has no connection with the clinical trial. The Patient Representative's telephone number is provided in the Informed Consent document.

II-C. Selection of Patients

" Estimate the number of patients to be involved in the proposed study. Describe recruitment procedures and patient eligibility requirements, paying particular attention to whether these procedures and requirements are fair and equitable."

Specifically:

These issues are described in detail in the Protocol on Page 29 in the sections on Rationale for Subject Selection and Recruitment Strategies.

1. *"How many patients do you plan to involve in the proposed study?"*
   We will enroll 5 patients.

2. *"How many eligible patients do you anticipate being able to identify each year?"*
   Given current inquiries and interest in this trial by patients, patient families and physicians generated about he conduct of this trial, it is likely that we will be able to enroll this planned number of patients (5) within 2-3 years.

3. *"What recruitment procedures do you plan to use?"*
   This is outlined in detail in the sections of the protocol indicated in the comments under the II-C introduction just above. To ensure effective local monitoring in the follow-up period, self-referring patients will not be accepted without a formal referral from a primary medical physician and confirmed diagnosis of X-linked CGD.

4. ***"What selection criteria do you plan to employ? What are the exclusion and inclusion criteria for the study?"***

Inclusion Criteria (Protocol Page 24)

1. Have a diagnosis of X-linked CGD (*i.e.*, a gp91-*phox* gene mutation/defect).
2. Have a minimum of 5.0 x10^6 CD34+ cells per kg body weight (collected and cryopreserved, prior to enrollment) available for transduction.
3. Weight greater or equal to 20 kg.
4. Unresponsive or incurable infection as defined by either/or:
   - Continued (stable or progressive) infection despite standard antimicrobial therapy
     - Stable and/or does not completely resolve despite a minimum of 2 months of treatment

     OR
     - Progressive as shown by increase in size or new sites of infection despite therapy for a minimum of two weeks.
   - Multidrug resistant organism as determined by tissue analysis
5. Not have a suitable sibling who is HLA-matched for stem cell or bone marrow donation.
6. Males aged 3-55 years.

7. Must use an approved method of contraception, such as barrier method (condom with spermicide).

Exclusion Criteria (Protocol Page 24)

1. Weigh less than 20 kg.
2. Be hemodynamically unstable, or requiring pressor support.
3. Require ventilatory assistance with high levels of oxygen.
4. Have an HLA-matched suitable sibling for stem cell or bone marrow donation.
5. Intolerance to busulfan.
6. Failure to use approved method of contraception, such as barrier method (such as a condom with spermicide).
7. Participation in another Gene Therapy clinical trial
8. If pre-conditioning and pre-infusion evaluations are found to match a criterion for Grade 4 toxicity as defined in the Appendix A, Toxicity Table*

5. *"How will patients be selected if it is not possible to include all who desire to participate?"*
We believe that there will be more patient volunteers seeking enrollment in this protocol who satisfy inclusion criteria than we can practically accommodate given our current resources. Therefore we have developed an algorithm for that will take precedence for enrollment given the goals and likely benefits from this therapy. This selection algorithm is indicated in the discussion in the Protocol in the last paragraph on Page 30 extending to the top of Page 31.

III. Informed Consent

"In accordance with the Protection of Human Subjects (45 CFR Part 46), investigators should indicate how subjects will be informed about the proposed study and the manner in which their consent will be solicited. They should indicate how the Informed Consent document makes clear the special requirements of gene transfer research. If a proposal involves children, special attention should be paid to the Protection of Human Subjects (45 CFR Part 46), Subpart D, Additional Protections for Children Involved as Subjects in Research."

A specific section of the Protocol entitled "Human Subject Protections" beginning at Page 29 addresses these issues and relates to the answers to the specific question below, including how consent or assent will be obtained from adults or children. The patient Informed Consent document and Minor Assent document include detailed discussion of the specific requirements of gene therapy research.

