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TITLE: DIAGNOSIS OF AIDS USING DESIGNED AMINO ACID PEPTIDES
REPRESENTING IMMUNODOMINANT EPITOPES OF HIV

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HIV causes a persistent infection that results in AIDS, a major health hazard to military and civilian populations. We have and continue to design and synthesize a variety of amino acid peptides from proteins of HIV-1 and HIV-2 viruses. Our purpose is to map the immunodominant domains of HIV-1 and HIV-2. This information and use of such reagents would accomplish three purposes. First, and under current evaluation, sensitive and specific reagents to diagnose HIV-1 and HIV-2 infected individuals, defining both viruses and marking emerging families of variants would be obtained. Second, the pathogenesis as regards the loss of, or conversely, the evolution of new immune (potentially immunopathologic) responses could be charted. Third, the data collected would be important for the design of subunit vaccines. Utilizing such designer peptides, the B cell (antibody)					
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19. Abstract (continued)

immunodominant domain of HIV-1 and HIV-2 have been defined and peptides having single amino substitutions within the HIV-1 epitope used to record emerging strains. A fusion peptide(s) designed to identify HIV-1 and HIV-2 has been constructed. Mapping T cell epitopes and their relationship to major histocompatibility complex glycoproteins has begun and the mechanism(s) for the presence of antibodies to both HIV-1 and HIV-2 in a single patient explored.



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MAAO 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).

MAAO For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

In conducting research utilizing recombinant DNA technology, the Investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

Michael RA Oestrich 2 May 1990
PI Signature Date

FINAL SCIENTIFIC REPORT

1. Introduction Overview

Efforts to solve the epidemiologic puzzle of AIDS especially in Africa are complicated by the presence of multiple human retroviruses. Simple serologic tests that unambiguously distinguish among infections by these retroviruses are essential. To that end, we defined a partially conserved immunoreactive epitope in the transmembrane glycoproteins of human immunodeficiency viruses (HIV) types 1 and 2. Synthetic peptides derived from these conserved domains were used in sensitive and specific immunoassays that detect antibodies in sera from patients infected with HIV-1 or HIV-2. By making single amino acid substitutions in the HIV-1 peptide it was possible to demonstrate HIV-1 strain-specific antibody responses to this epitope. From these results it is clear that such custom-designed peptides synthesized from this domain are likely to detect newly discovered HIV types, define infection with specific HIV strains, and allow detection of group-common antibodies.

In the first half of support (Mid-Term report) we focused on and completed two main areas of research. First, we mapped the immune response during primary acute infection to the HIV-1 immunodominant domain GP41 12 mer peptide LGIWGCSGKLIC, determined the contributions of T helper cells in raising antibody response to the peptide, studied T cell proliferation to the peptide and analyzed MHC restricted response and peptide structure (in a limited number of infected individuals). Second, we custom designed and synthesized a number of HIV-1 + HIV-2 hybrid peptides in order to detect both HIV infections with a single reagent and showed good correlation with peptides 7A:WGCAFRQVCGGGCSGKLIC and peptide 7B:WGCAFRQVGGGCSGKLIC.

During the time after the mid-term of the contract we focused on three major areas.

1. Generation and analysis of monoclonal antibodies to the HIV-1 and HIV-2 immunodominant GP41 domains.
- ii. Analysis of monoclonal antibody(s) that see both GP41 HIV-1 and HIV-2; study of sera from a subset of African patients in which individuals show a positive serologic response to both specific GP41 HIV-1 peptide (LGIWGCSGKLIC) and specific GP41 HIV-2 peptide (NSHWGCAFRQVC) against custom designed peptide.
- iii. Analysis of structure-function relationships of HIV-1 12 mer immunodominant domain.

2. Specific Accomplishments

1. Generation and analysis of monoclonal antibodies to the HIV-1 and HIV-2 immunodominant GP41 domains. Upon immunization with authentic peptides to the immunodominant domains of the transmembrane GP41 protein of HIV-1 or HIV-2, mice and rats

produced specific antibodies used as a source of monoclonals. As seen in Table 1, of these 39 monoclonal antibodies to HIV-1 GP41, aa 598-609, 16 (41%) also reacted with the minimal epitope flanked by cysteines -- aa 603-609; CSGKLIC. Most importantly, four of these monoclonal antibodies also reacted with the minimal HIV-2 epitope similarly flanked by cysteines -- aa 597-603; CAFRQVC. Similarly, when peptides that encompassed the HIV-2 GP41 immunodominant epitope were used to immunize mice, four resulting monoclonal antibodies specifically reacted with the minimal immunodominant domains of both HIV-1 (CSGKLIC) and HIV-2 (CAFRQVC).

