

**RESPONSES TO APPENDIX M-I-C-1  
HUMAN GENE TRANSFER PROTOCOLS**

**RECOMBINANT DNA ADVISORY COMMITTEE MEETING  
December 2001**

ID #	Letter	Protocol #	Response
255	08/15/2001	<b>9908-337</b>	<b>Transduction of CD34+ Cells from the Umbilical Cord Blood of Infants or the Bone Marrow of Children with Adenosine Deaminase (ADA)-Deficient Severe Combined Immunodeficiency (SCID)</b>
		<i>Response to M-I-C1:</i>	<p>This protocol was discussed at the March 2000 RAC meeting. This amendment was made prior to the October 2000 changes to the NIH Guidelines (material required after RAC review at a meeting). Received a copy of the latest version of the clinical protocol and informed consents for this study.</p> <p>The investigator indicated that they are ready to initiate this trial. Additions have been made to the section on risks regarding: stem cell factor, megakaryocyte growth and development factor, and the risk of increased intracranial pressure during ADA withdrawal. In addition, ophthalmologic examinations have been added to determine if there has been an increase in intracranial pressure prior to a tapering of the PEG-ADA dosage. An increase in intracranial pressure in two study participants with no other explanation other than PEG-ADA withdrawal is a new stopping criterion.</p>

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<b>0006-404</b>	<b>A Multicenter, Double-Blind, Placebo-Controlled, Phase II Study of Aerosolized AAVCF in Cystic Fibrosis Patients with Mild Lung Disease. Sponsor: Targeted Genetics</b>		
248	08/30/2001	<i>Response to M-I-C1:</i>	This submission from the sponsor (Targeted Genetics) contains a letter from the Cystic Fibrosis Foundation (CFF) (dated 8-27-01) which details their review of the bronchoscopy information from Cohort 1 subjects (all adults). Based on their review, the CFF Data Monitoring Committee recommends that the protocol may continue as currently written which includes proceeding with bronchoscopy at day 120 for "patients" in cohort 2.
246	10/01/2001	<i>Response to M-I-C1:</i>	<p>Protocol amendments for protocols 0006-404 and 0106-476 were submitted by the commercial sponsor, Targeted Genetic Corporation. This submission contains the following:</p> <p>a. A letter from the Cystic Fibrosis Foundation Data Monitoring Committee (dated August 27, 2001) stating that an interim analysis of subject safety data has been completed and that the study (protocol 404) may proceed as written.</p> <p>b. Changes to protocols 404 and 476. The changes specify that Hepatitis B vaccination is required in order to be entered into the study (due to the concern that the off-label use of alpha-1-antitrypsin, common among CF patients, may lead to infection with Hepatitis B, since this product is made from human plasma), define more clearly what is considered "hemoptysis", allow for the bronchoscopic procedures to be done on an inpatient basis (before was to be outpatient), allow for the use of PICC lines (percutaneous intravenous central catheters) and change the DSMB from the NHLBI (National Heart, Lung, and Blood Institute) to the CF Foundation.</p>
			The interim analysis by the CF Foundation was discussed at the September, 2001 RAC meeting.
<b>0101-441</b>	<b>A Phase I Trial of Intralesional rV-TRICOM Vaccine in the Treatment of Malignant Melanoma.</b>		
287	10/04/2001	<i>Response to M-I-C1:</i>	Received a copy of the final IBC, IRB approvals, IRB-approved informed consent, and clinical protocol.
<b>0101-452</b>	<b>A Multicenter, Randomized, Double-Blind, Placebo Controlled, Dose-Response Study to Evaluate the Efficacy and Safety of Ad5.1FGF-4 in Patients with Stable Angina. Sponsor: Berlex Laboratories.</b>		
264	10/11/2001	<i>Response to M-I-C1:</i>	Received a copy of the final IBC and IRB approvals and clinical protocol.

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278	10/29/2001	0102-458	<p><b>Pilot Phase II Study of Safety and Immunogenicity of a ALVAC-CEA/B7.1 Vaccine Administered with Chemotherapy, Alone or in Combination with Tetanus Toxoid or GM-CSF, as Compared to Chemotherapy Alone, in Patients with Metastatic Colorectal Adenocarcinoma. Sponsor: Aventis Pasteur Limited.</b></p> <p><i>Response to M-I-C1:</i> As outlined in Appendix M-I-C-1 of the NIH Guidelines (January 2001) received a copy of the final IBC and IRB approvals, final approved clinical protocol. Modifications to the clinical protocol include the following: 1) clarification of medications to be used for diarrhea, and the fact that it is considered as a toxicity; 2) deletion of cell-mediated immunity testing due to fact that little data will be generated from this test and the production of the test has been discontinued; and 3) changes in the informed consent concerning purpose, procedures, and risks.</p> <p>The initiation date for this study was September 27, 2001.</p>
247	10/01/2001	0106-476	<p><b>Evaluation of Anti-Inflammatory and Anti-Protease Pretreatment on the Delivery of Aerosolized tgAAVCF to Cystic Fibrosis Patients with Mild Lung Disease. Sponsor: Targeted Genetics Genetics.</b></p> <p><i>Response to M-I-C1:</i> Protocol amendments for protocols 0006-404 and 0106-476 were submitted by the commercial sponsor, Targeted Genetic Corporation. This submission contains the following:</p> <p>a. A letter from the Cystic Fibrosis Foundation Data Monitoring Committee (dated August 27, 2001) stating that an interim analysis of subject safety data has been completed and that the study (protocol 404) may proceed as written.</p> <p>b. Changes to protocols 404 and 476. The changes specify that Hepatitis B vaccination is required in order to be entered into the study (due to the concern that the off-label use of alpha-1-antitrypsin, common among CF patients, may lead to infection with Hepatitis B, since this product is made from human plasma), define more clearly what is considered "hemoptysis", allow for the bronchoscopic procedures to be done on an inpatient basis (before was to be outpatient), allow for the use of PICC lines (percutaneous intravenous central catheters) and change the DSMB from the NHLBI (National Heart, Lung, and Blood Institute) to the CF Foundation.</p>
285	10/09/2001	0106-477	<p><b>Intra-Lesional rF-B7.1 Versus rF-TRICOM Vaccine in the Treatment of Metastatic Cancer.</b></p> <p><i>Response to M-I-C1:</i> Received a copy of the final IBC, IRB approvals, IRB-approved informed consent, and clinical protocol.</p>