



(19) **United States**

(12) **Patent Application Publication**
Korber et al.

(10) **Pub. No.: US 2011/0150915 A1**

(43) **Pub. Date: Jun. 23, 2011**

(54) **POLYVALENT VACCINE**

Related U.S. Application Data

(75) Inventors: **Bette T. Korber**, Los Alamos, NM (US); **Simon Perkins**, Los Alamos, NM (US); **Tanmoy Bhattacharya**, Los Alamos, NM (US); **William M. Fischer**, Los Alamos, NM (US); **James Theiler**, Los Alamos, NM (US); **Norman Letvin**, Boston, MA (US); **Barton F. Haynes**, Durham, NC (US); **Beatrice H. Hahn**, Birmingham, AL (US); **Karina Yusim**, Los Alamos, NM (US); **Carla Kuiken**, Los Alamos, NM (US)

(63) Continuation of application No. 11/990,222, filed on Apr. 20, 2009, filed as application No. PCT/US2006/032907 on Aug. 23, 2006.

(60) Provisional application No. 60/710,154, filed on Aug. 23, 2005, provisional application No. 60/739,413, filed on Nov. 25, 2005.

Publication Classification

(73) Assignees: **Los Alamos National Security, LLC**, Los Alamos, NM (US); **Beth Israel Deaconess Medical Center**, Boston, MA (US); **Duke University**, Durham, NC (US); **The University of Alabama at Birmingham Research Foundation**, Birmingham, AL (US)

(51) **Int. Cl.**
A61K 39/21 (2006.01)
C07K 14/16 (2006.01)
C07H 21/00 (2006.01)
C12N 15/63 (2006.01)
A61K 39/295 (2006.01)
A61P 37/04 (2006.01)
A61P 31/18 (2006.01)

(52) **U.S. Cl.** **424/188.1**; 530/324; 530/350; 536/23.72; 435/320.1; 424/208.1

(57) **ABSTRACT**

The present invention relates, in general, to an immunogenic composition (e.g., a vaccine) and, in particular, to a polyvalent immunogenic composition, such as a polyvalent HIV vaccine, and to methods of using same. The invention further relates to methods that use a genetic algorithm to create sets of polyvalent antigens suitable for use, for example, in vaccination strategies.