Table 1

Generation of monoclonal antibodies to the gp41 immunodominant domain of either HIV-1 or HIV-2¹

Immunogen	Host	Total no.	HIV-1 aa		HIV-2 aa		HIV-1 HIV-2
			598-609	603-609	593-603	597-603	
HIV-1 gp41	Mouse	282	36	15	5	3	3
	Rat	86	3	1	1	1	1
598 603 609 L G L M G C S G K L I C or 595 598 609 C G G E Q L L G L M G C S G K L I C							
HIV-2 gp41	Mouse	610	14	4	30	4	4
593 597 603 N S M G C A F R Q V C or 583 593 603 C G G K Y L D Q D Q A R L N S M G C A F R Q V C							

¹ BALB mice or LOU/HN rats received a series of peptide injections (see Materials and Methods section). Spleen cells from animals with anti-peptide antibodies in their sera were fused to mouse 6351 or rat Y3 AG1.23 myeloma cells. After cloning and recloning 2x, supernatant fluids from each clone were tested for the ability to bind to HIV-1 aa 598-609 (LGLMGCSKLIC), HIV-1 aa 603-609 (CSKLIC), HIV-2 aa 593-603 (NSMGCAFRQVC), or HIV-2 aa 597-603 (CAFRQVC).

Three monoclonals generated after immunization with HIV-1 and three monoclonals resulting after immunization with HIV-2 were selected for further study. All six monoclonals demonstrated highly reactive titers, even at end point dilutions, when tested against the GP41 immunodominant domains of HIV-1 or HIV-2 (Table 2, Figure 1,2). However, when the CYS-CYS bond was broken by substitution of a serine for the N-terminal or C-terminal cysteine, none of the six monoclonal antibodies reacted with any of the peptides tested (Table 2). These results were repeated

in three other experiments. The Ig subset shown in Table 2 was typed by using isotype-specific murine and rat monoclonals.

Table 2

Generation of monoclonal antibodies that cross-react with the CYS-CYS loop of the immunodominant epitopes of HIV-1 and HIV-2¹

MoAb to	Ig subtype	HIV-1 gp41 peptides			HIV-2 gp41 peptides			
		LGLWGCSGKLIC	CSGKLIC	SGKLIC	NSMGCAFRVC	CAFRVC	SGKLIC	
HIV-1	41-6	IgG2b	520,000 ²	270,000	30	4,000	500	30
	4	IgG2b	28,480	25,000	10	1,280	420	30
	75	IgG	2,560	2,560	10	2,540	640	20
HIV-2	68.1	IgM	64,000	30,000	54	180,000	125,000	10
	68.11	IgM	31,000	100,000	73	32,000	155,000	30
	115.8	IgM	130,000	520	58	175,000	64,000	30
Normal Mouse			14	17	10	10	35	10

¹ Mouse monoclonal antibodies are HIV-1 41-6, 4 and HIV-2 68.1, 68.11, 115.8; 75 is a rat monoclonal.

² End point dilution of ascitic fluid. ELISA read at 492 nm using a concentration of 1 µg of peptide per well.