III-A. Communication about the Study to Potential Participants

1. *"Which members of the research group and/or institution will be responsible for contacting potential participants and for describing the study to them? What procedures will be used to avoid possible conflicts of interest if the investigator is also providing medical care to potential subjects?"*
All patients who are enrolled in clinical research protocols at NIH are expected to have a personal physician who is not on the Clinical Center staff. That physician will be provided with a copy of the Protocol and patient Informed Consent document and the patient is encouraged to consult with that

physician before enrolling in the protocol. The patient's personal physician, will be kept informed regarding medical care decisions about his/her patient and be encouraged to participate in such medical care decisions. Members of the NIH research team will be available to answer any questions that arise. Where the patient is an inpatient at NIH, and is being treated for an infection, and is also enrolled in the protocol, it is possible that the Principal Investigator may be involved in decisions relating to both the conduct of this research Protocol and with medical care decisions. In situations where a conflict of interest might be perceived, another physician on the clinical staff of the NIH Clinical Center who is not involved with the conduct of this Protocol will participate in the medical care decision, and this will be documented in the medical record of the patient.

2. *"How will the major points covered in Appendix M-II, Description of the Protocol, be disclosed to prospective participants and/or their parents or guardians in language that is understandable to them?"*
One of the main tasks of the NIAID IRB review of protocols is to ensure that the patient Informed Consent document and the Minor Assent document are written in easily understood lay language (or age appropriate language for the Assent) that is comprehensive in providing details about the protocol. The actual procedures for providing this informed consent is provided in detail in the Protocol on Page 29-30. All children will have the assent form read aloud to them and the study explained to them at an age-appropriate level by Dr. Kang and Dr. Malech. Minors who are able to do so will be invited to sign or mark the assent form. No child will be enrolled who does not understand and agree to participate.

3. *"What is the length of time that potential participants will have to make a decision about their participation in the study?"*
As outlined on Page 29-30 of the Protocol the patient will be asked to consider the Protocol for at least 24 hours before enrollment, but a potential participant also may take as long as necessary to consult with family, physician or other persons before making a decision about their participation.

4. *"If the study involves pediatric or mentally handicapped subjects, how will the assent of each person be obtained?"*
This is discussed in detail on Page 29-30 of the protocol. In brief, children will both read and have read to them aloud the Minor Assent. Children will be provided with a their own copies of both the Minor Assent and the Standard Consent. To the extent that they can and want to read the Standard Consent, they will be encouraged to do so. Furthermore, the Investigator will verbally discuss in detail in age appropriate language each item in the Standard Consent with the minor patient. Pediatric aged patients must be at least 3 years of age and must be alert, oriented, not mentally impaired, capable of asking questions about the Protocol, and capable of providing age appropriate Assent at the time of enrollment. The child will be present and may ask questions during the process of providing informed consent to the patient's parent or guardian. Minors who are able to do so will be invited to sign or mark the assent form. No child will be enrolled who does not understand and agree to participate.

III-B. Informed Consent Document

Submission of a human gene transfer experiment to NIH OBA must include a copy of the proposed informed consent document. A separate Informed Consent document should be used for the gene transfer portion of a research project when gene transfer is used as an adjunct in the study of another technique, e.g., when a gene is used as a "marker" or to enhance the power of immunotherapy for cancer. Because of the relative novelty of the procedures that are used, the potentially irreversible consequences of the procedures performed, and the fact that many of the potential risks remain undefined, the Informed Consent document should include the following specific information in addition to any requirements of the

DHHS regulations for the Protection of Human Subjects (45 CFR 46). Indicate if each of the specified items appears in the Informed Consent document or, if not included in the Informed Consent document, how those items will be presented to potential subjects. Include an explanation if any of the following items are omitted from the consent process or the Informed Consent document

III-B-1. General Requirements of Human Subjects Research

III-B-1-a. Description/Purpose of the Study *The subjects should be provided with a detailed explanation in non-technical language of the purpose of the study and the procedures associated with the conduct of the proposed study, including a description of the gene transfer component.*

Standard Informed Consent document: pages 2 to . 16

III-B-1-b. Alternatives *The Informed Consent document should indicate the availability of therapies and the possibility of other investigational interventions and approaches.*

Standard Informed Consent document: page 16.