(21) Appl. No.: **12/960,287**

(22) Filed: **Dec. 3, 2010**

Fig. 1A

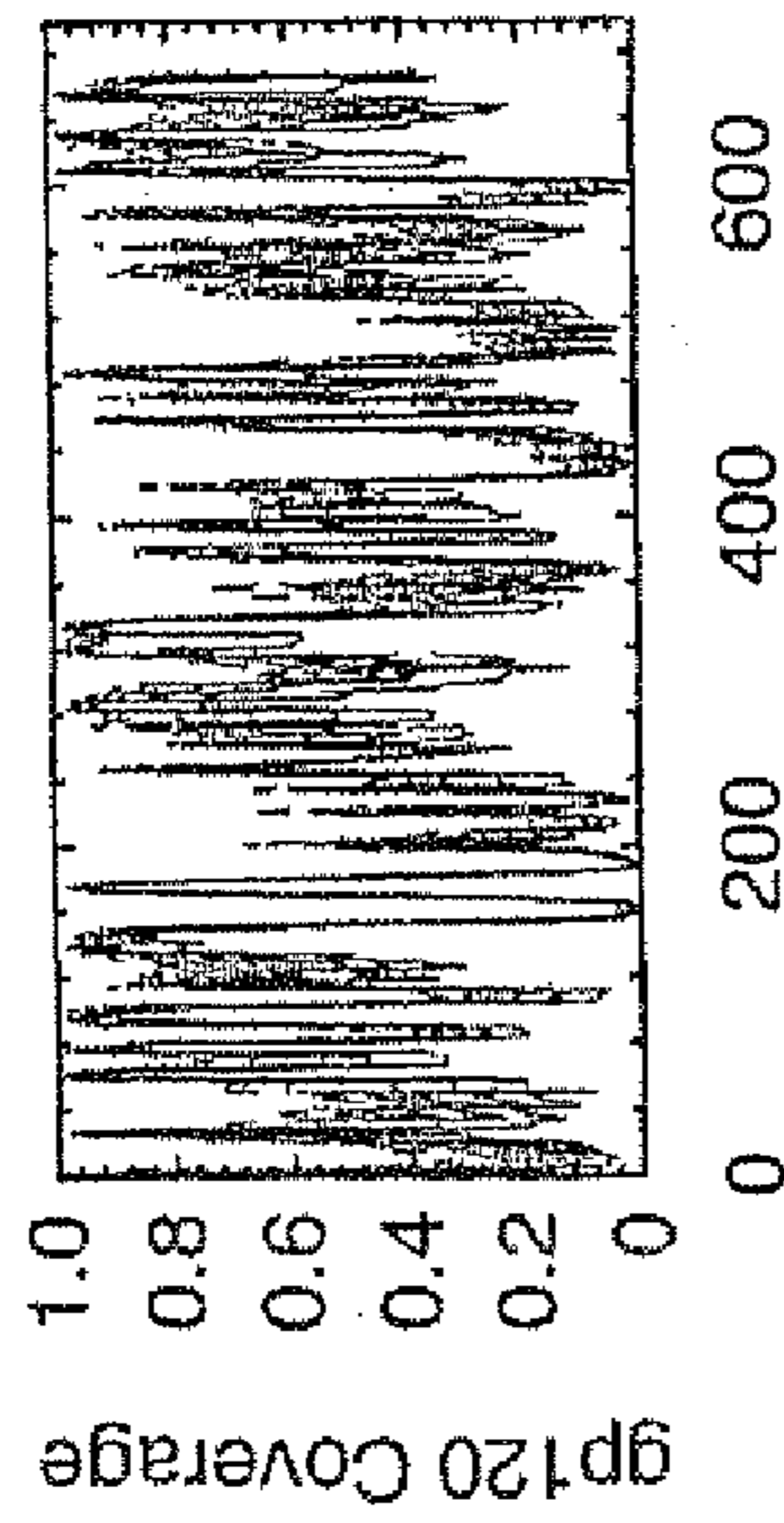


Fig. 1B

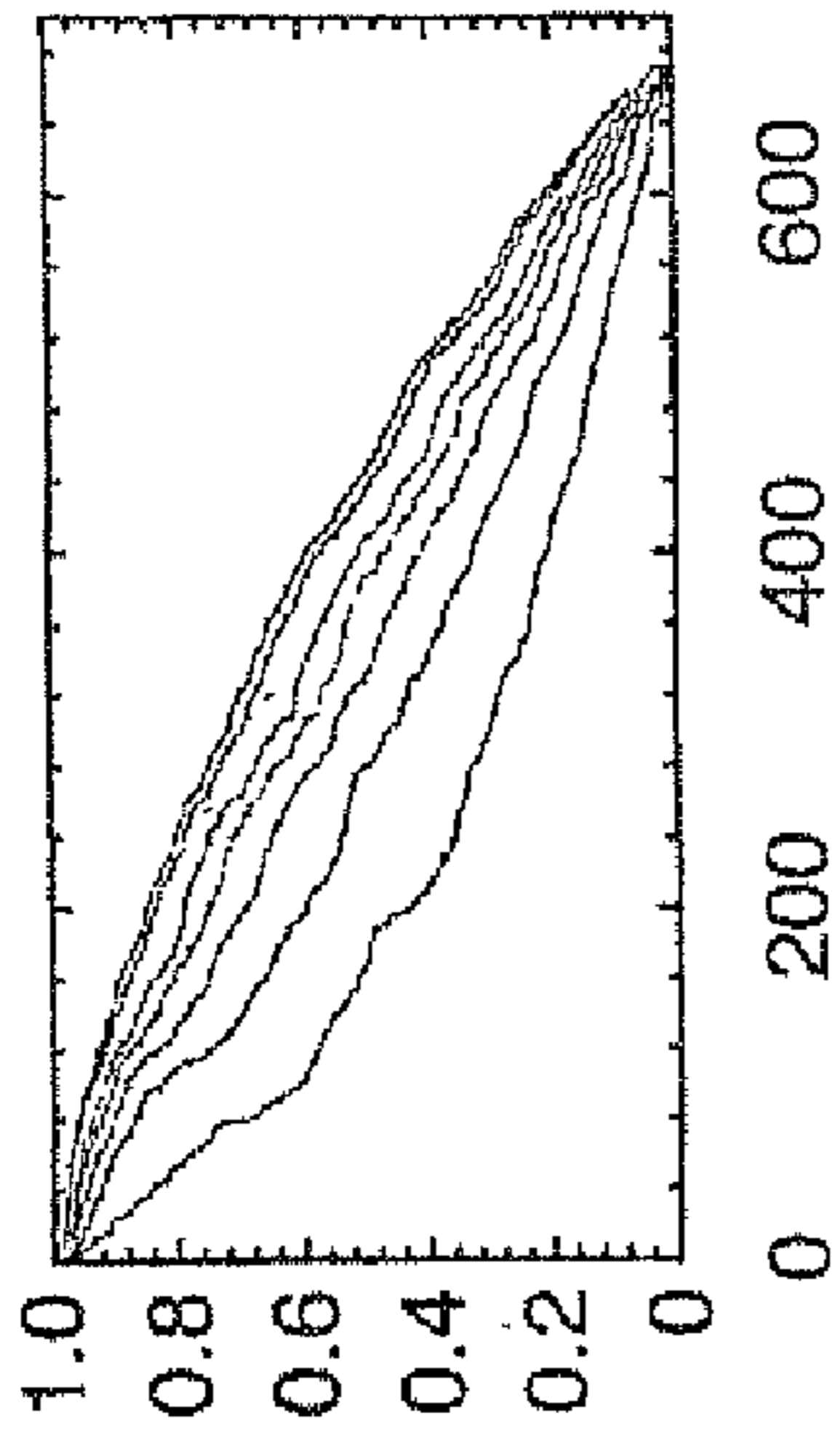


Fig. 1C

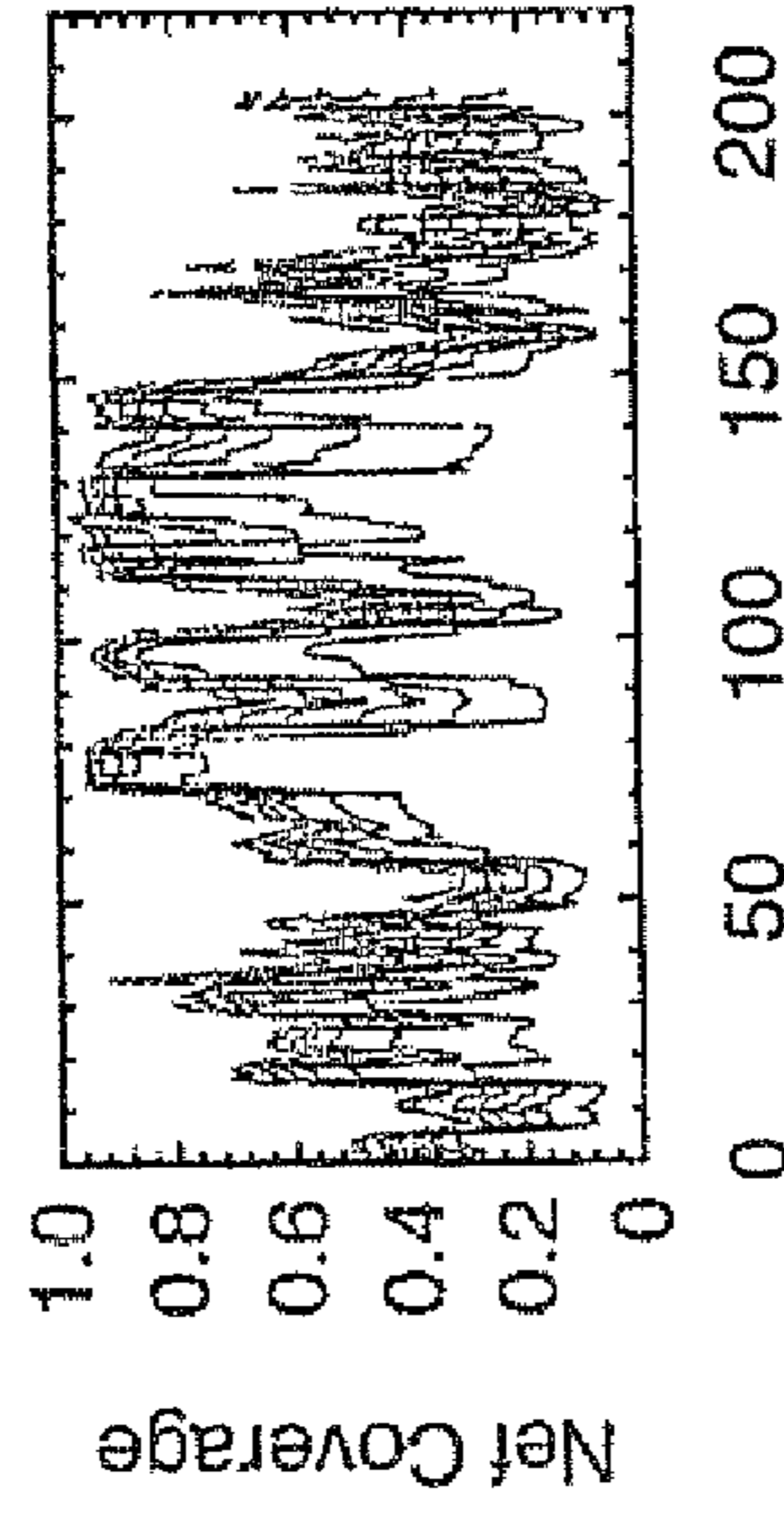


Fig. 1D

