

UCDHSC BIOSAFETY APPLICATION FOR HUMAN SOMATIC CELL/GENE TRANSFER CLINICAL TRIAL

This space is for Institutional Biosafety Committee Use ONLY

IBC Authorization Number _____

Forms Received by IBC/Biosafety Officer Date: _____

Reviewer 1 _____ Date: _____

Reviewer 2 _____ Date: _____

Full Committee Review Date: _____

Approved Deferred Disapproved

COMIRB # _____ Review Panel & Date _____

Please return the completed form and the required supporting documentation to: **Biosafety Officer, HSD, Mailstop F484**. Attach a cover letter, three (3) copies of the sponsor's clinical trial protocol and any amendments; the Clinical Investigators Brochure; the Informed Consent; the scientific abstract and non-technical abstract; the PI's Biosketch and the Biosketch for any co-investigators. Attach copy of sponsor's Standard Operating Procedures as appropriate.

Section I. Administrative Information

PRINCIPAL INVESTIGATOR: _____

DEPARTMENT/DIVISION: _____

PHONE NO: _____

Mailstop _____

CO-INVESTIGATORS: _____

OTHER PERSONNEL (List those involved in THIS clinical trial):

PROJECT TITLE: _____

COMIRB Number: _____

COMIRB Panel (if known) _____

FDA IND Number _____

SPONSOR/GRANT AGENCY [REDACTED]

PERIOD OF REQUEST: From: _____ To: _____

SITE(S) WHERE RESEARCH WILL BE DONE:

Building (s): [REDACTED]

Room No. (s) [REDACTED]

Other Committee Reviews, if applicable: [REDACTED]

I acknowledge all the requirements and restrictions of the most current NIH Guidelines for the Human Gene Transfer Clinical trial to be conducted. I accept responsibility for the safe conduct of the clinical trial to be conducted at UCDHSC.

I understand that it is my responsibility to assure that all personnel working on this clinical trial are informed of and trained about any of the potential hazards of the recombinant DNA or gene transfer material, the proper actions for safe use, the appropriate steps to take in case of accidents, spills or exposures and that they are provided with all necessary safety equipment/personal protective equipment and are instructed in its use.

_____ Date

_____ Signature of Principal Investigator

PLEASE FILL OUT THE REST OF THIS FORM BY ANSWERING ALL SECTIONS APPLICABLE TO THE PROJECT. Please check all that apply, and attach separate comments page(s) if necessary. The responses MUST be specific for clinical trials at UCDHSC facilities. You may request assistance from the study sponsor for the appropriate responses to these questions.

Section II. Which of the following categories does this study involve?

A. Categories of Human Gene Transfer Experiments that Require RAC Review and local IBC Review (including, but not limited to):

Many somatic cell gene transfer or therapy experiments are covered under the [NIH Guidelines, Appendix M](#). If the answer to any of the following questions is yes, then the experiments are subject to review by the Recombinant Advisory Committee at NIH and local review by the [Institutional Biosafety Committee \(IBC\)](#) and COMIRB.

1. New vectors/new gene delivery systems Yes No
2. New disease application for gene transfer vector/system Yes No
3. Unique applications of gene transfer Yes No
4. Other issues considered to require further public discussion. Yes No

B. Categories of Human Gene Transfer Experiments which require local IBC review and which may be Exempt from RAC Review (per 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, and when such an immune response has been demonstrated in model systems, and when the persistence of the vector-encoded immunogen is not expected, are exempt from the requirements for submission of the protocol to NIH OBA, RAC review, and subsequent reporting.

However, vaccine trials, like other human gene transfer trials subject to the NIH Guidelines, must be reviewed and approved by the [Institutional Biosafety Committee \(IBC\)](#) before research participants can be enrolled.

