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September 25, 2001

Boro Dropulic, Ph.D.
Chief Scientific Officer
VIRxSYS Corporation
200 Perry Parkway, Suite 1A
Gaithersburg, MD 20877
Phone: (301) 987-0480 Fax: (301) 987-0489

RE: Public RAC Discussion of Protocol #0107-488 entitled: *A Phase I, Open-Label Clinical Trial of the Safety and Tolerability of Single Escalating Doses of Autologous CD4 T-Cells Transduced With VRX486 in HIV-Positive Subjects*, Rob Roy MacGregor, M.D., University of Pennsylvania.

Dear Dr. Dropulic:

On behalf of the National Institutes of Health (NIH) and the NIH Recombinant DNA Advisory Committee (RAC), I want to thank you and your colleagues for participating in the September 6, 2001 meeting of the RAC. This letter conveys the major observations and recommendations made by the RAC during public discussion of your protocol.

During its preliminary review of your protocol, the RAC identified a number of issues that warranted public discussion. Prior to the RAC meeting, you received and had an opportunity to address comments of the RAC reviewers. Copies of the reviewers' written comments are enclosed for your records. A copy of the portion of the meeting transcript in which your protocol was discussed is also available upon request. The RAC appreciated your responsiveness to the reviewers' questions prior to and during the meeting and your willingness to make suggested changes to the protocol and the informed consent document.

During the RAC's public discussion of your protocol, the following additional observations and recommendations were made:

- With regard to pre-clinical studies:
 - Stricter testing for VSV-G (Vesicular stomatitis virus, strain G) prior to lot release has been proposed and should be implemented.
 - Further details about the focal lesions seen in several animals should be provided. Depending on the nature of these lesions, revisions to the clinical protocol and informed consent may be necessary.
 - Samples of all clinical lots of the vector should be archived.

- Comments made during the discussions regarding the use of 293 versus 293T cells and the use of a 2 plasmid versus a 4 plasmid production system should be considered, though no specific recommendations can be made.
- With regard to the clinical protocol:
 - Entry criteria about what constitutes a “HAART failure” should be clarified. The investigator should consider consulting with another HIV clinician to confirm that no other acceptable antiretroviral regimen is available as an alternative to study participation. Further details should be added as to which antiretroviral medications can be taken during the course of the study.
 - The proposed addition of T-cell repertoire testing by immunoscope technology should occur before administration of the vector product and at one point 4 to 12 weeks post-therapy. Responses to tetanus vaccine should be monitored, as outlined in the modified protocol.
 - The proposed 4 week follow-up period prior to advancing to the next subject was discussed extensively, with particular focus on whether 4 weeks would be long enough to confirm the presence of a new strain of lentivirus in the participant. The potential that new viral strains will develop and take longer than the proposed timeframe to appear was also discussed. These concerns should be discussed in both the protocol and the informed consent document and addressed in the sponsor’s response to these recommendations.
- With regard to the informed consent document:
 - It should be clearly stated that this is the first clinical use of a new vector class.
 - The concerns surrounding this vector class should be explained.
 - “HAART failure” should be defined more clearly. The antiretrovirals that may be taken during the study, as well as those that may not should be listed.
 - “The second paragraph of the “Purpose” section of the revised informed consent document should be made into a new section entitled “Possible Benefit”. It should replace the current “Benefits” section.
 - A copy of the final, IRB-approved informed consent document will be shared with the RAC following its submission.
- With regard to broader safety issues:
 - It is recommended that the definitions of which adverse events would lead to DSMB review should be better defined. For example, in order to establish what would constitute a significant decrease in CD4+ cell counts or increase in viral load, the participants’ normal variability in these counts should be established over a prolonged period of time (such as, 6 months or even one year prior to study enrollment).
 - Specific assays with which to monitor survival of transduced cells should be developed.
 - To reduce the possibility of generating a potentially more virulent HIV virus than would already be present in the test subjects, individuals with only CCR5-utilizing strains of HIV should be excluded from the study.
 - Specific tests to assess the genetic interaction between the vector and the resident HIV strain should be developed. Such tests could include assays for degenerate

gag/pol sequences; changes to mobilized vector and recombinant genomes; and the HIV viral genotype pre- and post-gene transfer.

The RAC voted to endorse these observations and recommendations by a vote of 9 in favor, 0 opposed, and 0 abstentions.