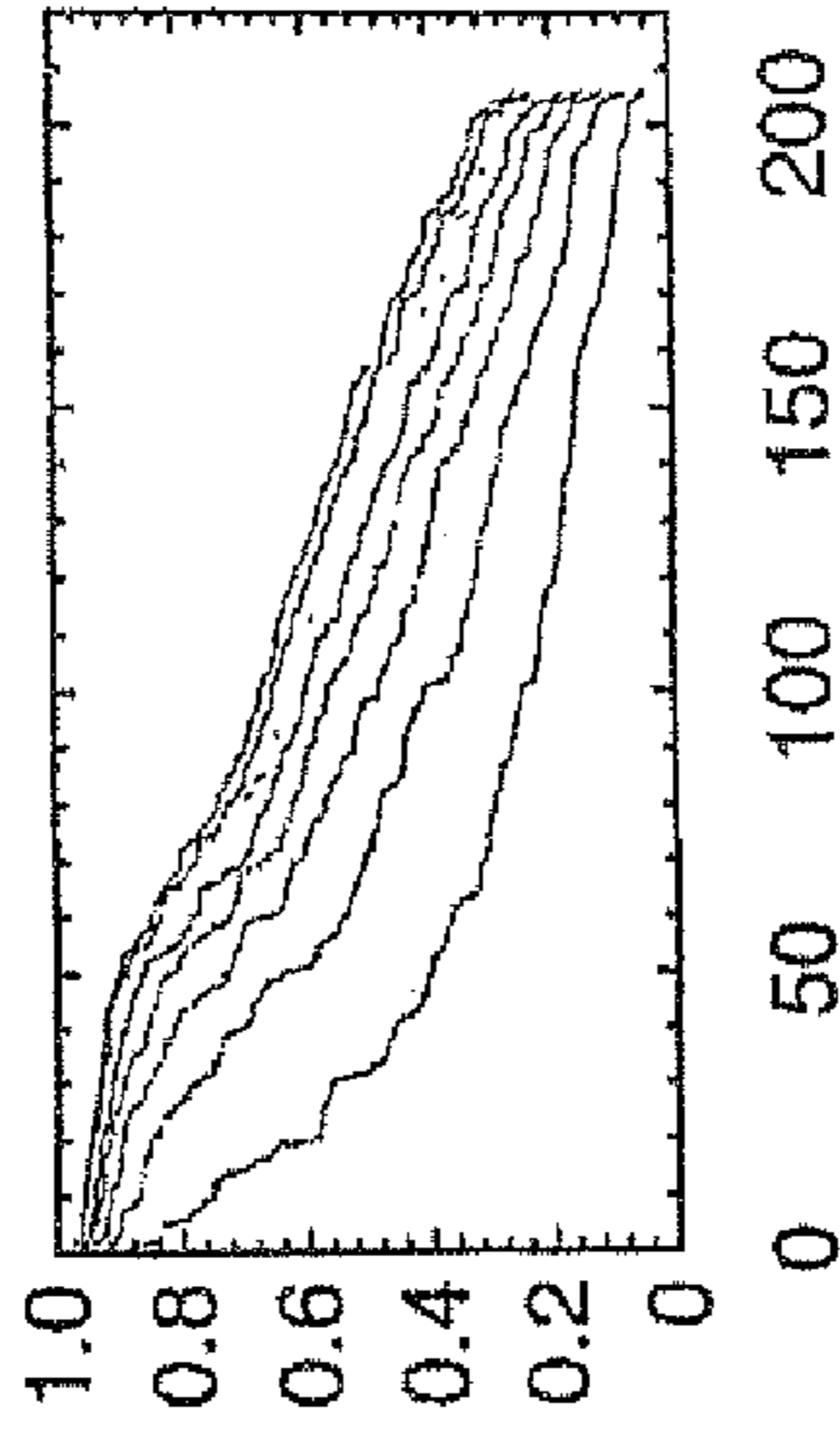


Fig. 1E

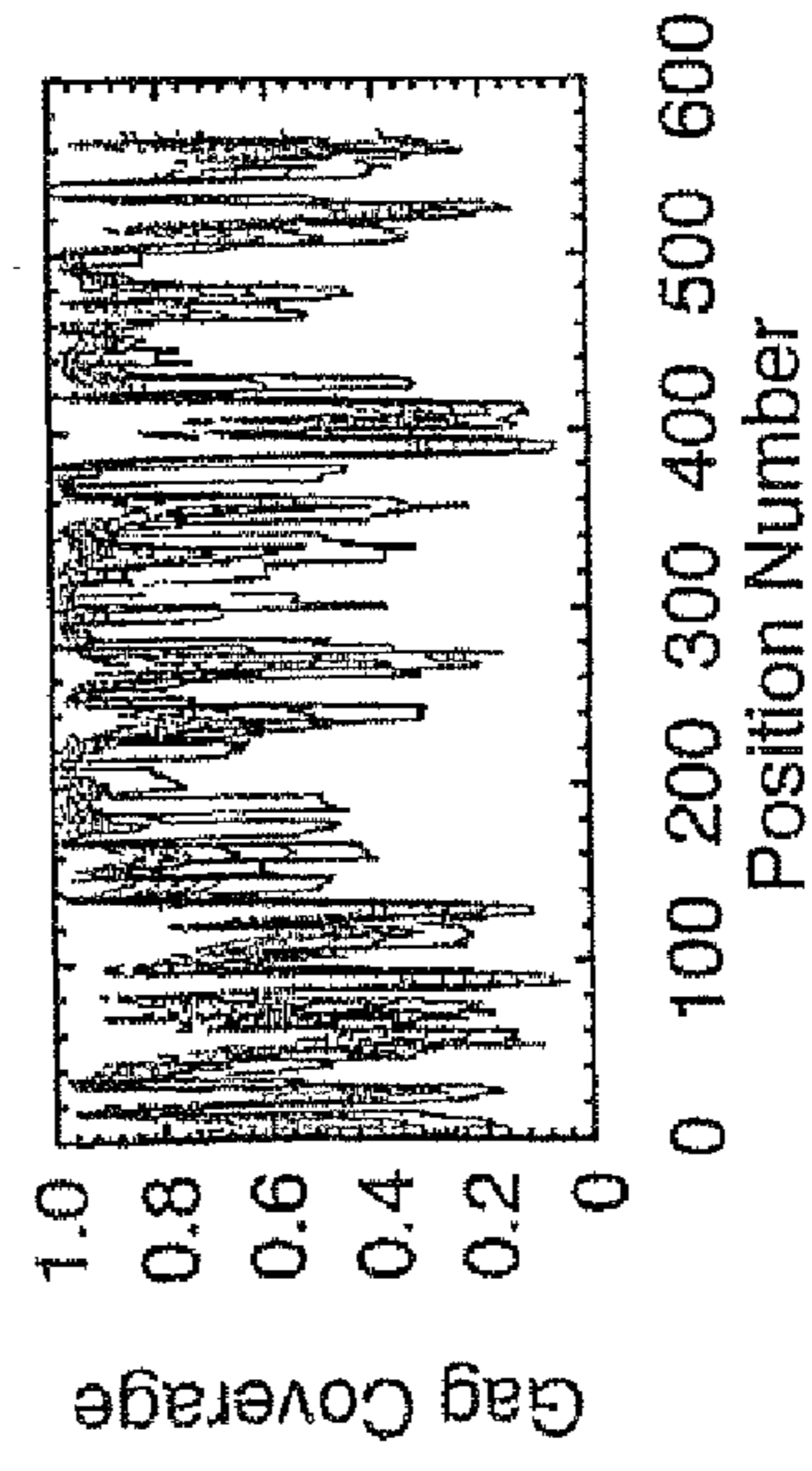


Fig. 1F

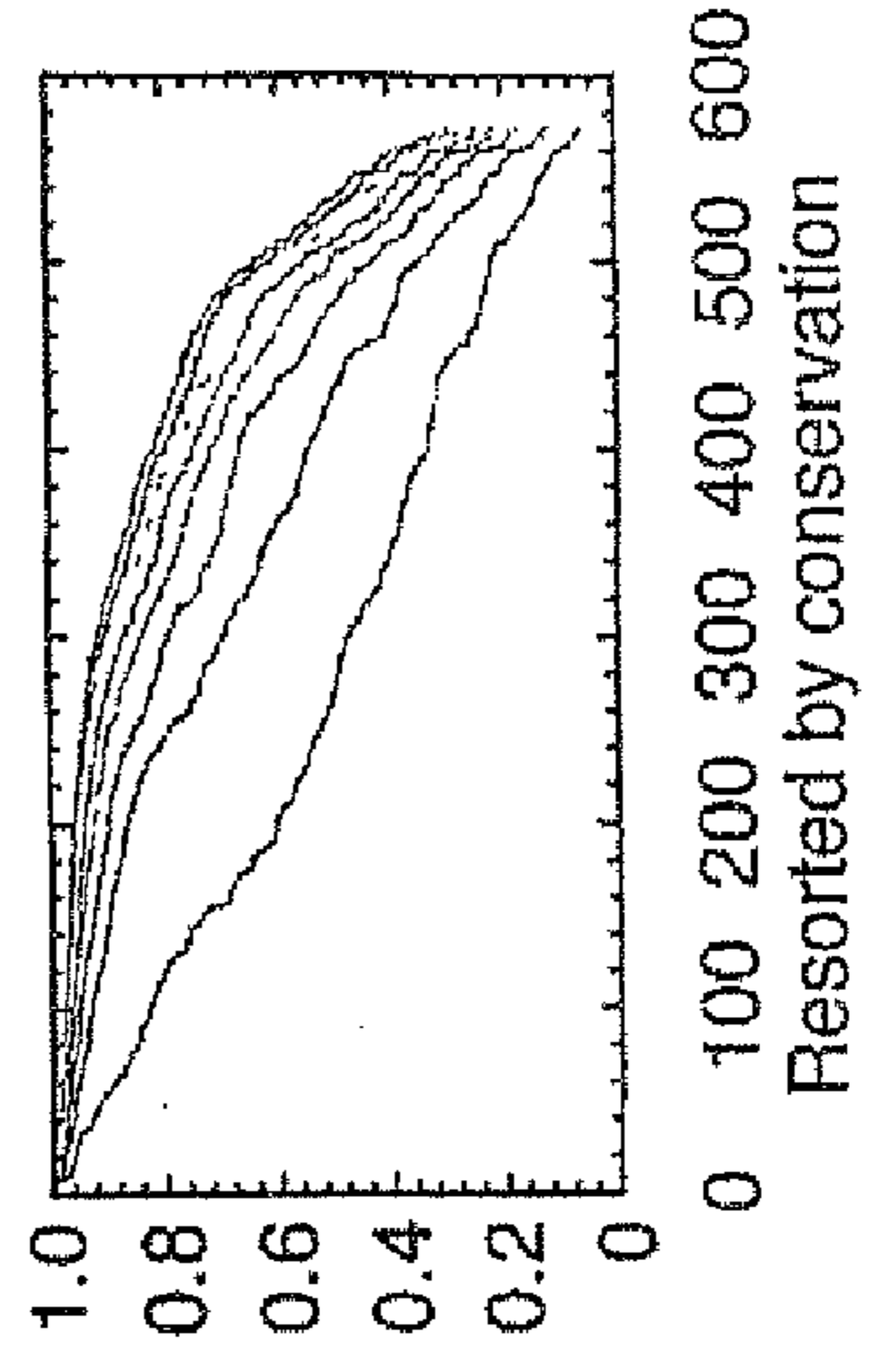


Fig. 2A

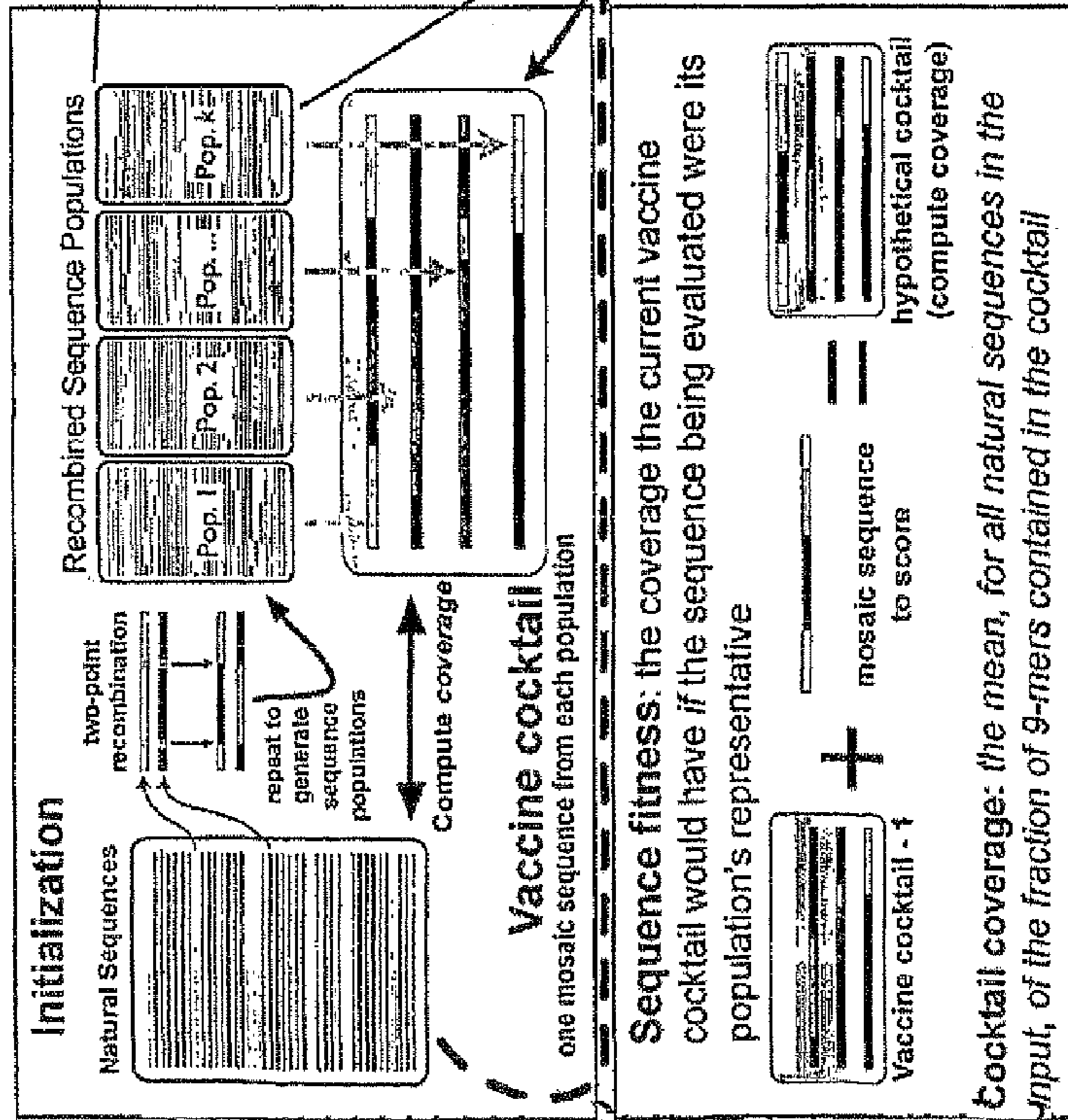


Fig. 2C