1. Vaccines (e.g. DNA Vaccines) Yes No
2. New phase (II or III) of gene transfer clinical trial of vector constructs previously approved by the RAC. Yes No
3. Lethally Irradiated Tumor Cells/No Replication-Competent Virus. This category includes experiments involving lethally irradiated tumor cells and vector constructs that have previously been approved by the RAC (or with the incorporation of minor modifications). Yes No
4. New Site/Original Investigator. This category includes the following: (1) initiation of a protocol at an additional site other than the site that was originally approved by the RAC, and (2) the investigator at the new site is the same as the investigator approved for the original study. Yes No

5. New Site/New Investigator. This category includes the following: (1) initiation of a protocol at an additional site other than the site that was originally approved by the RAC, and (2) the investigator at the new site is different than the investigator approved for the original site. Yes No

6. Gene Marking Protocols. This category includes human gene marking experiments involving vector constructs that have previously been approved by the RAC and: (1) minor modifications to the vector constructs, or (2) a different tumor cell target. Yes No

Section III. Description of the Proposal

A. State the Objectives and Rationale of the Proposed Research, using recombinant DNA for this experimental protocol answering the following questions: Why is the disease selected for experimental treatment by means of gene transfer a good candidate for such treatment? What objective and/or quantitative measures of disease activity are available? In your view, are the usual effects of the disease predictable enough to allow for meaningful assessment of the results of gene transfer?

[Redacted]

B. Is the protocol designed to prevent all manifestations of the disease, to halt the progression of the disease after symptoms have begun to appear, or to reverse manifestations of the disease in seriously ill victims?

[Redacted]

C. What alternative therapies exist? In what groups of subjects are these therapies effective? What are their relative advantages and disadvantages as compared with the proposed gene transfer?

[Redacted]

D. Into what cells will the recombinant DNA be transferred? Why is the transfer of recombinant DNA necessary for the proposed research? What questions can be answered by using recombinant DNA? What alternative methodologies exist? What are their relative advantages and disadvantages as compared to the use of recombinant DNA?

[Redacted]

E. Nature of the rDNA Material(s) to be used.

Provide a full description of the methods and reagents to be employed for gene delivery and the rationale for their use. The following are specific points to be addressed:

1. What is the structure of the cloned DNA that will be used?

[Redacted]

2. Describe the gene (genomic or cDNA), the bacterial plasmid or phage vector, and the delivery vector (if any). Provide complete nucleotide sequence analysis or a detailed restriction enzyme map of the total construct.

3. What regulatory elements does the construct contain (e.g., promoters, enhancers, polyadenylation sites, replication origins, etc.)? From what source are these elements derived? Summarize what is currently known about the regulatory character of each element.

4. Describe the steps used to derive the DNA construct.

5. What is the structure of the material that will be administered to the research participant?

6. Describe the preparation, structure, and composition of the materials that will be given to the human research subject or used to treat the subject's cells.

7. Describe any other material to be used in preparation of the material to be administered to the human research subject. For example, if a viral vector is proposed, what is the nature of the helper virus or cell line? If carrier particles are to be used, what is the nature of these?

F. Preclinical Studies, Including Risk-Assessment Studies

Provide results that demonstrate the safety, efficacy, and feasibility of the proposed procedures using animal and/or cell culture model systems, and explain why the model(s) chosen is/are most appropriate.

G. Delivery System:

1. What cells are the intended target cells of recombinant DNA?

2. IF target cells are to be treated ex vivo and returned to the human subject, how will the cells be characterized before and after treatment? Where will the cells be retrieved (building, room number, facility)? Where will the cells be cultured, characterized and treated?

3. What is the theoretical and practical basis for assuming that only the target cells will incorporate the DNA?

4. Is the delivery system efficient? What percentage of the target cells contain the added DNA?

5. How is the structure of the added DNA sequences monitored and what is the sensitivity of the analysis? Is the added DNA extrachromosomal or integrated? Is the added DNA unrearranged?

6. How many copies are present per cell? How stable is the added DNA both in terms of its continued presence and its structural stability?

H. Gene Transfer and Expression

1. What animal and cultured cell models were used in laboratory studies to assess the in vivo and in vitro efficacy of the gene transfer system? In what ways are these models similar to and different from the proposed human treatment?

2. What is the minimal level of gene transfer and/or expression that is estimated to be necessary for the gene transfer protocol to be successful in humans? How was this level determined?

3. Explain in detail all results from animal and cultured cell model experiments which assess the effectiveness of the delivery system in achieving the minimally required level of gene transfer and expression.

4. To what extent is expression only from the desired gene (and not from the surrounding DNA)? To what extent does the insertion modify the expression of other genes?

