DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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RE: Human Research Subject Protections Under Federal-Wide Assurance FWA-93

Research Project: 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 Cystic Fibrosis Transmembrane Conductance Regulator Gene in the Lung.
Principal Investigator: Ronald G. Crystal, M.D.
CUMC Project Number: 1193-231

Research Project: Evaluation of Repeat Administration of a Replication Deficient, Recombinant Adenovirus Vector Containing the Normal Cystic Fibrosis Transmembrane Conductance Regulator cDNA to the Airways of Individuals with Cystic Fibrosis.
Principal Investigator: Ronald G. Crystal, M.D.
CUMC Project Number: 1094-611

Research Project: 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.
Principal Investigator: Ronald G. Crystal, M.D.
CUMC Project Number: 0695-908

Research Project: Phase I study of Repetitive Administration of Different Serotypes of Replication Deficient Adenovirus Vectors Containing the Human Thrombopoietin cDNA as a Adjunct to Stem Cell Transplantations to Maintain Platelet Levels Following High Dose Chemotherapy for Advanced Malignancy
Principal Investigator: Ronald G. Crystal, M.D.
CUMC Project Number: 0696-394

Research Project: Systemic and Respiratory Epithelial Immune Response to an Adenovirus Type 5 Gene Transfer Vector in Normal Individuals
Principal Investigator: Ben-Gary Harvey, M.D.
CUMC Project Number: 0896-472

Research Project: Immune Responses to Intradermal Administration of an Adenovirus Type 5 Gene Transfer Vector in Normal Individuals
Principal Investigator: Ben-Gary Harvey, M.D.
CUMC Project Number: 1096-555

Research Project: Adenovirus Vector-Mediated Transfer of the gp75 Gene for Treatment of Metastatic Melanoma
Principal Investigator: Ronald G. Crystal, M.D.
CUMC Project Number: 1196-579

Research Project: Immune Response to Intradermal Administration of an Adenovirus Type 5 Gene Transfer Vector (Ad_{GV}CD.10)
Principal Investigator: Ben-Gary Harvey, M.D.
CUMC Project Number: 0297-693

Research Project: 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
Principal Investigator: Ronald G. Crystal, M.D.
CUMC Project Number: 0797-894

Research Project: Systemic and Respiratory Epithelial Immune Response to an Adenovirus Type 5 Gene Transfer Vector (Ad_{GV}CD.10)
Principal Investigator: Ronald G. Crystal, M.D.
CUMC Project Number: 0897-905

Research Project: **Phase I Study of Direct Administration of a Replication Deficient Adenovirus Vector (Ad_{GV}VEGF121.10) Containing the VEGF121 cDNA to the Ischemic Lower Limb of Individuals with Peripheral Vascular Disease**
Principal Investigator: **Ronald G. Crystal, M.D.**
CUMC Project Number: **0398-178**
Research Project: **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 Diffuse Coronary Artery Disease via Minimally Invasive Surgery**
Principal Investigator: **Ronald G. Crystal, M.D.**
CUMC Project Number: **0698-277**

Research Project: **Assessment of Direct Administration Via Minimally Invasive Surgery of a Replication Deficient Adenovirus Vector (Ad_{GV}VEGF121.10)Containing the VEGF121 cDNA to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease**
Principal Investigator: **Ronald G. Crystal, M.D.**
CUMC Project Number: **0899-826**

Dear Dr. Siskind and Dr. Hajjar:

The Office for Human Research Protections (OHRP) has reviewed your report of March 22, 2002, that was submitted in response to OHRP's August 21, 2001 letter regarding the above referenced research conducted at Cornell University Medical Center (CUMC).

Based upon its review, OHRP makes the following determinations regarding the above-referenced research projects.

(1) OHRP finds that unanticipated problems involving risks to subjects or others were not reported to the Institutional Review Board (IRB) and/or OHRP as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(a) and (b)(5). In particular, OHRP notes the following:

(a) According to a 6-28-96 letter to the Food and Drug Administration (FDA), a protocol deviation/error occurred on 9-29-95 for protocol #1094-611, in which a subject received the wrong dose of adenovirus vector. This was not reported to the CUMC IRB until a August 1996 revision request. OHRP has no record of receiving a report of this event.