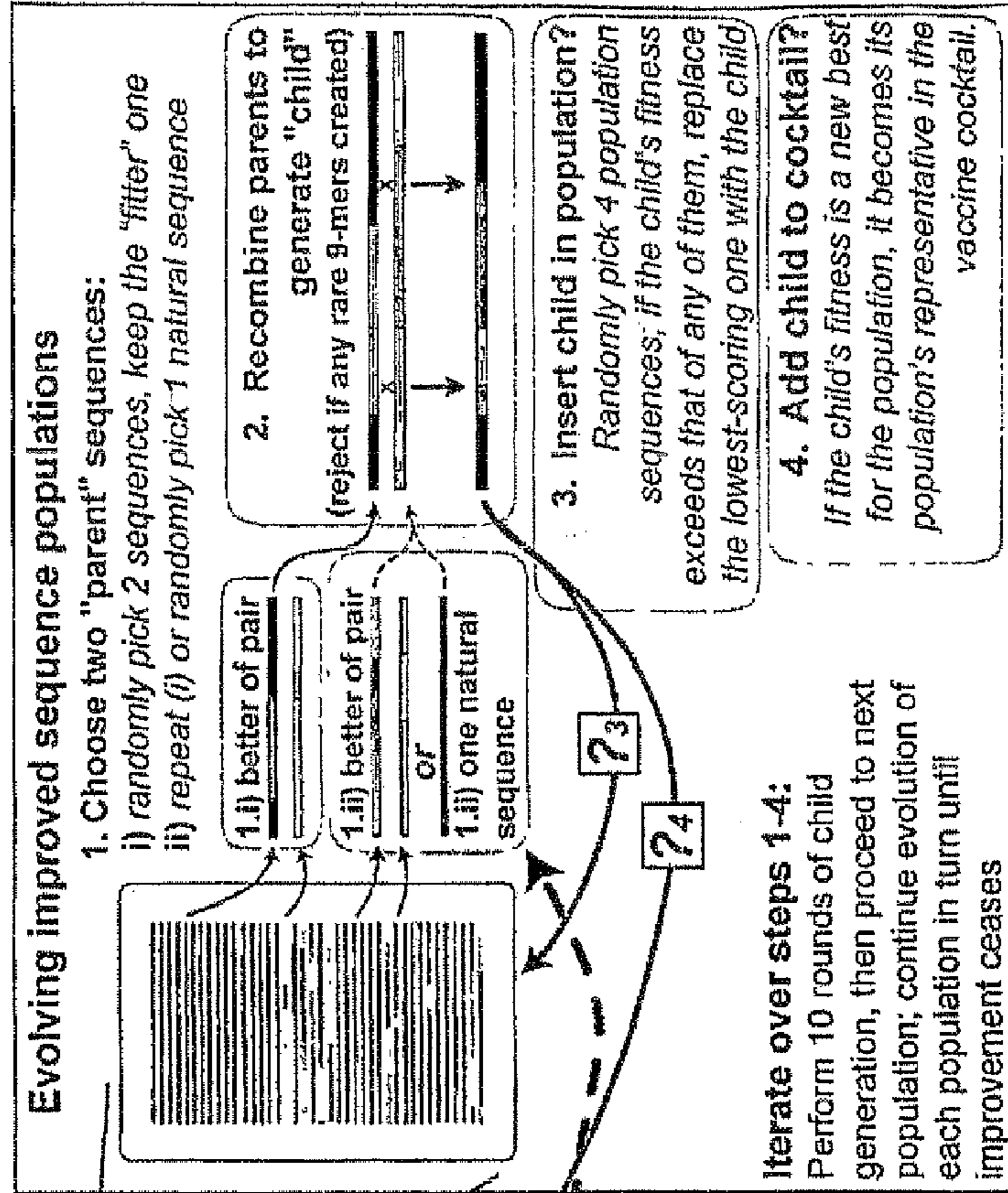


Fig. 2B

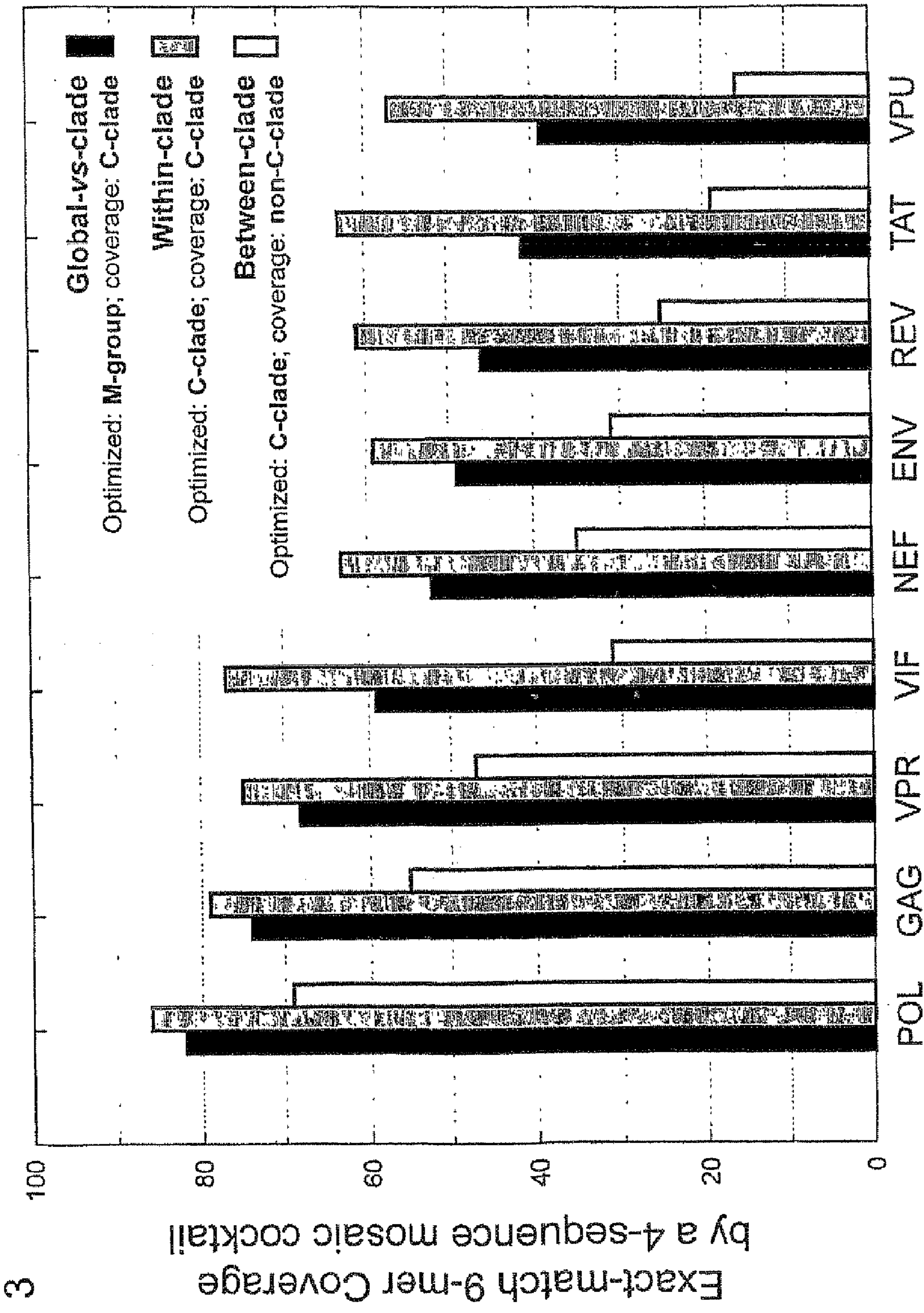


Fig. 3

Fig. 4A

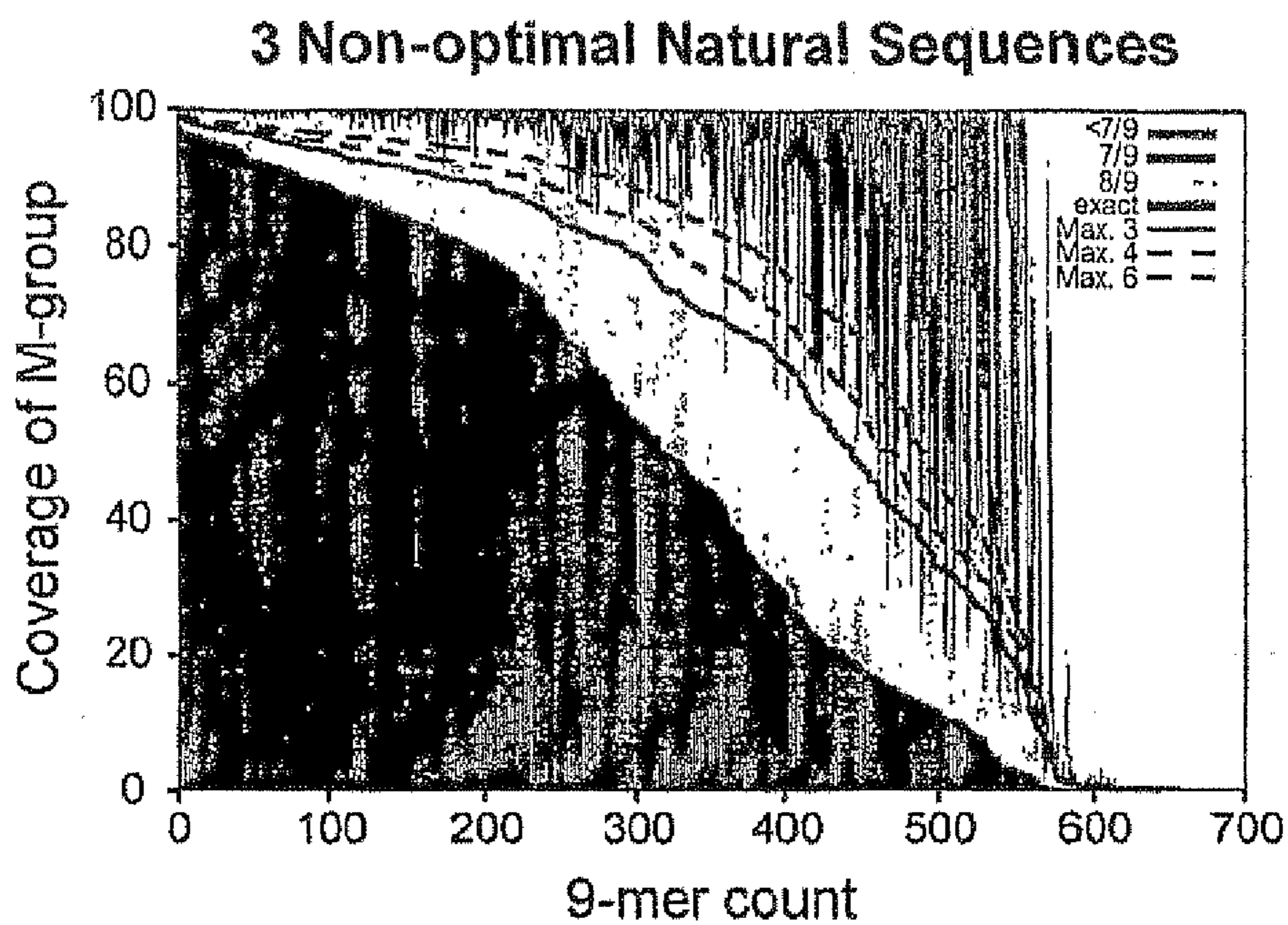


Fig. 4B

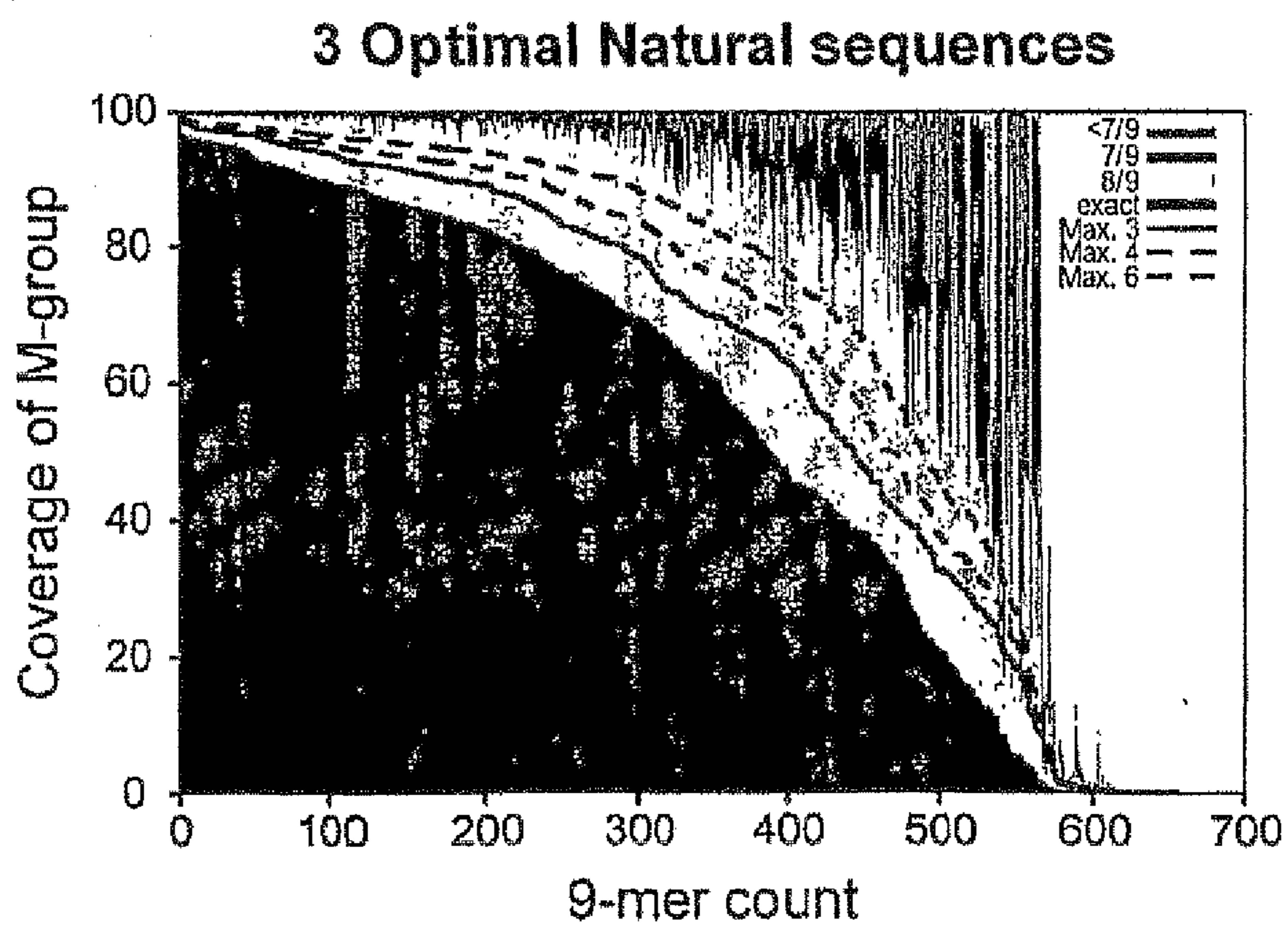


Fig. 4C

