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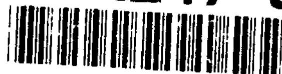

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This annual report describes our research effort in examining the use of synthetic peptides and anti-idiotypes (anti-Id) as two strategies for controlling human immunodeficiency virus (HIV) type 1 (HIV-1). Utilizing synthetic peptides to define linear epitopes on HIV-1 gp160, we compared the fine specificity of the humoral immune response to HIV-1 infection in humans representing two geographically diverse populations. In addition, we examined the anti-gp160 fine specificity in HIV-1 infected chimpanzees and recombinant gp160 immunized mice. We attempted to correlate reactivity to selected gp160 epitopes defined by peptides with disease progression and/or in vitro neutralizing activity. Immunization studies were performed using selected synthetic peptides and novel adjuvant formulations to assess the ability to induce anti-HIV-1 gp160 responses in experimental animals. Murine monoclonal anti-Id reagents, both noninternal image and internal image in nature, were also developed and tested for the ability to induce anti-gp160 Ab-3 responses in vivo. The molecular basis of monoclonal anti-Id was assessed by determining the variable (V) region gene sequence. These two strategies may serve to develop novel vaccination modalities and/or active immunization principles for controlling HIV-1 infection in vivo.

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FOREWORD

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources Commission on Life Sciences, National Research Council (DHHS, PHS, NIH Publication No. 86-23, Revised 1985).

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Introduction

The functional duality of the immunoglobulin variable (V) region imparts antigen recognition and idiotype (Id) expression. These two characteristics of the immunoglobulin V region represent important components when examining humoral immunity. The humoral immune response to a pathogen comprises one of the major modes that the immune system utilizes to control and abrogate infection and subsequent sequellae. A number of studies in experimental animal models for infection and disease have indicated that the humoral immune response to the envelope components of immunodeficiency viruses are important in protective immunity. Specifically, a recombinant form of gp120 from human immunodeficiency virus (HIV) type 1 (HIV-1) was shown to protect chimpanzees from a subsequent infectious viral challenge (1). Since recombinant subunit vaccines have been previously shown to be poor inducers of cell-mediated immune responses, protective immunity against HIV in this system most likely resulted from humoral immune responses associated with the production of neutralizing antibodies.

Two immunologic tools that can be used to analyze the functional duality of immunoglobulin V regions are synthetic peptides and anti-idiotypes (anti-Id). Synthetic peptides can be used to define and dissect both antigenic recognition and Id expression. Anti-Id are useful as serologic phenotypic markers for Id expression. Thus, synthetic peptides and anti-Id can be used to dissect the V region components of a given humoral immune response. An alternative use of these two tools is as active immunologic strategies to induce specific immune responses. Indeed, a number of studies have described the potential application of synthetic peptides and anti-Id as putative vaccines and/or immunologic intervention modalities for controlling chronic infections. It is the intent of this contract to examine these two immunologic tools for analyzing the humoral immune response to HIV-1 gp160. Based on these findings, we also propose to develop strategies for controlling HIV-1 infection _in vivo_ utilizing synthetic peptides and anti-Id.

The objectives of this research are to synthesize and characterize synthetic peptides corresponding to amino acid sequences from HIV-1 gp160. We propose to identify potential immunodominant and immunorecessive serologic reactive linear epitopes utilizing synthetic peptides and anti-gp160 produced in a number of species. We will determine whether serologic reactivity to selected peptide epitopes corresponds with disease progression and/or _in vitro_ neutralizing activity. Based on these results, selected peptides will be examined for their ability to induce anti-gp160 responses in experimental animals. In addition, we propose to generate and characterize murine monoclonal anti-Id. The anti-Id will be used to analyze the Id specificity of the anti-gp160 immune response. Anti-Id will also be examined _in vivo_ to assess their ability to induce anti-gp160 Ab-3 responses. The molecular basis of murine monoclonal anti-Id V regions that induce anti-gp160 Ab-3 responses will be determined.

