Interleukin-2 Alone, or with Recombinant Interleukin-2 and Recombinant Alpha Interferon.*

RAC Approval: 2-11-92/NIH Approval: 4-17-92
Closed: 6-94

9202-016 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug
In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intraperitoneal Administration

Freeman, Scott M.; Tulane University Medical Center, New Orleans, Louisiana; *Gene Transfer for the Treatment of Cancer.*

RAC Approval: 2-10-92/NIH Approval: 2-5-93

9202-017 (Open) Gene Therapy/Infectious Disease/Human Immunodeficiency Virus
In Vitro/CD8+ Allogeneic Cytotoxic T Lymphocytes/CD8+ Syngeneic Cytotoxic T Lymphocytes/Retrovirus/Hygromycin Phosphotransferase/Herpes Simplex Virus Thymidine Kinase cDNA/Intravenous

Greenberg, Philip D. and Riddell, Stanley; Fred Hutchinson Cancer Research Center, University of Washington, Seattle; *Phase I Study to Evaluate the Safety of Cellular Adoptive Immunotherapy Using Genetically Modified CD8+ HIV-Specific T Cells in HIV Seropositive Individuals.*

RAC Approval: 2-11-92/NIH Approval: 4-17-92

9206-018 (Open) Gene Therapy/Phase I/Cancer/Relapsed-Refractory Neuroblastoma/Immunotherapy
In Vitro/Autologous Neuroblastoma Cells/Allogeneic Partially HLA-Matched/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Brenner, Malcolm K.; Furman, Wayne; Santana, Victor; Bowman, Laura; and Meyer, William; St. Jude Children's Research Hospital, Memphis, Tennessee; *Phase I Study of Cytokine-Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma.*

RAC Approval: 6-1-92/NIH Approval: 8-14-92

9206-019 (Closed) Gene Therapy/Phase I/Cancer/Brain/Pro-Drug
In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Stereotactic Injection

Oldfield, Edward; National Institutes of Health, Bethesda, Maryland; *Gene Therapy for the Treatment of Brain Tumors Using Intra-Tumoral Transduction with the Thymidine Kinase Gene and Intravenous Ganciclovir.* Sponsor: Genetic Therapy, Inc./Novartis

RAC Approval: 6-1-92/NIH Approval: 8-14-92
Closed: 12-94

9206-020 (Closed) Gene Marking/Cancer/Chronic Myelogenous Leukemia
In Vitro/Autologous Bone Marrow Cells/Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Deisseroth, Albert B.; MD Anderson Cancer Center, Houston, Texas; *Use of Two Retroviral Markers to Test Relative Contribution of Marrow and Peripheral Blood Autologous Cells to Recovery After Preparative Therapy.*

RAC Approval: 6-2-92/NIH Approval: 8-14-92
Closed: 2-13-96

9206-021 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Allogeneic Partially HLA-Matched/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Gansbacher, Bernd; Houghton, Alan; and Livingston, Philip; Memorial Sloan Kettering Cancer Center, New York, New York; *Immunization with HLA-A2 matched Allogeneic Melanoma Cells that Secrete Interleukin-2 in Patients with Metastatic Melanoma.*

RAC Approval: 6-2-92/NIH Approval: 8-14-92
Closed: 10-19-94

9206-022 (Open) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vitro/Allogeneic Partially HLA-Matched/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Gansbacher, Bernd; Motzer, Robert; Houghton, Alan; and Bander, Neil; Memorial Sloan Kettering Cancer Center, New York, New York; *Immunization with Interleukin-2 Secreting Allogeneic HLA-A2 Matched Renal Cell Carcinoma Cells in Patients with Advanced Renal Cell Carcinoma.*

RAC Approval: 6-2-92/NIH Approval: 8-14-92

9206-023 (Open) Gene Marking/Cancer/Multiple Myeloma
In Vitro/CD34+ Autologous Peripheral Blood Cells/Intravenous/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Dunbar, Cynthia; National Institutes of Health, Bethesda, Maryland; *Retroviral-Mediated Gene Transfer of Bone Marrow and Peripheral Blood Stem Cells During Autologous Bone Marrow Transplantation for Multiple Myeloma.*

RAC Approval: 6-2-92/NIH Approval: 8-14-92

9206-024 (Open) Gene Marking/Cancer/Breast
In Vitro/CD34+ Autologous Peripheral Blood Cells/Intravenous/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Dunbar, Cynthia; National Institutes of Health, Bethesda, Maryland; *Retroviral-Mediated Gene Transfer of Bone Marrow and Peripheral Blood Stem Cells During Autologous Bone Marrow Transplantation for Metastatic Breast Cancer.*

RAC Approval: 6-2-92/NIH Approval: 8-14-92

9206-025 (Open) Gene Marking/Cancer/Chronic Myelogenous Leukemia
In Vitro/CD34+ Autologous Peripheral Blood Cells/Intravenous/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Dunbar, Cynthia; National Institutes of Health, Bethesda, Maryland; *Retroviral-Mediated Gene Transfer of Bone Marrow and Peripheral Blood Stem Cells During Autologous Bone Marrow Transplantation for Chronic Myelogenous Leukemia.*

RAC Approval: 6-2-92/NIH Approval: 8-14-92

9209-026 (Open) Gene Marking/Infectious Disease/Human Immunodeficiency Virus
In Vitro/Syngeneic Peripheral Blood Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Walker, Robert E.; National Institutes of Health, Bethesda, Maryland; *A Study of the Safety and Survival of the Adoptive Transfer of Genetically Marked Syngeneic Lymphocytes in HIV Infected Identical Twins.*

RAC Approval: 9-14-92/NIH Approval: 9-3-93

9209-027 (Closed) Gene Marking/Cancer
In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Schuening, Friedrich G.; Miller, A. Dusty; and Kiem, Hans-Peter; Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington; *Study on Contribution of Genetically Marked Peripheral Blood Repopulating Cells to Hematopoietic Reconstitution after Transplantation.*

RAC Approval: 9-14-92/NIH Approval: 2-5-93
Closed: 4-29-97

9209-028 (Closed) Gene Marking/Cancer/Lymphoid Malignancies/
In Vitro/G-CSF Mobilized Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Schuening, Friedrich G.; Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington; *Evaluation of the Use of Recombinant Human G-CSF Stimulated Peripheral Blood Progenitor Cell Supplementation in Autologous Bone Marrow Transplantation in Patients with Lymphoid Malignancies.*

RAC Approval: 9-14-92/NIH Approval: 2-5-93
Closed: 2-25-94 (Merged with protocol # 9209-027)

9209-029 (Closed) Gene Marking/Cancer/
In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Schuening, Friedrich G.; Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington; *A Trial of G-CSF Stimulated Peripheral Blood Stem Cells for Engraftment in Identical Twins.*

RAC Approval: 9-14-92/NIH Approval: 2-5-93
Closed: Protocol Never Initiated

9209-030 (Open) Gene Marking/Cancer/Chronic Lymphocytic Leukemia/Follicular Non-hodgkins Lymphoma
In Vitro/Autologous Bone Marrow Cells/Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Deisseroth, Albert B.; University of Texas MD Anderson Cancer Center, Houston, Texas; *Use of Retroviral Markers to Identify Efficacy of Purging and Origin of Relapse Following Autologous Bone Marrow and Peripheral Blood Cell Transplantation in Indolent B Cell Neoplasms (Follicular Non-Hodgkin's Lymphoma or Chronic Lymphocytic Leukemia) Patients.*

RAC Approval: 9-14-92/NIH Approval: 12-2-93

9403-031 (Open) Gene Therapy/Phase I/Cancer/Non-small Cell Lung Cancer/Antisense/Tumor Suppressor Gene
In Vivo/Autologous Tumor Cells/Retrovirus/p53 cDNA/kras Antisense/Intratumoral/Bronchoscope

Roth, Jack A.; The University of Texas MD Anderson Cancer Center, Houston, Texas; and Garver, Robert I., Jr.; University of Alabama at Birmingham, Birmingham, AL; *Clinical Protocol for Modification of Oncogene and Tumor Suppressor Gene Expression in Non-Small Cell Lung Cancer (NSCLC).*

RAC Approval: 3-4-94/NIH Approval: 1-4-95

9209-032 (Open) Gene Marking/Cancer/Neuroblastoma
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; St. Jude Children's Research Hospital, Memphis, Tennessee; *A Phase II Trial of the Baxter Neuroblastoma Bone Marrow Purging System Using Gene Marking to Assess Efficacy.*

RAC Approval: 9-15-92/NIH Approval: 2-5-93

9209-033 (Open) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vitro/Autologous Fibroblasts/Lethally Irradiated/In Combination with Untransduced Autologous Tumor Cells/Retrovirus/Cytokine/Interleukin-4 cDNA/Subcutaneous Injection

Lotze, Michael T. and Rubin, Joshua T.; University of Pittsburgh, Pittsburgh, Pennsylvania; *Gene Therapy of Cancer: A Pilot Study of IL-4 Gene Modified Antitumor Vaccines.*

RAC Approval: 9-15-92/NIH Approval: 2-5-93

9212-034 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Crystal, Ronald G.; Rockefeller University Hospital, New York, New York; *A Phase I Study, in Cystic Fibrosis Patients, of the Safety, Toxicity, and Biological Efficacy of a Single Administration of a Replication Deficient, Recombinant Adenovirus Carrying the cDNA of the Normal Human Cystic Fibrosis Transmembrane Conductance Regulator Gene in the Lung.*

RAC Approval: 12-3-92/NIH Approval: 4-16-93

9212-035 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adenovirus/Serotype 5/E2a Temperature Sensitive Mutant/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Wilson, James M., University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; Simon, Richard H., University of Michigan Medical Center, Ann Arbor, Michigan; McCoy, Karen, Cystic Fibrosis Center at Ohio State University; *Gene Therapy of Cystic Fibrosis Lung Diseases Using E1 Deleted Adenoviruses: A Phase I Trial.*

RAC Approval: 12-3-92/NIH Approval: 8-26-93

9212-036 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Adenovirus/Serotype 2/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal

Welsh, Michael J.; Howard Hughes Medical Institute, Iowa City, Iowa; and Smith, Alan E.; Genzyme Corporation, Framingham, Massachusetts; *Cystic Fibrosis Gene Therapy Using an Adenovirus Vector: In Vivo Safety and Efficacy in Nasal Epithelium*. Sponsor: Genzyme Corporation

RAC Approval: 12-4-92/NIH Approval: 4-16-93

9303-037 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma/Pro-Drug
In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Van Gilder, John C.; University of Iowa, Iowa City, Iowa; Berger, Mitchell; University of California San Francisco, California; Prados, Michael; University of Washington, Seattle, Washington; Warnick, Ronald; University of Cincinnati Medical Center, Cincinnati, Ohio; Schold, Clifford; University of Texas Southwestern Medical Center, Dallas, Texas; Fetell, Michael; Columbia Presbyterian Medical Center, New York, New York; Schramm, Johannes; Neurochirurgische Universitatsklinik, Bonn, Germany; Westphal, Manfred; University Clinic Eppendorf, Hamburg, Germany; Tonn, Jorg-Christian, University Kliniken, Wurzburg, Germany; Moumdjian, Robert; Notre-Dame Hospital, Montreal, Quebec, Canada; Shaffrey, Mark; University of Virginia, Charlottesville, Virginia; Asher, Anthony; Charlotte Neurological Associates and Presbyterian Hospital, Charlotte, North Carolina; Epstein, Mel; Brown University, Providence, Rhode Island; Schmitz-Schackert, Gabriele Anna Maria; University Klinik "Carl Gustav-Carus, Dresden, Germany; Mendez, Ivar; Victoria General Hospital, Nova Scotia, Canada; Bernstein, Mark; The Toronto Hospital, Toronto, Ontario, Canada; *Gene Therapy for the Treatment of Recurrent Glioblastoma Multiforme with In Vivo Tumor Transduction with the Herpes Simplex Thymidine Kinase Gene/Ganciclovir System*. Sponsor: Genetic Therapy, Inc./Novartis

RAC Approval: 3-1-93/NIH Approval: 4-16-93

9303-038 (Open) Gene Marking/Cancer/Leukemia/Non-malignant Disorders
In Vitro/Epstein-Barr Virus Specific Allogeneic Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Heslop, Helen E.; Brenner, Malcolm K.; and Rooney, Cliona; St. Jude Children's Research Hospital, Memphis, Tennessee; *Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes to Recipients of Mismatched-Related or Phenotypically Similar Unrelated Donor Marrow Grafts.*

RAC Approval: 3-2-93/NIH Approval: 4-16-93

9303-039 (Open) Gene Marking/Cancer/Acute Myelogenous Leukemia
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; Krance, Robert; Heslop, Helen E.; Santana, Victor; and Ihle, James; St. Jude Children's Research Hospital, Memphis, Tennessee; *Assessment of the Efficacy of Purging by Using Gene-Marked Autologous Marrow Transplantation for Children with Acute Myelogenous Leukemia in First Complete Remission.*

RAC Approval: 3-2-93/NIH Approval: 4-16-93

9303-040 (Open) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Subcutaneous Injection

Simons, Jonathan; Johns Hopkins Oncology Center, Baltimore, Maryland; *Phase I Study of Non Replicating Autologous Tumor Cell Injections Using Cells Prepared With or Without Granulocyte-Macrophage Colony Stimulating Factor Gene Transduction in Patients with Metastatic Renal Cell Carcinoma.*

RAC Approval: 3-1-93/NIH Approval: 12-2-93

9303-041 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Wilmott, Robert W. and Whitsett, Jeffrey; Children's Hospital Medical Center, Cincinnati, Ohio; and Trapnell, Bruce; Genetic Therapy, Inc., Gaithersburg, Maryland; *A Phase I Study of Gene Therapy of Cystic Fibrosis Utilizing a Replication Deficient Recombinant Adenovirus Vector to Deliver the Human Cystic Fibrosis Transmembrane Conductance Regulator cDNA to the Airways.* Sponsor: Genetic Therapy, Inc./Novartis

RAC Approval: 3-2-93/NIH Approval: 4-16-93
Closed: 4-28-97 (IND Withdrawn)

9303-042 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator CDNA/Intranasal

Boucher, Richard C. and Knowles, Michael R.; University of North Carolina, Chapel Hill, North Carolina; *Gene Therapy for Cystic Fibrosis Using E1 Deleted Adenovirus A Phase I Trial in the Nasal Cavity.*

RAC Approval: 3-2-93/NIH Approval: 10-7-93
Closed: 10-94

9306-043 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Gamma Interferon cDNA/Subcutaneous Injection

Seigler, Hilliard F.; Duke University Medical Center, Durham, North Carolina; and Merritt, James A.; Viagene, Inc., San Diego, California; *A Phase I Trial of Human Gamma Interferon-Transduced Autologous Tumor Cells in Patients With Disseminated Malignant Melanoma.*

RAC Approval: 6-7-93/NIH Approval: 9-3-93

9306-044 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Chemoprotection
In Vitro/CD34+ Autologous Bone Marrow Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Bone Marrow Transplant

Deisseroth, Albert B.; Kavanagh, John; and Champlin, Richard; University of Texas MD Anderson Cancer Center, Houston, Texas; *Use of Safety-Modified Retroviruses to Introduce Chemotherapy Resistance Sequences into Normal Hematopoietic Cells for Chemoprotection During the Therapy of Ovarian Cancer: A Pilot Trial.*

RAC Approval: 6-7-93/NIH Approval: 12-2-93

9306-045 (Open) Gene Therapy/Phase I/Cancer/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Direct Injection/Catheter Delivery to Pulmonary Nodules

Nabel, Gary J.; University of Michigan Medical Center, Ann Arbor, Michigan; *Immunotherapy for Cancer by Direct Gene Transfer into Tumors.*

RAC Approval: 6-7-93/NIH Approval: 9-3-93

9306-046 (Open) Gene Therapy/Phase I/Monogenic Disease/Gaucher Disease
In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Glucocerebrosidase cDNA/Bone Marrow Transplant

Barranger, John A.; University of Pittsburgh, Pittsburgh, Pennsylvania; *Gene Therapy for Gaucher Disease: Ex Vivo Gene Transfer and Autologous Transplantation of CD34(+) Cells.*

RAC Approval: 6-7-93/NIH Approval: 9-3-93

9306-047 (Closed) Gene Therapy/Phase I/Monogenic Disease/Gaucher Disease
In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Glucocerebrosidase cDNA/Bone Marrow Transplant

Karlsson, Stefan and Dunbar, Cynthia; National Institutes of Health, Bethesda, Maryland; and Kohn, Donald B.; Childrens Hospital Los Angeles, Los Angeles, California; *Retroviral Mediated Transfer of the cDNA for Human Glucocerebrosidase into Hematopoietic Stem Cells of Patients with Gaucher Disease.* Sponsor: Genetic Therapy, Inc./Novartis

RAC Approval: 6-7-93/NIH Approval: 9-3-93
Closed: 4-30-97 (IND Withdrawn)

9306-048 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy
In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1IIIB Envelope Protein/Intramuscular Injection

Galpin, Jeffrey E.; University of Southern California; Casciato, Dennis A.; Shared Medical Research Foundation, Tarzana, California; and Merritt, James A.; Viagene, Inc., San Diego, California; *A Preliminary Study to Evaluate the Safety and Biologic Effects of Murine Retroviral Vector Encoding HIV-1 Genes [HIV-IT(V)] in Asymptomatic Subjects Infected with HIV-1.* Sponsor: Chiron Corporation

RAC Approval: 6-7-93/NIH Approval: 9-3-93
Closed: 9-8-94

9306-049 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense
In Vitro/CD4+ Autologous Peripheral Blood Cells/Retrovirus/Particle Mediated Gene Transfer (Accell®)/RSV-tar/Rev M10/Intravenous

