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HUMAN IMMUNE RESPONSE TO HTLV-III VIRUS INFECTION IN ACQUIRED IMMUNODEFICIENCY SYNDROME

ANNUAL REPORT

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NOVEMBER 10, 1988

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-86-C-6279

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SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION: Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT: Approved for public release distribution unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION: University of Massachusetts Medical School; 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code): 55 Lake Avenue North, Worcester, MA 01655	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: US Army Medical Research & Development Command; 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: DAMD17-86-C-6279
8c. ADDRESS (City, State, and ZIP Code): Fort Detrick, Frederick, MD 21701-5012	10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
63105A	3M2-63105DH29	AD	019

11. TITLE (Include Security Classification)

(U) Human Immune Response to HIV-III Virus Infection in Acquired Immunodeficiency Syndrome

12. PERSONAL AUTHOR(S)

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13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Annual	FROM 10/87 TO 10/88	November 10, 1988	6

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
06	03		AIDS: HIV-1; Retrovirus, Lentivirus, Immunology
06	13		

RA 1

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The purpose of the research program is to define immune responses of humans to Human Immunodeficiency Virus (HIV) infection and the cause of the Acquired Immune Deficiency Syndrome (AIDS). Immunodeficiency caused by HIV infections may be due to immune mediated lysis (by antibody and/or HIV specific cytotoxic T lymphocytes [CTL]) of infected macrophages and T4 lymphocytes. The definitions of these immune responses to HIV virus are needed for rational approaches for therapy and prevention.

Since the project began in October, 1986, we have developed an integrated program of research projects to develop experimental systems required for defining the immune responses of humans to HIV.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL
Mary Frances Bostian	301-663-7325	SGRD-RMI-S

DD Form 1473, JUN 86 *Previous editions are obsolete* SECURITY CLASSIFICATION OF THIS PAGE

A. Summary

The purpose of the research program is to define immune responses of humans to Human Immunodeficiency Virus (HIV-1) infection and the cause of the Acquired Immune Deficiency Syndrome (AIDS). Immunodeficiency caused by HIV infections may be due to immune mediated lysis (by antibody and/or HIV specific cytotoxic T lymphocytes [CTL]) of infected macrophages and T4 lymphocytes. Enhanced infection of macrophages and other Fc receptor bearing cells by virus-antibody complexes may contribute to the pathogenesis of HIV-1 infections. The definitions of these immune response to HIV are needed for rationa. approaches for therapy and prevention.

Since the project began in October, 1986, we have developed an integrated program of research projects to develop experimental systems required for defining the immune responses of humans to HIV.

B. Foreword

a) Copyright material - NA

b) Limited distribution material - NA

c) Commercial organizations, etc - NA

d) Animal experimentation - NA

e) For the protection of human subjects the investigators have adhered to policies of applicable Law 45CFR46.

f) The investigators have abided by the NIH Guidelines for Research involving recombinant DNA Molecules (April 1982) and the Administrative Practices Supplement.

C. Body of Report

1. Antibody-enhanced infection by HIV-1 via Fc Receptor-Mediated Entry.

a) Brief summary

Cells of macrophage lineage can be infected by HIV-1 via three possible mechanisms. Virus can attach to the CD4 receptor and infect macrophages similar to the mechanism of infection of CD4 + cells. Macrophages could pinocytose the virus particle. In addition, virus could enter macrophages complexed to antibody via binding to Fc receptors for IgG or C3b. We have recently reported evidence that the serum of some HIV-1 antibody positive individuals can complex with HIV-1 and augment HIV-1 infection of a human monocytic cell line, U937. This enhancement of infection occurs at serum dilutions beyond the neutralization endpoint,and is detectable at very high dilutions in some sera, and mediated by Fc receptors.

In the coming year, we will extend these data by measuring levels of neutralizing and enhancing antibody in sera selected from:

b) Studies Planned for this year

1) A cohort of individuals in a high risk group for HIV-1 infection have been prospectively followed at Johns Hopkins from 1983 in a study of the epidemiology of HIV-1 infection. Selected sets of sera have been given to us under code. These sera were obtained from individuals in the group some of whom have become infected with HIV-1 and were followed clinically. Our results will be given to the clinical epidemiologists performing the study and they may provide some evidence for or against a possible role for infection-enhancing antibodies in the progression of HIV-1 infections.

2) We have been asked by Dr. Wayne Koff, Director, Prevention Branch, AIDS Program, NIAID, to study under code for neutralizing and enhancing antibodies selected sera from some volunteers who have been injected with baculovirus expressed HIV gp 160 experimental vaccine. It is important to avoid the induction of infection enhancing antibodies in developing candidate experimental HIV-1 vaccines, and our results should provide useful information concerning this aspect of HIV-1 vaccine development.

3) We will initiate studies to identify the viral epitopes responsible for enhancement using monoclonal antibodies and polyclonal antisera obtained from a number of collaborating laboratories. We have identified one serum which has high levels of HIV-1 antibody but does not enhance infection at dilutions beyond the neutralization endpoint. There are no obvious differences in western blots in the antibodies to HIV-1 structural antigens between this serum and the other sera which neutralize HIV at low dilutions but enhance infection at dilutions above the neutralization endpoint.

2. <u>HIV-1 specific cytotoxic T lymphocyte responses</u>.

a) Autologous EBV transformed B cell lines infected with Vaccinia gp 160 hybird virus (obtained from B. Moss) as target cells.

We have established 20 autologous EBV transformed B cell lines from HIV-1 antibody positive donors. We are assessing whether the peripheral blood lymphocytes of these HIV-1 antibody-positive donors contain HIV-1 specific CTL, as reported by Walker, et al. We have found 2 donors' PBL that have some specific lytic activity of their

autologous, EBV-transformed B cell lines infected with the Vaccinia - gp 160 hybrid virus, out 8 other donors PBL do not. Most of the donors' PBL lyse their autologous EBV-transformed cell lines to a high degree, so this makes it difficult to use these donors' B cell lines as target cells for HIV specific killing.

b. Stimulation of HIV-1 specific T cells.

We have stimulated the PBL of 20 HIV antibody-positive donors with live HIV-1 (HTLV-III_B) virus, and only 30% respond. These donors were selected because they appeared to be in Walter Reed Stages 1 or 2. Thus, our results with live virus HIV-1 antigen are similar to those published by Wahren et al using a heat killed HTLV III_B antigen.

In an effort to improve the T cell response of the PBL of HIV-1 antibody positive donors, we have added IL-2 to these assays, and tested the PBL of several of the non-responders again. Our results show that Il-2 at high concentrations non-specifically increases lymphocyte growth but at low concentrations specifically augments the growth of HIV-1 specific lymphocytes.

We will continue to analyse T cell responses to HIV-1, and we hope to establish human T cell lines for epitope mapping now that we are succeeding in showing higher levels of HIV-1 specific stimulation.