III-B-1-c. Voluntary Participation *The subjects should be informed that participation in the study is voluntary and that failure to participate in the study or withdrawal of consent will not result in any penalty or loss of benefits to which the subjects are otherwise entitled.*

Standard Informed Consent document: page 1 (Introduction) and page 16 (Study Withdrawal).

III-B-1-d. Benefits *The subjects should be provided with an accurate description of the possible benefits, if any, of participating in the proposed study. For studies that are not reasonably expected to provide a therapeutic benefit to subjects, the Informed Consent document should clearly state that no direct clinical benefit to subjects is expected to occur as a result of participation in the study, although knowledge may be gained that may benefit others.*

Standard Informed Consent document: page 7-8.

III-B-1-e. Possible Risks, Discomforts, and Side Effects *There should be clear itemization in the Informed Consent document of types of adverse experiences, their relative severity, and their expected frequencies. For consistency, the following definitions are suggested: side effects that are listed as mild should be ones which do not require a therapeutic intervention; moderate side effects require an intervention; and severe side effects are potentially fatal or life-threatening, disabling, or require prolonged hospitalization. If verbal descriptors (e.g., "rare," "uncommon," or "frequent") are used to express quantitative information regarding risk, these terms should be explained.*

Standard Informed Consent document: from page 8 through page 16.

The Informed Consent document should indicate any possible adverse medical consequences that may occur if the subjects withdraw from the study once the study has started.

Patients will receive only a single infusion gene transfer study design. Withdrawal from the study only affects the conduct of safety evaluations, which are important to assure that no adverse effects have occurred. This is outlined on page11 of the consent document. Additionally, in the event the patient withdraws from the study, the consent emphasizes the continuation of the scheduled cell infusion once a patient receives busulfan in order to decrease potential for developing or worsening of infection.

III-B-1-f. Costs *The subjects should be provided with specific information about any financial costs associated with their participation in the protocol and in the long-term follow-up to the protocol that is not covered by the investigators or the institution involved. Subjects should be provided an explanation about the extent to which they will be responsible for any costs for medical treatment required as a result of research-related injury.*

It is current policy at the National Institutes of Health that all medical care and procedures performed on the inpatient service or in the outpatient clinics at NIH in the course of patient participation in a clinical research protocol at the NIH Clinical Center are at no cost to the patient. Furthermore, it has been our customary practice for NIAID protocols that patients who do not live local to the NIH Clinical Center and are outpatients participating in this program will be provided with reimbursement for travel (except for the first evaluation visit) and be provided with lodging at no cost during the time when it is required that they remain local to NIH for clinical research protocol procedures or follow-up. Patient participants will be told the above information verbally, but this information will not be included in the written Informed Consent document. Included in the written Standard Informed Consent document on page 16 (item #2.) is the NIH and US Government policy on regarding research-related injuries. Additionally, no financial payment will be provided for study participants, as outlined on page 8 of the Standard Informed Consent document.

III-B-2. Specific Requirements of Gene Transfer Research

III-B-2-a. Reproductive Considerations *To avoid the possibility that any of the reagents employed in the gene transfer research could cause harm to a fetus/child, subjects should be given information concerning possible risks and the need for contraception by males and females during the active phase of the study. The period of time for the use of contraception should be specified.*

The ex vivo transduction and single re-infusion trial design pose no known risk to reproduction in any case.

Standard Informed Consent document: page 5. Use of barrier or other effective form of birth control is required in order to address the potential for teratogenicity related effects from receiving busulfan as a conditioning agent. X-linked CGD primarily affects males, thus, females are excluded from this study.

III-B-2-b. Long Term Follow-Up *To permit evaluation of long-term safety and efficacy of gene transfer, the prospective subjects should be informed that they are expected to cooperate in long-term follow-up that extends beyond the active phase of the study.*

Standard Informed Consent document: page 7.