Nabel, Gary J.; University of Michigan Medical Center, Ann Arbor, Michigan; *A Molecular Genetic Intervention for AIDS - Effects of a Transdominant Negative Form of Rev.*

RAC Approval: 6-7-93/NIH Approval: 9-3-93

9306-050 (Open) Gene Therapy/Phase I/Cancer/Astrocytoma/Pro-Drug
In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Ommaya Injection

Raffel, Corey; Mayo Clinic, Rochester, Minnesota; Villablanca, Judith; Childrens Hospital Los Angeles, Los Angeles, California; Packer, Roger, Childrens National Medical Center, Washington, DC; Tonn, Jorg-Christian, Neurochirurgische Klinik und Poliklinik, Universitats-Klinikin, Wurzburg, Germany; and Burdach, Stefan; University Center for Paediatrics, Heinrich-Heine Universitat, Dusseldorf, Germany; *Gene Therapy for the Treatment of Recurrent Pediatric Malignant Astrocytomas with In Vivo Tumor Transduction with the Herpes Simplex Thymidine Kinase Gene.* Sponsor: Genetic Therapy, Inc./Novartis

RAC Approval: 6-8-93/NIH Approval: 9-3-93

9306-051 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Brain/Chemoprotection
In Vitro/CD34+ Autologous Bone Marrow Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Bone Marrow Transplant

Hesdorffer, Charles and Antman, Karen; Columbia University College of Physicians and Surgeons, New York, New York; *Human MDR Gene Transfer in Patients with Advanced Cancer.*

RAC Approval: 6-8-93/NIH Approval: 9-3-93

9306-052 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma/Antisense
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Lipofectin (Gibco BRL)/Insulin-like Growth Factor Antisense/Subcutaneous Injection

Ilan, Joseph; Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, Ohio; *Gene Therapy for Human Brain Tumors Using Episome-Based Antisense cDNA Transcription of Insulin-Like Growth Factor I*

RAC Approval: 6-8-93/NIH Approval: 12-2-93

9309-053 (Open) Gene Therapy/Phase I/Cancer/Small Cell Lung Cancer/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Lipofectin (Gibco BRL)/Cytokine/Interleukin-2 cDNA/Neomycin Phosphotransferase cDNA/Subcutaneous Injection

Cassileth, Peter; Podack, Eckhard R.; Sridhar, Kasi; University of Miami; and Savaraj, Niramol; Miami Veterans Administration Hospital, Miami, Florida; *Phase I Study of Transfected Cancer Cells Expressing the Interleukin-2 Gene Product in Limited Stage Small Cell Lung Cancer.*

RAC Approval: 9-9-93/NIH Approval: 12-2-93

9309-054 (Open) Gene Therapy/Phase I/Cancer/Breast/Chemoprotection
In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Intravenous

O'Shaughnessy, Joyce;Kentuckiana Medical Oncology Association, Louisville, Kentucky; *Retroviral Mediated Transfer of the Human Multi-Drug Resistance Gene (MDR-1) into Hematopoietic Stem Cells During Autologous Transplantation after Intensive Chemotherapy for Breast Cancer.*

RAC Approval: 9-9-93/NIH Approval: 10-7-93

9309-055 (Open) Gene Therapy/Phase I/Cancer/Brain Tumors/Pro-Drug
In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Kun, Larry E.; Sanford, R. A.; Brenner, Malcolm K.; and Heideman, Richard L.; St. Jude Childrens Research Hospital, Memphis, Tennessee; and Oldfield, Edward H.; National Institutes of Health, Bethesda, Maryland; *Gene Therapy for Recurrent Pediatric Brain Tumors.* Sponsor: Genetic Therapy, Inc./Novartis

RAC Approval: 9-9-93/NIH Approval: 10-7-93

9309-056 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Interleukin-2 cDNA/Neomycin Phosphotransferase cDNA/Subcutaneous Injection

Das Gupta, Tapas K. and Cohen, Edward P.; University of Illinois at Chicago, Chicago, Illinois; *Immunization of Malignant Melanoma Patients with Interleukin 2-Secreting Melanoma Cells Expressing Defined Allogeneic Histocompatibility Antigens.*

RAC Approval: 9-10-93/NIH Approval: 4-19-94

9309-057 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus-1/Replication Inhibition/Hairpin Ribozyme In Vitro/CD4+ Peripheral Blood Cells/Retrovirus/Hairpin Ribozyme/Intravenous

Wong-Staal, Flossie; Poeschla, Eric; and Looney, David; University of California, San Diego, California; *A Phase I Clinical Trial to Evaluate the Safety and Effects in HIV-1 Infected Humans of Autologous Lymphocytes Transduced with a Ribozyme that Cleaves HIV-1 RNA.*

RAC Approval: 9-10-93/NIH Approval: 10-25-94

9309-058 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/In Combination with Untransduced Autologous Tumor Cells/Retrovirus/Interleukin-2 cDNA/Subcutaneous Injection

Economou, James S. and Glasby, John A.; University of California Medical Center, Los Angeles, California; *Genetically Engineered Autologous Tumor Vaccines Producing Interleukin-2 for the Treatment of Metastatic Melanoma.*

RAC Approval: 9-10-93/NIH Approval: 12-2-93

9312-059 (Closed) Gene Therapy/Phase I/Cancer/Leptomeningeal Carcinomatosis/Pro-Drug In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intraventricular Injection/Subarachnoid Injection

Oldfield, Edward H. and Ram, Zvi; National Institutes of Health, Bethesda, Maryland; *Intrathecal Gene Therapy for the Treatment of Leptomeningeal Carcinomatosis.* Sponsor: Genetic Therapy, Inc./Novartis

RAC Approval: 12-2-93/NIH Approval: 1-20-94
Closed 1/95

9312-060 (Open) Gene Therapy/Phase I/Cancer/Colon/Immunotherapy In Vitro/Autologous Fibroblasts/Lethally Irradiated/In Combination with Untransduced Autologous Tumor Cells/Retrovirus/Interleukin-2 cDNA/Subcutaneous Injection

Sobol, Robert E. and Royston, Ivor; San Diego Regional Cancer Center, San Diego, California; *Injection of Colon Carcinoma Patients with Autologous Irradiated Tumor Cells and Fibroblasts Genetically Modified to Secrete Interleukin-2.*

RAC Approval: 12-2-93/NIH Approval: 1-4-95

9312-061 (Closed) Gene Therapy/Phase I/Monogenic Disease/Gaucher Disease In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/Glucocerebrosidase cDNA/Intravenous

Schuening, Friedrich; Fred Hutchinson Cancer Research Center, Seattle, Washington; *Retrovirus-Mediated Transfer of the cDNA for Human Glucocerebrosidase into Peripheral Blood Repopulating Cells of Patients with Gaucher's Disease.*

RAC Approval: 12-2-93/NIH Approval: 11-15-94
Closed: 4-29-97

9312-062 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1IIIB Envelope Protein/Intramuscular Injection

Haubrich, Richard; University of California at San Diego Treatment Center, San Diego, California; and Merritt, James A.; Viagene, Inc., San Diego, California, *An Open Label, Phase I/II Clinical Trial to Evaluate the Safety and Biological Activity of HIV-IT(V) (HIV-1 IIIBenv/Retroviral Vector) in HIV 1 Infected Subjects.*

RAC Approval: 12-3-93/NIH Approval: 4-19-94
Closed: 10-13-94

9312-063 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Lipofectin (Gibco BRL)/B7 (CD80) cDNA/Neomycin Phosphotransferase cDNA/Subcutaneous Injection

Sznol, Mario; National Institutes of Health, Frederick, Maryland; *A Phase I Trial of B7-Transfected Lethally Irradiated Allogeneic Melanoma Cell Lines to Induce Cell Mediated Immunity Against Tumor-Associated Antigens Presented by HLA-A2 or HLA-A1 in Patients with Stage IV Melanoma.*

RAC Approval: 12-3-93/NIH Approval: 4-19-94

9312-064 (Closed) Gene Therapy/Phase I/Cancer/Colon/Hepatic Metastases/Immunotherapy

In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Hepatic Injection

Rubin, Joseph; Mayo Clinic, Rochester, Minnesota; *Phase I Study of Immunotherapy of Advanced Colorectal Carcinoma by Direct Gene Transfer into Hepatic Metastases.* Sponsor: Vical, Incorporated

RAC Approval: 12-3-93/NIH Approval: 4-19-94
Closed: 3-16-95 (Closed to accrual - maximum number of subjects entered)

9312-065 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Used in Combination with Anti-CD3 and Interleukin-2 Primed Autologous Lymph Node Cells to Prime Autologous Peripheral Blood Cells In Vitro/Retrovirus/GM-CSF cDNA/Intravenous

Chang, Alfred E.; University of Michigan, Ann Arbor, Michigan; *Adoptive Immunotherapy of Cancer with Activated Lymph Node Cells Primed In Vivo with Autologous Tumor Cells Transduced with the GM-CSF Gene.*

RAC Approval: 12-3-93/NIH Approval: 8-23-94

9312-066 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Cationic Liposome Complex/DMRIE-DOPE/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal

Sorscher, Eric J. and Logan, James L.; University of Alabama, Birmingham, Alabama; *Gene Therapy for Cystic Fibrosis Using Cationic Liposome Mediated Gene Transfer: A Phase I Trial of Safety and Efficacy in the Nasal Airway.*

RAC Approval: 12-3-93/NIH Approval: 1-4-95

9312-067 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Maxillary Sinus Epithelial Cells/Adenovirus/Serotype 2/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Maxillary Sinus Administration

Welsh, Michael J.; Howard Hughes Medical Institute, Iowa City, Iowa; *Adenovirus-Mediated Gene Transfer of CFTR to the Nasal Epithelium and Maxillary Sinus of Patients with Cystic Fibrosis.* Sponsor: Genzyme Corporation

RAC Approval: 12-3-93/NIH Approval: 2-10-94

9403-068 (Open) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Gamma Interferon cDNA/Subcutaneous Injection

Rosenblatt, Joseph; University of California, Los Angeles, California; Seeger, Robert; Childrens Hospital, Los Angeles, California; and Merritt, James A.; Viagene, Inc., San Diego, California; *A Phase I Study of Immunization with Gamma Interferon Transduced Neuroblastoma Cells.*

RAC Approval: 3-3-94/NIH Approval: 10-25-94

9403-069 (Closed) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy
In Vitro/CD8+ Syngeneic Peripheral Blood Cells/Retrovirus/CD4-zeta Chimeric Receptor/Intravenous/Concurrent Interleukin-2 Therapy

Walker, Robert; National Institutes of Health, Bethesda, Maryland; *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

RAC Approval: 3-3-94/NIH Approval: 8-23-94
Closed: 2-97

9403-070 (Open) Gene Therapy/Phase I/Monogenic Disease/Alpha-1-Antitrypsin Deficiency
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Cationic Liposome Complex/DC-Chol-DOPE/Alpha-1 Antitrypsin cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Brigham, Kenneth; Clinical Research Center at Vanderbilt University Medical Center, Nashville, Tennessee; *Expression of an Exogenously Administered Human Alpha-1-Antitrypsin Gene in the Respiratory Tract of Humans.* Sponsor: Gene Medicine, Inc

RAC Approval: 3-3-94/NIH Approval: 10-25-94

9403-071 (Closed) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Direct Injection

Vogelzang, Nicholas; the University of Chicago, Chicago, Illinois; *Phase I Study of Immunotherapy for Metastatic Renal Cell Carcinoma by Direct Gene Transfer into Metastatic Lesions.* Sponsor: Vical, Incorporated

RAC Approval: 3-4-94/NIH Approval: 4-19-94
Closed: 4-5-95 (Closed to accrual - maximum number of subjects entered)

9403-072 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Direct Injection

Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; and Akporiaye; Harris; Stopeck; Unger; and Warneke; University of Arizona, Tucson, Arizona; *Phase I Study of Immunotherapy of Malignant Melanoma by Direct Gene Transfer.* Sponsor: Vical, Incorporated

RAC Approval: 3-4-94/NIH Approval: 4-19-94
Closed: 3-27-95 (Closed to accrual - maximum number of subjects entered)

9406-073 (Open) Gene Therapy/Phase I/Colon/Immunotherapy
In Vivo/Autologous Tumor Cells/Plasmid DNA/Carcinoembryonic Antigen Plasmid Expression Vector/Kanamycin Resistance cDNA/Intratumoral/Direct Injection

Curiel, David; University of Alabama, Birmingham, Alabama; *Phase I Trial of a Polynucleotide Augmented Anti-Tumor Immunization to Human Carcinoembryonic Antigen in Patients with Metastatic Colorectal Cancer.*

RAC Approval: 6-10-95/NIH Approval: 7-27-95

9406-074 (Open) Gene Therapy/Phase I/Other/Rheumatoid Arthritis
In Vivo/Autologous Synovial Cells/Retrovirus/Interleukin-1 Receptor Antagonist Protein cDNA/Intrajoint/Metacarpal Phalangeal Joints

Evans, C. H. and Robbins, Paul; University of Pittsburgh, Pittsburgh, Pennsylvania; *Clinical Trial to Assess the Safety, Feasibility, and Efficacy of Transferring a Potentially Anti-arthritic Cytokine Gene to Human Joints with Rheumatoid Arthritis.*

RAC Approval: 6-9-94/NIH Approval: 7-27-95

9406-075 (Open) Gene Marking/Cancer/Ovarian
In Vitro/Autologous Peripheral Blood Cells/Autologous Tumor Infiltrating Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intraperitoneal

Freedman, Ralph; MD Anderson Cancer Center, Houston, Texas; *Use of a Retroviral Vector to Study the Trafficking Patterns of Purified Ovarian TIL Populations Used in Intraperitoneal Adoptive Immunotherapy of Ovarian Cancer Patients: A Pilot Study.*

RAC Approval: 6-9-94/NIH Approval: 7-12-94

9406-076 (Open) Gene Marking/Cancer/Pediatric Malignancies
In Vitro/CD34+ Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Heslop, Helen; Brenner, Malcolm, K.; and Krance, Robert; St. Jude Childrens Research Hospital, Memphis, Tennessee; *Use of Double Marking with Retroviral Vectors to Determine the Rate of Reconstitution of Untreated and Cytokine Expanded CD34(+) Selected Marrow Cells in Patients Undergoing Autologous Bone Marrow Transplantation.*

RAC Approval: 6-9-94/NIH Approval: 7-12-94

9406-077 (Open) Gene Therapy/Phase I/Cancer/Breast/Chemoprotection
In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Intravenous

Deisseroth, Albert; Hortobagyi, Gabriel; Champlin, Richard; and Holmes, Frankie; MD Anderson Cancer Center, Houston, Texas; *Use of Safety-Modified Retroviruses to Introduce Chemotherapy Resistance Sequences into Normal Hematopoietic Cells for Chemoprotection During the Therapy of Breast Cancer: A Pilot Trial.*

RAC Approval: 6-9-94/NIH Approval: 7-12-94

9406-078 (Open) Gene Therapy/Phase I/Monogenic Disease/Fanconi Anemia
In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Fanconi Anemia Complementation Group C cDNA/Intravenous

Liu, Johnson, M. and Young, Neal S.; National Institutes of Health, Bethesda, Maryland; *Retroviral Mediated Gene Transfer of the Fanconi Anemia Complementation Group C Gene to Hematopoietic Progenitors of Group C Patients.*

RAC Approval: 6-9-94/NIH Approval: 2-12-95

9406-079 (Open) Gene Therapy/Phase I/Cancer/Non-small Cell Lung Cancer/Tumor Suppressor Gene In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral/Bronchoscope

Roth, Jack A.; MD Anderson Cancer Center, Houston, Texas; *Clinical Protocol for Modification of Tumor Suppressor Gene Expression and Induction of Apoptosis in Non-Small Cell Lung Cancer (NSCLC) with an Adenovirus Vector Expressing Wildtype p53 and Cisplatin.*

RAC Approval: 6-10-94 and 9-11-95/NIH Approval: 9-21-95

9406-080 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma/Immunotherapy In Vitro/Autologous Fibroblasts/Lethally Irradiated/In Combination with Untransduced Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Sobol, Robert and Royston, Ivor; San Diego Regional Cancer Center; San Diego, California, *Injection of Glioblastoma Patients with Tumor Cells Genetically Modified to Secrete Interleukin-2 (IL-2): A Phase I Study.*

RAC Approval: 6-10-94/NIH Approval: 7-12-94

9406-081 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Lymphoma/Breast/Head and Neck Cancer/Immunotherapy In Vitro/Autologous Fibroblasts/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-12 cDNA/Neomycin Phosphotransferase cDNA/Intratumoral/Direct Injection

Lotze, Michael T; University of Pittsburgh, Pittsburgh Pennsylvania; *IL-12 Gene Therapy Using Direct Injection of Tumor with Genetically Engineered Autologous Fibroblasts.*

RAC Approval: 6-10-94/NIH Approval: 2-10-95

9408-082 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Subcutaneous Injection

Simons, Jonathan; Johns Hopkins Oncology Center, Baltimore, Maryland; *Phase I/II Study of Autologous Human GM-CSF Gene Transduced Prostate Cancer Vaccines in Patients with Metastatic Prostate Carcinoma.*
NIH/ORDA Approval: 8-3-94 (Accelerated Review)

9409-083 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Flotte, Terence R.; The University of Florida, Gainsville, Florida; Zeitlin, Pamela L.; Johns Hopkins Childrens Center, Baltimore, Maryland; *A Phase I Study of an Adeno-associated Virus-CFTR Gene Vector in Adult CF Patients with Mild Lung Disease* Sponsor: Targeted Genetics Corporation