5. In what percentage of cells does expression from the added DNA occur? Is the product biologically active? What percentage of normal activity results from the inserted gene?

6. Is the gene expressed in cells other than the target cells? If so, to what extent?

I. Retrovirus Delivery Systems

If your gene transfer product uses a retroviral delivery system, you must complete the following section. If not, please indicate Not Applicable

1. What cell types have been infected with the retroviral vector preparation? Which cells, if any, produce infectious particles?

2. How stable are the retroviral vector and the resulting provirus against loss, rearrangement, recombination, or mutation?

3. What information is available on how much rearrangement or recombination with endogenous or other viral sequences is likely to occur in the human subject's cells?
[REDACTED]
4. What steps have been taken in designing the vector to minimize instability or variation?
[REDACTED]
5. What laboratory studies have been performed to check for stability, and what is the sensitivity of the analyses?
[REDACTED]
6. What laboratory evidence is available concerning potential harmful effects of the transfer (e.g., development of neoplasia, harmful mutations, regeneration of infectious particles, or immune responses)?
[REDACTED]
7. What steps will be taken in designing the vector to minimize pathogenicity? What laboratory studies have been performed to check for pathogenicity, and what is the sensitivity of the analyses?
[REDACTED]
8. Is there evidence from animal studies that vector DNA has entered untreated cells, particularly germ-line cells? What is the sensitivity of these analyses?
[REDACTED]
9. Has a protocol similar to the one proposed for a clinical trial been conducted in non-human primates and/or other animals? What were the results? Specifically, is there any evidence that the retroviral vector has recombined with any endogenous or other viral sequences in the animals?
[REDACTED]

J. Non-Retrovirus Delivery/Expression Systems

If your gene transfer product uses a non-retroviral delivery system, you must complete the following section. If not, please indicate Not Applicable.

1. What animal studies have been conducted to determine if there are pathological or other undesirable consequences of the protocol (including insertion of DNA into cells other than those treated, particularly germ-line cells)?
[REDACTED]
2. How long have the animals been studied after treatment?
[REDACTED]
3. What safety studies have been conducted? (Include data about the level of sensitivity of such assays.)
[REDACTED]

Section IV. Clinical Procedures, Including Research Participant Monitoring

Describe the experimental treatment that will be administered to the human subjects and the diagnostic methods that will be used to monitor the success or failure of the experimental treatment, addressing the following questions. If previous clinical studies using similar methods have been performed by yourself or others, indicate their relevance to the proposed study.

1. Will cells (e.g., bone marrow cells) be removed from human subjects and treated *ex vivo*? If so, describe the type, number, and intervals at which these cells will be removed.

██████████

2. Will human subjects be treated to eliminate or reduce the number of cells containing malfunctioning genes (e.g., through radiation or chemotherapy)?

██████████

3. What treated cells (or vector/DNA combination) will be given to human subjects?

██████████

4. How will the treated cells be administered? What volume of cells will be used? Will there be single or multiple experimental treatments? If so, over what period of time?

██████████

5. How will it be determined that new gene sequences have been inserted into the subject's cells and if these sequences are being expressed? Are these cells limited to the intended target cell populations? How sensitive are these analyses?

██████████

6. What studies will be conducted to assess the presence and effects of any contaminants?

██████████

7. What are the clinical endpoints of the study? Are there objectives and quantitative measurements to assess the natural history of the disease? Will such measurements be used in human subject follow-up?

██████████

8. How will subjects be monitored to assess specific effects of the treatment on the disease? What is the sensitivity of the analyses?

██████████

9. How frequently will follow-up studies be conducted? How long will follow-up continue? Is this addressed in the Informed Consent document?

██████████

10. What are the major beneficial and adverse effects of the experimental treatment that you anticipate? What measures will be taken in an attempt to control or reverse these adverse effects if they occur? Compare the probability and magnitude of deleterious consequences from the disease if recombinant DNA transfer is not used.

██████████

If a treated human subject dies, what special post-mortem studies will be performed? Is this addressed in the Informed Consent document?

██████████

Section V. Public Health Considerations

The IBC is specifically charged with review of the environmental and public health considerations for the use of gene transfer.