(b) The 5-1-97 continuing review report for protocol #0695-908 noted an "unexpected complication secondary to intramuscular injection" (dermal

hypersensitivity) and that a subject C03 experienced jaundice "with duration longer than expected," both in footnotes to a table. OHRP has no record of receiving reports of these events.

(c) A 5-13-98 letter to the FDA for protocol #0297-693 reported an adverse event for this protocol in which a subject undergoing screening for this protocol developed Guillian-Barre syndrome. This was reported to the CUMC IRB 5-13-98, but not to OHRP.

(d) The continuing review report submitted April 17, 1999 for protocol #0698-277 included subject safety data, including hepatic toxicity. This appears to be the only reporting of adverse events to the CUMC IRB for this protocol. A death was reported "possibly related to procedure" in a footnote of a table. According to the footnote, the deceased subject experienced gastrointestinal bleeding prior to death. OHRP has no record of receiving a report of this event.

Corrective Actions: OHRP acknowledges that CUMC has made numerous corrective actions to respond to this finding and others, including (i) developing new procedures for the IRB; (ii) expanding the IRB staff; (iii) revising the definition of and clarifying the reporting requirements for adverse events; (iv) establishing an adverse event subcommittee to review all adverse event reports; (v) adding statements which describe reporting requirements to all approval letters; (vi) and initiating an audit program. In addition, OHRP acknowledges that the principal investigator for the above-referenced research has instituted numerous corrective actions such as (i) quality assurance review of study regulatory files; (ii) developing an adverse event recording and reporting standard operating procedure; (iii) undertaking training in human subject protections, and (iv) revamping the monitoring of its clinical trials. OHRP notes that "unanticipated problems involving risks to subjects or others" may involve risks only, not actual proven harm (such as was the case in the vector overdose described in (1)(a) above). OHRP recommends that the principal investigator's standard operating procedures include discussion of this distinction.

Additional Guidance: CUMC's written IRB policies and procedures should be expanded to include additional operational details for ensuring prompt reporting to the IRB, appropriate institutional officials, and Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval. In particular, the New York Hospital-Cornell Medical Center Committee on Human Rights in Research Principles and Procedures Governing Use of Human Subjects in Research should describe the need to report unanticipated problems involving risks to subjects or others, or suspension or termination of IRB approval to OHRP and the procedures for accomplishing this reporting.

(2) OHRP finds that the informed consent documents reviewed and approved by the CUMC IRB for these projects did not adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1):

(i) A statement that the study involves research (particularly protocol #1193-231 and 1094-611).

(ii) An explanation of the purposes of the research (i.e., several of the objectives of protocol #0696-394 were not mentioned in the informed consent document: "Does ...administration of these vectors in the presence of a chemotherapeutic regimen that induces alkylating agents evoke an anti-Ad vector humoral response....is there expression following the repetitive administration of a vector of the same serotype, and if not, can use of an alternative serotype achieve the desired expression?").

(iii) A complete description of the procedures to be followed, and identification of any procedures which are experimental:

– Lung function tests outlined in the IRB-approved protocol #1193-231 (spirometry, He Dilution, Body box and ABG) are not described in the informed consent document (which only states "Breathing tests. These tests are harmless..." or refers the subject to the protocol.)

– An attachment to the informed consent document listing study procedures for protocol #0696-394 included "Multiple gated angiography." This procedure was not described in the informed consent document nor the protocol.

– The informed consent document for Part B of protocol #0696-394, which involved transfer of the vector to the liver, stated "[t]he basis for this experimental therapy is to transfer the gene for thrombopoietin...to the cells in the skin." This is the route of administration for Part A, not Part B.

– The informed consent document for protocol #0696-394 included an appendix regarding exposure to ionizing radiation and the protocol stated that such exposure was part of standard treatment or optional. Use of X-rays or CT scans was not otherwise described in the informed consent document.

– The fact that the vector would be administered under local anesthesia was described in the protocol but not in the informed consent document for protocol #0398-178.

– Informed consent document for protocol #0698-277 stated "Surgery will be scheduled as it would have been despite participation in any experimental study." It is not clear what this means since subjects are undergoing surgery only for research purposes.

(b) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts.

(i) The informed consent document for protocol # 1193-231 and #1094-611 did not describe what the consequences or treatments would be for the possible adverse events outlined in the form.