RAC Approval: 9-12-94/NIH Approval: 11-15-94

9409-084 (Open) Gene Therapy/Phase I/Cancer/Breast/Antisense In Vivo/Autologous Tumor Cells/Retrovirus/c-fos Antisense RNA/c-myc Antisense/Intrapleural/Intraperitoneal

Holt, Jeffrey, and Arteaga, Carlos B.; Clinical Research Center at Vanderbilt University Medical Center, Nashville, Tennessee; *Gene Therapy for the Treatment of Metastatic Breast Cancer by In Vivo Infection with Breast-Targeted Retroviral Vectors Expressing Antisense c-fos or Antisense c-myc RNA.*

RAC Approval: 9-12-94/NIH Approval: 1-4-95

9409-085 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)/Multiple Dose

Crystal, Ronald G.; New York Hospital-Cornell Medical Center, New York, New York; *Evaluation of Repeat Administration of a Replication Deficient, Recombinant Adenovirus Containing the Normal Cystic Fibrosis Transmembrane Conductance Regulator cDNA to the Airways of Individuals with Cystic Fibrosis.*

RAC Approval: 9-12-94/NIH Approval: 11-30-94

9409-086 (Open) Gene Therapy/Phase I/Cancer/Breast/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Avectin™/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Lyerly, H. Kim; Duke University Medical Center, Durham, North Carolina; *A Pilot Study of Autologous Human Interleukin-2 Gene Modified Tumor Cells in Patients with Refractory or Recurrent Metastatic Breast Cancer.*

RAC Approval: 9-12-94/NIH Approval: 10-25-94

9409-087 (Open) Gene Therapy/Phase I/Monogenic Disease/Hunter Syndrome
In Vitro/Autologous Peripheral Blood Cells/Retrovirus/Iduronate-2-Sulfatase cDNA/Intravenous

Whitley, Chester B.; University of Minnesota, Minneapolis, Minnesota; *Retroviral-Mediated Transfer of the Iduronate-2-Sulfatase Gene into Lymphocytes for Treatment of Mild Hunter Syndrome (Mucopolysaccharidosis Type II).*

RAC Approval: 9-13-94/NIH Approval: 8-20-95

9409-088 (Open) Gene Therapy/Phase I/Other/Peripheral Artery Disease
In Vivo/Vascular Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor cDNA/Intraarterial/Angioplasty Catheter/Hydrogel Coated Balloon

Isner, Jeffrey M. and Walsh, Kenneth; St. Elizabeth's Medical Center, Tufts University, Boston, Massachusetts; *Arterial Gene Transfer for Therapeutic Angiogenesis in Patients with Peripheral Artery Disease.*

RAC Approval: 9-13-94/NIH Approval: 11-15-94

9409-089 (Open) Gene Therapy/Phase I/Cancer/Central Nervous System/Pro-Drug
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Stereotactic Injection

Eck, Stephen L. and Alavi, Jane B.; University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *Treatment of Advanced CNS Malignancy with the Recombinant Adenovirus H5.020RSVTK: A Phase I Trial.*

RAC Approval: 9-13-94/NIH Approval: 2-2-96

9409-090 (Open) Gene Therapy/Phase I/Cancer/n/Pro-Drug
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intrapleural

Albelda, Steven M.; University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *Treatment of Advanced Mesothelioma with the Recombinant Adenovirus H5.010RSVTK: A Phase I Trial.*

RAC Approval: 9-13-94/NIH Approval: 1-4-95

9409-091 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Respiratory Epithelial Cells/Adenovirus/Serotype 2/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Respiratory Epithelial Cells/Bronchoscope

Dorkin, Henry L.; New England Medical Center, Tufts University, Boston, Massachusetts; and Lapey, Allen; Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; *Adenovirus Mediated Gene Transfer for Cystic Fibrosis: Safety of Single Administration in the Lung (lobar instillation).* Sponsor: Genzyme Corporation

NIH/ORDA Approval: 10-5-94 (Accelerated Review)

9411-092 (Open) Gene Marking/Cancer/Lymphoma/Breast
In Vitro/CD34+ Autologous Bone Marrow Cells/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Douer, Dan; University of Southern California; Kenneth Norris Comprehensive Cancer Center and Hospital, Los Angeles, California; *High Dose Chemotherapy and Autologous Bone Marrow plus Peripheral Blood Stem Cell Transplantation for Patients with Lymphoma or Metastatic Breast Cancer: Use of Marker Genes to Investigate the Biology of Hematopoietic Reconstitution in Adults.*

NIH/ORDA Approval: 11-18-94 (Accelerated Review)

9411-093 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor

cDNA/Subcutaneous Injection

Dranoff, Glen; Dana Farber Cancer Institute, Boston, Massachusetts; *A Phase I Study of Vaccination with Autologous, Irradiated Melanoma Cells Engineered to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor.*

NIH/ORDA Approval: 11-23-94 (Accelerated Review)

9412-094 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Respiratory Epithelial Cells/Adenovirus/Serotype 2/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Respiratory Epithelial Cells/Aerosol Administration

Dorkin, Henry L.; New England Medical Center, Tufts University, Boston, Massachusetts; and Lapey, Allen; Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; *Adenovirus Mediated Gene Transfer for Cystic Fibrosis: Safety of a Single Administration in the Lung (aerosol administration).* Sponsor: Genzyme Corporation

RAC Approval: 12-1-94/NIH Approval: 7-24-95

9412-095 (Open) Gene Therapy/Phase I/Solid Tumors/Lymphoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1102/Cytokine/Interleukin-2 cDNA/Intratumoral/Direct Injection

Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; and Rinehart, John; Scott and White Clinic, Temple Texas. *Phase I Trial of Interleukin-2 Plasmid DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Solid Malignant Tumors or Lymphomas by Direct Gene Transfer.* Sponsor: Vical, Incorporated

RAC Approval: 12-1-94/NIH Approval: 3-2-95

9412-096 (Open) Gene Therapy/Phase I/Cancer/Head and Neck Squamous Cell/Tumor Suppressor Gene
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral/Bronchoscope

Clayman, Gary; MD Anderson Cancer Center, Houston, Texas; *Clinical Protocol for Modification of Tumor Suppressor Gene Expression in Head and Neck Squamous Cell Carcinoma (HNSCC) with an Adenovirus Vector Expressing Wild-type p53.*

RAC Approval: 12-2-94 and 9-11-95/NIH Approval: 9-21-95

9412-097 (Open) Gene Therapy/Phase I/Cancer/Colon/Hepatic Metastases/Tumor Suppressor Gene
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intrahepatic/Hepatic Artery/Bolus Infusion

Venook, Alan and Warren, Robert; Moffitt-Long Hospital of the University of California, San Francisco Medical Center; Gene Therapy of *Primary and Metastatic Malignant Tumors of the Liver Using ACN53 Via Hepatic Artery Infusion: A Phase I Study* Sponsor: Schering Plough Corporation (formerly Canji)

RAC Approval: 12-2-94/Sole FDA Review Recommended by NIH/ORDA: 5-15-96

9412-098 (Open) Gene Therapy/Phase I/Cancer/Central Nervous System Malignancies/Pro-Drug
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intra- tumoral/Stereotactic Injection

Grossman, Robert and Woo, Savio;The Methodist Hospital, Houston, Texas; *Phase I Study of Adenoviral Vector Delivery of the HSV-TK Gene and the Intravenous Administration of Ganciclovir in Adults with Malignant Tumors of the Central Nervous System.*

RAC Approval: 12-2-94/NIH Approval: 2-2-96

9502-099 (Open) Gene Therapy/Phase I/Cancer/Astrocytoma/Pro-Drug
In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Stereotactic Injection

Fetell, Michael; Columbia Presbyterian Medical Center, New York, New York; Warnick, Ronald; University of Cincinnati, Cincinnati, OH; Yung, W.K. Alfred; M.D. Anderson Cancer Center, Houston, Texas; Maria, Bernard L.; University of Florida, Gainesville, Florida; Shaffrey, Mark; University of Virginia Health Sciences Center, Charlottesville, Virginia; Ram, Zvi; Chaim Sheba Medical Center, Tel Aviv University Sackler School of Medicine, Tel Hashomer, Israel; Prados, Michael; University of California, San Francisco, California; and Grossman, Stuart; Johns Hopkins University Hospital Oncology Center; Baltimore, Maryland; *Stereotaxic Injection of Herpes Simplex Thymidine Kinase Vector Producer Cells (PA317/G1TkSvNa.7) and Intravenous Ganciclovir for the Treatment of Recurrent Malignant Glioma.* Sponsor: Genetic Therapy, Inc./Novartis

NIH/ORDA Approval: 2-10-95 (Accelerated Review)

9503-100 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug
In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intraperitoneal/Catheter

Link, Charles; Human Gene Therapy Research Institute; and Moorman, Donald; Iowa Methodist Medical Center, Des Moines, Iowa; *A Phase I Trial of In Vivo Gene Therapy with Herpes Simplex Thymidine Kinase/Ganciclovir System for the Treatment of Refractory or Recurrent Ovarian Cancer*
RAC Approval: 3-6-95/NIH Approval: 7-27-95

9503-101 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-7 cDNA/Hygromycin Phosphotransferase/Herpes Simplex Virus Thymidine Kinase cDNA/Subcutaneous Injection

Economou, James; Glaspy, John; and McBride, William; University of California, Los Angeles, California; *A Phase I Testing of Genetically Engineered Interleukin-7 Melanoma Vaccines.*

RAC Approval: 3-6-95/NIH Approval: 8-20-95
Closed: 3-97

9503-102 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/HLA-Matched Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-2 cDNA/Gamma Interferon cDNA/Subcutaneous Injection

Gansbacher, Bernd; Memorial Sloan Kettering Cancer Center, New York, New York; *Phase I/II Study of Immunization with MHC Class I Matched Allogeneic Human Prostatic Carcinoma Cells Engineered to Secrete Interleukin-2 and Interferon-γ.*

RAC Approval: 3-6-95/Sole FDA Review Recommended by NIH/ORDA: 5-14-96

9503-103 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense
In Vitro/Antisense TAR/Transdominant Rev/Intravenous

Morgan, Richard and Walker, Robert; National Institutes of Health, Bethesda, Maryland; *Gene Therapy for AIDS using Retroviral Mediated Gene Transfer to deliver HIV-1 Antisense TAR and Transdominant Rev Protein Genes to Syngeneic Lymphocytes in HIV Infected Identical Twins.*

RAC Approval: 3-7-95/NIH Approval: 4-1-95

9503-104 (Open) Gene Therapy/Phase I/Monogenic Disease/Chronic Granulomatous Disease
In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/p47phox/Intravenous

Malech, Harry; National Institutes of Health, Bethesda, Maryland; *Gene Therapy Approach for Chronic Granulomatous Disease.*

RAC Approval: 3-7-95/NIH Approval: 4-15-95

9503-105 (Open) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy
In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1IIIB Envelope Protein/Intramuscular Injection

Parenti, David; George Washington University Medical Center, Washington, D.C.; Haubrich, Richard; University of California San Diego Treatment Center, San Diego, California; Frame, Peter; University of Cincinnati AIDS Treatment Center, Cincinnati, Ohio; Powderly, William; Washington University AIDS Clinical Trials Unit; St. Louis, Missouri; and Loveless, Mark; Oregon Health Sciences University, Portland, Oregon; *A Repeat Dose Safety and Efficacy Study of HIV-IT(V) in HIV-1 Infected Subjects with Greater Than or Equal to 100 CD4+ T Cells and No AIDS Defining Symptoms.*

NIH/ORDA Approval: 3-11-95 (Accelerated Review)

9506-106 (Open) Gene Marking/Cancer/Chronic Myelogenous Leukemia
In Vitro/Autologous G-CSF and ATA-C Mobilized Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Verfaillie, Catherine; University of Minnesota, Minneapolis, Minnesota; *Autologous Marrow Transplantation for Chronic Myelogenous Leukemia Using Stem Cells Obtained After In Vivo Chemotherapy Cytokine Priming.*

NIH/ORDA Approval: 5-5-95

9506-107 (Open) Gene Therapy/Phase I/Cancer/Multiple Myeloma/Pro-Drug
In Vitro/Allogeneic T Lymphocytes/Retrovirus/Herpes Simplex Thymidine Kinase/Ganciclovir/Intravenous

Munshi, Nikhil C. and Barlogie, Bart; University of Arkansas for Medical Sciences, Little Rock, Arkansas; *Thymidine Kinase (TK) Transduced Donor Leukocyte Infusions as a Treatment for Patients with Relapsed or Persistent Multiple Myeloma after T-cell Depleted Allogeneic Bone Marrow Transplant.*

Sponsor: Genetic Therapy, Inc./Novartis

RAC Approval: 6-9-95/NIH Approval: 7-27-95

9506-108 (Open) Gene Therapy/Phase I/Cancer/Renal Cell/Melanoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Subcutaneous Injection

Fox, Bernard A. and Urba, Walter J.; Earle A. Chiles Research Institute, Providence Medical Center, Portland, Oregon; *Adoptive Cellular Therapy of Cancer Combining Direct HA-B7/β-2 Microglobulin Gene Transfer with Autologous Tumor Vaccination for the Generation of Vaccine-Primed Anti-CD3 Activated Lymphocytes.*

RAC Approval: 6-9-95/NIH Approval: 9-30-95

9506-109 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Immunotherapy
In Vitro/Anti-CD3 Stimulated Autologous Peripheral Blood Lymphocytes/Retrovirus/Antibody/MOv-gamma (Reactive with Folate Binding Protein)/Intravenous/Intraperitoneal

Hwu, Patrick; National Institutes of Health, Bethesda, Maryland; *Treatment of Patients with Advanced Epithelial Ovarian Cancer using Anti-CD3 Stimulated Peripheral Blood Lymphocytes Transduced with a Gene Encoding a Chimeric T-cell Receptor Reactive with Folate Binding Protein*

RAC Approval: 6-9-95/Sole FDA Review Recommended by NIH/ORDA: 5-14-96

9506-110 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/DDAB-DOPE/Cytokine/Interleukin-2 cDNA/Intradermal Injection

Berchuck, Andres and Lyerly, H. Kim; Duke University Medical Center, Durham, North Carolina; *A Phase I Study of Autologous Human Interleukin-2 (IL-2) Gene Modified Tumor Cells in Patients with Refractory Metastatic Ovarian Cancer.*

RAC Approval: 6-10-95/NIH Approval: 9-30-95

9506-111 (Open) Gene Therapy/Phase I/Monogenic Disease/Purine Nucleoside Phosphorylase Deficiency
In Vitro/Autologous Peripheral Blood Lymphocytes/Retrovirus/Purine Nucleoside Phosphorylase cDNA/Intravenous

McIvor, R. Scott; Institute of Human Genetics, University of Minnesota, Minneapolis, Minnesota; *Gene Therapy for Purine Nucleoside Phosphorylase Deficiency.*

RAC Approval: 6-9-95/NIH Approval: 7-27-95

9506-112 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Single Chain Antibody Gene/In Vitro/CD4+ Autologous Peripheral Blood Lymphocytes/Retrovirus/sFv105 Anti-HIV-1 Envelope Protein(gp160)Gene/Intravenous

Marasco, Wayne A.; Dana Farber Cancer Institute, Boston, Massachusetts; *Intracellular Antibodies Against HIV-1 Envelope Protein for AIDS Gene Therapy.*

RAC Approval: 6-9-95/NIH Approval: 7-27-95

9504-113 (Closed) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus-1/Immunotherapy
In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1IIIB Envelope Protein/Intramuscular Injection

Conant, Marcus, Conant Medical Group; Lang, William, ViRx, Inc.; and Merritt, James, Viagene, Inc., San Francisco, California; *A Randomized, Double Blinded, Phase I/II Dosing Study to Evaluate the Safety and Optimal CTL Inducing Dose of HIV-IT(V) in Pre-Selected HIV-1 Infected Subjects.*

RAC Approval: NA/NIH Approval: NA (Non-NIH funded institution)
FDA Approval: 5-6-94

9507-114 (Open) Gene Therapy/Phase I-II/Monogenic Disease/Cystic Fibrosis
In Vivo/Maxillary Sinus Epithelial Cells/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Maxillary Sinus Administration

Gardner, Phyllis; Stanford University School of Medicine, Stanford, California; *A Phase I/II Study of Ig-CF for the Treatment of Chronic Sinusitis in Patients with Cystic Fibrosis.* Sponsor: Targeted Genetics Corporation

Sole FDA Review Recommended by NIH/ORDA: 7-11-95

9508-115 (Open) Gene Therapy/Phase II/Cancer/Metastatic Malignancies(Breast Adenocarcinoma, Renal Cell Carcinoma, Melanoma, Colorectal Adenocarcinoma, non-Hodgkin's Lymphoma)/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL 1005/HLA-B7/Beta-2 Microglobulin cDNA/Direct Intratumoral Injection

Chang, Alfred E.; University of Michigan Medical Center, Ann Arbor, Michigan; Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; Vogelzang, Nicholas; University of Chicago Medical Center, Chicago, Illinois; Levy, Ronald; Stanford University Medical Center, Palo Alto, California; Redman, Bruce; Wayne State University School of Medicine; Detroit, Michigan; Figlin, Robert; University of California Medical Center, Los Angeles, California; Rubin, Joseph; Mayo Foundation for Medical Evaluation and Research, Rochester, Minnesota; Rinehart, John J.; Scott and White Hospital, Texas A & M University, Temple Texas; Doroshow, James H.; City of Hope National Medical Center, Duarte, California; Klasa, Richard; British Columbia Cancer Agency, Vancouver, British Columbia; Sobol, Robert; Sidney Kimmel Cancer Center, San Diego, California; *Phase II Study of Immunotherapy of Metastatic Cancer by Direct Gene Transfer.* Sponsor: Vical, Incorporated