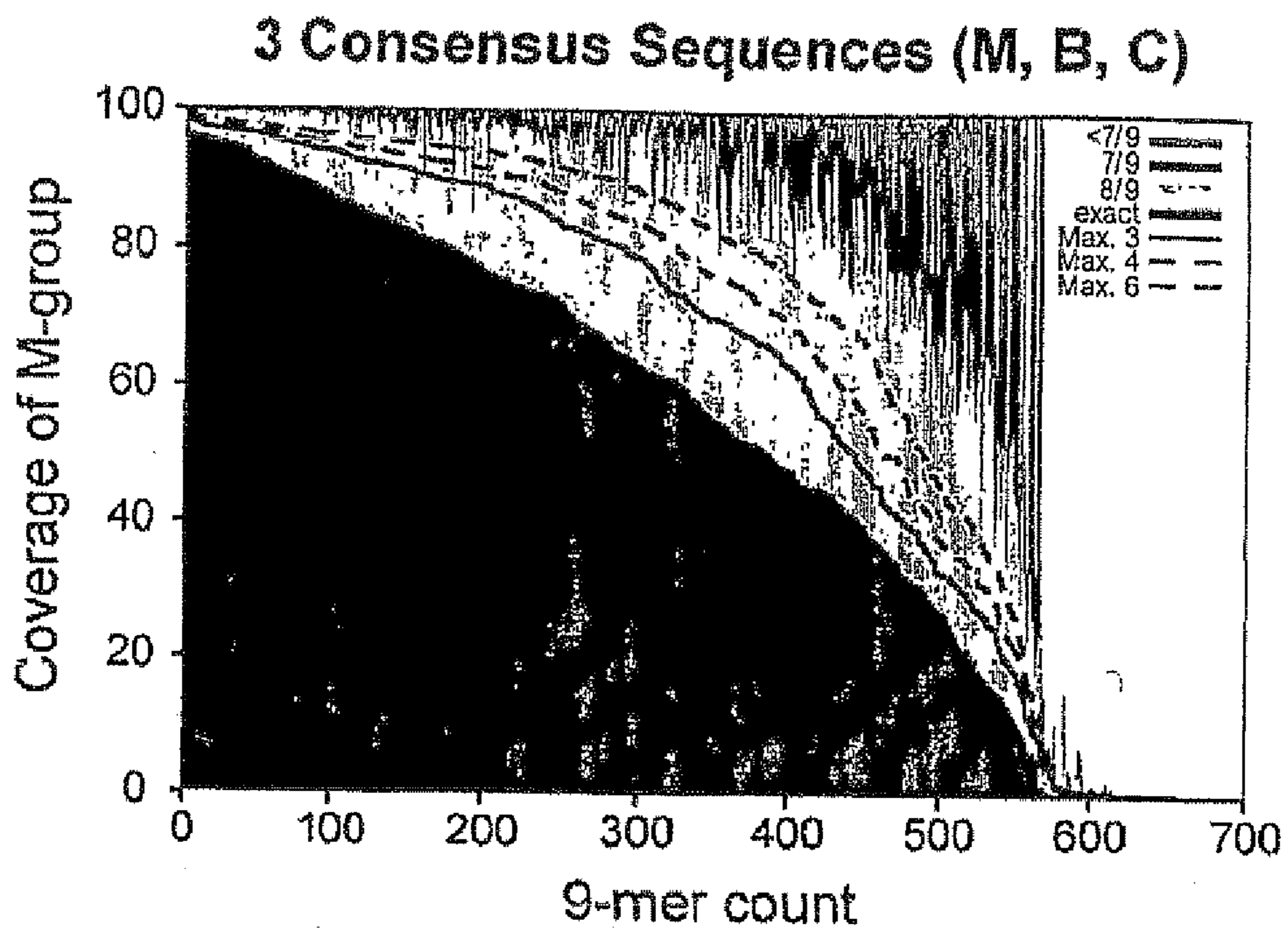


Fig. 4D

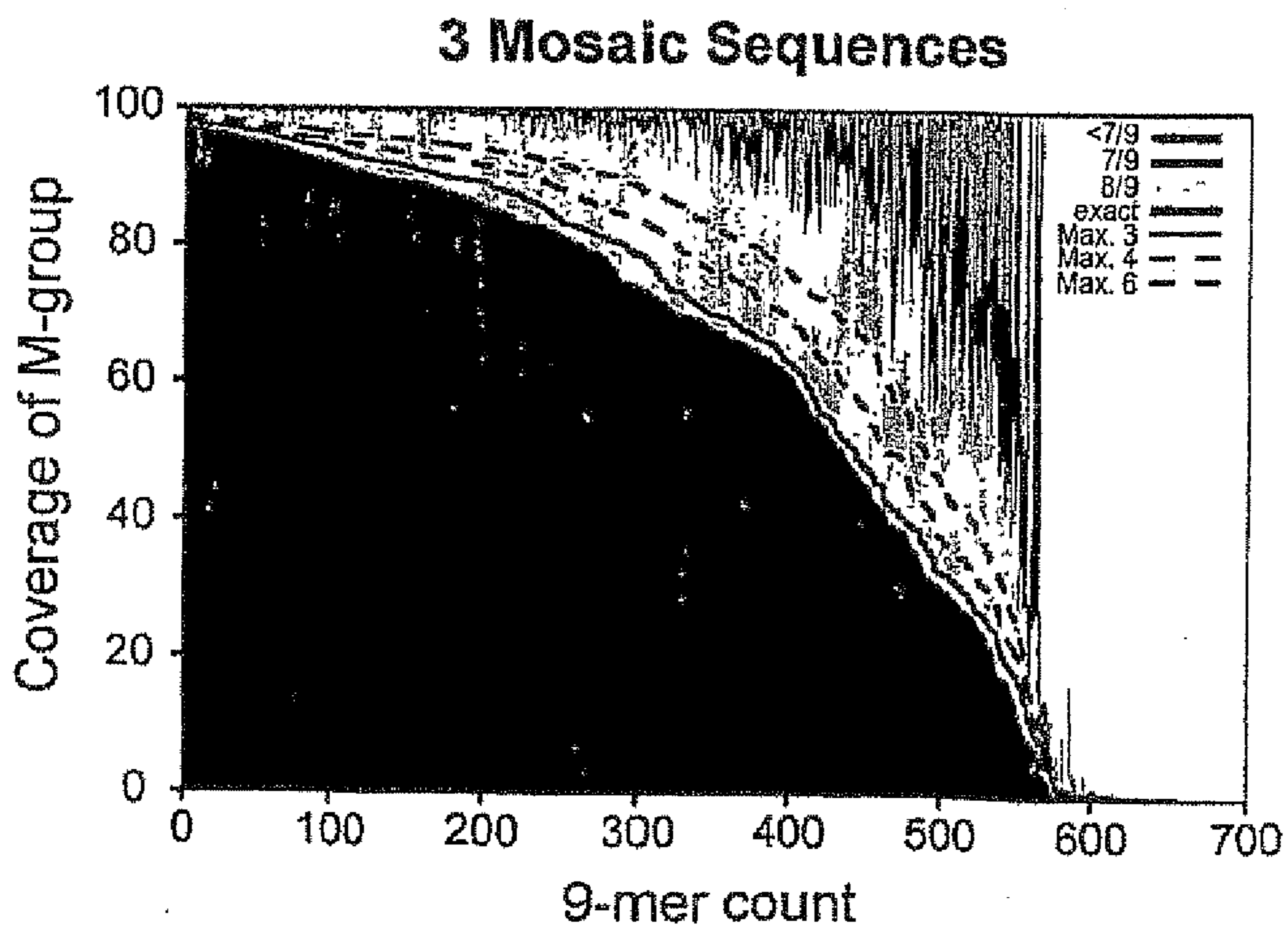


Fig. 4E

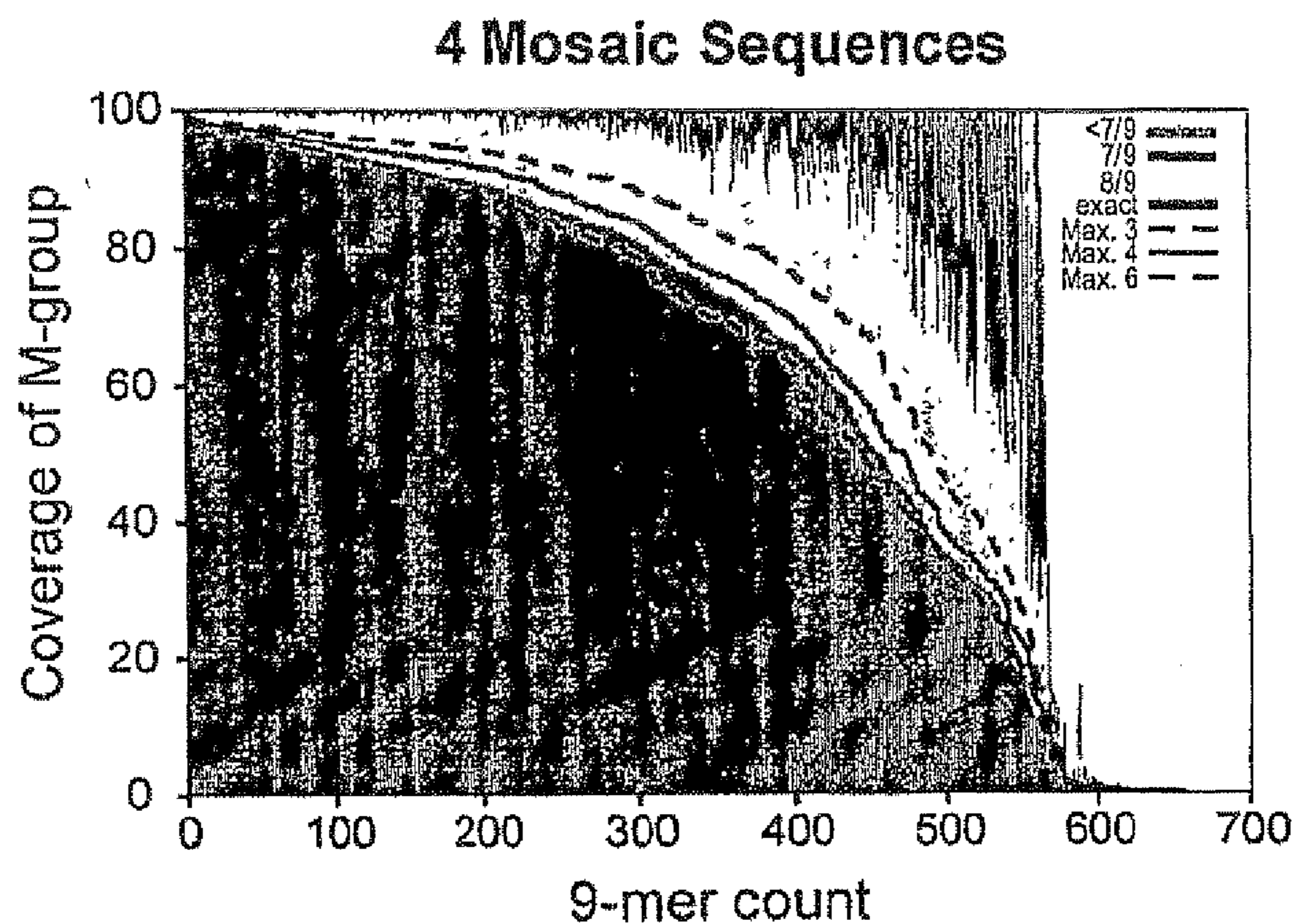


Fig. 4F

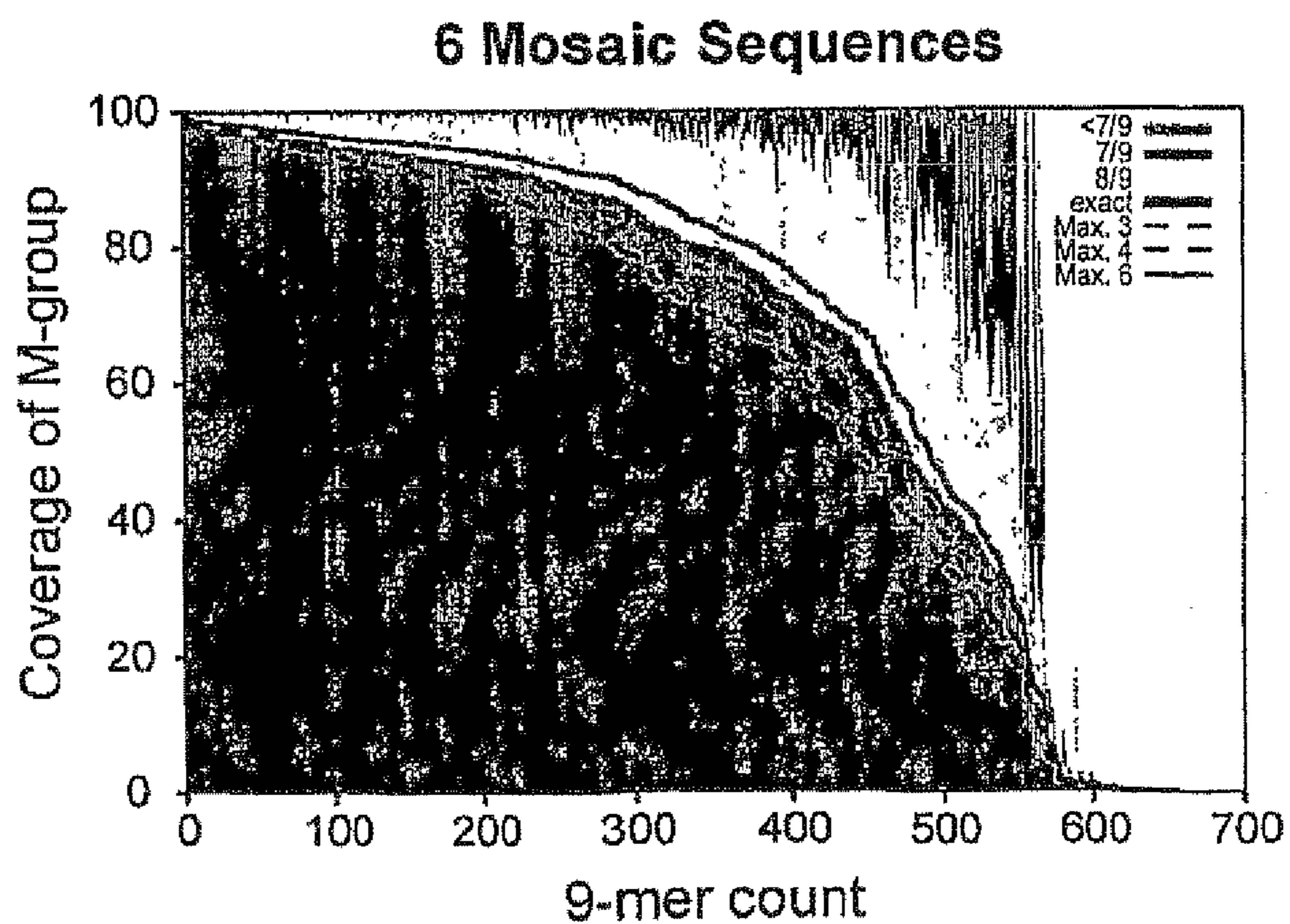
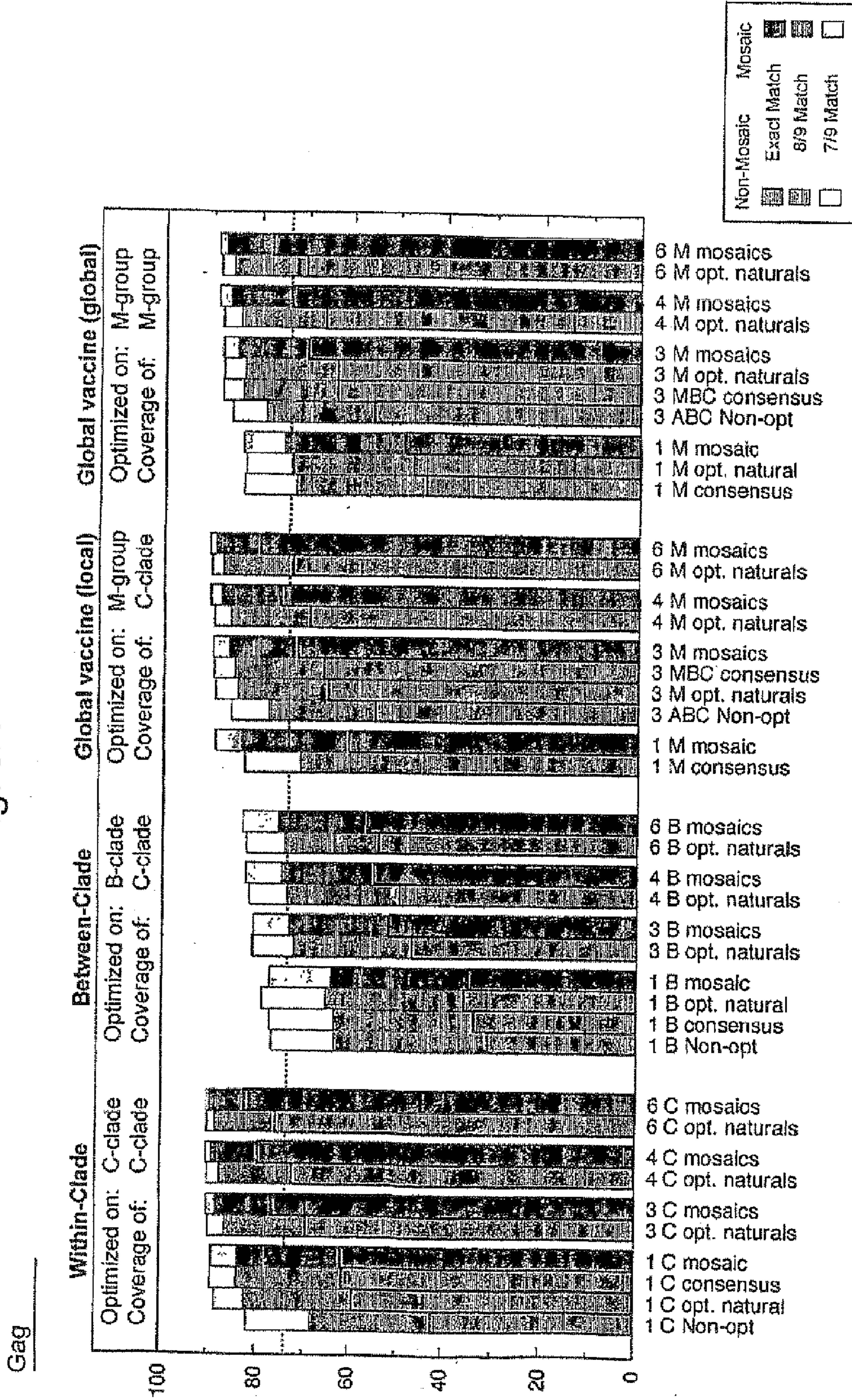