(ii) Risks outlined in the 1997 version of "Consent for Fiberoptic Brochoscopy" for protocol #0695-908 include the risks of aspiration pneumonia, hypoxemia, bronchospasm, and abnormal changes in heart rhythm. These same risks were not described in the informed consent document for protocol #s 1094-611 or 1193-231.

(iii) Informed consent document for protocol #0695-908 stated that 5-FC is nontoxic. However, publications from 1992 refer to hematolgic, gastrointestinal, and hepatic toxicities of this drug (Francis P, Walsh TJ; Clin Infect Dis 1992 Dec; 15(6): 1003-18). Indeed, in the 5-1-97 continuing review report, the investigators noted several apparent adverse reactions to 5-FC that were never noted in the informed consent document– nausea, vomiting, and increase in liver function tests and coagulation parameters.

(iv) The informed consent document for Part A of protocol #0696-394 and protocol # 1196-579 did not include a description of the risks and discomforts of skin biopsy.

(v) The following risk described in protocol #0696-394 was not described in the informed consent document: "Studies in experimental animals show that administration of the vector to the normal liver will induce mild inflammation within the liver...."

(vi) Several risks of bronchoalveolar lavage (transient fever and cardiac arrhythmias) were described in the protocol but not in the informed consent document for protocol #s 0896-472, 0297-693, 0897-905 and 1096-555.

(vii) In slides for a presentation to the RAC on 12-9-99, it was stated that "infequent minor AE possibly linked to Ad vectors, mostly fevers, leukocytosis, or elevated

transaminases." These events were apparently anticipated but were not described in the informed consent documents.

(viii) A report to the FDA dated 4-19-99 regarding protocol #1094-611 indicated several adverse reactions, including "unexpected premature ventricular contractions for 10 minutes during bronchoscopy..." and a 38% FEV1 decrease. These events were apparently anticipated but were not described in the informed consent documents.
(ix) Adverse events that occurred in protocol #0797-894 included anemia, pulmonary edema, pneumonia, respiratory failure, elevated liver enzymes, and renal abnormalities. These events were apparently anticipated but were not described in the informed consent documents.

(x) At their March 18, 1998 review of protocol #0398-178 the IRB requested that the investigator discuss in the informed consent document that unforeseen risks may occur. The principal investigator responded "[w]e ... have discussed all theoretical risks associated with delivery of the adenovirus...." There was no description in the revised informed consent document regarding unforeseen risks as the IRB requested.

(c) Section 46.116(a)(3): A description of any benefits to the subject or others that may *reasonably* be expected from the research. In particular, OHRP finds that the following informed consent document overstated potential for benefits: The informed consent document for protocol #1193-231 referred to the research as "treatment of cystic fibrosis."

(d) Section 46.116(a)(4): A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject (e.g., the alternative treatments listed in the informed consent document for protocol #0398-178 do not include any for those with limb-threatening disease.).

(e) Section 46.116(a)(8): A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. Most, if not all, of the informed consent documents stated "[y]our decision whether or not to participate will not prejudice future relations with the New York Hospital-Cornell Medical Center." They also stated "[y]ou are free to withdraw from the study without jeopardizing future care by the doctors carrying out this study." Penalty or loss of benefits could include things other than future relations with CUMC or care by the investigators.

Corrective Action: OHRP acknowledges that the CUMC IRB has made numerous corrective actions to address this finding, including (i) enhanced training on appropriate inclusion of required elements in informed consent documents; (ii) development of new IRB review forms to assist members in identifying and recording informed consent elements; and (iii) establishment of

a second IRB to reduce the IRB workload. OHRP also acknowledges that the principal investigator has established standardized operating procedures for the preparation of the informed consent document. In addition, CUMC will undertake a specific review of all statements regarding side effects of drugs by a pharmacist member of the IRB or qualified consultant and is redrafting the IRB's informed consent template so as to conform to regulations at 45 CFR 46.116.

(3) HHS regulations at 45 CFR 46.116 require that the information that is given to subjects must be in language understandable to the subject. OHRP finds that some of the informed consent documents approved by the IRB for these studies appeared to include complex language that would not be understandable to all subjects. In particular, OHRP notes the following:

(i) Informed consent document for protocol #s 1193-231, 0797-894, and 1094-611 were very complex and technical, including such terms as "respiratory manifestations," "genotype," "expressing," myocardial infarction," "intravenous contrast solution," "infusion," "radiopharmaceuticals."