Sole FDA Review Recommended by NIH/ORDA: 8-2-95

9508-116 (Open) Gene Therapy/Phase I/Cancer/Glioma/Immunotherapy
In Vitro/Autologous Tumor (Glioma) Cells/Non-Irradiated/Retrovirus/Cytokine/Interleukin-4 cDNA/Subcutaneous Injection

Bozik, Michael; Gilbert, Mark; and Lotze, Michael T.; University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania; *Gene Therapy of Malignant Gliomas: A Phase I Study of IL-4 Gene -Modified Autologous Tumor to Elicit an Immune Response.*

Sole FDA Review Recommended by NIH/ORDA: 8-7-95

9508-117 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus-1/Replication Inhibition
In Vitro/Autologous CD34+ Peripheral Blood Cells/Retrovirus/Hammerhead Ribozyme/Intravenous

Mitsuyasu, Ronald; University of California Los Angeles, California; *A Phase I Trial of Autologous CD34+ Hematopoietic Progenitor Cells Transduced with an Anti-HIV-1 Ribozyme.*

Sole FDA Review Recommended by NIH/ORDA: 8-7-95

9508-118 (Open) Gene Therapy/Phase I/Other/Restenosis
In Vivo/Vascular Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor cDNA/Intraarterial/Angioplasty Catheter/Hydrogel Coated Balloon

Isner, Jeffrey, M.; St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Massachusetts; *Accelerated Re-endothelialization and Reduced Neointimal Thickening Following Catheter Transfer of phVEGF165.*

Sole FDA Review Recommended by NIH/ORDA: 8-7-95

9508-119 (Open) Gene Therapy/Phase I/Human Immunodeficiency Virus-1
In Vitro/CD8+ Allogeneic Cytotoxic T Lymphocytes/CD8+ Syngeneic Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase/Herpes Simplex Virus Thymidine Kinase cDNA/Retrovirus/Intravenous

Riddell, Stanley R.; Fred Hutchinson Cancer Research Center, Seattle, Washington; *Phase I Study to Evaluate the Safety of Cellular Adoptive Immunotherapy using Autologous Unmodified and Genetically Modified CD8+ HIV-Specific T Cells in HIV Seropositive Individuals.* Sponsor: Targeted Genetics Corporation

Sole FDA Review Recommended by NIH/ORDA: 8-7-95

9508-120 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Used to Derive Tumor Infiltrating Lymphocytes/HLA-B7 cDNA/Intravenous

Chang, Alfred E. and Nabel, Gary J.; University of Michigan Medical Center, Ann Arbor, Michigan; *Phase I Study of Tumor-Infiltrating Lymphocytes Derived from In Vivo HLA-B7 Gene Modified Tumors in the Adoptive Immunotherapy of Melanoma.*

Sole FDA Review Recommended by NIH/ORDA: 8-14-95

9508-121 (Open) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vivo/Autologous Tumor Cells/HLA B7 cDNA/Intratumoral/Concurrent Interleukin-2 Therapy

Figlin, Robert A.; University of California Los Angeles Medical Center, Los Angeles, California; *Phase I Study of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Renal Cell Carcinoma by Direct Gene Transfer with Concurrent Low Dose Bolus IL-2 Protein Therapy.* Sponsor: Vical, Incorporated

Sole FDA Review Recommended by NIH/ORDA: 8-14-95

9508-122 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies (type of cancer not specified)/Immunotherapy In Vivo/Autologous Muscle Cells/Canarypox Virus/Carcinoembryonic Antigen cDNA/Intramuscular Injection

Hawkins, Michael J. and Marshall, John L.; Georgetown University Medical Center, Washington, D.C.; *A Study of Recombinant ALVAC Virus that Expresses Carcinoembryonic Antigen in Patients with Advanced Cancers.*

Sole FDA Review Recommended by NIH/ORDA 8-14-95

9509-123 (Open) Gene Therapy/Phase I/Cancer/Prostate/Antisense In Vivo/Autologous Tumor Cells/Retrovirus/Antisense c-myc RNA/Intraprostate Injection

Steiner, Mitchell S., Clinical Research Center at Vanderbilt University Medical Center, Nashville, Tennessee; and Holt, Jeffrey T., Vanderbilt University School of Medicine, Nashville, Tennessee; *Gene Therapy for the Treatment of Advanced Prostate Cancer by In Vivo Transduction with Prostate-Targeted Retroviral Vectors Expressing Antisense c-myc RNA.*

RAC Approval: 9-11-95/NIH Approval: 9-30-95

9509-124 (Open) Gene Therapy/Phase I/Cancer/Ovarian and Extraovarian/Anti-erbB-2 Single Chain Antibody Gene In Vivo/Autologous Tumor Cells/Adenovirus/Anti-erbB-2 (oncoprotein/extracellular domain) Single-chain Antibody Gene/Intraperitoneal Injection

Curiel, David T. and Alvarez, Ronald D.; University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I Study of Recombinant Adenovirus Vector-Mediated Delivery of an Anti-erbB-2 Single Chain (sFv) Antibody Gene for Previously Treated Ovarian and Extraovarian Cancer Patients.*

RAC Approval: 9-11-95/Sole FDA Review Recommended by NIH/ORDA: 5-15-96

9509-125 (Open) Gene Therapy/Phase I/Cancer/Colon Carcinoma (Hepatic Metastases)/Pro-Drug In Vivo/Autologous Tumor Cells/Adenovirus/E. coli Cytosine Deaminase cDNA/Intratumoral (Hepatic) Injection/Combined with Oral 5-Fluorocytosine

Crystal, Ronald, G.; Hershowitz, Edward; and Lieberman, Michael; New York Hospital-Cornell Medical Center, New York, New York; *A Phase I Study of Direct Administration of a Replication-Deficient Adenovirus Vector Containing the E. coli Cytosine Deaminase Gene to Metastatic Colon Carcinoma of the Liver in Association with the Oral Administration of the Pro-Drug 5-Fluorocytosine.*

RAC Approval: 9-11-95/NIH Approval: 9-30-95

9509-126 (Open) Gene Therapy/Phase I/Cancer/Prostate Adenocarcinoma/Immunotherapy In Vivo/Vaccination/Vaccinia Virus/Prostate Specific Antigen/Intradermal Injection

Chen, A.P.; National Naval Medical Center, Bethesda, Maryland; *A Phase I Study of Recombinant Vaccinia that Expresses Prostate Specific Antigen in Adult Patients with Adenocarcinoma of the Prostate.*

Sole FDA Review Recommended by NIH/ORDA: 9-22-95

9509-127 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis In Vivo/Nasal Epithelial Cells/Cationic Liposome Complex/DOPE/Cystic Fibrosis Transmembrane Conductance Regulator cDNA; Intranasal Administration

Welsh, Michael J. and Zabner, Joseph; Howard Hughes Medical Institute, University of Iowa College of Medicine, Iowa City, Iowa; *Cationic Lipid Mediated Gene Transfer of CFTR: Safety of a Single Administration to the Nasal Epithelia.* Sponsor: Genzyme Corporation

Sole FDA Review Recommended by NIH/ORDA: 9-26-95

9510-128 (Open) Gene Therapy/Phase I/Cancer/Gastrointestinal Tract, Breast, or Lung Adenocarcinoma (CEA-Expressing Malignancies)/Immunotherapy/In Vivo/Vaccination/Vaccinia Virus/Carcinoembryonic Antigen/Intradermal Injection in Combination with Subcutaneous Peptide Challenge

Cole, David J.; Medical University of South Carolina, Charleston, South Carolina; *Phase I Study of Recombinant CEA Vaccinia Virus Vaccine with Post Vaccination CEA Peptide Challenge.*

Sole FDA Review Recommended by NIH/ORDA: 10-16-95

9510-129 (Open) Gene Marking/Cancer/EBV-Positive Hodgkin Disease
In Vitro/EBV-Specific Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Roskrow, Marie; Hudson, Melissa; Rooney, Cliona; Heslop, Helen; and Brenner, Malcolm; St. Jude Children's Research Hospital, Memphis, Tennessee; *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.*

Sole FDA Review Recommended by NIH/ORDA: 10-17-95

9510-130 (Open) Gene Marking/Cancer/EBV-Positive Hodgkin Disease
In Vitro/EBV-Specific Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotranspherase cDNA/Intravenous Administration

Roskrow, Marie; Hudson, Melissa; Rooney, Cliona; Heslop, Helen; and Brenner, Malcolm; St. Jude Children's Research Hospital, Memphis, Tennessee; *Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes to Patients with Relapsed EBV-Positive Hodgkin Disease.*

Sole FDA Review Recommended by NIH/ORDA: 10-17-95

9510-131 (Closed) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus
In Vitro/Autologous CD8+ T Cells/Retrovirus/CD4-Zeta Chimeric Receptor/Intravenous

Connick, Elizabeth; University of Colorado Health Sciences Center, Denver, Colorado; and Deeks, Steven G.; University of California, San Francisco General Hospital, San Francisco, California; *A Randomized, Controlled, Phase II Study of the Activity and Safety of Autologous CD4-Zeta Gene-Modified T Cells in HIV-Infected Patients.* Sponsor: Cell Genesys, Inc.

Sole FDA Review Recommended by NIH/ORDA: 10-17-95
Closed 8-6-97 (No longer enrolling patients)

9510-132 (Open) Gene Therapy/Phase I/Cancer/Locally Advanced or Metastatic Prostate/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Cytokine/Interleukin-2 cDNA/Intradermal Injection

Paulson, David; and Lyerly, H. Kim; Duke University Medical Center, Durham, North Carolina; *A Phase I Study of Autologous Human Interleukin-2 (IL-2) Gene Modified Tumor Cells in Patients with locally Advanced or Metastatic Prostate Cancer.*

Sole FDA Review Recommended by NIH/ORDA: 10-19-95

9511-133 (Open) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy
In Vitro/Autologous Tumor Cells (Non-Irradiated)/Type 5 Adenovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Brenner, Malcolm K.; Dilloo, Dagmar; and Bowman, Laura; St. Jude Children's Research Hospital, Memphis, Tennessee; Phase I Study of Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using an Adenoviral Vector.

Sole FDA Review Recommended by NIH/ORDA: 11-1-95

9511-134 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition
In Vitro/Autologous CD4+ T Cells/Retrovirus/Neomycin Phosphotransferase Gene/PolyTAR Decoy Gene/RRE-polyTAR Decoy Gene

Greenberg, Philip D.; Fred Hutchinson Cancer Research Center, University of Washington Medical Center, Seattle, Washington; *Phase I Study to Evaluate the Safety and In Vivo Persistence of Adoptively Transferred Autologous CD4+ T Cells Genetically Modified to Resist HIV Replication.*

Sole FDA Review Recommended by NIH/ORDA: 11-1-95

9511-135 (Open) Gene Therapy/Phase I/Cancer/Ovarian and Extraovarian Cancer/Single Chain Antibody
In Vivo/Autologous Tumor Cells/Adenovirus/Herpes Simplex Thymidine Kinase Gene/Intraperitoneal Injection/Combined with Intravenous Ganciclovir Administration

Alvarez, Ronald D. and Curiel, David T.; University of Alabama Comprehensive Cancer Center, Birmingham, Alabama; *A Phase I Study of Recombinant Adenovirus Vector-Mediated Intraperitoneal Delivery of Herpes Simplex Virus Thymidine Kinase (HSV-TK) Gene and Intravenous Ganciclovir for Previously Treated Ovarian and Extraovarian Cancer Patients.*

Sole FDA Review Recommended by NIH/ORDA: 11-1-95

9511-136 (Open) Gene Therapy/Phase I/Cancer/Metastatic Melanoma/Immunotherapy In Vitro/Autologous CD8+ Tyrosinase-Specific TCells/Retrovirus/Hygromycin Phosphotranspherase/Intravenous Administration

Yee, Cassian and Greenberg, Philip D.; Fred Hutchinson Cancer Research Center, University of Washington Medical Center, Seattle, Washington; *Phase I Study to Evaluate the Safety of Cellular Adoptive Immunotherapy Using Autologous Unmodified and Genetically Modified CD8+ Tyrosinase-Specific T Cells in Patients with Metastatic Melanoma.*

Sole FDA Review Recommended by NIH/ORDA: 11-1-95

9512-137 (Open) Gene Therapy/Phase I/Cancer/Ovarian,Breast/Oncogene Regulation/HER-2/*neu*
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intraperitoneal, Intrapleural Administration

Hortobagyi, Gabriel N.; Lopez-Berstein, Gabriel; and Hung, Mien-Chien; MD Anderson Cancer Center, Houston, Texas; Kilbourn, Robert, Rush-Presbyterian/St. Luke's Medical Center, Chicago, Illinois; Weiden, Paul, Virginia Mason Medical Center, Seattle, Washington; *Phase I Study of E1A Gene Therapy for Patients with Metastatic Breast or Ovarian Cancer that Overexpresses Her-2/neu.* Sponsor: Targeted Genetics Corporation

RAC Approval: 12-4-95/NIH Approval: 2-2-96

9512-138 (Open) Gene Therapy/Phase I/Cancer/Malignant Glioma/Antisense
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Plasmid DNA--Electroporation/TGF-β2/Subcutaneous Injection

Black, Keith L.; and Fakhrai, Habib; University of California, Los Angeles, School of Medicine, Los Angeles, California; *A Phase I Study of the Safety of Injecting Malignant Glioma Patients with Irradiated TGF-β2 Antisense Gene Modified Autologous Tumor Cells.*

RAC Approval: 12-4-95/NIH Approval: 4-2-96

9512-139 (Open) Gene Therapy/Phase I/Monogenic Disease/Partial Ornithine Transcarbamylase (OTC) Deficiency
In Vivo/Autologous Peripheral Blood Cells/Adenovirus/Type 5 (E2a Temperature-Sensitive Mutant)/Ornithine Transcarbamylase cDNA/Intravenous

Batshaw, Mark; Institute for Human Gene Therapy, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *A Phase I Study of Adenoviral Vector Mediated Gene Transfer to Liver in Adults with Partial Ornithine Transcarbamylase Deficiency.*

RAC Approval: 12-4-95/Sole FDA Review Recommended by NIH/ORDA: 5-14-96

9512-140 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/
In Vivo/Adenovirus/Type 2/MART-1 Melanoma Antigen/Subcutaneous Injection/Immunization

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Phase I Trial in Patients with Metastatic Melanoma of Immunization with a Recombinant Adenovirus Encoding the MART-1 Melanoma Antigen.*

Sole FDA Review Recommended by NIH/ORDA 12-1-95

9512-141 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus-1/Replication Inhibition
In Vitro/Autologous CD4+ Peripheral Blood Lymphocytes/Retrovirus/Anti-Rev SFv/Intravenous

Pomerantz, Roger J; Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania; *Intracellular Immunization Against HIV-1 Infection Using an Anti-Rev Single Chain Variable Fragment (SFv).*

Sole FDA Review Recommended by NIH/ORDA: 12-13-95

9512-142 (Open) Gene Therapy/Phase I/Gene Therapy/Cancer/Head and Neck Squamous Cell Carcinoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL 1005/HLA-B7/Beta-2 Microglobulin cDNA/Direct Intratumoral Injection

Gluckman, Jack L.; University of Cincinnati Medical Center, Cincinnati, Ohio; *Allovectin-7 in the Treatment of Squamous Cell Carcinoma of the Head and Neck.*

Sole FDA Review Recommended by NIH/ORDA: 12-15-95

9601-143 (Open) Gene Therapy/Phase I/Cancer/Breast/Chemoprotection
In Vitro/Autologous CD34+ Peripheral Blood Lymphocytes//Retrovirus/Multi-Drug Resistance-1 cDNA/Neomycin Phosphotransferase cDNA/Intravenous

Cowen, Kenneth H.; National Institutes of Health, Bethesda, Maryland; *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.*

Sole FDA Review Recommended by NIH/ORDA: 1-26-96

9601-144 (Open) Gene Therapy/Phase I/Cancer/Prostate/Pro-Drug
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Intra-prostatic Tumor Injection

Scardino, Peter T.; Thompson, TImothy C.; and Woo, Savio L.C.; Baylor College of Medicine, Houston, Texas; *Phase I Study of Adenoviral Vector Delivery of the HSV-tk Gene and the Intravenous Administration of Ganciclovir in Men with Local Recurrence of Prostate Cancer after Radiation Therapy.*

Sole FDA Review Recommended by NIH/ORDA: 1-29-96

9601-145 (Closed) Gene Therapy/Phase I/Cancer/Bladder/Tumor Suppressor Gene
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Retinoblastoma cDNA/Intravesical Catheter Administration

Small, Eric J. and Carroll, Peter R.; University of California, San Francisco, California; *Gene Therapy of Bladder Cancer Using Recombinant Adenovirus Containing the Retinoblastoma Gene (ACNRB): A Phase IA Study.* Sponsor: Schering Plough Corporation (formerly Canji)

Sole FDA Review Recommended by NIH/ORDA: 1-30-96
Canceled: 4-4-97

9602-146 (Open) Gene Therapy/Phase I/Cancer/Hematologic Malignancies Following Allogeneic Bone Marrow Transplant/Pro-Drug/Elimination of Graft Versus Host Disease
In Vitro/Allogeneic Peripheral Blood Lymphocytes/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intravenous

Link, Charles J.; Human Gene Therapy Research Institute, Des Moines, Iowa; Burt, Richard K. and Traynor, Ann; Northwestern University School of Medicine, Chicago, Illinois; *Adoptive Immunotherapy for Leukemia: Donor Lymphocytes Transduced with the Herpes Simplex Thymidine Kinase Gene for Remission Induction.*