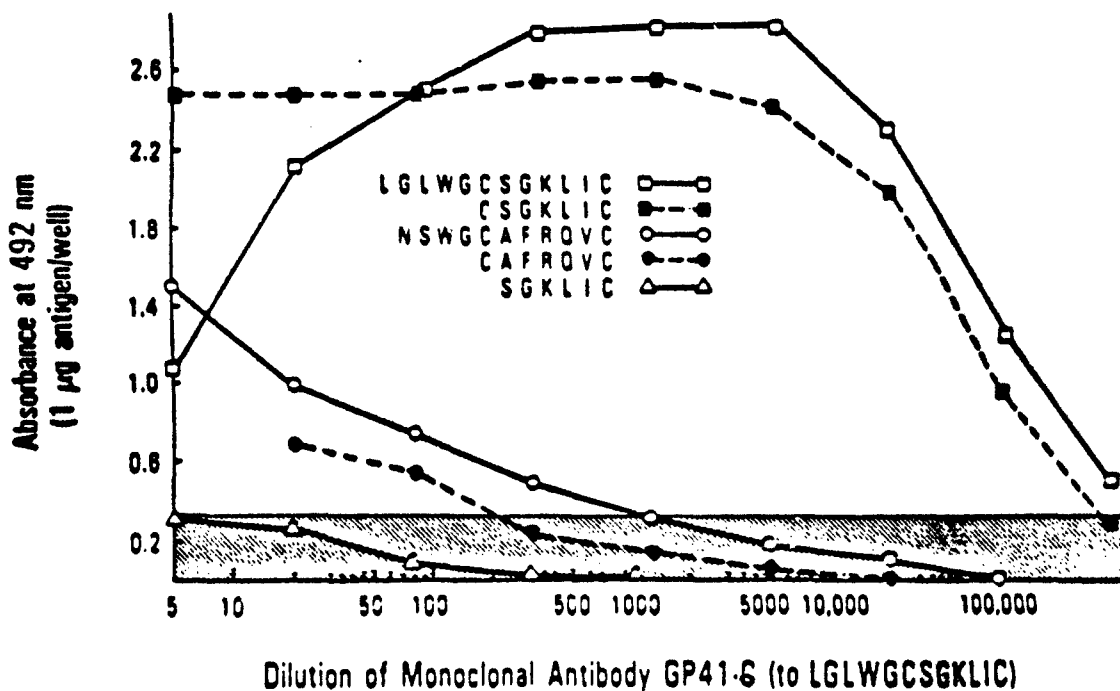


Figure 1

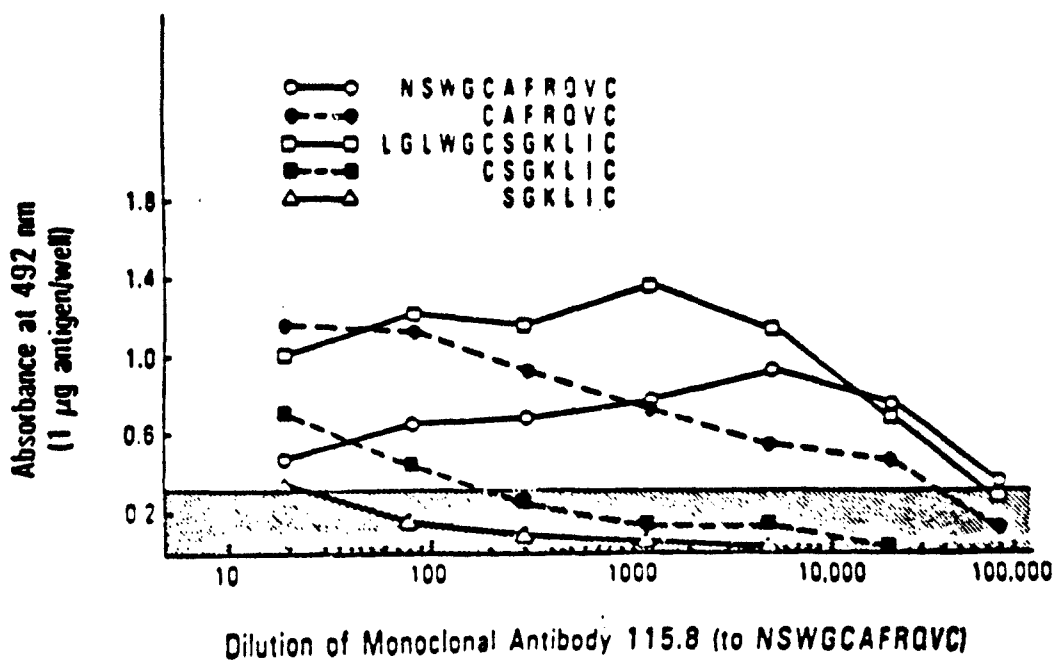


Figure 2

Next we judged the relative binding affinities of HIV-1 monoclonal antibody GP41-6 and of HIV-2 monoclonal antibody 115.8 to the cysteine loop of HIV-1 (CSGKLIC) or HIV-2 (CAFRQVC). As Table 3 shows, concentrations of peptide antigens varying from 10 μ g to 0.01 μ g bound better to the CYS-CYS loop contained in the immunizing peptide than to the non-immunizing CYS-CYS loop. The binding observed at this wide range of antigen dosages induced reasonable efficiency and affinity of the antibodies under study.