I. Fine Specificity of HIV-1 gp160 humoral immune responses

This section of the report describes studies that examined the humoral immune response to selected HIV-1 gp160 epitopes defined by synthetic peptides. We examined and compared the fine specificity of the anti-gp160 responses in HIV-1 infected individuals from two geographically diverse populations, HIV-1 experimentally infected chimpanzees, and six inbred strains of mice immunized with recombinant gp160. Our selection of HIV-1 gp160 epitopes defined by synthetic peptides included: (i) peptide 304-321 which corresponds to the amino portion of the HIV-1 IIIB V3 loop; (ii) peptides RP135, RP142, and RP145 which correspond to the entire V3 loop and principle neutralizing determinant of gp120 from the HIV-1 IIIB, MN, and HAN/SC isolates, respectively; (iii) peptide 425-448 which corresponds to the putative CD4 binding site on gp120; (iv) peptide 502-528 which corresponds to the carboxyl terminus epitope of gp120; (v) peptide 600-611 which corresponds to the major immunodominant epitope expressed on gp41 and has been associated with distinguishing HIV-1 versus HIV-2 serologic reactivity; (vi) peptide 616-632 which corresponds to a gp41 epitope that induces *in vitro* HIV-1 inhibiting antibodies when immunized into mice; (vii) peptide 735-752 which corresponds to a gp41 neutralizing epitope and; (viii) peptide 846-860 which represents a native gp41 epitope on the carboxyl terminus of gp41 and has been correlated with the cytopathogenicity of HIV-1 *in vitro* utilizing deletion mutation analysis. Each of these peptides when coupled to carrier proteins and used to immunize experimental animals induces anti-peptide antibodies that recognize HIV-1 gp160 and therefore represents B cell epitopes on gp160 (reviewed in 2).

A. Humoral immune responses in HIV-1 infected humans

We examined sera from 160 HIV-1 infected USAF personnel for antibodies reactive to HIV-1 gp160 synthetic peptide epitopes. Seropositive individuals were placed into three groups based on levels of circulating CD4+ cells. These groups consisted of individuals with: (i) greater than 400 CD4+ cells; (ii) between 200-400 CD4+ cells and; (iii) less than 200 CD4+ cells. The percentage of sera containing antibodies to immunodominant epitopes (analogous to V3 sequences and peptide 600-611) were unchanged between groups, regardless of CD4 cell numbers. The percentage of sera containing antibodies reactive with weakly immunogenic gp160 epitopes, such as those defined by peptides 425-448 and 846-860, declined in groups as CD4 values decreases. However, this decrease was not statistically significant. Only antibodies to a carboxyl terminal epitope of gp120 defined by peptide 502-528 demonstrated a statistically significant decrease in serologic reactivity as CD4+ cell numbers declined. This decrease was not reflected in overall anti-gp160 antibody titers and may reflect a narrowing or change in the fine specificity to gp160 epitopes as disease progression occurs (3).

We have extended this study and compared the fine specificity of the anti-gp160 response among HIV-1 infected individuals from the United States and Tanzania. These two geographically diverse populations reflect different epidemiologic patterns of HIV-1 infection. In the United States and Europe, HIV-1 infection occurs mostly in homosexual males and intravenous drug abusers. In Tanzania, along with the remainder of Africa, HIV-1 infection is predominantly characterized by heterosexual spread. While the clinical and

immunologic profiles of HIV-1 infected individuals in the United States and Europe have been well characterized, information concerning HIV-1 infection in Africa is far less complete. We observed the greatest difference in antibody fine specificity between these two populations in the recognition of an immunodominant gp41 epitope defined by peptide 600-611. This highly conserved region was recognized by only 50% of sera from HIV-1 infected Tanzanians, whereas, greater than 90% of sera from the United States contained reactive antibodies (4). Differences were also observed in the recognition of gp160 epitopes defined by peptides 502-528 and 846-860. These differing patterns of antibody fine specificity may be partially due to the presence of regional HIV-1 isolates which differ in envelope amino acid sequences.

In addition, we examined whether any difference in fine specificity was observed among asymptomatic and symptomatic individuals within these two HIV-1 infected populations. No difference in serologic reactivity to the selected gp160 epitopes that were examined was observed among asymptomatic versus symptomatic individuals from Tanzania. This result differed when comparing asymptomatic and symptomatic individuals from the United States. Confirming our previous results based on CD4+ cells numbers, a statistically significant reduction in antibody reactivity to peptide 502-528 was observed in symptomatic individuals. We also examined sera obtained from these two populations for reactivity to V3 peptides whose sequences were obtained from divergent HIV-1 isolates. The predominant reactivity that was observed was with the V3 peptide corresponding to the HIV-1 MN isolate. More than 60% of HIV-1 infected individuals from these two populations recognized this V3 peptide. We attempted to correlate V3 peptide reactivity and in vitro neutralizing activity. Selected sera that recognized various V3 peptides by ELISA were examined for their ability to neutralize divergent HIV-1 isolates in vitro. In our limited study (n=30), no concordance was observed between in vitro neutralizing activity and V3 peptide recognition. However, HIV-1 infected sera from Tanzania were more likely to neutralize HIV-1 IIIB and/or MN isolates in vitro when compared to sera from the United States (5). The information obtained from comparing antibody fine specificity among geographically diverse populations will be useful in the design of more effective diagnostic and therapeutic products worldwide.