Fig. 5A



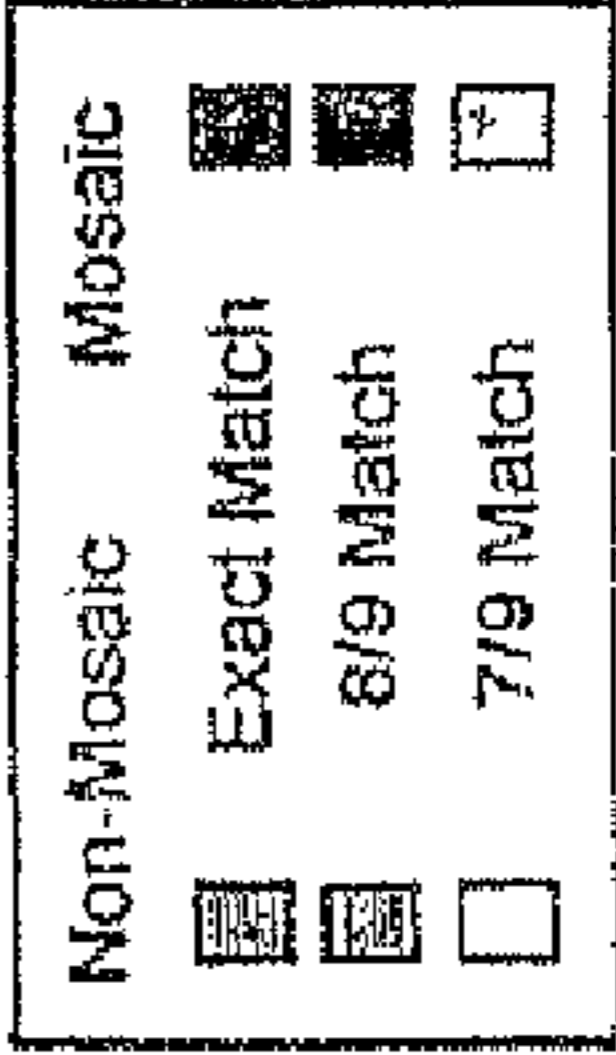
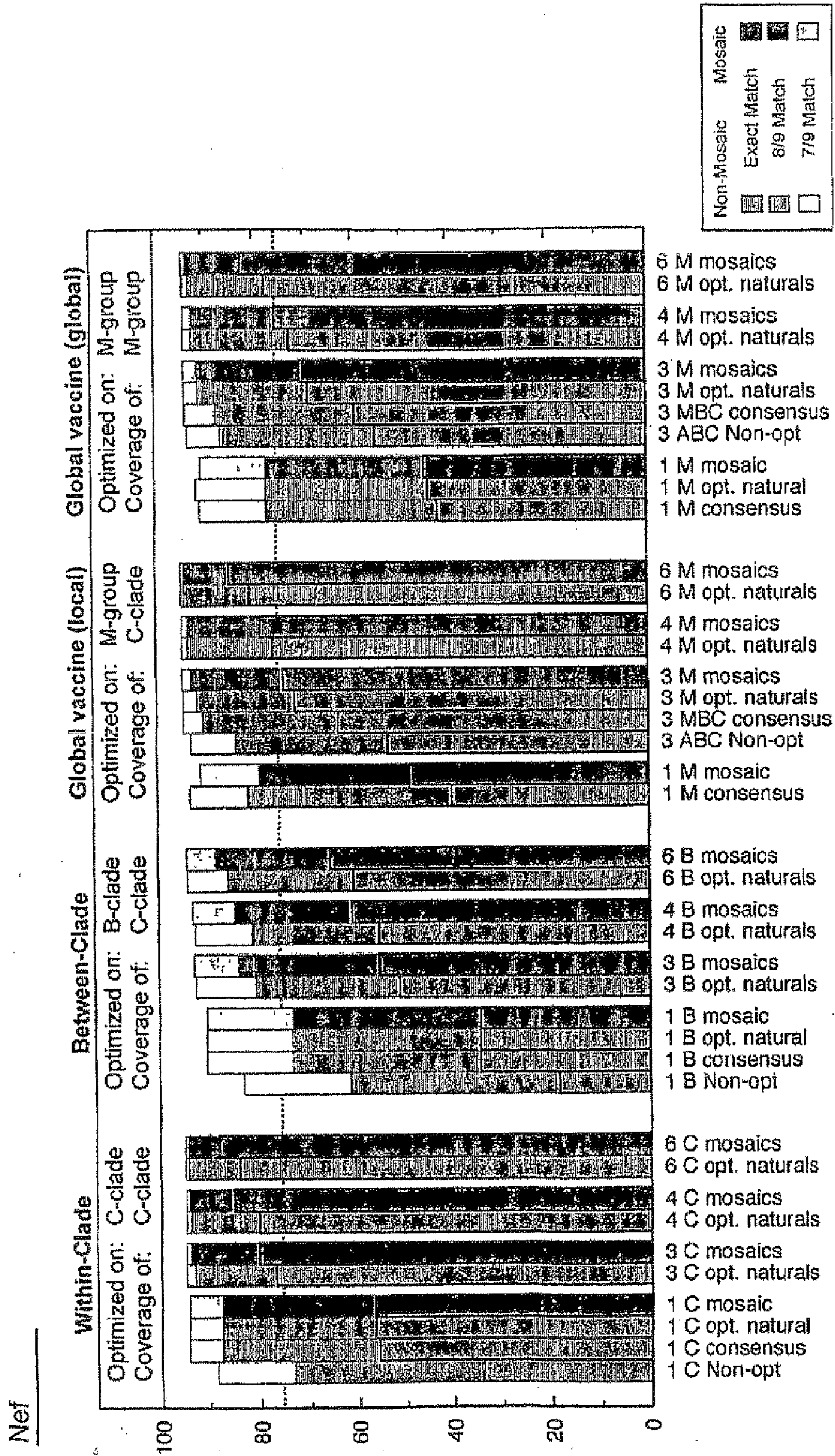


Fig. 6A

Gag coverage

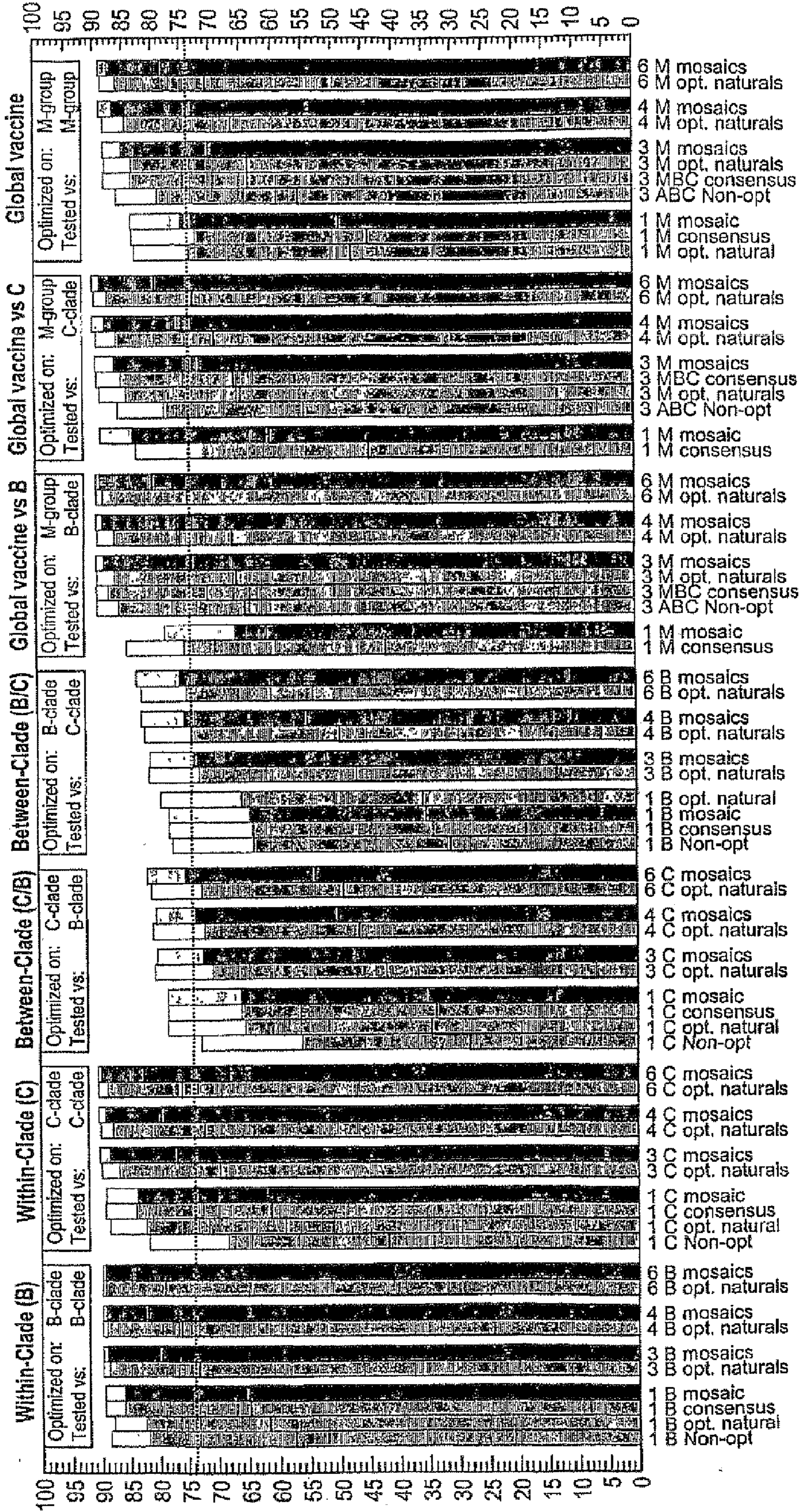


Fig. 6B

Nef coverage (central region)

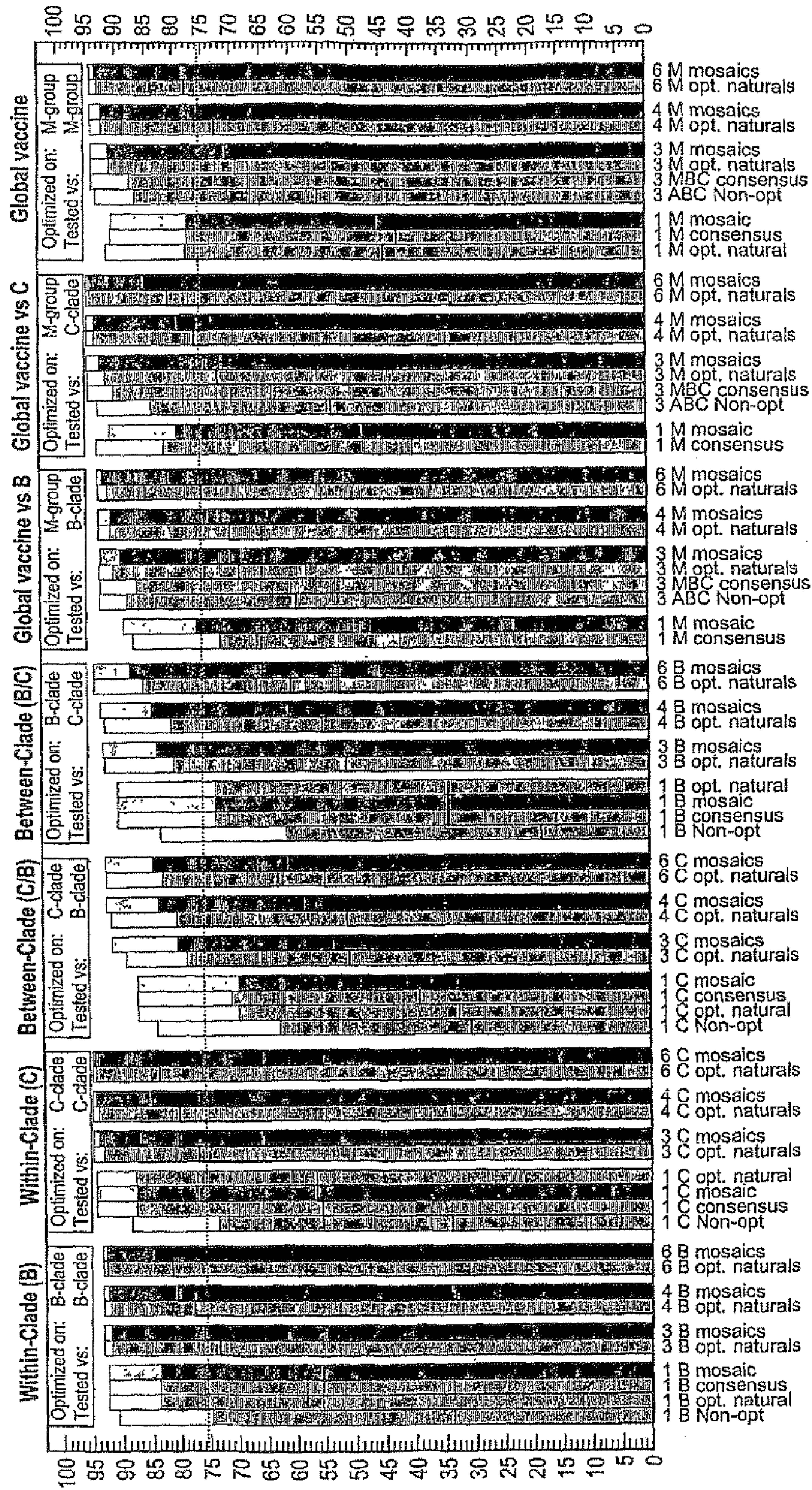


Fig. 7A

9-mer Frequencies (0-60%)