Table 3

Binding of monoclonal antibodies to varying concentrations of CYS-CYS loop peptides of the immunodominant GP41 epitope of HIV¹

Concentration of peptide (μ G)	MoAb of HIV-1 binding to		MoAb of HIV-2 binding to	
	HIV-1 peptide CSGKLIC	HIV-2 peptide CAFRQVC	HIV-1 peptide CSGKLIC	HIV-2 peptide CAFRQVC
10	4,700	1,100	1,400	92,000
1	300,000	150,000	6,000	240,000
0.2	1,200,000	400,000	680	2,700,000
0.1	190,000	80,000	110	660,000
0.2	14,000	13	43	320
0.01	20,000	21	40	620

1 Monoclonal antibody (MoAb) to HIV-1 was GP41-6 and to HIV-2 was 115.8.

11. Analysis of monoclonal antibody(s) that see both GP41 HIV-1 and HIV-2: study of sera from a subset of African patients in which individuals show a positive serologic response to both specific GP41 HIV-1 peptide (LGIWGCSGKLIC) and specific GP41 HIV-2 peptide (NSWGCAFRQVC) against custom designed peptide. Studies presented above in Table 2 and Figure 1, indicated the importance of the CYS-CYS loop in both HIV-1 and HIV-2 for monoclonal antibody binding. To confirm and extend this observation, a series of HIV peptides was synthesized in which the amino-terminal or carboxy-terminal cysteine was replaced by a serine. Similarly the amino terminal cysteine was replaced by a serine in the larger HIV-1 and HIV-2 authentic peptides. As shown in Table 4, only when the CYS-CYS bond was present did significant binding of either monoclonal antibody (GP41-6 or 115.8) occur to either HIV-1 or HIV-2 immunodominant domain. Varying concentrations of HIV-1 peptide aa 603-609 (CSGKLIC) were used to inhibit binding of HIV-1 GP41 peptide aa 598-609 to monoclonal antibody GP41-6. At a 20 μ g concentration, the binding of peptide aa 603-609 was inhibited >90%, with 50% inhibition at a concentration of 8 μ g. Peptides SGKLIC or CSGKLIS showed negligible inhibition at 50 μ g concentration. Further, peptide CSGKLIC inhibited the binding of monoclonal antibody to the HIV-2 GP41 12-mer peptide.

Table 4

Cross-reaction between HIV-1 and HIV-2 shown by binding of monoclonal antibodies to the CYS-CYS loop peptides of the immunodominant GP41 epitope¹

HIV-1 peptides	End point dilution of MoAb to	
	HIV-1:CSGKLIC ²	HIV-2:CAFRQVC ³
CSGKLIC	126,000	1,400
SGKLIC	N11	150
CSGKLIC	N11	N11
LGLWGSSGKLIC	1,000	140
<u>HIV-2 peptides</u>		
CAFRQVC	680	34,000
SAFRQVC	N11	N11
CAFRQVS	N11	N11
NSHGSAFRQVC	N11	400

¹Normal mouse sera or ascites fluid were not positive against these peptides in a dilution >1/30. Values of 1/30 or less are recorded as N11.

²Monoclonal antibody (MoAb) used was GP41-6.

³MoAb used was 115.8.

Finally, in preliminary experiments we found evidence that sera from HIV+ individuals that is dually positive for HIV-1 and HIV-2 GP41 immunodominant domains contained antibodies to the CYS-CYS loop. As documented in our mid term report and elsewhere (Science 237:1347, 1987; Nature 329:248, 1987; J. Virol. 61:2639, 1987) HIV-1 infection could be distinguished from HIV-2 infection, and vice versa, by using designed peptides from the N-terminus region of the GP41 transmembrane domain. For HIV-1, this region consisted of amino acid residues 598-609 (LGLWGCSGKLIC) and for HIV-2 amino acid residues 593-603 (NSHGCAFRQVC). However, several sera collected from patients in the African Ivory Coast (obtained from CDC, Joseph McCormick) had dual reactivity against HIV-1 and HIV-2, according to multiple serologic procedures. Yet, both viruses were never isolated from any one subject. Sera from 10 of these individuals with antibodies reactive to GP41 of HIV aa 598-609 and GP41 of HIV-2 aa 593-603 were then selected for this study. As shown in Table 5, with 5 sera of which material was available, all reacted with the CYS-CYS loop peptides from HIV-1 and HIV-2. However, when the CYS-CYS loop was linearized by a serine substitution for a cysteine, none of the sera reacted with peptide SGKLIC (Table 5). Unfortunately, too little dually reactive sera was available to perform CSGKLIC, SGKLIC AND CSGKLIS peptide absorption studies or repeat studies with SGKLIC peptide binding. We are hoping to obtain additional sera from the Army to complete and confirm these preliminary observations.