B. Fine specificity of anti-gp160 responses in HIV-1 infected chimpanzees

We have examined the fine specificity of the humoral immune response to HIV-1 gp160 in HIV-1 infected chimpanzees (6). Chimpanzees can be readily infected in vivo with HIV-1, however, they fail to develop any symptoms associated with HIV induced AIDS. Thus, chimpanzees represent a relevant nonhuman primate model to study HIV-1 infection, but not disease. Indeed, a number of reports have utilized chimpanzees to assess protective immunity induced by various prototypic HIV-1 vaccine candidates (reviewed in 7). In our studies, twenty-three HIV-1 experimentally infected chimpanzees were examined for selected anti-gp160 responses defined by synthetic peptide epitopes. Of particular interest was the observation that 50% of HIV-1 infected chimpanzees recognized a carboxyl terminal epitope on gp41 defined by peptide 846-860. This compares with less than 20% of 320 HIV-1 infected humans recognizing this epitope (3-5). Other serologic differences were detected with peptide 600-611 when comparing anti-gp160 responses among HIV-1 infected chimpanzees and humans. Less than 40% of the HIV-1 infected chimpanzees recognized this immunodominant gp41 epitope. These studies

indicate that differences in the fine specificity of the anti-gp160 responses exist among HIV-1 infected chimpanzees versus humans. It remains to be determined whether these differences in serologic reactivity reflect the inability of chimpanzees to develop disease symptoms following HIV infection.

C. Fine specificity of the anti-gp160 response in gp160 immunized inbred strains of mice

We have assessed the anti-gp160 humoral immune response in inbred strains of mice immunized with baculovirus-derived recombinant HIV-1 gp160 (rgp160). Six inbred strains of mice were each immunized with two different concentrations of rgp160, and anti-gp160 fine specificity was examined. Within a given inbred strain of mice, no significant difference in antibody titers to gp160 was observed in those groups receiving the two different concentrations (7). Differences in anti-gp160 titers were observed among the various inbred strains, however, these differences became less apparent following additional injections with rgp160. In addition, each mouse strain exhibited a unique pattern of reactivity to selected gp160 epitopes defined by synthetic peptides. Epitopes defined by peptide 735-752 which were immunorecessive in HIV-1 infected humans and chimpanzees, appeared to be immunodominant in some of the inbred strains of mice that were examined. Other differences in antibody fine specificity among mice immunized with rgp160 and HIV-1 infected individuals were also observed. The kinetics of the anti-gp160 immune response indicated that multiple immunizations with rgp160 resulted in responses to selected epitopes that were initially not detectable. The observed differences in the fine specificity of the humoral immune response to distinct gp160 epitopes among the six inbred strains suggests a genetic basis for regulating the antibody response to these epitopes. This apparent regulation can be overcome by multiple injections with rgp160. The analysis of the fine specificity and possible genetic regulation of the humoral immune response to gp160 is warranted in light of the fact that rgp160 has been approved by the Food and Drug Administration to be tested as a vaccine and therapeutic modality in multi-center phase I and II safety and efficacy trials in the United States. The strains of mice that were examined in this study were major histocomptability complex H-2 locus and immunoglobulin IgCh locus disparate. These strains included Balb/c, A/J, CBA, C57BL, DBA and SJL.

D. Immunogenicity studies using gp160 synthetic peptides

In collaborative studies, we have also been examining the in vivo effects of various adjuvants on inducing anti-gp160 response to gp160 synthetic peptides. We have compared the ability of alumina hydroxide (alum) and various derivatives of stearyl tyrosine for inducing anti-gp160 responses to peptide 503-535 in experimental animals. Studies indicate that both alum and stearyl tyrosine induce comparable anti-peptide and anti-gp160 titers in mice, rabbits and baboons, however, groups of mice and baboons immunized with stearyl tyrosine also produced detectable levels of neutralizing antibodies when compared to alum (8). Previous studies have indicated that this peptide can induce neutralizing antibodies when immunized into experimental animals (9). The neutralizing antibodies induced by peptide 503-535 in stearyl tyrosine were assessed by an in vitro cell cytotoxicity assay using the IIIB isolate and appeared to be specific (50% inhibition of cytotoxicity was observed with sera dilutions between 1:100 and 1:400). The observation that

stearyl tyrosine can alter the quality of the antibody response when compared to alum (neutralizing versus non-neutralizing) suggests that this adjuvant may have some utility in studies involving immune responses to HIV-1 gp160.

II. Studies on idiotypy and anti-gp160

In this section of the annual report, we will describe our studies involving idiotypy. This includes the production and characterization of murine monoclonal anti-Id reagents, their in vivo modulating characteristics, serologic recognition of anti-gp160 responses, and preliminary studies on the structural and molecular basis of murine monoclonal anti-Id.