As you know, the current reporting requirements set forth at Appendix M-I-C-1 of the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* require the principal investigator to submit a written statement responding to each of the RAC's observations and recommendations and to provide additional documentation as specified to this office no later than 20 working days after enrollment of the first research participant. These reporting requirements are excerpted and enclosed for your convenience.

The Internet site < <http://www4.od.nih.gov/oba/> > of the NIH Office of Biotechnology Activities (OBA) includes a copy of the complete *NIH Guidelines*, minutes of RAC meetings, and information about gene transfer research protocols registered with our office. Contact information for our office is as follows:

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Thank you for your detailed responses to the questions from the RAC reviewers, which you provided to us at the meeting. Please let us know if you have any questions about the RAC's recommendations on your protocol or the requirements of the *NIH Guidelines*.

Sincerely,

Amy P. Patterson, M.D.
Director
Office of Biotechnology

Enclosures

cc (letter only):

Rob Roy MacGregor, M.D., University of Pennsylvania
Harriet Izenberg, IBC Contact, University of Pennsylvania
Joseph Sherwin, Ph.D., IRB Chair, University of Pennsylvania
Claudia Mickelson, Ph.D., Chair, NIH RAC
Philip D. Noguchi, M.D., Director, Division of Cellular and Gene Therapies, OTRR, CBER, FDA
Stephanie Simek, Ph.D., Division of Application and Review and Policy, OTRR, CBER, FDA
Greg Koski, M.D., Ph.D., Director, OHRP, DHHS
RAC Reviewers: Ms. King and Drs. Markert and Aguilar-Cordova
Ad Hoc Reviewers: Drs. Coffin, Yee, and Zaia

**Reporting Requirements
of the
NIH Guidelines for Research Involving Recombinant DNA Molecules
(Appendix M-I-C)**

Appendix M-I-C-1. Initiation of the Clinical Investigation

No later than 20 working days after enrollment (see definition of enrollment in Section I-E-7) of the first research participant on a human gene transfer experiment, the Principal Investigator(s) shall submit the following documentation to NIH OBA: (1) a copy of the informed consent document approved by the Institutional Review Board (IRB); (2) a copy of the protocol approved by the Institutional Biosafety Committee (IBC) and IRB; (3) a copy of the final IBC approval from the clinical trial site; (4) a copy of the final IRB approval; (5) a brief written report that includes the following information: (a) how the investigator(s) responded to each of the RAC's recommendations on the protocol (if applicable); and (b) any modifications to the protocol as required by FDA; (6) applicable NIH grant number(s); (7) the FDA Investigational New Drug Application (IND) number; and (8) the date of the initiation of the trial. The purpose of requesting the FDA IND number is for facilitating interagency collaboration in the Federal oversight of human gene transfer research.

Appendix M-I-C-2. Additional Clinical Trial Sites

No research participant shall be enrolled (see definition of enrollment in Section I-E-7) at a clinical trial site until the following documentation has been submitted to NIH OBA: (1) Institutional Biosafety Committee approval (from the clinical trial site); (2) Institutional Review Board approval; (3) Institutional Review Board-approved informed consent document; (4) curriculum vitae of the principal investigator(s) (no more than two pages in biographical sketch format); and (5) NIH grant number(s) if applicable.

Appendix M-I-C-3. Annual Reporting

Investigators shall comply with annual data reporting requirements. Annual data report forms will be forwarded by NIH OBA to investigators. Information submitted in these annual reports will be evaluated by NIH OBA and the RAC, and possibly considered at a future RAC meeting. Information obtained through the annual data reporting process will be included in the NIH Human Gene Transfer Information System to: (1) provide clinical trial information; (2) provide administrative details of protocol registration; (3) provide annual status reports of protocols; (4) facilitate risk assessment of individual applications of human gene transfer; and (5) enhance public awareness of relevant scientific, safety, social, and ethical issues.

Appendix M-I-C-4. Serious Adverse Event Reporting

Investigators who have received authorization from FDA to initiate a human gene transfer protocol must report any serious adverse event immediately to the local Institutional Review Board, Institutional Biosafety Committee, Office for Human Research Protections (if applicable), and NIH OBA, followed by the submission of a written report filed with each group. Reports submitted to NIH OBA shall be sent to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax).