Sole FDA Review Recommended by NIH/ORDA: 2-8-96

9602-147 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense
In Vitro/CD34+ Autologous Bone Marrow Cells/Retrovirus/RRE Decoy Gene, and Retrovirus/Neomycin Phosphotransferase Gene/Intravenous

Kohn, Donald B.; Childrens Hospital Los Angeles, Los Angeles, California; *Transduction of CD34+ Cells from the Bone Marrow of HIV-1 Infected Children: Comparative Marking by and RRE Decoy.*

Sole FDA Review Recommended by NIH/ORDA: 2-8-96

9602-148 (Open) Gene Therapy/Phase I/Cancer/Head and Neck Squamous Cell Carcinoma/Pro-Drug
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

O'Malley, Bert W.; Johns Hopkins University, Baltimore, Maryland; *Phase I Study of Adenoviral Vector Delivery of the HSV-tk Gene and the Intravenous Administration of Ganciclovir in Adults with Recurrent or Persistent Head and Neck Cancer.*

Sole FDA Review Recommended by NIH/ORDA: 2-13-96

9603-149 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Tumor Suppressor Gene

In Vivo/Autologous Tumor Cells/Retrovirus/BRCA-1 Gene/Intraperitoneal Administration (Ultrasound Guided)
Holt, Jeffrey T.; Clinical Research Center at Vanderbilt University Medical Center, Nashville, Tennessee; *Ovarian Cancer Gene Therapy with BRCA-1.*

Sole FDA Review Recommended by NIH/ORDA: 3-6-96

9603-150 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy In Vivo/Autologous Tumor Cells/HLA B7 cDNA/Intratumoral/Concurrent Interleukin-2 Therapy

Hersh, Evan M., Arizona Cancer Center, Tucson, Arizona; and Sondak, Vernon K., University of Michigan Medical Center, Ann Arbor, Michigan; *Evaluation of Intratumoral Gene Therapy with HLA-B7/DMRIE/DOPE plus Subcutaneous Low Dose Il-2.*
Sole FDA Review Recommended by NIH/ORDA; 3-26-96

Closed: 3-11-97. Protocol Never Initiated

9604-151 (Open) Gene Therapy/Phase I/ Cancer/Melanoma/Immunotherapy In Vivo/AutologousTumor Cells/Adenovirus/Serotype 2/GP100 Melanoma Antigen/Subcutaneous or Intramuscular Injection/Concurrent Interleukin-2 Therapy

Rosenberg, Steven A.,National Institutes of Health, Bethesda, Maryland; *Phase I Trial in Patients with Metastatic Melanoma of Immunization with a Recombinant Adenovirus Encoding the the GP100 Melanoma Antigen.*

Sole FDA Review Recommmended by NIH/ORDA: 4-19-96

9604-152 (Open) Gene Therapy/Phase I/Inherited Genetic Disorder/Monogenic Disease/X-Linked Severe Combined Immune Deficiency/Correction In Vitro/CD34+ Autologous Umbilical Cord Blood or Bone Marrow/Retrovirus/cDNA for Common γ Chain of Multiple Cytokine Receptors/Intravenous

Weinberg, Kenneth I.,Childrens Hospital Los Angeles (CHLA) ; Los Angeles, California; *Gene Therapy for X-linked Severe Combined Immune Deficiency using Retroviral Mediated Transduction of the γc cDNA into CD34+ Cells.*

Sole FDA Review Recommmended by NIH/ORDA: 4-24-96

9604-153 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Hammerhead Ribozyme/In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Tat and Rev Hammerhead Ribozyme/Intravenous

Kohn, Donald B.,Childrens Hospital of Los Angeles (CHLA), Los Angeles, California; and Zaia, John A., City of Hope National Medical Center, Duarte, California; *Transduction of CD34+ Autologous Peripheral Blood Progenitor Cells from HIV-1 Infected Persons: a Phase I Study of Comparative Marking Using a Ribozyme Gene and a Neutral Gene.*

Sole FDA Review Recommended by NIH/ORDA: 4-24-96

9605-154 (Open) Gene Therapy/Phase I/Cancer/Brain Tumors/Pro-Drug/In Vivo/Autologous Tumor Cells/psiCRIP-MFG-S-TK1-67 Cells/Retrovirus/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Harsh IV, Griffith R., Chiocca, E. Antonio; Hochberg, Fred H.; Harvard Medical School, Boston, Massachusetts; *Phase I Study of Retroviral-Mediated Incorporation of the HSV Thymidine Kinase Gene and Ganciclovir in Malignant Gliomas.*

Sole FDA Review Recommended by NIH/ORDA: 5-1-96

9605-155 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Cationic Liposome Complex/B7(CD80) cDNA/Retrovirus/Herpes Simplex Thymidine Kinase/Ganciclovir/Intraperitoneal

Freeman, Scott M., and Robinson III, William R.; Tulane University School of Medicine, New Orleans, Louisiana; *Tumor Vaccination With HER-2/Neu Using a B7 Expressing Tumor Cell Line Prior To Treatment With HSV-TK Gene-Modified Cells*

Sole FDA Review Recommended by NIH/ORDA: 5-2-96

9608-156 (Open) Gene Therapy/Phase I/Cancer/Breast/Immunotherapy/InVitro/Allogeneic Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/B7(CD80) cDNA/Subcutaneous Injection

Urba, Walter J., Providence Portland Medical Center, Portland, Oregon; *Phase I Trial Using a CF-80 Modified Allogeneic Breast Cancer Line to Vaccinate HLA-A2-Positive Women with Breast Cancer.*

Sole FDA Review Recommended by NIH/ORDA: 8-6-96

9608-157 (Open) Gene Therapy/Phase III of #9303-037/Cancer/Glioblastoma/Pro-Drug/In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Maria, Bernard, University of Florida, Gainsville, Florida; Royston,Ivor, Sharp Healthcare, Sidney Kimmel Cancer Center, San Diego, California; Bucholz, Richard, St. Louis University, St. Louis, Missouri; Olson, Jeffrey, Winship Cancer Center, Atlanta, Georgia; Lillehei, Kevin, University of Colorado, Denver, Colorado; Van Gilder, John, University of Iowa College of Medicine, Iowa City, Iowa; Nemunaitis, John; Texas Oncology P.A., Baylor University Medical Center, Dallas, Texas; Origitano, Thomas, Loyola University Medical Center, Maywood, Illinois; Warnick, Ronald, University of Cincinnati Medical Center, The Christ Hospital, Good Samaritan Hospital, Jewish Hospital of Cincinnati, Veterans Affairs Medical Center, Cincinnati, Ohio; Weber, Friederich Dr. med., Heinrich Heine Universtat, Dusseldorf, Germany; Rainov, Nikolai, PD Dr. med. Martin Luther Universtat, Halle, Germany; Cloughesy, Timothy, UCLA Department of Neurology, Reed Neurological Research Center, Boyiver Oncology Clinic, Los Angeles, California; Markert, James, University of Alabama at Birmingham, Birmingham, Alabama; Matti Vapalahti, Kuopio University Hopsital, Kuopio, Finland; Yasuhiro Yonekawa, University Hospital, Zurich, Switzerland; Nanno Harrie Mulder, Academic Hospital Groningen, Groningen, The Netherlands; Susanne Osante, Academic Hospital Leiden, Leiden, The Netherlands; Fetell, Michael, Columbia-Presbyterian Medical Center Neurological Institute, New York, New York; Schramm, Johannes, Prof. Dr. med., Univ. Klinikum Neurochirurgische Klinik, Bonn, Germany; Westphal, Manfred, PD Dr. med., Klinikum Eppendorf Neurochirurgie/Univ. Martinstr. 52, Hamburg, Germany; Tonn, Jorg-Christian, PD Dr. med., u. Poliklinik/Univ. Kliniken, Wurzberg, Germany; Moumdjian, Robert, Dr.,Hospital Notre-Dame, Montreal, Quebec, Canada; Shaffrey, Mark, University of Virginia, Charlottesville, Virginia; Asher, Anthony, Presbyterian Hospital, Cancer Center, Charlotte, North Carolina; Epstein, Mel, Brown University, Providence, Rhode Island; Schmidt-Schackert,

Frau.Prof. Dr. med., Gabriele, Univ.-Klin. Kar-G. Carus, Klinik f. Neurochirurgie, Dresden, Germany; Mendez, Ivar, Victoria General Hospital, Halifax, Nova Scotia, Canada; Bernstein, Mark, The Toronto Hospital, Toronto, Ontario, Canada; Quigley, Mathew, Alleghemy University of Health Sciences, Pittsburgh, Pennsylvania; Payner, Troy, Indianapolis Surgical Group, Indianapolis, Indiana; Kivipelto, Leena, Helsinki University Central Hospital, Helsinki, Finland; Seiler, Rolf W., University Hospital, Bern, Switzerland; Weiss, Martin Harvey, University of Southern California, Department of Neurosurgery, Los Angeles, California; Fick, James R., Medical College of Georgia, Department of Surgery, Augusta, Georgia; Leblanc, Richand, Montreal Neurological Institute, Montreal, Quebec, Canada; Buchfelder, Michael, Neurochirurgische Klinik mit Poliklinik der Universtat Erlangen-Nurnberg, Erlangen, Germany; Brotchi, Jacques, Hopital Erasme, Neruosergery, Cliniques Universiaites de Bruxelles, Bruxelles, Belgium; Astrup, Jens, Arhus Kommunehospital, Arhus C, Denmark; Henriksson, Roger, University Hospital, Umea, Sweden; Maciunas, Robert J., Vanderbilt University Medical Center, Nashville, Tennessee; Ram, Zvi; The Chaim Sheba Medical Center; Tel-Hashomer, Israel; Andrews, David; Thomas Jefferson University Hospital; Philadelphia, Pennsylvania; and Verlooy, Jan; University Hospital Antwerp; Antwerp, Belgium; *Prospective, Open-Label, Parallel-Group, Randomized Multicenter Trial Comparing the Efficacy of Surgery, Radiation, and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir Against the Efficacy of Surgery and Radiation in the Treatment of Newly Diagnosed, Previoulsy Untreated Glioblastoma.* Sponsor: Genetic Therapy, Inc./Novartis

Sole FDA Review Recommended by NIH/ORDA: 8-22-96

9608-158 (Open) Gene Therapy/Phase I-IB/Cancer/Melanoma or Sarcoma/Immunotherapy/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Plasmid DNA/Particle Mediated Gene Transfer (Accell®)/Cytokine/GM-CSF cDNA/Subcutaneous Injection

Mahvi, David M., University of Wisconsin Hospital and Clinics Comprehensive Cancer Center, Madison, Wisconsin; *Phase I/IB Study of Immunization with Autologous Tumor Cells Transfected with the GM-CSF Gene by Particle-Mediated Transfer in Patients with Melanoma or Sarcoma.*

Sole FDA Review Recommended by NIH/ORDA: 8-26-96

9605-159 (Open) Gene Marking/Cancer/Pediatric Malignancies/In Vitro/CD34+ Autologous Bone Marrow and Peripheral Blood/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Heslop, Helen E.; Brenner, Malcolm K.; Krance, Robert A.; St. Jude Children's Research Hospital, Memphis, Tennessee; *A Comparative Evaluation of the Utility of Hemopoietic Progenitor Cells Derived from Peripheral Blood vs Bone Marrow.*

Sole FDA Review Recommended by NIH/ORDA: 5-15-96

9609-160 (Open) Gene Therapy/Phase I/Cancer/Prostate Adenocarcinoma/Immunotherapy/In Vivo/Vaccination/Vaccinia Virus/Prostate Specific Antigen/Intradermal Injection

Kufe, Donald W., and Eder, Joseph Paul, Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I Trial Of Recombinant Vaccina Virus That Expresses PSA In Patients With Adenocarcinoma Of The Prostate.*

Sole FDA Review Recommended by NIH/ORDA: 9-18-96

9609-161 (Closed) Gene Therapy/Phase I/Cancer/Small Cell Lung Cancer/Immunotherapy/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Lipofectin(GibcoBRL)/B7-1(CD80) cDNA/Subcutaneous Injection

Antonia, Scott J., H. Lee Moffitt Cancer Center, Tampa, Florida; *Treatment of Small Cell Lung Cancer Patients In Partial Remission Or At Relapse With B7-1 Gene-Modified Autologous Tumor Cells As A Vaccine With Systemic Interferon Gamma.*

Sole FDA Review Recommended by NIH/ORDA: 10-10-96
Closed: 1-23-98. Protocol Never Initiated

9610-162 (Open) Gene Therapy/Phase I/Cancer/Solid Tumors/Oncogene Regulation/HER-2/neu/ In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intratumoral Injection

LaFollette, Suzanne, Rush/Presbyterian/St. Luke's Medical Center, Chicago, Illinois; Murray, James L., M.D. Anderson Cancer Center, Houston, Texas; Yoo, George, Wayne State University, Detroit, Michigan; *A Phase I Multicenter Study of Intratumoral E1A Gene Therapy for Patients with Unresectable or Metastatic Solid Tumors that Overexpress HER-2/neu.* Sponsor: Targeted Genetics Corporation

Sole FDA Review Recommended by NIH/ORDA: 10-29-96

9610-163 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Fowlpox Virus/MART-1 Melanoma Antigen/Intramuscular Injection

Rosenberg, Steven A., NIH, Bethesda, Maryland; *Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Fowlpox Virus Encoding The MART-1 Melanoma Antigen.*

Sole FDA Review Recommended by NIH/ORDA: 5-23-96

9610-164 (Open) Gene Therapy/Phase I/Cancer/Liver(Hepatic)Metastases/Pro-Drug/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase Gene/Ganciclovir/Intratumoral Injection

Sung, Max W., and Woo, Savio L.C., Mount Sinai Medical Center, New York, New York; *Phase I Trial of Adenoviral Vector Delivery of the Herpes Simplex Thymidine Kinase Gene by Intratumoral Injection Followed by Intravenous Ganciclovir in Patients with Hepatic Metastases.*

Sole FDA Review Recommended by NIH/ORDA: 11-12-96

9611-165 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Fowlpox Virus/gp100 Melanoma Antigen/Intramuscular Injection

Rosenberg, Steven A., NIH, Bethesda, Maryland; *Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Fowlpox Virus Encoding the GP100 Melanoma Antigen.*

NIH/ORDA Receipt Date: 11-13-96 . Sole FDA Review Recommended: 1-17-96

9611-166 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Vaccinia Virus/MART-1 Melanoma Antigen/Intramuscular Injection

Rosenberg, Steven A., NIH, Bethesda, Maryland; *Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Vaccinia Virus Encoding the MART-1 Melanoma Antigen.*

NIH/ORDA Receipt Date: 11-13-96. Sole FDA Review Recommended: 1-17-96

9611-167 (Open)Gene Therapy/Phase II/Cancer/Glioblastoma/Pro-Drug/In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Maria, Bernard, et.al. (All #9608-157 sites are eligible to participate in this study.) *Prospective, Open-Label, Multicenter, Extension Trial for the Treatment of Recurrent Glioblastoma Multiforme with Surgery and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir for Patients with Disease Progression Following Standard Treatment on Protocol GTI-0115.* Sponsor: Genetic Therapy, Inc./Novartis
This protocol is an extension of #9608-157.