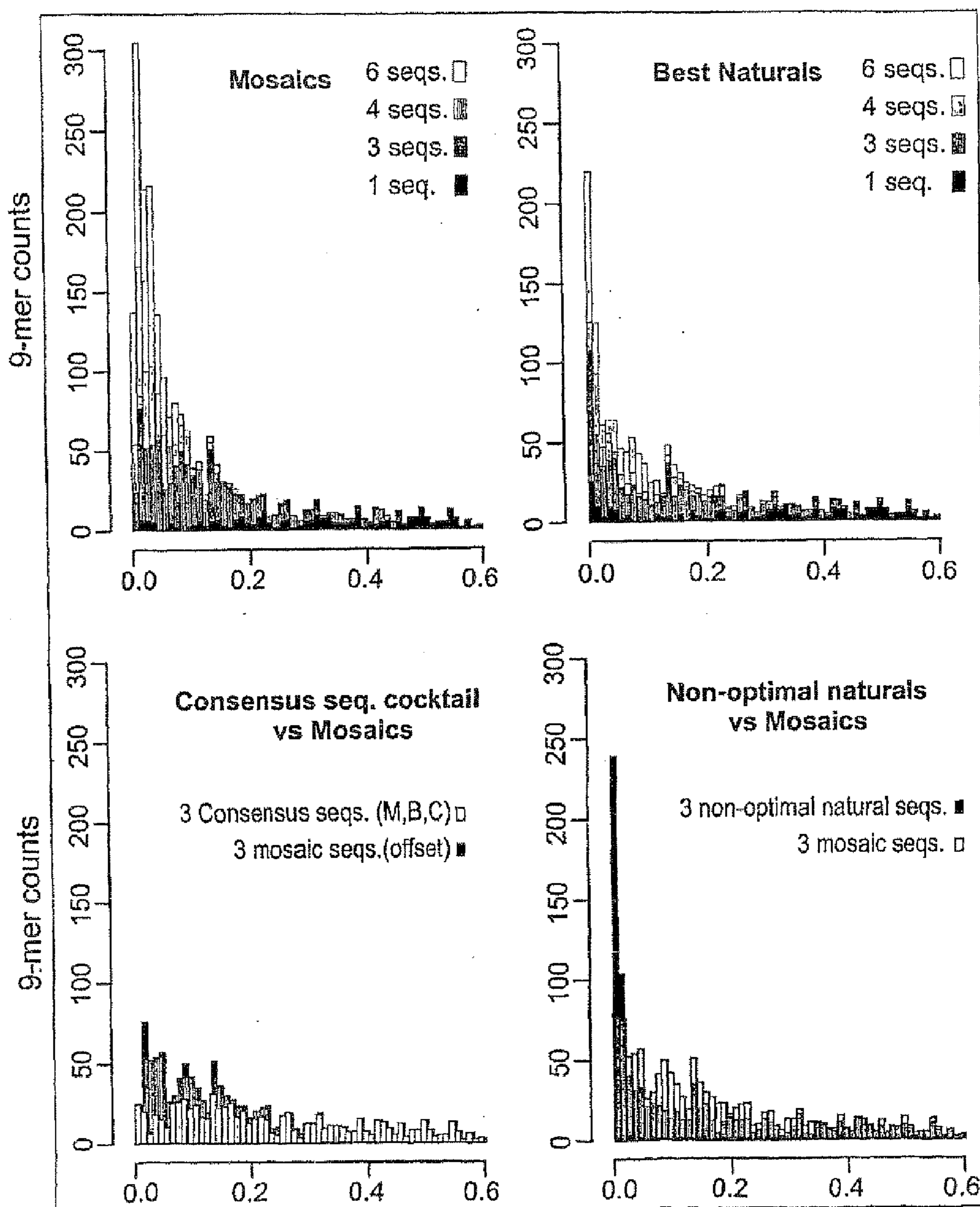
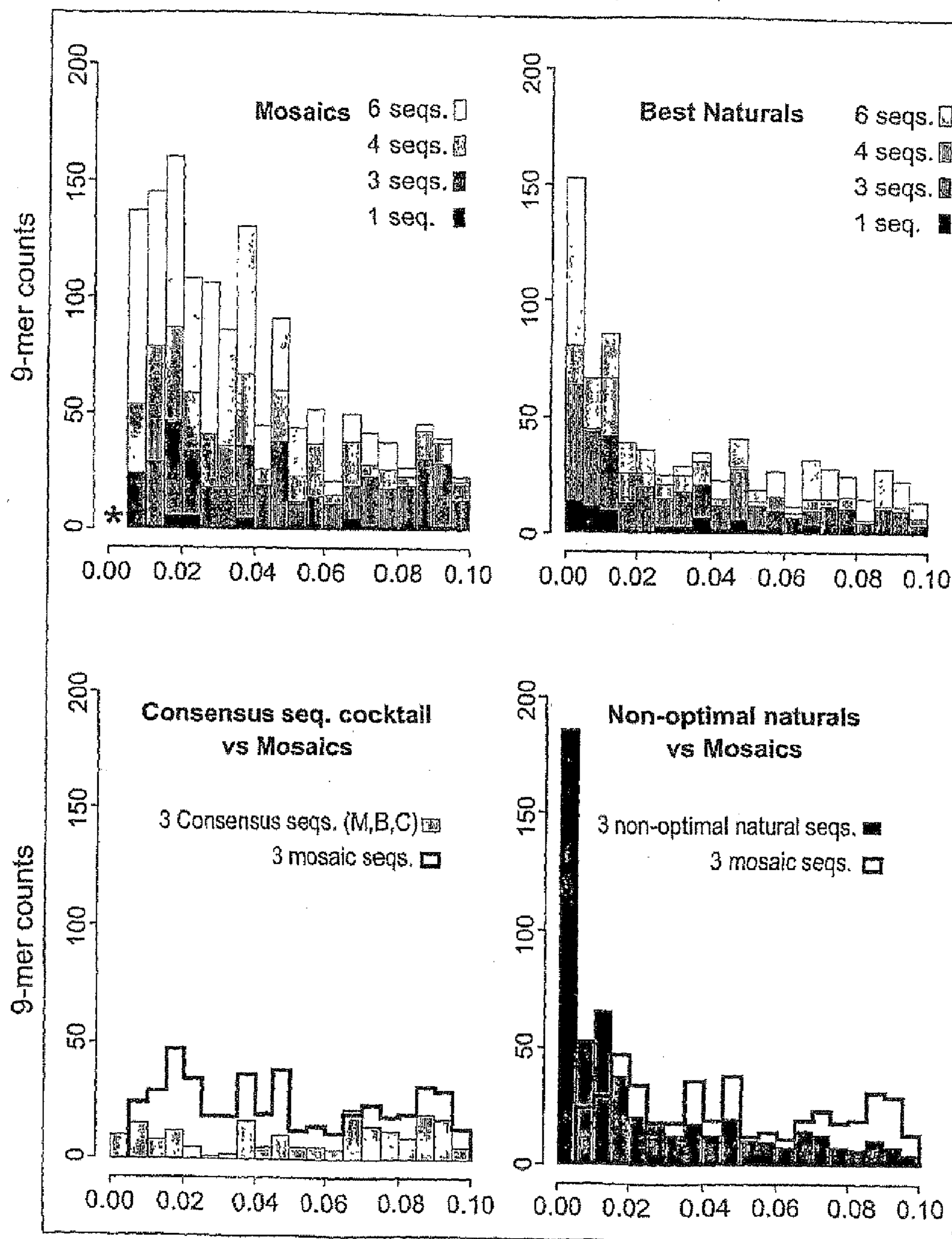
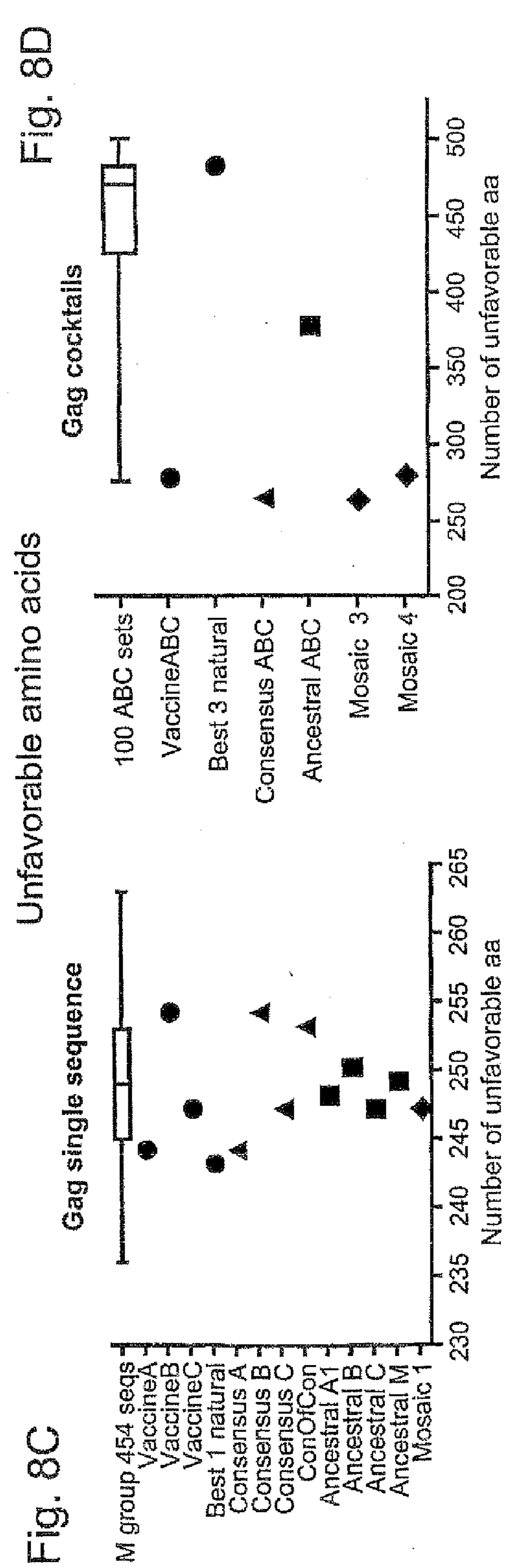
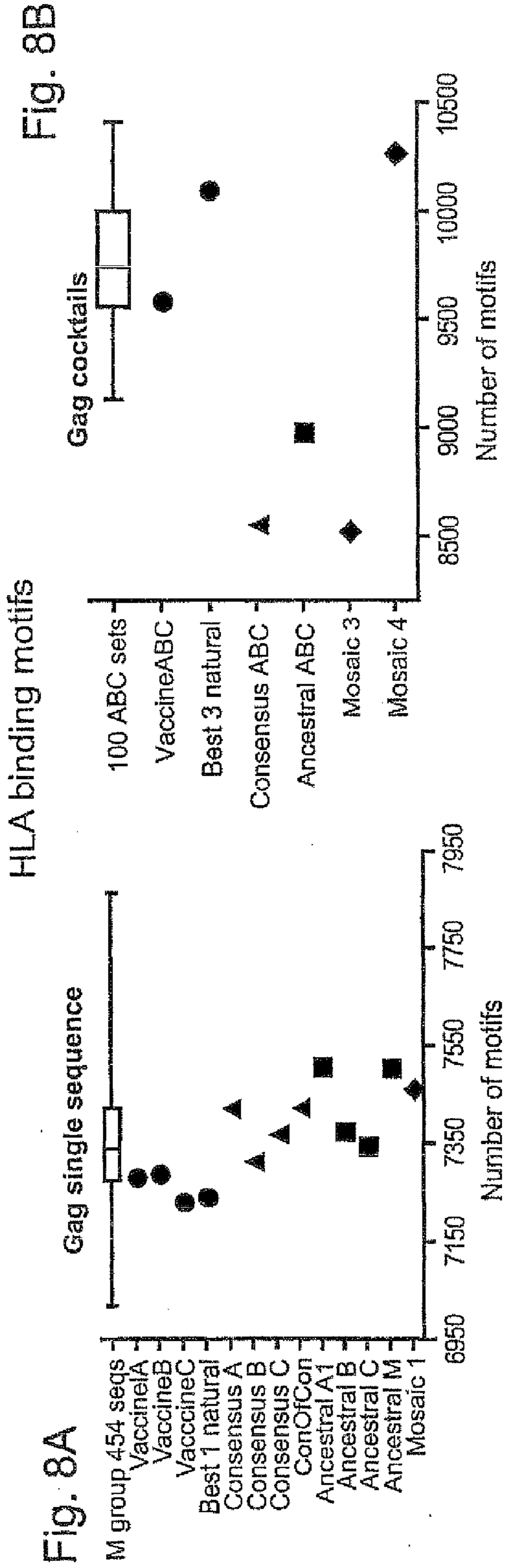


Fig. 7B

9-mer Frequencies (0-10%)