Table 5

Antibody responses of HIV-1 or HIV-2 infected individuals to
HIV GP41 immunodominant domains

Subjects	HIV-1 gp41 peptides			HIV-2 gp41 peptides	
	LGLWGCSGKLIC	CSGKLIC	SGKLIC	NSWGCAFRQVC	CAFRQVC
HIV-1 AIDS	150/150*	10/10	0/10	0/10	0/10
HIV-2 AIDS	0/11	0/11	0/11	11/11	11/11
SIV	0/3	0/3	0/3	3/3	3/3
HIV-1 + HIV-2** Ivory Coast	10/10	5/5	ND	10/10	5/5

*Total number positive/total number in the group.

**Experiment performed only once due to limited amounts of sera available

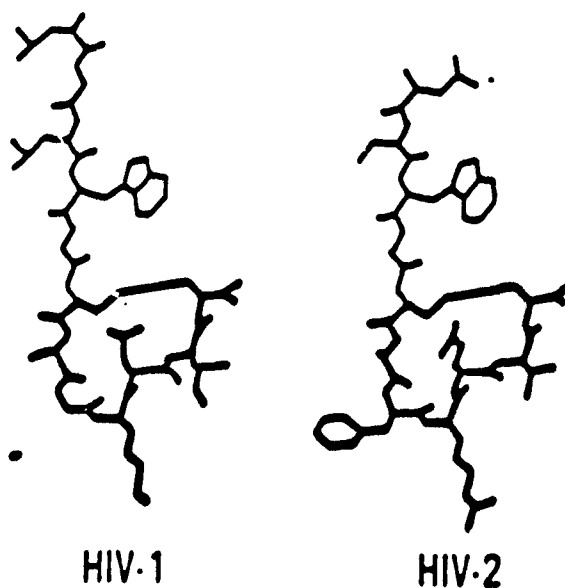
ND - not determined.

The observations made here have two major potential implications. First, we predict that the CYS-CYS peptides, CSGKLIC for HIV-1 or CAFRQVC for HIV-2, would be valuable reagents in determining whether patients with dually positive sera are so because of immunologic cross-reactivity. Although dual infection with both viruses can occur (see Rayfield et al., J. Infect. Dis 158:1170, 1988; Evans et al., Lancet 2: 1389, 1988), the extremely few incidents reported indicate either difficulties with their isolation or identification by polymerase chain reaction or that dual infection is rare. Hence, documentation of both types of HIV in some individuals may well be attributed to cross-reactive antigenic determinants. The use of CSGKLIC, SGKLIC, CSGKLIS, CAFRQVC, CAFRQVS, LGLWGSSGKLIC, LGLWGSCGKLIS, NSWGSAFRQVC or NSWGCAFRQVS reagents should be of value in resolution of this issue.

111. Analysis of structure-function relationships of HIV-1 12 mer immunodominant domain. Molecular modeling and dynamic studies were performed as follows in collaboration with U.C. Singh and V.N. Balaji of the Molecular Biology Department of Scripps. To simulate the favorable conformations of the HIV-1 GP41 aa sequence 598-609, computer graphics model building, constrained minimization, and molecular dynamics with several cycles of heating and slow cooling were used. The initial structures were model built by AMBER (Singh et al., Amber, version 3.0, UCSF; and U.C. Singh 1989, unpublished) in all trans conformation and was subjected to 500 cycles of minimization for both linear and cyclic (CYS-CYS) forms. In the cyclic form, a soft constraint to cyclize the disulfide bridge in CYS-Cys was included. The resultant structures were minimized without constraints for another 1000 cycles (or until the