NIH/ORDA Receipt Date: 11-13-96. Sole FDA Review Recommended by NIH/ORDA: 1-6-97

9611-168 (Open) Gene Therapy/Phase II/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL 1005/HLA-B7/Beta-2 Microglobulin cDNA/Direct Intratumoral Injection

Hersh, Evan M., Arizona Cancer Center, Tucson, Arizona; Klasa, Richard, British Columbia Cancer Agency, Vancouver, B.C., Canada; Gonzales, Rene, University of Colorado Cancer Center, Denver, Colorado; Silver, Gary, Northern California Melanoma Clinic, San Francisco, California;Thompson, John A.,U. of Washington Medical Center, Seattle, Washington; *Phase II Study of Immunotherapy of Metastatic Melanoma by Direct Gene Transfer.* Sponsor: Vical, Incorporated

NIH/ORDA Receipt Date: 11-26-96. Sole FDA Review Recommended by NIH/ORDA: 1-6-97

9611-169 (Open) Gene Therapy/Phase I/II/Cancer/Solid Tumors/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL 1102/Cytokine/Interleukin-2 cDNA/Direct Intratumoral Injection

Hersh, Evan, M., Arizona Cancer Center, Tucson, Arizona; Rinehart, John, Scott and White Clinic, Temple, Texas; Rubin, Joseph, Mayo Clinic, Rochester, Minnesota; Sondak, Vernon K., University of Michigan Medical Center, Ann Arbor, Michigan; Gonzales, Rene, University of Colorado Cancer Center, Denver, Colorado; Sobol, Robert E., Sharp HealthCare, San Diego, California; and Forscher, Charles A., Cedars-Sinai Comprehensive Cancer Center, Los Angeles, California; *Phase I/II Trial of Interleukin-2 DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Cancer by Direct Gene Transfer.* Sponsor: Vical, Incorporated

NIH/ORDA Receipt Date: 11-26-96. Sole FDA Review Recommended by NIH/ORDA: 1-17-97

9612-170 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Lung and Nasal Epithelial Cells/Cationic Liposome Complex/DOPE/CFTR cDNA/Aerosol Administration

Sorscher, Eric, University of Alabama, Birmingham, Medical Center; *Safety and Efficiency of Gene Transfer of Aerosol Administration of a Single Dose of a Cationic Lipid/DNA Formulation fo the Lungs and Nose of Patients with Cystic Fibrosis.* Sponsor: Genzyme Corporation

NIH/ORDA Receipt Date: 12-17-96. Sole FDA Review Recommended by NIH/ORDA: 1-6-97

9701-171 (Open) Non-Therapeutic/In Vivo/Intradermal Cells/Adenovirus/Serotype 5/E.coli Cytosine Deaminase/Intradermal Injection

Harvey, Ben-Gary, and Crystal, Ronald G., Rockefeller University Hospital, New York, New York; *Immune Response to Intradermal Administration of an Adenovirus Type 5 Gene Transfer Vector ($Ad_{GV}CD.10$) in Normal Individuals.*

NIH/ORDA Receipt Date: 1-9-97. RAC Approval: 3-6-97/NIH Approval: 4-21-97

9701-172 (Open) Gene Therapy/Phase I/Cancer/Germ Cell Tumors (Testicular Cancer)/Chemoprotection/In Vitro/G-CSF Mobilized Autologous CD34+ Peripheral Blood Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Bone Marrow Transplant

Cornetta, Kenneth, and Abonour, Rafat, Indiana University Department of Medicine, Indianapolis, Indiana; *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.*

NIH/ORDA Receipt Date: 1-9-97. Sole FDA Review Recommended by NIH/ORDA: 2-26-97

9701-173 (Open) Gene Therapy/Phase I/Cancer/Brain Tumors/Chemoprotection/In Vitro/Peripheral Blood CD34+ Cells/Retrovirus/O^6-Methylguanine DNA Methyltransferase cDNA/Intravenous Infusion

Williams, David A., Indiana University School of Medicine, Indianapolis, Indiana; *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.*

NIH/ORDA Receipt Date: 1-13-97. Sole FDA Review Recommended by NIH/ORDA: 2-4-97

9701-174 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Interleukin-2 cDNA/Neomycin Phosphotransferase cDNA/Immunoisolation Device/Subcutaneous Implantation

Das Gupta, Tapas K., University of Illinois at Chicago, Chicago, Illinois; *A Pilot Study Using Interleukin-2 Transfected Irradiated Allogeneic Melanoma Cells Encapsulated in an Immunoisolation Device In Patients with Metastatic Malignant Melanoma.*

NIH/ORDA Receipt Date: 1-13-97. Sole FDA Review Recommended by NIH/ORDA: 2-21-97

9701-175 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma/Pro-Drug/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Stereotactic Injection

Lieberman, Frank, Germano, Isabelle, and Woo, Savio, Mount Sinai Medical Center, New York, New York; *Gene Therapy for Recurrent Glioblastoma Multiforme: Phase I Trial of Intraparenchymal Adenoviral Vector Delibvery of the HSV-TK Gene and Intravenous Administration of Ganciclovir.*

NIH/ORDA Receipt Date: 1-22-97. Sole FDA Review Recommended by NIH/ORDA: 2-12-97

9702-176 (Open) Gene Therapy/Phase I/II/Cancer/Prostate Adenocarcinoma/Immunotherapy/In Vivo/Vaccination/Vaccinia Virus/Prostate Specific Antigen/Intradermal Injection

Sanda, Martin G., University of Michigan Urology Clinics, Ann Arbor, Michigan; *A Phase I/II Clinical Trial Evaluating the Safety and Biological Acivity of Recombinant Vaccinia-PSA Vaccine in Patients with Serological Recurrence of Prostate Cancer Following Radical Prostatectomy.*

NIH/ORDA Receipt Date: 2-19-97. Sole FDA Review Recommended by NIH/ORDA: 5-13-97

9702-177 (Open) Gene Marking/Cancer/Chronic Myelogenous Leukemia/In Vitro/Autologous Peripheral Blood Cells Mobilized by Cyclophosphamide and G-CSF/Retrovirus/Neomycin Phosphotransferase cDNA/Autologous Bone Marrow Transplant

Verfaille, Catherine, McIvor, Scott, McCullough, Jeff, and McGlave, Philip, University of Minnesota, Minneapolis, Minnesota; *Autologous Marrow Transplantation for Chronic Myelogenous Leukemia Using Retrovirally Marked Peripheral Blood Progenitor Cells Obtained after In Vivo Cyclophosphamide/G-CSF Priming.*

NIH/ORDA Receipt Date: 2-21-97. Sole FDA Review Recommended by NIH/ORDA: 3-14-97

9703-178 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/CD34+ Autologous Cord Blood Cells/Retrovirus/Transdominant Trev/Intravenous

Belmont, John W., Texas Children's Hospital, Houston, Texas; *Phase I Clinical Trial of TREV Gene Therapy for Pediatric AIDS.*

NIH/ORDA Receipt Date: 3-10-97. Sole FDA Review Recommended by NIH/ORDA: 3-31-97

9703-179 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Carcinoembryonic Antigen/Intravenous

Lyerly, Kim H., Duke University Medical Center, Durham, North Carolina; *A Phase I Study of Active Immunotherapy With Carcinoembronic Antigen RNA-Pulsed Autologous Human Cultured Dendritic Cells In Patients With Metastatic Malignancies Expressing Carcinoembryonic Antigen.*

NIH/ORDA Receipt Date: 3-14-97. Sole FDA Review Recommended by NIH/ORDA: 6-24-97

9703-180 (Open) Gene Therapy/Phase I/Other/Cubital Tunnel Syndrome/In Vivo/Autologous Muscle Cells/Plasmid DNA/Polyvinylpyrrolidone (PVP)/Human Insulin-Like Growth Factor-1(hIGF-1)/Intramuscular Injection

Netscher, David, Hand Clinic at the Veteran's Affairs (VA) Medical Center, Houston, Texas. *Phase I Single Dose-Ranging Study Of Formulated hIGF-I Plasmid In Subjects With Cubital Tunnel Syndrome* Sponsor: Gene Medicine, Inc.

NIH/ORDA Receipt Date: 3-17-97. Sole FDA Review Recommended: 4-7-97

9703-181 (Open) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/In Vitro/Autologous CD8 + and CD4+ T Lymphocytes/Retrovirus/CD4-Zeta Chimeric Receptor/Intravenous/Concurrent Interleukin-2 Therapy

Connick, Elizabeth, University of Colorado Health Sciences Center, Denver, Colorado, Deeks, Steven G., University of California, San Francisco General Hospital, San Francisco, California, Scadden, David, Massachusetts General Hospital (East), Charlestown, Massachusetts, Mitsuyasu, Ronald, University of California, Los Angeles Medical Center, Los Angeles, California; *A Phase II Study of the Activity and Safety of Autologous CD4-Zeta Gene-Modified T Cells With or Without Exogenous Interleukin-2 in HIV Infected Patients.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 3-19-97. Sole FDA Review Recommended: 4-18-97

9703-182 (Open) Gene Therapy/Phase II/Monogenic Inherited Disorder/Cystic Fibrosis/Sinusitis/Correction/In Vivo/Maxillary Sinus Epithelial Cells/ Adeno-associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Maxillary Sinus Administration

Gardner, Phyllis, Stanford University's General Clinical Research Center (GCRC), Palo Alto, California. *A Phase I/II Study of tgAAVCF for the Treatment of Chronic Sinusitis With Cystic Fibrosis* Sponsor: Targeted Genetics Corporation

NIH/ORDA Receipt Date: 3-13-97. Sole FDA Review Recommended: 4-1-97

9703-183 (Closed) Gene Marking/Cancer/EBV-Positive Hodgkin Disease/In Vitro/EBV-Specific Hodgkin Disease/In Vitro/EBV-Specific Cytotoxic Lymphocytes/Retrovirus/Neomycin Phosphotransferase/Bone Marrow Transplant

Straus, Stephan E., National Institutes of Health, Bethesda, Maryland; *Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T-Lymphocytes To Patients With Relapsed EBV-Positive Hodgkin Disease.*
Compassionate Case

NIH/ORDA Receipt Date: 3-19-97. Sole FDA Review Recommended by NIH/ORDA: 3-25-97

Patient never treated (closed as of 11-18-97)

9703-184 (Open) Gene Therapy/Phase I/Cancer/Prostate Cancer/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1102/Cytokine/Interleukin-2 cDNA/Intratumoral Injection

Belldegrun, Arie, University of California, Los Angeles, School of Medicine, Los Angeles, California; *A Phase I Study Evaluating the Safety and Efficacy of Interleukin-2 Gene Therapy Delivered by Lipid Mediated Gene Transfer (Leuvectin) in Prostate Cancer Patients.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 3-24-97. Sole FDA Review Recommended by NIH/ORDA: 5-21-97

9704-185 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Melanoma Cell/Canarypox Virus/Cytokine/Interleukin-12 cDNA/Intratumoral Injection

Conry, Robert M., University of Alabama at Birmingham, Birmingham, Alabama; *Phase Ib Trial of Intratumoral Injection of a Recombinant Canarypox Virus Encoding the Human Interleukin-12 Gene (ALVAC-hIL-12) in Patients with Surgically Incurable Melanoma* Sponsor: NCI- Cancer Therapy Evaluation Program

NIH/ORDA Receipt Date: 4-1-97. Sole FDA Review Recommended by NIH/ORDA: 7-2-97

9704-186 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Nasal Epithelial Cells/Cystic FibrosisTransmembrane Conductance Regulator cDNA/Cationic Liposome Complex/EDMPC/Intranasal Administration

Noone, Peadar G., Knowles, Michael R., University of North Carolina at Chapel Hill, North Carolina. *A Double-Blind, Placebo Controlled, Dose Ranging*

Study to Evaluate the Safety and Biological Efficacy of the Lipid-DNA Complex GR213487B in the Nasal Epithelium of Adult Patients with Cystic Fibrosis. Sponsor: Glaxo Wellcome Inc.

NIH/ORDA Receipt Date: 4-23-97. Sole FDA Review Recommended by NIH/ORDA: 5-13-97

9705-187(Open) Gene Therapy/Phase I/Cancer/Prostate/Pro-Drug/In Vivo/AutologousTumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase Gene/Ganciclovir/Intratumoral Injection

Hall, Simon J., Woo, Savio L.C., Mount Sinai School of Medicine, New York, New York; *Phase I Trial of Adenoviral-Mediated Herpes Simplex Thymidine Kinase Gene Transduction in Conjuction with Ganciclovir Therapy as Neo-adjuvant Treatment for Patients with Clinically Localized (Stage T1c and T2b&c)Prostate Cancer Prior to Radical Prostatectomy.*

NIH/ORDA Receipt Date: 5-7-97. Sole FDA Review Recommended by NIH/ORDA: 5-28-97

9705-188 (Open) Gene Therapy/Phase I/Cancer/Chronic Myelogenous Leukemia/Chemoprotection/Tyr-22 Murine Dihydrofolate Reductase Gene/Antisense/Anti-b3a2BCR/ABL Gene/In Vitro/Autologous Peripheral Blood CD34+ Cells Mobilized by Cyclophosphamide and G-CSF/Retrovirus/Autologous Bone Marrow Transplant

Verfaillie, Catherine, McIvor, Scott, McCullough, Jeff, McGlave, Philip; University of Minnesota, Minneapolis, Minnesota; *Autologous Transplantation for Chronic Myelogenous Leukemia with Stem Cells Transduced with a Methotrexate Resistant DHFR and Anti-BCR/ABL Containing Vector and Post Transplant Methotrexate Administration.*

NIH/ORDA Receipt Date: 5-16-97. Sole FDA Review Recommended by NIH/ORDA: 6-6-97

9705-189 (Open) Gene Therapy/Phase I/Cancer/Hepatocellular Carcinoma/Tumor Supressor Gene/In Vivo/AutologousTumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Belani, Chandra P., University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Phase I Study of Percutaneous Injections of Adenovirus p53 Construct (Adeno-p53) for Hepatocellular Carcinoma.

NIH/ORDA Receipt Date: 5-27-97. Sole FDA Review Recommended by NIH/ORDA: 9-19-97

9705-190 (Open) Gene Therapy/Phase I/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DOTMA-Cholesterol/Cytokine/Interleukin-2 cDNA/Intratumoral Injection

O'Malley, Bert W., Johns Hopkins Medical Institutions, Baltimore, Maryland; *A Double-Blind, Placebo-Controlled, Single Rising-Dose Study of the Safety and Tolerability of Formulated hIL-2 Plasmid in Patients with Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponser: Gene Medicine, Inc.

NIH/ORDA Receipt Date: 5-27-97. Sole FDA Review Recommended by NIH/ORDA: 6-16-97

9706-191 (Open) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Direct Intratumoral Injection

Gluckman, Jack L..; Gleich, Lyon L., University of Cincinnati Medical Center, Cincinnati, Ohio; Swinehart, James M., Colorado Medical Research Center, Denver, Colorado; Hanna, Ehab, University of Arkansas for Medical Sciences/Arkansas Cancer Research Center (UAMS), Little Rock, Arkansas; Castro, Dan J., University of California, Los Angeles, Los Angeles, California; Gapany, Markus, Veterans Affairs Medical Center, Minneapolis, Minnesota; Carroll, William, R., University of Alabama at Birmingham, Birmingham, Alabama; Coltrera, Marc D., University of Wahington Medical Center, Seattle, Washington; Wolf, Gregory T., University of Michigan Medical Center, Ann Arbor, Michigan; and Okuno, Scott, Mayo Clinic, Rochester, Minnesota; *Phase II Study of Immunotherapy by Direct Gene Transfer with Allovectin-7 for the Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 6-6-97. Sole FDA Review Recommended by NIH/ORDA: 7-7-97

9706-192 (Open) Gene Therapy/Phase I/Cancer/Prostate/Tumor suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Belldegrun, Arie, and Figlin, Robert., UCLA School of Medicine, Los Angeles, California; *A Phase I Study in Patients with Locally Advanced or Recurrent Adenocarcinoma of the Prostate Using SCH58500 (rAd/p53) Administered by Intratumoral Injection* Sponsor: Schering-Plough Corporation

NIH/ORDA Receipt Date: 6-9-97. Sole FDA Review Recommended by NIH/ORDA: 9-17-97

9706-193 (Open) Gene Therapy/Phase I/Cancer/Immunotherapy/CEA-Expressing Malignancies/In Vivo/Autologous Muscle Cells/Canarypox Virus/Vaccinia Virus/Carcinoembryonic Antigen cDNA/Intramuscular and Percutaneous Injection

Marshall, John L., Vincent T. Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, D.C.; *A Pilot Study of Sequential*

Vaccinations with ALVAC-CEA and Vaccina-CEA with the addition of IL-2 and GM-CSF in Patients with CEA Expressing Tumors Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 6-18-97. Sole FDA Review Recommended by NIH/ORDA: 9-18-97

9706-194 (Open) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy/In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1 IIIB Envelope Protein/Intramuscular Injection

Aboulafia, David; Virginia Mason Clinic, Seattle, Washington; Campbell, Thomas; University of Colorado Health Sciences Center, Denver, Colorado; Kumar, Princy; Georgetown University Medical Center, Washington, D.C.; Murphy, Robert; Northwestern University Medical School, Chicago, Illinois; Skolnik, Paul; New England Medical Center, Boston, Massachusetts; Wheat, Joseph; Indiana University Hospital, Indianapolis, Indiana; *A Phase II, Randomized, Double Blind Placebo Controlled Study of Combination Drug Anti-Retroviral Therapy to Include a Reverse Transcriptase Inhibitor and a Protease Inhibitor Plus HIV-IT(V) or Placebo in HIV Patients with CD4+ Counts ≥ 100, and HIV RNA ≥ 1K, and ≤ 10K* Sponsor: Chiron Corporation

NIH/ORDA Receipt Date: 6-23-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

9706-195 (Open) Gene Therapy/Phase I/Cancer/Immunotherapy/CEA-Expressing Malignancies/In Vivo/Vaccinia Virus/Carcinoembryonic Antigen cDNA/Intradermal and Subcutaneous Injections

Conry, Robert M.;The University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I Trial of a Recombinant Vaccinia-CEA (180 Kd) Vaccine Delivered by Intradermal Needle Injection Versus Subcutaneous Jet Injection in Patients with Metastatic CEA-Expressing Adenocarcinoma* Sponsor: Drug Regulatory Affairs Branch, Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment, Diagnosis and Centers, NCI, NIH

NIH/ORDA Receipt Date: 6-26-97. Sole FDA Review Recommended by NIH/ORDA: 9-5-97

9706-196 (Open) Gene Therapy/Phase I/Monogenic Disease/Chronic Granulomatous Disease/In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/gp91phox/Intravenous Infusion

Smith, Franklin O., and Dinauer, Mary C.; Indiana University School of Medicine, Indianapolis, Indiana; *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*

NIH/ORDA Receipt Date: 6-30-97. Sole FDA Review Recommended by NIH/ORDA: 7-21-97

9706-197 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/InVivo/Autologous Melanoma Cell/Canarypox Virus/B7(CD80)/Interleukin-12/Cytokine/Intratumoral Injection

Conry, Robert M.; University of Alabama at Birmingham, Birmingham, Alabama; *Phase Ib Trial of Intratumoral Injection of a Recombinant Canarypox Virus Encoding Human B7.1 (ALVAC-hB7.1) or a Combination of ALVAC-hB7.1 and a Recombinant Canarypox Virus Encoding Human Interleukin-12 (ALVAC-hIL-12) in Patients with Surgically Incurable Melanoma* Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 6-30-97. Sole FDA Review Recommended by NIH/ORDA: 9-5-97

9707-198 (Open) Gene Therapy/Phase I/II/Cancer/Colorectal Carcinoma Expressing TAG-72/In Vitro/Autologous CD8+ and CD4+ T Lymphocytes/Retrovirus/CC49-Zeta T Cell Receptor/Intravenous Infusion