A. Generation and characterization of murine monoclonal anti-Id

In our initial experiments, we generated monoclonal anti-Id, designated MC1, against a chimpanzee anti-gp41 response specific for peptide 735-752. Based on serologic characterization, the monoclonal anti-Id recognized a noninternal image anti-Id. This anti-Id detected a shared Id expressed on two chimpanzee anti-gp41 preparations specific for peptide 735-752, but failed to detect an interspecies Id cross-reaction. Immunization of this anti-Id into syngeneic hosts induced an anti-gp41 Ab-3 response that recognized peptide 735-752. The Ab-3 response in mice also shared an Id specificity with the chimpanzee Ab-1 used to generate the monoclonal anti-Id. Thus, in syngeneic hosts, immunization with noninternal image anti-Id induced Ab-3 responses exhibiting both the antigen specificity (Ag+) and Id expression (Id+) shared by the Ab-1. We also immunized a heterologous species with the anti-Id and induced Ab-3 responses that failed to recognize gp41. Further serologic characterization of this Ab-3 response indicated that the Id specificity was shared by the Ab-1. In the instance of heterologous immunization, the noninternal image anti-Id appeared to induce Ab-3 responses that exhibited Ag-,Id+ specificities (10). This apparent genetic restriction by noninternal image anti-Id in the induction of antigen specific responses places a major limitation on the use of these preparations as putative vaccines. However, the ability to induce Id responses that reflect the Id expressed on the Ab-1 preparation indicates the noninternal image anti-Id may be useful in priming Id specific responses prior to administration of the antigen. If the Id represents a serologic marker that is associated with the lack of disease progression, then priming for Id specific responses may be advantageous in humoral immune response induce by a given antigen. Thus, noninternal image anti-Id could be utilized to preprogram the immune response prior to exposure to an antigen. This represents a potential novel facet of active immunotherapeutic strategies for treating chronic infections.

We have also generated three monoclonal anti-Id preparations specific for a rabbit anti-gp120 preparation that recognized peptide 503-535. This peptide encompasses the carboxyl terminus of gp120 and the amino terminus of gp41. Based on radioimmunoprecipitation studies, it appears that the specificity of the Ab-1 preparation used to generate the anti-Id is for gp120. These anti-Id preparations each appeared to recognize an interspecies cross-reactive Id expressed on anti-gp120 produced by immunizing with peptide 503-535. The interspecies Id was combining-site related and was expressed on Ab-1 preparations from rabbits, mice and baboons. This indicated that the anti-Id serologically exhibited internal image characteristics. Heterologous immunization of rabbits with the three murine monoclonal anti-Id induced anti-

gp120 Ab-3 responses specific for peptide 503-535 by ELISA and radioimmunoprecipation (11). These data support our notion that an internal image anti-Id should not exhibit <u>in vivo</u> genetic restriction and induce antigen specific responses in heterologous species. Preliminary studies indicate that the Ab-3 responses induced in rabbits contains neutralizing antibodies and inhibits HIV-1 IIIB cytotoxicity of CD4+ target cell lines. The neutralizing antibody titers in the Ab-3 sera are comparable to that observed for Ab-1 sera produced by immunizing with peptide 503-535. We propose to continue studies with these anti-Id reagents during the upcoming year.

B. Molecular basis for monoclonal anti-Id

We have cloned and sequenced the cDNA encoding the V region of the noninternal image monoclonal anti-Id, designated MC1. The V region heavy chain (V_H) sequence shared homology with a group of mouse monoclonal antibodies specific for the 2-phenyl-oxazalone hapten. This group of antibodies expressed a V_H region encoded by a gene designated V_HOx-1 which is a member of the murine V_HQ52 gene family. In addition, the D_H and J_H regions appear to be encoded by DSP2.8 and J_H2 gene segments, respectively. The V region kappa chain (V_k) of MC1 is encoded by the V_k21 gene family and the J_k region is derived from the J_k4 germline gene family (12). This data represents our preliminary characterization of the molecular basis on murine monoclonal anti-Id. Since no primary amino acid sequence homology exists between the V region sequence of MC1 and peptide 735-752, the mechanism of how this noninternal image anti-Id induced anti-gp41 Ab-3 responses specific for peptide 735-752 in mice remains to be determined. We propose to sequence additional murine monoclonal anti-Id V regions as they become available and assess whether noninternal image versus internal image utilize similar or different V region genes. In addition, we will determine whether V region gene usage by murine monoclonal anti-Id in the HIV-1 gp160 system is biased or represents a random event reflecting V region gene frequencies. The biased utilization of V region genes may be associated with proximity of V genes to the constant region genes or the possibility that genetic mechanisms, such as gene conversion, select particular V regions for association with a given population of anti-Id subclass.

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