change in energy reached less than 0.001 KCal/mol³). These structures were the starting point for a series of molecular dynamics simulations using the NEWTON module of AMBER 3.3 (U.C. Singh, unpublished version). These structures were artificially heated to 600°K and cooled to 300°K over a period of 100 ps. The dynamics simulation was continued for another 200 ps. This protocol was repeated for more than 10 cycles to arrive at the statistically most probable common conformation in each case. The resultant structures were then put in a water bath (containing approximately 2242 water molecules - TIP3P) with periodic boundary conditions. The molecular dynamics simulations continued for 300 ps, and structures were sampled with an r.m.s. deviation of more than 0.5 Å. All computer simulations were carried out on CRAY XMP/116 at the Research Institute of Scripps Clinic, and the structures were examined by using the MOGLI (molecular graphics library) on an Evans and Sutherland Computer Graphics System (PS390) driven by a micro-Vax.

Figure 3 displays a computer graphic model of the CYS-CYS epitopes recognized by these cross-reactive monoclonal antibodies, represented by the heavy lines.. Considering the radical substitutions within the CYS-CYS loop of HIV-1 compared to that of HIV-2, these monoclonal antibodies most likely recognized conformation rather than linear determinants.



HIV-1	LEU	GLY	LEU	TRP	GLY	CYS	SER	GLY	LYS	LEU	ILE	CYS
HIV-2	ASN	SER	TRP	GLY		CYS	ALA	PHE	ARG	Gln	VAL	CYS

The probable conformations deduced from molecular dynamic simulation for both linear and cyclic structure of HIV-1 aa 598-609 are shown in stereo in Figure 4. In the linear structure (upper panel) we observed the aa LEU to CYS sequence in an α helical conformation. The next residues in sequence (SER) terminate the continuation of this α helix and GLY lies in the left handed α helical region. The sulfur atoms (SG) on cysteine residues are 15 Å apart. The cyclic structure (lower panel) is compact, and the disulfide bridge formation is in the g^+ conformation (CB-SG-SG-CB + 91.5 degrees). There is no helical content in this structure. Residues GLY(3)-LEU(4)-TRP(5)-GLY(6) form a type II B-turn and residue GLY(9), LYS(10) are in the 27 hydrogen bonded formation.