Venook, Alan and Warren, Robert S., University of California, San Francisco, California and Fisher, George; Stanford University, Palo Alto, California; *A Phase I/II Study of Autologous CC49-Zeta Gene-Modified T Cells and α-Interferon in Patients with Advanced Colorectal Carcinomas Expressing the Tumor-Associated Antigen, TAG-72* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 7-7-97. Sole FDA Review Recommended by NIH/ORDA: 8-28-97

9707-199 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Breast/Head and Neck Cancer/Cutaneous T-Cell Lymphoma/Immumotherapy/In Vitro/Autologous Fibroblasts/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-12/Intratumoral Injection

Park, Chan H.; Samsung Medical Center, Seoul, Korea; Kim, Sunyoung; Seoul National University, Seoul, Korea; Lotze, Michael; Tahara, Hideaki; and Robbins, Paul; University of Pittsburgh, Pittsburgh, Pennsylvania; *IL-12 Gene Therapy Using Direct Injection of Tumors with Genetically Engineered Autologous Fibroblasts*

NIH/ORDA Receipt Date: 7-22-97. Sole FDA Review Recommended by NIH/ORDA: 10-30-97

9707-200 (Open) Gene Therapy/Phase I/II/Cancer/Non-Hodgkin's B-Cell Lymphoma/Mantle Cell Lymphoma/Immumotherapy/In Vivo/Naked Plasmid DNA/Tumor Idiotype/Intramuscular Injection

Levy, Ronald; Stanford University School of Medicine, Stanford, California; *A Phase I/II Study of Vaccine Therapy for B-Cell Lymphoma Utilizing Plasmid DNA Coding for Tumor Idiotype* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 7-24-97. Sole FDA Review Recommended by NIH/ORDA: 8-13-97

9707-201 (Open) Gene Therapy/Phase I/ Cancer/Ovarian/Immunotherapy/In Vitro/Autologous Tumor Cells/Canarypox Virus/B7.1 (CD80)/Intraperitoneal Injection

Freedman, Ralph; The University of Texas, M.D. Anderson Cancer Center, Houston, Texas; *Intraperitoneal (IP) Auatologous Therapeutic Tumor Vaccine (AUT-OV-ALVAC-hB7.1) plus IP rIFN-γ for Patients with Ovarian Cancer. A Pilot Study* Sponsor: NCI Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 7-28-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

9707-202 (Open) Gene Therapy/Phase I/Immunotherapy/Cancer/Melanoma/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)/Subcutaneous Injection

Dranoff, Glenn and Soiffer, Robert; Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; *A Phase I Study of Vaccination with Autologous, Lethally Irradiated Melanoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor*

NIH/ORDA Receipt Date: 7-28-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

9707-203 (Open) Gene Therapy/Phase I/Immunotherapy/Cancer/Non-Small Cell Lung Carcinoma (NSCLC)/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)/Subcutaneous Injection

Dranoff, Glenn and Salgia, Ravi; Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; *A Phase I Study of Vaccination with Autologous, Lethally Irradiated Non-Small Cell Lung Carcinoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor*

NIH/ORDA Receipt Date: 7-28-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

9707-204 (Open) Gene Therapy/Phase I/Monogenic Disease/Leukocyte Adherence Deficiency (LAD)/In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/CD18/Intravenous Infusion

Hickstein, Dennis; University of Washington School of Medicine, Seattle, Washington; *Retrovirus-Mediated Transfer of the cDNA for Human CD18 into Perpheral Blood Repopulating Cells of Patients with Leukocyte Adherence Deficiency*

NIH/ORDA Receipt Date: 7-31-97. Sole FDA Review Recommended by NIH/ORDA: 9-17-97

9708-205 (Open) Gene Therapy/Phase I/II/Cancer/Prostate/Immunotherapy/ In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Subcutaneous Injection

Simons, Jonathan W.; Johns Hopkins Oncology Center, Baltimore, Maryland; *Phase I/II Study of Allogeneic Human GM-CSF Gene Transduced Irradiated Prostate Cancer Cell Vaccines in Patients with Prostate Cancer*

NIH/ORDA Receipt Date: 8-19-97. Sole FDA Review Recommended by NIH/ORDA: 9-9-97

9708-206 (Open) Gene Therapy/Phase I/II/Cancer/Chronic Myelogenous Leukemia/Adoptive Immunotherapy/In Vitro/Donor CD8+ and CD4+ Lymphocytes/Retrovirus/Hygromycin Phosphotransferase-Herpes Simplex Thymidine Kinase Fusion Gene/Intravenous Infusion

Flowers, Mary E. D. and Riddell, Stanley; Fred Hutchinson Cancer Research Center, Seattle, Washington; *Infusion of Polyclonal HyTK (hygromycin phosphotransferase and HSV thymidine kinase gene)-transduced Donor T Cells for Adoptive Immunotherapy in Patients with Relapsed CML after Allogeneic Stem Cell Transplant: Phase I-II Clinical Trial*

NIH/ORDA Receipt Date: 8-19-97. Sole FDA Review Recommended by NIH/ORDA: 9-26-97

9708-207 (Open) Gene Therapy/Phase I/Cancer/Colorectal/Immunotherapy/In Vivo/Autologous Tumor Cells/Canarypox Virus/Carcinoembryonic Antigen/B7.1 (CD80)/Intradermal Scarification

Kaufman, Howard L.; Albert Einstein Cancer Center, Bronx, New York; *Phase I Clinical Trial of a Recombinant ALVAC-CEA-B7 Vaccine in the Treatment of Advanced Colorectal Carcinoma.* Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 8-21-97. Sole FDA Review Recommended by NIH/ORDA: 11-25-97

9708-208 (Open) Gene Therapy/Phase I/Cancer/Mesothelioma/Pro-Drug/In Vivo/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Herpes Simplex Virus Thymidine Kinase/Ganciclovir/Intrapleural Administration

Schwarzenberger, Paul; Louisiana State University Medical Center, New Orleans, Louisiana; *The Treatment of Malignant Pleural Mesothelioma with a Gene-Modified Cancer Vaccine: A Phase I Study*

NIH/ORDA Receipt Date: 8-25-97. Sole FDA Review Recommended by NIH/ORDA: 9-16-97

9708-209 (Open) Non-Therapeutic/In Vivo/Bronchial Epithelial Cells/Adenovirus/Serotype 5/*E. coli* Cytosine Deaminase/Intrabronchial Administration

Harvey, Ben-Gary and Crystal, Ronald G.; Rockefeller University Hospital, New York, New York; *Systemic and Respiratory Immune Response to Administration of an Adenovirus Type 5 Gene Transfer Vector ($Ad_{GV}CD.10$)*

NIH/ORDA Receipt Date: 8-26-97. Discussed at the December 16, 1997 RAC meeting

---

9709-210 (Open) Gene Therapy/Phase I-II/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1005/HLA-B7/β2-Macroglobulin cDNA/Direct Intratumoral Injection

Gonzales, Rene; University of Colorado Cancer Center, Denver, Colorado and Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; *Compassionate Use Protocol for Retreatment with Allovectin-7 Immunotherapy for Metastatic Cancer by Direct Gene Transfer* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 9-8-97. Sole FDA Review Recommended by NIH/ORDA: 9-26-97

9708-211 (Open) Gene Therapy/Phase I/Monogenetic Disease/Canavan Disease/In Vivo/Autologous Brain Cells/Plasmid DNA/Adeno-associated Virus/Poly-L-Lysine/Cationic Liposome Complex/DC-Chol/DOPE/Aspartoacylase cDNA/Intracranial (Ommaya Reservoir) Administration

Seashore, Margretta, R.; Yale University, New Haven, Connecticut; *Gene Therapy of Canavan Disease: Retreatment of Previously Treated Children*

NIH/ORDA Receipt Date: 8-28-97. Discussed at the December 16, 1997 RAC meeting

---

9709-212 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Vical-1102/Interleukin-2 cDNA/Intratumoral Injection

Gonzales, Rene; University of Colorado Health Sciences Center, Denver, Colorado; and Hersh, Evan M.; Arizona Cancer Center, Tucson, Arizona; *Phase I Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) with IL-2 Plasmid DNA/DMRIE/DOPE Lipid Complex (Leuvectin) as an Immunotherapeutic Regimen in Patients with Metastatic Melanoma* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 9-18-97. Sole FDA Review Recommended by NIH/ORDA: 10-8-97

9709-213 (Open) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/In Vitro/Autologous CD8+ T Cells/Retrovirus/CD4-Zeta Chimeric Receptor/Intravenous

Deeks, Steven G.; University of California, San Francisco General Hospital, San Francisco, California; *A Phase II Study of Autologous CD4-Zeta Gene-Modified T Cells in HIV-Infected Patients with Undectable Plasma Viremia on Combination Antiretroviral Drug Therapy* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 9-22-97. Sole FDA Review Recommended by NIH/ORDA: 10-10-97

9709-214 (Open) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53

Breau, Randall L.; University of Arkansas for Medical Sciences, Little Rock, Arkansas; Clayman, Gary L.; The University of Texas MD Anderson Cancer Center, Houston, Texas; Yoo, George H.; Wayne State University/Barbara Ann Karmanos Cancer Center, Detroit, Michigan; Medina, Jesus E., University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; Murphy, Barbara S., Vanderbilt University Medical Center, Nashville, Tennessee; Goodwin, W. Jarrard, University of Miami Hospitals and Clinics, Miami, Florida; Weber, Jeffery S., University of Southern California, Los Angeles, California; Schuller, David E., Ohio State University Medical Center, Columbus, Ohio; and Bukowski, Ronald M., The Cleveland Clinic Foundation, Cleveland, Ohio; *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: Gencell (Division of Rhone-Poulenc Rorer Pharmaceuticals)

NIH/ORDA Receipt Date: 9-22-97. Sole FDA Review Recommended by NIH/ORDA: 10-21-97

9709-215 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vivo/Autologous Tumor Cells/Canarypox Virus/Carcinoembryonic Antigen/B7.1 (CD80)/Intramuscular and Intradermal Injections

von Mehren, Margaret; Fox Chase Cancer Center, Philadelphia, Pennsylvania; *Phase I/Pilot Study of ALVAC-CEA-B7.1 Immunization in Patients with Advanced Adenocarcinoma Expressing CEA* Sponsor: National Cancer Institue - Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 9-24-97. Sole FDA Review Recommended by NIH/ORDA: 10-28-97

9709-216 (Open) Gene Therapy/Phase I/Cancer/Breast/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Cutaneous or Subcutaneous

von Mehren, Margaret; Fox Chase Cancer Center, Philadelphia, Pennsylvania; *Phase I/Pilot Study of p53 Intralesional Gene Therapy with Chemotherapy in Breast Cancer* Sponsor: National Cancer Institue - Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 9-24-97. Sole FDA Review Recommended by NIH/ORDA: 10-28-97

9710-217 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Logothetis, Christopher J.; University of Texas MD Anderson Cancer Center, Houston, Texas; *A Tolerance and Efficacy Study of Intraprostatic INGN 201 Followed by Pathological Staging and Possible Radical Prostatectomy in Patients with Locally Advanced Prostate Cancer* Sponsor: Introgen Therapeutics, Inc.

NIH/ORDA Receipt Date: 10-3-97. Sole FDA Review Recommended by NIH/ORDA: 11-6-97

9710-218 (Open) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Hammerhead Ribozyme/In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Tat and Rev Hammerhead Ribozyme/Intravenous

Krishnan, Amrita and Zaia, John, A.; City of Hope Medical Center, Duarte, California; *High Dose Chemotherapy and Autologous Peripheral Stem Cell Transplantation for HIV Lymphomas: A Phase IIa Study of Comparative Marking Using a Ribozyme Gene and a Neutral Gene* Sponsor: Ribozyme Pharmaceuticals, Inc.

NIH/ORDA Receipt Date: 10-6-97. Sole FDA Review Recommended by NIH/ORDA: 10-27-97

9710-219 (Open) Gene Therapy/Phase I/Cancer/Bladder/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intravesical Administration

Pagliaro, Lance C.; The University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase I Trial of Intravesical Ad-p53 Treatment in Locally Advanced and Metastatic Bladder Cancer*

NIH/ORDA Receipt Date: 10-21-97. Sole FDA Review Recommended by NIH/ORDA: 11-10-97

9710-220 (Open) Gene Therapy/Phase II/Cancer/Non-Small Cell Lung Cancer/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Bronchoscopy or Percutaneous Intratumoral Injection

Dobbs, Tracy W.; East Tennessee Oncology/Hematology, P.C., Knoxville, Tennessee; *A Phase II Gene Therapy Study in Patients with Non-Small Cell Lung Cancer Using SCH 58500 (rAd/p53) in Combination with Chemotherapy for Multiple Cycles* Sponsor: Schering Plough Research Institute

NIH/ORDA Receipt Date: 10-31-97. Sole FDA Review Recommended by NIH/ORDA: 12-15-97

9711-221 (Open) Gene Therapy/Phase I/Other/ Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor (VEGF) cDNA/Cardiac Administration

Crystal, Ronald G.; The New York Hospital-Cornell Medical Center, New York, New York; *Phase I Study of Direct Administration of a Replication-Deficient Adenovirus Vector (Ad_{GV}VEGF121.10) Containing the VEGF121 cDNA to the Ischemic Myocardium of Individuals with Life Threatening Diffuse Coronary Artery Disease* Sponsor: GenVec, Inc.

NIH/ORDA Receipt Date: 11-4-97. Discussed at the December 16, 1997 RAC meeting

---

9711-222 (Open) Gene Therapy/Phase I/Monogenetic Disease/Canavan Disease/In Vivo/Autologous Brain Cells/Plasmid DNA/Adeno-Associated Virus/Protamine/Cationic Liposome Complex/DC-Cholesterol-DOPE/Aspartoacylase cDNA/Intracranial (Ommaya Reservoir)

Freese, Andrew; Thomas Jefferson University, Philadelphia, Pennsylvania; *Gene Therapy of Canavan Disease*

NIH/ORDA Receipt Date: 11-12-97. Sole FDA Review Recommended by NIH/ORDA: 1-26-98

9712-223 (Open) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy/In Vitro/Allogeneic Neuroblastoma Cell

Lines/Retrovirus/Cytokine/Interleukin-2 (IL-2)/Plasmid/Electroporation/Chemokine/Lymphotactin/Subcutaneous Injection

Bowman, Laura; St. Jude Children's Research Hospital, Memphis, Tennessee; *Phase I Study of Chemokine and Cytokine Gene Modified Allogeneic Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using a Retroviral Vector*

NIH/ORDA Receipt Date: 12-3-97. Sole FDA Review Recommended by NIH/ORDA: 12-29-97

9712-224 (Open) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy/In Vitro/Autologous Tumor Cells (Non-Irradiated)/Type 5 Adenovirus/Cytokine/Interleukin-2 (IL-2)/Chemokine/Lymphotactin/Subcutaneous Injection

Bowman, Laura; St. Jude Children's Research Hospital, Memphis, Tennessee; *Phase I Study of Chemokine and Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using an Adenoviral Vector*

NIH/ORDA Receipt Date: 12-3-97. Sole FDA Review Recommended by NIH/ORDA: 12-29-97

9712-225 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense/In Vitro/Antisense TAR/Transdominant Rev/Intravenous

Isola, Luis M.; Mount Sinai Medical Center, New York, New York; *A Phase I Trial of Autologous and Allogeneic Bone Marrow Transplantation with Genetically Marked Cells for the Treatment of HIV Associated Lymphoid Malignancies*

NIH/ORDA Receipt Date: 12-15-97. Sole FDA Review Recommended by NIH/ORDA: 1-7-98

9712-226 (Open) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injections

Dreicer, Robert; University of Iowa College of Medicine, Iowa City, Iowa; *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)* Sponsor: Gencell (Division Rhone-Poulenc Rorer Pharmaceuticals, Inc.)

NIH/ORDA Receipt Date: 12-17-97. Sole FDA Review Recommended by NIH/ORDA: 1-9-98

9801-227 (under review) Gene Therapy/Phase II/Cancer/Melanoma/Head and Neck Cancer/Immunotherapy/In Vitro/Autologous Fibroblasts/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-12 cDNA/Neomycin Phosphotransferase cDNA/Intrtumoral Injection

Lotze, Michael T.; University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania; *IL-12 Gene Therapy Using Direct Injection of Tumors with Genetically Engineered Autologous Fibroblasts (A Phase II Study)*

NIH/ORDA Receipt Date: 1-2-98.

9801-228 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug/In Vivo/ Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase cDNA/Acyclovir/Intraperitoneal Injection

Kieback, Dirk G.; Baylor College of Medicine, Houston, Texas; *Phase I Study of Concomitant Adenovirus-Mediated Transduction of Ovarian Cancer with HSV-tk Gene Followed by Intravenous Administration of Acyclivor and Chemotherapy with Topotecan in Patients after Optimal Debulking Surgery for Recurrent Ovarian Cancer*

NIH/ORDA Receipt Date: 1-14-98. Sole FDA Review Recommended by NIH/ORDA: 2-5-98

9801-229 (under review) Gene Therapy/Phase I/Cancer/Prostate/Pro-Drug/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

Kadmon, Dov; Baylor College of Medicine, Houston, Texas; *Neoadjuvant Pre-radical Prostatectomy Gene Therapy (HSV-tk Gene Transduction Followed by Ganciclovir) in Patients with Poor Prognostic Indicators*

NIH/ORDA Receipt Date: 1-16-98.

9801-230 (under review) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense/Antisense TAR/Antisense tat/rev/In Vitro/CD34+ Cells/Intravenous

Cowan, Morton J. and Conant, Marcus A.; University of California, San Francisco, San Francisco, California; *Evaluation of the Safety and Effects of Ex Vivo Modification and Re-infusion of CD34+ Cells by an Antisense Construct Against HIV-1 in a Retroviral Vector* Sponsor: Enzo Therapeutics, Inc.