(ii) The informed consent document for several of these protocols referred subjects to the protocol, which is very complex and technical.

(iii) On 10-11-99, the IRB approved the addition of sweat chloride tests for protocol #1094-611. The descriptions of these in the informed consent documents were very technical and complex, including the following terms: "cholinergic agent" "a few ml" "flexor surface" "the current generator is battery supplied to prevent patient exposure to a power line surge" "5cm below the antecubital fossa in the midline..." "intradermal" "parafilm" and "tachycardia."

Corrective Action: OHRP acknowledges that the CUCM IRB has taken numerous corrective actions as already mentioned. In addition, OHRP acknowledges CUCM's statement that the IRB now requires informed consent documents to be written at an eighth grade reading level, and in the future will avoid referring subjects to the protocol if they have any questions regarding the research study.

(4) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364. OHRP finds that use of expedited review by the IRB has not been restricted to these categories. For example:

(a) The continuing review of protocol #0797-894 on 8-10-99 was conducted in an expedited manner, but 3 subjects had been accrued since the last continuing review.

(b) Continuing review of protocol #0698-277 on 6-29-99 was conducted in an expedited manner, although subjects had been enrolled since the last review and

subjects were still being followed-up. The follow-up of subjects in the protocols appears to have included research-related interventions (e.g., bronchoscopies) and therefore expedited continuing review would not seem to have been appropriate.

Corrective Action: OHRP acknowledges that, in addition to the actions already mentioned, the CUMC IRB is (i) revising its policies and procedures to contain an updated description of the regulations at 45 CFR 46.110 and 63 FR 60364; (ii) developing new forms for submission and review of protocols to be handled in an expedited manner which allow for the identification of the specific permissible category justifying the expedited review; and (iii) has enhanced IRB member training on this issue.

(5) OHRP finds that when reviewing this research, the IRB sometimes appeared to lack sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, the continuing review forms for protocol #1193-231 did not indicate any enrollment of subjects. However, references to protocol #1193-231 in protocol #1094-611 indicated that 7 subjects had been studied.

Corrective Action: OHRP acknowledges that the CUMC IRB has taken numerous corrective actions mentioned above to address this and other findings.

(6) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that the following protocol changes were implemented prior to obtaining IRB approval:

(a) A memo from the principal investigator to Dr. William Schwieterman dated 5-2-94 regarding protocol #1193-231 indicated that the investigators were going to delete certain immune studies from the protocol.

(b) A 9-16-99 letter to the FDA from the principal investigator regarding protocol #0897-905 indicated a change in the protocol, increasing the number of bronchoscopies to be performed per subject.

(c) CUMC's 2-23-00 response to OHRP's 11-12-99 letter stated "[t]he FDA IND and sponsorship of the study [protocol #0797-894] was transferred to PD/WL on September 2, 1998....The FDA IND and sponsorship of the study [protocol #0398-178] was transferred to PD/WL on July 24, 1998...."

Corrective Action: OHRP acknowledges that the CUMC IRB is initiating an audit program which will check individual protocols to assure that the study is being conducted as approved

by the IRB and that changes are approved by the IRB prior to implementation. In addition, IRB approval letters have been modified to emphasize the need for IRB review of any changes prior to their implementation.

(7) Regarding project number 0896-472, OHRP finds that the procedures for enrolling subjects may have failed to minimize the possibility of coercion or undue influence as required by HHS regulations at 45 CFR 46.116. The April 1998 submission to the IRB had a new advertisement which was not pointed out to the IRB; this ad promised "$1000 at completion." The IRB had asked the principal investigator to state in the informed consent document that the subjects would be compensated $150 for each bronchoscopy, thereby reducing undue influence of offering large amounts of money for completing the trial. This advertisement appears to ignore the IRB's concern.

Corrective Action: OHRP acknowledges that the CUMC IRB has taken numerous corrective actions to address this and other findings.

OHRP finds that the corrective actions taken by CUMC adequately address the above findings and are consistent with the CUMC MPA. As a result, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact me if you have any questions regarding this matter.

Sincerely,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Owen K. Davis, IRB Chair
Dr. Ronald Crystal, PI
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. John Mather, VA
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Mr. Barry Bowman, OHRP