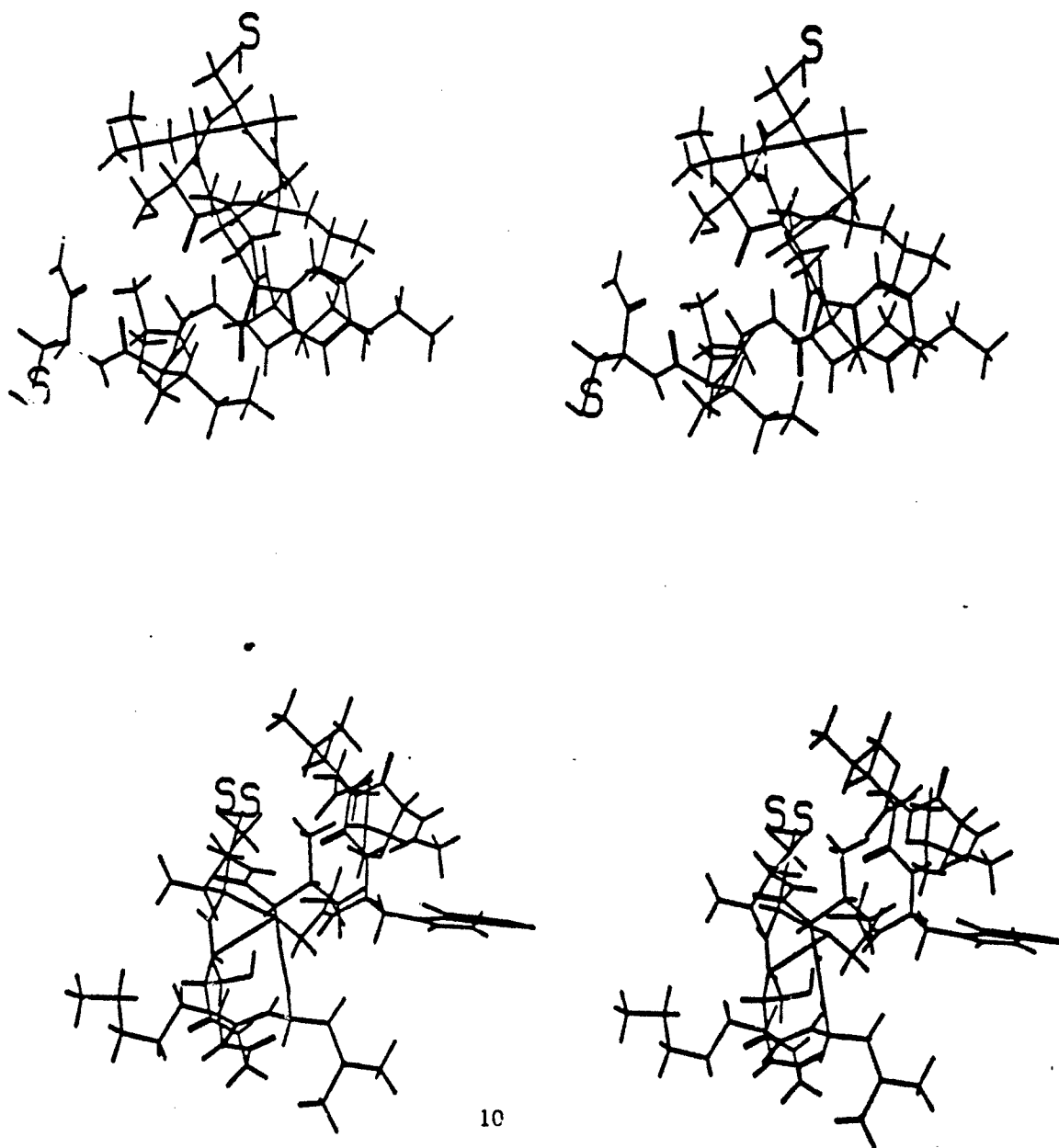


Figure 4. Stereo views of the predominant structure found for HIV-1 aa 598-609 based on molecular dynamics simulations: (a) linear (free Cys, Cys) and (b) cyclic forms (in which Cys-Cys -S-S bridge is formed).

3. Summary of the Final Term Scientific Report

Thirty-six monoclonal antibodies from mice and three from rats were raised against the immunodominant domain of the transmembrane GP41 protein of HIV type 1 (LGLWGCSGKLIC; amino acid residues 598-609). Of these, three monoclonals from the mice and one from a rat also reacted with the corresponding immunodominant domain of the HIV type 2 transmembrane GP41 protein (amino acid residues 593-603; NSWGCAFRQVC). Immunochemical studies employing a variety of synthetic peptides indicated that the cross-reactivity was due to antibody binding to CSGKLIC of HIV type 1 or CAFRQVC of HIV type 2. Single amino acid substitutions for a cysteine at either the amino or carboxy end of the peptide interrupted antibody binding, indicating that the site recognized was the CYS-XXXXX-CYS loop. Similar results occurred when the 11-mer HIV type 2 GP41 immunodominant epitope (amino acids 593-603) was inoculated into mice to raise monoclonal antibodies. In this instance, of thirty monoclonal antibodies developed, four reacted with both HIV type 1 and HIV type 2. Analysis of individual sera from HIV infected individuals reactive to HIV type 1 as well as HIV type 2 similarly demonstrated cross-reactivity to the CYS-XXXXX-CYS loop structure. Thus, custom-designed peptides synthesized from immunodominant domains of HIV types 1 and 2 are likely to be of value in documenting HIV serologic cross-reactivity.

Molecular modeling and dynamic studies indicate that, for HIV-1, the LEU (aa 598) to CYS (aa 603) segment is in an α helical conformation, whereas the next SER (aa 604) terminates the α helix. The C (aa 603) to C (aa 609) loop is compact, and the disulfide bridge formation is in the g^+ conformation. The sulfur atoms on cysteine residues are 15 Å apart. Residues GLWG (aa 599-602) form a type II B turn.

4. Publications

Schriner, R.D., J.W. Gnann, A.J. Langlois, K. Shriver, J.A. Nelson and M.B.A. Oldstone. B and T lymphocyte responses to an immunodominant epitope of human immunodeficiency virus. *J. Virol.* 62:2531-2536, 1988.

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6. Resulting Graduate Degrees

None