NIH/ORDA Receipt Date: 1-20-98.

9802-231 (under eview) Gene Therapy/Phase I/II/Monogenic Disease/Chronic Granulomatous Disease/In Vitro/CD 34+ Autologous Peripheral Blood Cells/Retrovirus/p47phox/gp91phox/Intravenous

Malech, Harry L.; National Institutes of Health, Bethesda, Maryland; *Gene Therapy Approach for Chronic Granulomatous Disease*

NIH/ORDA Receipt Date: 2-2-98.

9802-232 (under review) Gene Therapy/Phase I/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/Vascular Enothelial Growth Factor (VEGF) cDNA/Cardiac Administration

Isner, Jeffrey M.;Tufts University School of Medicine, Boston, Massachusetts; *Gene Therapy for Myocardial Angiogenesis*

NIH/ORDA Receipt Date: 2-3-98.

(Scroll down for Summary Table)

HUMAN GENE TRANSFER PROTOCOLS								
	Review Level 1	Review Level 2	Review Level 3	Review Level 4	Review Level 5	Review Level 6	Review Level 7	TOTAL
MARKING	23	2	5	0	0	0	0	30
THERAPY	83	5	92	[illegible]	5	12	2	200
NON-THERAPEUTIC	1	0	0	0	0	0	1	2
INFECTIOUS DISEASES	8	1	11	[illegible]	1	1	0	23
1. Human Immunodeficiency Virus	8	1	11	1	1	1	0	23
MONOGENIC DISEASES	20	1	9	0	1	1	1	33
1. Alpha-1-Antitrypsin Deficiency	1	0	0	0	0	0	0	1
2. Chronic Granulomatous Disease	1	0	1	0	1	0	0	3
3. Cystic Fibrosis	10	1	5	0	0	0	0	16
4. Familial Hypercholesterolemia	1	0	0	0	0	0	0	1
5. Fanconi Anemia	1	0	0	0	0	0	0	1
6. Gaucher Disease	3	0	0	0	0	0	0	3
7. Hunter Syndrome	1	0	0	0	0	0	0	1
8. Ornithine Transcarbamylase Deficiency	0	0	1	0	0	0	0	1
9. Purine Nucleoside Phosphorylase Deficiency	1	0	0	0	0	0	0	1
10. SCID-ADA	1	0	0	0	0	0	0	1
11. X-linked SCID	0	0	1	0	0	0	0	1
12. Leukocyte Adherence Deficiency	0	0	1	0	0	0	0	1
13. Canavan Disease	0	0	0	0	0	1	1	2
OTHER DISEASES/DISORDERS	2	0	2	0	1	0	1	6
1. Peripheral Artery Disease	1	0	0	0	0	0	0	1
2. Rheumatoid Arthritis	1	0	0	0	0	0	0	1
3. Arterial Restenosis	0	0	1	0	0	0	0	1
4. Cubital Tunnel Syndrome	0	0	1	0	0	0	0	1
5. Coronary Artery Disease	0	0	0	0	1	0	1	2
CANCER (BY THERAPEUTIC APPROACH)	53	3	70	0	2	10	0	138
1. Antisense	4	0	0	0	0	0	0	4
2. Chemoprotection	4	0	4	0	0	0	0	8
3. Immunotherapy/In Vitro Transduction	22	2	19	0	1	2	0	46
4. Immunotherapy/In Vivo Transduction	7	0	28	0	0	2	0	37
5. Pro-drug/HSV-TK and Ganciclovir	12	1	10	0	1	1	0	25
6. Tumor Suppressor Gene	3	0	6	0	0	5	0	14
7. Single Chain Antibody	0	0	2	0	0	0	0	2
8. Oncogene Down-Regulation	1	0	1	0	0	0	0	2
TOTAL GENE TRANSFER PROTOCOLS (THERAPY, MARKING and NON-THERAPEUTIC)	107	7	97	1	5	12	3	232

Review Level 1 = Full RAC review + NIH Director approval + FDA Investigational New Drug (IND) approval. This review process is no longer in effect.

Review Level 2 = Accelerated RAC Review + NIH Office of Recombinant DNA Activities (ORDA) Approval + FDA IND Approval. This review process is no longer in effect.
Review Level 3 = Sole FDA Review Recommended by NIH/ORDA. Simultaneous submission to NIH(ORDA) required for the purpose of data monitoring and adverse event reporting. This revew process is no longer in effect.
Review Level 4 = Sole FDA Review [submission to NIH(ORDA) not required]. This is only for non-NIH funded (either direct or collaborative) institutions who elect to submit to NIH(ORDA) under voluntary compliance.
Review Level 5 = Received by NIH(ORDA). Review level pending.
Review Level 6 = Sole FDA Review Recommended by NIH/ORDA. Submission to NIH(ORDA) required for the purpose of data monitoring and adverse event reporting. This review process is currently in effect.
Review Level 7 = Full RAC discussion + FDA approval. This review process is currently in effect.

AMENDMENTS TO
HUMAN GENE TRANSFER PROTOCOLS
MARCH 10, 1998 RECOMBINANT DNA ADVISORY COMMITTEE

11-20-97 (letter date)	9706-191 Gluckman *et al.*	**Phase II Study of Immunotherapy by Direct Gene Transfer with Allovectin-7 for the Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck** **Amendment:** One principal investigator/site is added to the protocol. The PI at the new site; University of Michigan Medical Center; Ann Arbor, Michigan; is Gregory T. Wolf, M.D.
12-2-97	9409-088 Isner and Walsh	**Arterial Gene Transfer for Therapeutic Angiogenesis in Patients with Peripheral Artery Disease** **Amendment:** Received reversed protocol from PI, Dr. Isner, for intramuscular gene transfer of naked DNA encoding for vascular endothelial growth factor in patients with peripheral artery disease. Dr. Isner stated "...that this protocol was pursued as an amendment to the intr-arterial protocol. The only remarkable difference between the two protocols is the route of administration. The plasmid vector is the same and the clinical endpoints are unchanged."
12-4-97	9706-196 Smith and Dinauer	**Fibronectin-Assisted, Retroviral-Mediated Transduction of CD34+ Peripheral Blood Cell with gp91 phox in Patients with X-Linked Chronic Granulomatous Disease: A Phase I Study** **Amendments:** Minor amendments have been made to the clinical protocol. 1) Patients will undergo aphereis for a maximum of two days. 2) New "stratification." If number of cells, peripheral blood progenitor cells, collected exceeds 7.5×10^8, patients will receive both fresh and cryopreserved transduced cells. If the number is less than 7.5×10^8 cells, patients will only receive fresh cells. In either case, at most two transfusions will be done. One transfusion of fresh cells and if possible one transfusion, six months later, of cryopreserved transduced cells. 3) Other changes in the cryoprservation procedure and the transduction procedure have been made to reflect the new "stratification."
12-12-97	9703-184 Belldegrun	**A Phase I Study Evaluating the Safety and Efficacy of Interleukin-2 Gene Therapy Delivered by Lipid Mediated Gene Transfer (Leuvectin) in Prostate Cancer Patients** **Amendments:** 1) Pre-treatment biopsy has been added to obtain a baseline for comparison to the post-treatment biopsy. 2) Change in the inclusion criteria so that creatinine levels must now be in the normal range instead of less than 0.8mg/dL.
12-15-97	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:** Two principal investigators/sites are added to the protocol. The new PIs are David E. Schuller, M.D. at Ohio State University Medical Center; Columbus, Ohio; and Ronald M. Bukowski, M.D. at The Cleveland Clinic Foundation; Cleveland, Ohio.
12-22-97	9706-191 Gluckman *et al.*	**Phase II Study of Immunotherapy by Direct Gene Transfer with Allovectin-7 for the Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck** **Amendment:** One principal investigator/site is added to the protocol. The PI at the new site; Mayo Clinic; Rochester, Minnesota; is Scott Okuno, M.D.
1-6-98	9706-191 Gluckman *et al*	**Phase II Study of Immunotherapy by Direct Gene Transfer with Allovectin-7 for the Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck** **Amendment:** To allow investigation of the effects of Allovectin-7 in patients with advanced or recurrent non-squamous cell cancer of the head and neck or aerodigestive tract. Patients with certain skin cancers such as melanoma or basal cell carcinoma are excluded. The amendment will initially be conducted at the U. of Cincinnati Medical Center by Dr. Jack Gluckman. The amendment has been approved by the U of Cincinnati IBC and IRB.

1-7-98	9406-078 Johnson and Young	**Retroviral Mediated Gene Transfer of the Franconi Anemia Complementation Group C Gene to Hematopoietic Progenitors of Group C Patients** **Amendments:** 1) Transduce autologous hematopoietic progenitor and stem cells isolated from bone marrow rather than from mobilized peripheral blood in 3 patients. 2) One principal investigator/site is added to the protocol. The PI at the new site; University of Minnesota; Minneapolis, Minnesota; is John E. Wagner, M.D.
1-30-98	9701-173 Williams	**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:** Changes have been made to the eligibility criteria to state more clearly the types of poor prognosis brain tumor patients who may enroll in the study. Minor changes have been made to the clinical protocol to reduce confusion with respect to the eligibility of patients currently undergoing radiation therapy. The protocol has been amended to allow admission of patients either prior to radiation therapy or following completion of radiation therapy. The investigators state that: "We do not anticipate that timing of radiation therapy in relation to the chemotherapy/stem cells would affect the objectives of the study, nor do we anticipate that the proposed revisions will effect the risk/benefit ratio for the patients."
2-13-98	9709-212 Gonzalez *et al.*	**Phase I Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) with IL-2 Plasmid DNA/DMRIE/DOPE Lipid Complex (Leuvectin) as an Immunotherapeutic Regimen in Patients with Metastatic Melanoma** **Amendment:** One principal investigator/site is added to the protocol. The PI at the new site; Mayo Clinic; Rochester, Minnesota; is Joseph Rubin, M.D.
2-13-98	9608-157 Maria *et al.*	**Prospective, Open-Label, Parallel-Group, Randomized Multicenter Trial Comparing the Efficacy of Surgery, Radiation, and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir Against the Efficacy of Surgery and Radiation in the Treatment of Newly Diagnosed, Previously Untreated Glioblastoma** **Amendments:** 1) Dr. John Gutheil has replaced Dr. Ivor Royston as the PI at the Sharp HealthCare/Sidney Kimmell Cancer Center and Dr. Martti Kulvik has replaced Dr. Leena Kivipelto as the PI at Helsinki University Central Hospital. 2) Three principal investigators sites are added to the protocol. The PI at Universitatsklinik fur Neurologie is Gunther Stockhammer, M.D., the PI at Centre Leon Berard is Professeur Marie Lavrot, and the PI at Unita' Neuroncologia Molecolare e Terapia Genica is Dr. Gaetano Finocchiaro.
2-17-98	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 principal investigator/site is added to the protocol. The PI at the new site; University of Louisville Health Sciences Center; Louisville, Kentucky; is John Hamm, M.D.

SAFETY REPORTS, ADVERSE EVENTS, AND UPDATES FOR HUMAN GENE TRANSFER PROTOCOLS MARCH 10, 1998 RECOMBINANT DNA ADVISORY COMMITTEE MEETING

11-17-97 (letter date)	9512-137 Hortobagyi *et al.*	**Phase I Study of E1A Gene Therapy for *Patients with Metastatic Breast or* Ovarian Cancer that Overexpresses Her-2/neu** **Adverse event:** Occurred at Virginia Mason Medical center under the direction of Dr. Paul Weiden. Patient received 7.2 mg DNA/m^2 on 10-30-97. One and a half hours after infusion of the plasmid DNA/lipid complex, patient experienced severe abdominal pain and vomiting. Patient required IV morphine to relieve the pain. Due to labored breathing, caused by the pain, oxygen was administered. Patient was admitted to the hospital for pain control; patient continued vomiting for several hours. Patient spiked a fever of 39°C. Patient was released form the hospital on 10-31-97 and fully recovered on 11-2-97. **Update:** To date, 6 patients have been enrolled in the breast cancer arm of this study. This arm of the study is going to be closed by Targeted Genetics to accrual. Targeted Genetics does not intend to pursue this indication. Twelve ovarian cancer patients have been treated under this protocol. Dosing has stopped past the 7.2 mg DNA/m^2 group. Maximum tolerated dose has been determined to be 3.6 mg DNA/m^2 for this formulation of plasmid: lipid (25 µg DNA: 250 nmole lipid).
11-24-97	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)** **Adverse event:** Patient received first dose of Ad5CMV-p53 on Sept. 8, 1997 and second dose the following day. After second injection of study drug, patient experienced fatigue, chills, and a fever of 103.5°F. Two ibuprofen tablets were given and fever was reduced to 99.4°F. Minimal bleeding at injection site occurred, packed with surgicel. One day after second dose, patient experienced moderate bleeding which quickly ceased. Patient received third injection of drug; moderate bleeding at injection site, packed with surgicel. Patient stayed in hospital overnight for observation. On Sept. 11, 1997 mild amount of bleeding, but no obstruction or inflammation. Temperature was normal and bleeding resolved. Patient discharged from hospital. The fever experienced by the patient was considered by the investigator as possibly related to the study drug. Patient went on to receive cycle 2 of study from October 6-8, 1997 and did not experience any complications.
11-18-97	9703-183 Straus	**Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T-Lymphocytes to Patients with Relapsed EBV-Positive Hodgkin Disease** Compassionate Case **Update:** Compassionate single patient protocol was terminated due to inability to grow out EBV-specific cytotoxic T lymphocytes (after multiple attempts) from the patient. Patient was never treated under this compassionate protocol. Patient underwent aggressive courses of chemotherapy, that as of this date have led to clinical remission.

11-26-97	9512-137 Hortobagyi *et al.*	**Phase I Study of E1A Gene Therapy for Patients with Metastatic Breast or Ovarian Cancer that Overexpresses Her-2/neu** **Adverse event:** Patient received third infusion of lipid:DNA complex (3.6mg DNA/m^2) on November 13, 1997. Patient went back to complain of nausea, vomiting, and severe constipation; nausea and vomiting had occurred for the past 10 days. Patient was admitted to the hospital for IV fluids to control nausea and vomiting and remained in the hospital for 6 days. During this hospitalization, patient received chemotherapy and was taken off study. According to the report filed by the sponsor (Targeted Genetic): "The investigator did not believe these events were related to E1A Lipid Complex; however, the Targeted Genetics medical monitor could not rule out the possibility considering the frequency of previous reports of patients experiencing nausea and vomiting treated with E1A Lipid Complex in this trial."
1-23-98	9609-161 Antonia	**Treatment of Small Cell Lung Cancer in Partial Remission or at Relapse with B7-1 Gene-Modified Autologous Tumor Cells as a Vaccine with Systemic Interferon Gamma** **Update:** Protocol has been closed. Investigators were able to culture autologous tumor cells from several patients. However, they were unable to transfect the cells with their plasmid construct expressing B7-1; even though a variety of transfection techniques were tried.
1-30-98	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)** **Adverse event:** On day 14 of third course of treatment, patient experienced bleeding from the oral cavity with decreased blood pressure and decreased hematocrit. In addition, patient had bloody emesis with clots. Patient was hospitalized and treated with promethazine and IV fluids. An electrocardiogram showed sinus rhythm, sinus tachycardia with occasional premature ventricular contractions. Hematocrit was 25-29% compared to 38% two days before start of third course. Bleeding continued for approximately 6 hours; a similar episode occurred two days prior to this event (no hospitalization was required). "This event was considered by the investigator as possibly related to [the] study medication."
2-16-98	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, a total of ten patients, 15 total over two years, have been enrolled. Of the ten patients, three failed to mobilize sufficient number of CD34+ cells and therefore did not meet the eligibility requirements for the study. However, enough cells were obtained from these three patients to allow for transplantation with untransduced cells. Failure to mobilize sufficient number of cells is not unexpected given that many of the patients are heavily pre-treated. The other seven have either completed the tandem transplantation regimen (five patients) or are in the midst of the first transplant. Drug resistant transduced progenitors have been detected in the five patients that have completed the tandem transplantations. The investigators report that: "The range of gene transfer into progenitors is 10 to 27 %. Analysis for replication competent retrovirus of infused product and patients samples post-BMT have all been negative to date." In addition, the investigators report that no safety reports have been filed, no patients have dropped out of the study due to an adverse event, and all patients are still alive.

ACRONYMS

ASGPR	asialoglycoprotein receptor
ASPA	aspartoacylase
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
EIAV	equine infectious anemia virus
FDA	Food and Drug Administration
GFP	green flourescent protein
GTAC	Gene Therapy Advisory Committee
GTPC	Gene Therapy Policy Conference
HIV	human immunodeficiency virus
HSV-1	Herpes Simplex Virus-Type 1
HSV-TK	Herpes Simplex Virus-Thymidine Kinase
IBC	Institutional Biosafety Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITR	inverted terminal repeat
LTR	long terminal repeat
MRI	magnetic resonance imaging
NCI-CTEP	National Cancer Institute--Cancer Therapy Evaluation Program
NFP	non-flourescent protein
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
NMR	nuclear magnetic resonance
ORDA	Office of Recombinant DNA Activities
PCR	polymerase chain reaction
pfu	plaque forming units
PI	principal investigator
Points to Consider	*Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects*
RAC	Recombinant DNA Advisory Committee
RCR	replication-competent retrovirus
RCV	replication-competent virus
RFA	Request for Applications
SIV	simian immunodefiency virus
TK	thymidine kinase
UK	United Kingdom
VEGF	vascular endothelial growth factor
VSV	vesicular stomatitis virus