MIPR NO: 93MM3578

TITLE: VACCINE-INDUCED ENHANCEMENT OF EIAV REPLICATION AND DISEASE

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REPORT DATE: January 14, 1994

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Development Command, Fort Detrick Frederick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
The purpose of this funding was to initiate the expansion of ongoing research in which the equine infectious anemia virus (EIAV)/Shetland pony animal lentivirus system is being used as a model for human AIDS vaccines with respect to the elucidation of the mechanisms of vaccine enhancement, the evaluation of in vitro enhancement assays as correlates of in vivo enhancement, and the development of vaccination strategies that minimize the potential for deleterious immune responses. The current funding was specifically provided as a supplement to expand isolation facilities for housing EIAV-infected ponies, for the purchase of additional ponies to be used in vaccine trials, and for the production and biochemical characterization of recombinant protein vaccine, rgp90. All of these objectives have now been accomplished in anticipation of additional funding that will facilitate more detailed studies of vaccine-induced enhancement of EIAV replication and disease.
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In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 32 CFR 219 and Subparts B, C, and D.

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In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Principal Investigator's Signature Date
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A. Introduction

The United States Army is currently involved in the design and evaluation of potential AIDS vaccines based on the use of selected HIV-1 antigens produced in various recombinant expression systems. Among the most thoroughly studied candidate AIDS vaccine is a baculovirus-expressed HIV-1 envelope glycoprotein, designated gp160 (Koff et al. 1990). This gp160 vaccine is being considered for human trials in Thailand under the auspices of the US Army.

However, there remains significant controversy regarding the potential efficacy of the gp160 vaccine based on initial limited human trials and additional concerns have been raised about the potential for eliciting deleterious immune responses that could result in a greater susceptibility to HIV-1 infection or an enhancement of virus replication and disease (Burke 1992). Vaccine-induced enhancement of viral infections has been documented in several viral systems, including dengue virus, respiratory syncytial virus, and feline infectious peritonitis virus (Porterfield 1986). In many of these cases, the enhancement phenomenon can be correlated with the presence of antibodies that bind to virus and enhance infection of target cells, especially monocytes and macrophages. Since monocytic cells are a primary target in all natural lentivirus infections, including HIV-1 infection of humans, the potential for antibody dependent enhancement (ADE) of HIV-1 infection and disease in humans needs to be considered carefully.

Enhancing antibodies have been demonstrated in vitro in serum from HIV-1 infected individuals (Robinson et al. 1988, Homsy et al. 1989), SIV-infected macaques (Montefiori et al. 1990), visna virus-infected sheep (Jolly et al. 1989), and CAEV-infected goats (McGuire et al. 1986). The potential role of enhancing antibodies in the development of AIDS has also been suggested, although the in vivo relevance of ADE remains uncertain and controversial (Homsy et al. 1990). To date there has been no reliable in vivo model to examine the mechanisms of ADE of lentivirus infections or to evaluate the prognostic value of in vitro assays of ADE.

In previous studies using the equine infectious anemia virus (EIAV)/Shetland pony system as a model for evaluating AIDS vaccine strategies, we have demonstrated a range of efficacy from sterile protection against homologous virus challenge by inactivated whole virus vaccines and viral envelope subunit vaccines, to severe enhancement of EIAV replication and disease in ponies immunized with a baculovirus-expressed envelope glycoprotein vaccine designated rgp90 (Issel et al. 1992, Wang et al. 1994). These vaccine trial suggest that immune responses to EIAV vaccine can elicit either protection against or enhancement of EIAV replication and disease, thus providing a novel in vivo model for characterizing both host and viral determinants associated with vaccine-induced protection and enhancement of a lentivirus
infection.

The use of EIAV as a model for evaluating potential strategies for AIDS vaccine development is an ongoing program funded by the National Institutes of Health. However, the objectives of this NIH funding are to characterize the immune correlates of protection that evolve naturally during persistent EIAV infection of ponies and to evaluate vaccine strategies for eliciting protective immune responses. To expand the studies to examining the recently discovered enhancement phenomenon, funding was requested and provided by the US Army by means of a one time supplement to the current NIH grant via interagency transfer. The specific objectives of the supplemental funding were: (i) construct 14 isolation stalls for housing EIAV-infected ponies, (ii) to purchase 16 ponies dedicated to vaccine enhancement studies, and (iii) to produce and characterize baculovirus-expressed EIAV gp90 to be used as vaccine in proposed enhancement studies. These preparations were in anticipation of funding of a pending grant application to the US Army (932110044) to facilitate a detailed study of EIAV vaccine enhancement that would begin in January 1994.

B. Body

As of December 31, 1993 we have completed the construction of dedicated isolation stalls at the University of Kentucky for housing ponies to be used in the EIAV enhancement studies. In addition, we have purchased 16 Shetland ponies for use in future experiments and are in the process of preparing these animals for use in the near future. At the University of Pittsburgh we have completed the preparation and standard characterizations of a stock of baculovirus rgp90 to be used in the planned vaccine trials.

C. Conclusions

As a result of the supplemental funding received in 1993, we are now poised to initiate extensive EIAV vaccine enhancement studies as soon as the pending application with the US Army is finalized. We have recently evaluated the rgp90 vaccine stock in a 4 pony pilot immunization trial and demonstrated a vaccine-induced enhancement of EIAV replication and disease, as reported in earlier trials (Wang et al., 1994).

D. References