You must specifically address and explain, whether or not there is a significant possibility that the added DNA or vector will be shed or otherwise spread:

1. Is there a risk of transmission (horizontal transmission) of the viral vector, from the patient to other persons (health care workers, intimate contacts, etc)
[REDACTED]
2. Is there a risk of vertical transmission to offspring? Will birth control measures be recommended to subjects?
[REDACTED]
3. Is there a risk of vertical transmission to offspring of health care personnel?
[REDACTED]
4. What precautions will be taken against such spread (e.g., patients sharing a room, health-care workers, or family members)?
[REDACTED]
5. Is there a significant possibility that the DNA and/or vector could contaminate the clinical facility, ie, the environment, in which treatment will be administered or where patients will be domiciled after treatment?
[REDACTED]
6. What measures will be undertaken to mitigate the risks, if any, to public health?
[REDACTED]

Section V. Personnel

1. In addition to the PI, what professional personnel (medical and nonmedical) will be involved in the proposed study and what is their relevant expertise?
[REDACTED]

2. What training, specific to this protocol, is to be conducted by the PI and/or the sponsor for these medical personnel?
[REDACTED]

Section VI. Adequacy of Laboratory and Clinical Facilities

Describe the laboratory, pharmacy and clinical facilities where the proposed study will be performed. Specifically:

1. At what hospital(s) or clinic(s) will the treatment be given?
[REDACTED]

2. Will the study be conducted as an inpatient or outpatient procedure or a combination?
[REDACTED]

3. Which facilities of the hospital or clinic will be especially important for the proposed study?
[REDACTED]

4. Will patients occupy regular hospital beds or clinical research center beds?
[REDACTED]

5. Where will patients reside during the follow-up period?
[REDACTED]

6. What protocols will be followed for scheduling patients to outpatient clinics and to assure terminal cleaning of any room used in the study?
[REDACTED]

7. Where will study drugs be prepared and by whom?
[REDACTED]

8. List any biological safety cabinet to be used in the preparation of the study drug, with location, serial number and the date of its most recent certification.
[REDACTED]

9. What specific protocols are to be followed for the receipt, storage, preparation and disposal of study drug?
[REDACTED]

Section VII. Safety Reporting Functions

Explain the how safety reporting for all adverse events, serious adverse events, and any finding from tests in laboratory animals that suggests a significant risk for human research participants (including reports of mutagenicity, teratogenicity, or carcinogenicity) will be handled for this clinical trial. Who will be responsible for the notification to NIH and the FDA, COMIRB and the IBC?

██████████

Section VIII. Informed Consent

A. General Requirements of the Informed Consent

Investigators submitting human gene transfer proposals must include the Informed Consent document as submitted to the COMIRB and specific to UCDHSC clinical trial site(s).

Information must be disclosed to potential participants and/or their parents or guardians in language that is understandable to them.

Investigators must address, and the Informed Consent document must adequately describe:

- a) The recombinant DNA/genetic material component of the proposed study;
- b) Include specific statements regarding the release of information to other parties;
- c) Include a specific statement regarding requests for autopsy;
- d) Include information regarding 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. The Informed Consent document should include a list of persons who can be contacted in the event that questions arise during the follow-up period. The investigator should request that subjects continue to provide a current address and telephone number.

The subjects should be informed that any significant findings resulting from the study will be made known in a timely manner to them and/or their parent or guardian including new information about the experimental procedure, the harms and benefits experienced by other individuals involved in the study, and any long-term effects that have been observed.

B. Specific Requirements of Gene Transfer Research: 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, in the Informed Consent document, 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 inclusion of pregnant or lactating women should be addressed in the Informed Consent if they are not excluded from the parameters of the clinical trial.

C. Interest of the Media and Others in the Research, Privacy and Confidentiality Issues

The Informed Consent should include appropriate language 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.

The Informed Consent should 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.

The Informed Consent should include what provisions will be made to honor the wishes of individual patients (and the parents or guardians of pediatric or mentally handicapped patients) as to whether, when, or how the identity of patients is publicly disclosed.

The Informed Consent should include what provisions will be made to maintain the confidentiality of research data, at least in cases where data could be linked to individual patients.