III-B-2-c. Request for Autopsy *To obtain vital information about the safety and efficacy of gene transfer, subjects should be informed that at the time of death, no matter what the cause, permission for an autopsy will be requested of their families. Subjects should be asked to advise their families of the request and of its scientific and medical importance.*

Standard Informed Consent document: page 7.

III-B-2-d. Interest of the Media and Others in the Research *To alert subjects that others may have an interest in the innovative character of the protocol and in the status of the treated subjects, the subjects should be informed of the following: (i) that the institution and investigators will make efforts to provide protection*

from the media in an effort to protect the participants' privacy, and (ii) that representatives of applicable Federal agencies (e.g., the National Institutes of Health and the Food and Drug Administration), representatives of collaborating institutions, vector suppliers, etc., will have access to the subjects' medical records.

Standard Informed Consent document page 11,under Stored Samples and Future Research and also on the next page, 12, under Release of Medical Records.

IV. Privacy and Confidentiality *Indicate what measures will be taken to protect the privacy of patients and their families as well as to maintain the confidentiality of research data.*

Standard Informed Consent document: page 16, item #1.

IV-A. *"What provisions will be made to honor the wishes of patients as to whether, when, or how identity is disclosed."*

Standard Informed Consent document: page 11,under Labeling of Stored Samples. Also please refer to page 16, item #1.

IV-B. *"What provisions will be made to maintain the confidentiality of research data, at least in cases where data could be linked to individual patients."*
No identifiers such as names, initials, dates of birth, address, or city of domicile or other specific information that could strongly or even weakly link data results to individual patients will be used to indicate patients in any public disclosure of research results. Patients will be assigned a code number identifier, and all samples will be labeled with only the code number, not by name or initials. In order to protect subject confidentiality the research data generated in this study will be stored in a locked drawer or password-protected database, accessible only to study investigators. Research data that contains identifiers will be maintained under lock and will be available only to members of the research team or those involved in providing clinical care to a patient

V. Special Issues

V-A. " *What steps will be taken, consistent with Appendix M-IV, Privacy and Confidentiality, to ensure that accurate and appropriate information is made available to the public with respect to such public concerns as may arise from the proposed study?* "
Current practice of the NIH Clinical Center is to provide summaries of all approved protocols and the complete Informed Consent document on the Web page for public access. In addition, any adverse events associated with the protocol or any issues which raise public health concerns will be communicated as soon as possible to the FDA, DSMB, IBC, the NIAID IRB and the NIH Biosafety Office. Information and data from this study will be published in peer-reviewed journals. In addition, findings will be made known to the medical gene transfer community by means of written and oral presentations at public national and international meetings. In all presentations dealing with this work, the identity of participating subjects will remain confidential, using code numbers rather than initials or names. No subject will be identified by name, and no information will be made public from which the specific identities of individuals could be inferred.

V-B. *"Do you or your funding sources intend to protect under patent or trade secret laws either products or procedures developed in the proposed study? If so, what steps will be taken to permit full communications as possible among investigators and clinicians concerning research methods and results?"*

It is the intent of NIH that all novel research results from all studies performed at NIH laboratories and clinics are to be published in as timely fashion as possible. There is no intention to protect any product or procedure of this study by means of patents or trade secret laws. It is the intent of the investigators to present as soon as appropriate the scientific findings resulting from this protocol at public forums and meetings and to submit written manuscripts describing the results of these studies for peer review and publication in the scientific literature.

VI. Footnotes of Appendix M

VI-A. *Human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected, are exempt from Appendix M-I, Submission Requirements, and Appendix M-I-C, Reporting Requirements-Human Gene Transfer Experiment.*

Not applicable.

Dave, U. P., N. A. Jenkins, et al. (2004). "Gene Therapy Insertional Mutagenesis Insights." Science 303(5656): 333-.

Hacein-Bey-Abina, S., F. Le Deist, et al. (2002). "Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy." N Engl J Med 346(16): 1185-93.

Hacein-Bey-Abina, S., C. von Kalle, et al. (2003). "A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency." N Engl J Med 348(3): 255-6.

Hacein-Bey-Abina, S., C. Von Kalle, et al. (2003). "LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1." Science 302(5644): 415-9.

Malech, H. L., M. E. Horwitz, et al. (1998). "Extended production of oxidase normal neutrophils in X-linked chronic granulomatous disease (CGD) following gene therapy with gp^{91phox} transduced CD34+ cells." Blood 92(10 (Suppl)): 690a.

Ott, M. G., M. Schmidt, et al. (2006). "Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of MDS1-EVI1, PRDM16 or SETBP1." Nat Med 12(4): 401-9.

MFGS-gp91 sequence ATG 2278

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AGAACTCTGT AGCACCGCCT ACATACCTCG CTCTGCTAAT CCTGTTACCA 6900
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GTCCGGCGTA GAGCGCCACA GGACGGGTGT GGTCGCCATG ATCGCGTAGT 9450
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CGATATCCCG CAAGAGGCCC GGCAGTACCG GCATAACCAA GCCTATGCCT 9650
ACAGCATCCA GGGTGACGGT GCCGAGGATG ACGATGAGCG CATTGTTAGA 9700
TTTCATACAC GGTGCCTGAC TGCGTTAGCA ATTTAACTGT GATAAACTAC 9750
CGCATTA 9757

慢性肉芽腫症に対する遺伝子治療の実績一覧

2007年12月現在

症例	年齢	病　型	実施者 国	実施時期	導入 細胞	ベクター	前処置	効　果	経　　過	備考
1	26	gp91欠 (X連鎖)	Ott ドイツ	2004.Jan	PBSC	SF71gp91phox	BU (8mg)	あり	死(2006, Apr.10, day820) 敗血症、モノソミー7	
2	25	gp91欠 (X連鎖)	Ott ドイツ	2003	PBSC	SF71gp91phox	BU (8mg)	あり	MDS、モノソミー7	
3	5	gp91欠 (X連鎖)	Seger スイス	2003	PBSC	SF71gp91phox	BU (8mg)	あり	生	
4	12	gp91欠 (X連鎖)	Thrasher イギリス	2001.11.09	PBSC	MFGS-gp91phox	Mel (140mg)	あり	生、gene marked cells <1%	
5	27	gp91欠 (X連鎖)	Thrasher イギリス	2005.11.12	BMSC	SF71gp91phox	Mel (140mg)	なし	生、gene marked cells <1%	
6	6	gp91欠 (X連鎖)	Thrasher イギリス	2006.04.28	PBSC	SF71gp91phox	Mel (140mg)	なし	生、gene marked cells <1%	
7	9	gp91欠 (X連鎖)	Thrasher イギリス	2007.08.03	PBSC	SF71gp91phox	Mel (140mg)	あり	生、gene marked cells <1%	
8-12	37F 21M 18F 27M 27F	p47欠	Malech 米国NIH	1995～	PBSC	MFGS-p47phox	なし	Oxidase陽性率 0.004-0.051% (平均0.019%)	生	＊1
13	20	gp91欠 (X連鎖)	Malech 米国NIH	1998-2000	PBSC	MFGS-gp91phox	なし	0.13%	生	
14-17	未発表	gp91欠 (X連鎖)	Malech 米国NIH	1998-2000	PBSC	MFGS-gp91phox	なし	数週間あり	生	＊2
18	28	gp91欠 (X連鎖)	Malech 米国NIH	2006～	PBSC	MFGS-gp91phox	BU (10mg)	あり	生、gene marked cells <1%	(13と同一患者)
19	31	gp91欠 (X連鎖)	Malech 米国NIH	2006～	PBSC	MFGS-gp91phox	BU (10mg)	あり	死、感染症 (day?で死亡)	
20	37	gp91欠 (X連鎖)	Malech 米国NIH	2008年1-2月 に実施予定	PBSC	MFGS-gp91phox	BU (10mg)			

PBSC：G-CSF mobilized peripheral blood CD34+ stem cells, BMSC: Bone marrow CD34+ stem cells

SF71gp91phox developed by Dr. Grez (Germany), MFGS-based vectors developed by Dr. Malech

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資料 4

研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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