HLA binding motifs

Unfavorable amino acids

Fig. 8B

Fig. 8D

Fig. 9

>nef_coreB.syn1.1
EVGFVVRPQVPLRPMTYKALDLSHFLKEKGGLEGLIYSQKRQDILDLWVYHTQGYFPDW
QNYTPGPGIRYPLTFGWCFKLVPE

>nef_coreB.syn3.1
EVGFVVKPQVPLRPMTYKAAVDLSHFLKEKGGLEGLVYSQKRQDILDLWYHTQGYFPDW
QNYTPGPGTRFPLTFGWCFKLVPE

>nef_coreB.syn3.2
EVGFVVTQVPLRPMTYKALDLSHFLREKGGLEGLIYSQKRQEIIDLWVYHTQGYFPDW
HNYTPGPGVRYPLTFGWCFKLVPE

>nef_coreB.syn3.3
EVGFVVRPQVPLRPMTYKAAVDLSHFLKEKGGLEGLIHSQRRQDILDLWVYHTQGFPPDW
QNYTPGPGIRYPLTFGWCFKLVPE

>nef_coreB.syn4.1
EVGFVVTQVPLRPMTYKAAVDLSHFLREKGGLEGLIHSQKRQDILDLWYHTQGYFPDW
QNYTPGPGIRYPLTFGWCFKLVPE

>nef_coreB.syn4.2
DVGFVVRPQIPLRPMTYKAAVDLSHFLREKGGLEGLVYSQKRQDILDLWVYHTQGFPPDW
QNYTPGPGTRFPLTFGWCFKLVPE

>nef_coreB.syn4.3
EVGFVVRPQVPLRPMTYKAAVDLSHFLKEKGGLEGLIYSQKRQEIIDLWVYHTQGYFPDW
GNYTPGPGTRYPLTFGWCFKLVPE

>nef_coreB.syn4.4
EVGFVVKPQVPLRPMTYKALDLSHFLKEKGGLEGLIYSQRRQDILDLWVYHTQGYFPDW
HNYTPGPGVRYPLTFGWCFKLVPE

>nef_coreB.syn6.1
EVGFPIRPQVPLRPMTYKALDLSHFLKEKGGLEGLIYSQKRQEIIDLWVYHTQGYFPDW
HNYTPGPGIRYPLCFGWCFKLVPE

>nef_coreB.syn6.2
EVGFVVTQVPLRPMTYKAAVDLSHFLKEKGGLEGLIYSQRRQDILDLWYHTQGYFPDW
QCYTPGPGVRFPLTFGWCFKLVPE

>nef_coreB.syn6.3
EVGFVVKPQVPLRPMTYKAAVDLSHFLKEKGGLEGLIYSQKRQDILDLWYHTQGYFPDW
QNYTPGPGIRYPLTFGWCFKLVPE

>nef_coreB.syn6.4
DVGFVVRPQVPLRPMTYKAAVDLSHFLKEKGGLEGLIYSQRRQDILDLWVYHTQGFPPDW
QNYTPGPGTRYPLTFGWCFKLVPE

>nef_coreB.syn6.5
EVGFVVRPQIPLRPMTYKALDLSHFLREKGGLEGLVYSQKRQDILDLWVYHTQGYFPDW
GNYTPGPGTRFPLTFGWCFKLVPE

>nef_coreB.syn6.6
EVGFVVRPQVPLRPMTYKAAFDLSHFLKDKGGLEGLIHSQKRQDILDLWVYHTQGYFPDW
QNYTPGPGVRYPLTFGWCFKLVPE

>nef_coreC.syn1.1
EVGFVVRPQVPLRPMTYKAAFDLSHFLKEKGGLEGLIYSKQRQEIIDLWVYHTQGFPPDW
QNYTPGPGVRYPLTFGWCFKLVPE

Fig. 9 cont'd-1

>nef_coreC.syn3.1
EVGF^PVTPQVPLRPMTFKGAFDLGFFLKEKGGLDGLIYSKKRQDILDLWVYHTQGYFPDW
QNYTPGGVRYPLTFGW^CYKLV^PV^D
>nef_coreC.syn3.2
EVGF^PVKPQVPLRPMTYKAAF^DLSFFLKDKGGLEGLIWSKKRQEILDLWVYHTQGF^FPDW
QNYTPGGGIRYPLTFGW^PPKLV^PV^D
>nef_coreC.syn3.3
EVGF^PVRPQVPLRPMTYKAAF^DLSFFLKEKGGLEGLIYSKKRQEILDLWVYNTQGF^FPDW
HNYTPGGVRFPLTFGW^CFKLV^PV^D

>nef_coreC.syn4.1
EVGF^PVRPQVPLRPMTYKAAF^DLSFFLKEKGGLEGLIWSKKRQEILDLWVYNTQGYFPDW
QCYTPGGVRFPLTFGW^CFKLV^PV^D
>nef_coreC.syn4.2
DVGF^PVRPQV^PVRPMTYKAAF^DLSFFLKDKGGLEGLIHSKRRQDILDLWVYNTQGF^FPDW
HNYTPGGGIRYPLTFGW^CFKLV^PV^D
>nef_coreC.syn4.3
EVGF^PVKPQVPLRPMTYKAAV^DLSFFLKEKGGLEGLIYSKKRQEILDLWVYHTQGF^FPDW
QNYTPGGGTRYPLTFGW^PPKLV^PV^D
>nef_coreC.syn4.4
EVGF^PVTPQVPLRPMTFKGAFDLGFFLKEKGGLDGLIYSKKRQDILDLWVYHTQGYFPDW
QNYTPGGVRYPLTFGW^CYKLV^PV^D

>nef_coreC.syn6.1
DVGF^PVRPQVPLRPMTYKAAF^DLSFFLKEKGGLDGLIYSKKRQEILDLWVYNTQGYFPDW
QCYTPGGVRYPLTFGW^CYKLV^PV^D
>nef_coreC.syn6.2
EVGF^PVKPQV^PVRPMTYKAAF^DLSFFLKDKGGLEGLIWSKKRQEILDLWVYHTQGF^FPDW
QNYTPGGGIRYPLTFGW^CFKLV^PV^D
>nef_coreC.syn6.3
EVGF^PVKPQVPLRPMTFKGAFDLGFFLKEKGGLEGLIYSKQRQDILDLWVYHTQGF^FPDW
HNYTPGGVRLPLTFGW^CFKLV^PV^D
>nef_coreC.syn6.4
GVGF^PVRPQV^PVRPMTYKAAF^DLGFFLKDKGGLEGLIYSKKRQDILDLWVYNTQGF^FPDW
QNYTPGGVRFPLTFGW^CFKLV^PV^D
>nef_coreC.syn6.5
EVGF^PVTPQVPLRPMTYKAAV^DLSWFLKEKGGLDGLIYSRKRQEILDLWVHHTQGF^FPDW
QNYTPGGGTRFPLTFGW^CFKLV^PV^D
>nef_coreC.syn6.6
EVGF^PVRPQV^PVRPMTYKAAV^DLSFFLKEKGGLEGLIHSKRRQDILDLWVYHTQGYFPDW
QNYTPGGGTRYPLTFGW^PPKLV^PV^D

>nef_coreM.syn1.1
EVGF^PVRPQVPLRPMTYKAAV^DLSHFLKEKGGLEGLIYSKKRQEILDLWVYHTQGYFPDW
QNYTPGGVRYPLTFGW^CFKLV^PV^D

Fig. 9 cont'd-2

>nef_coreM.syn3.1
DVGFPVVRPQVPLRPMTYKAAVDLSHFLKEKGGLEGLVYSQKRQDILDLWVYHTQGFFPDW
QNYTPGPGVRYPLTFGWICYKLVVD
>nef_coreM.syn3.2
EVGFPVVRPQVVRPMTYKGAFDLSFFLKEKGGLEGLIYSKKRQEILDLWVYHTQGYFPDW
HNYTPGPGTRFPLTFGWCFKLVVD
>nef_coreM.syn3.3
EVGFPVKPQVPLRPMTYKALDLSHFLKEKGGLDGLIYSKKRQDILDLWVYNTQGYFPDW
QNYTPGPGIRYPLTFGWCFKLVVE

>nef_coreM.syn4.1
EVGFPVTPQVPLRPMTFKGAFDLGFFLKEKGGLEGLIYSKKRQEILDLWVYHTQGFFPDW
QNYTPGPGTRYPLCFGWCFKLVVE
>nef_coreM.syn4.2
EVGFPVKPQVPLRPMTYKAAVDLSHFLKEKGGLEGLVYSQKRQDILDLWVYHTQGYFPDW
QNYTPGPGIRYPLTFGWICYKLVVD
>nef_coreM.syn4.3

DVGFPVVRPQVPLRPMTYKALDLSHFLKEEGGLEGLIYSQKRQEILDLWVYNTQGYFPDW
QNYTPGPGVRYPLTFGWCFKLVVD
>nef_coreM.syn4.4
EVGFPVVRPQVVRPMTYKGAFDLSFFLKEKGGLDGLIYSKKRQDILDLWVYNTQGFFPDW
HNYTPGPGTRFPLTFGWCFELVVD

>nef_coreM.syn6.1
EVGFPVVRPQVTRPMTYKAVDLSHFLKEKGGLEGLVYSQKRQDILDLWVHHTQGFFPDW
QNYTPGPGTRYPLTFGWPFKLVVD

>nef_coreM.syn6.2
DVGFPVVRPQVVRPMTYKAAFDSLFFLREKGGLDGLIYSKKRQDILDLWVYNTQGYFPDW
QNYTPGPGVREPLTFGWCFELVVD

>nef_coreM.syn6.3
NVGFPVVRPQVPLRPMTFKGAFDLGFFLKEKGGLEGLIYSKKRQEILDLWVYHTQGYFPDW
HNYTPGPGTRFPLTFGWCFKLVVE

>nef_coreM.syn6.4
EVGFPVTPQVPLRPMTYKGAFDLSFFLKEKGGLDGLIYSRKRQEILDLWVYNTQGFFPDW
QNYTPGPGIRYPLTFGWCFKLVPM

>nef_coreM.syn6.5
EVGFPVKPQVPLRPMTYKAAVDLSHFLREKGGLEGLIHSQRRQDILDLWIYHTQGYFPDW
QCYTPGPGVRYPLTFGWICYKLVVD

>nef_coreM.syn6.6
GVGFPVVRPQIPLRPMTYKALDLSHFLKEEGGLEGLIYSQKRQDILDLWVYHTQGFFPDW
HNYTPGPGIRYPLCFGWCFKLVVD

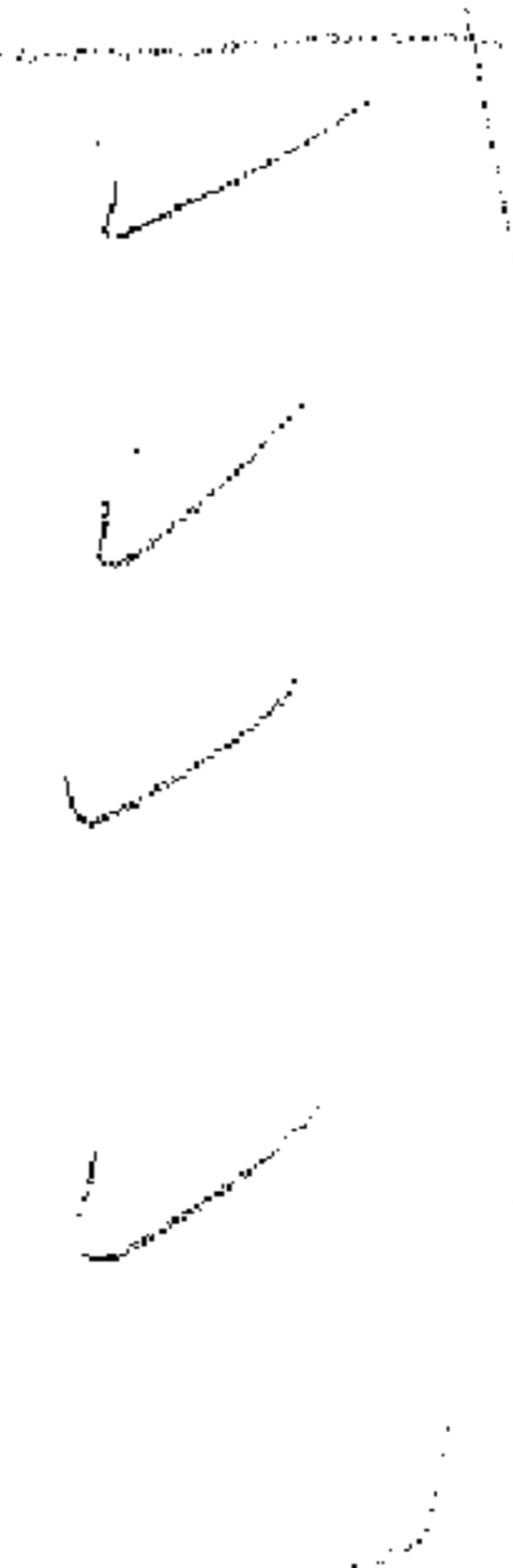


Fig. 9 cont'd-3

>gagB.syn1.1

MGARASVLSGGELDRWEKIRLRPGGKKKYKPKHIVWASRELERFAVNPGLLETSEGCRQI
LGQLQPSLQGTGSEELRSLYNTVATLYCVHQRIEVKDTKEALDKIEEEQNKSKKKAQQAAA
DTGNS SQVSNYPYIVQNLQGMVHQAI SPRTLNAWVKVVEEKAFSPEVIMFSALESEGAT
PQDLNNTMLNNTVGGHQAAMQMLKETINEEAAEWDRHLHPVHAGPIAPGQMREPRGSDIAGTT
STLQEQIGWMTNPPPIPVGEIYKRWIILGLNKIVRMYSPTSILDIRQGPKEPFRDYVDRF
YKTLRAEQASQEVKNWMTETLLVQANANPDCKTILKALGPAATLEEMMTACQGVGGPFGHKA
RVLAEAMSQVTNSATIMMQRGNFRNQRKTVKCFNCGKEGHI AKNCRAPRKKGCWKCGKEG
HQMDC-TERQANFLGKIWPSHKG-RPGNFLQSRP-----EPTAP
PEESFRFGEETTPSQKQEPIDKELYPLASLRSFLGNDPSSQ

>gagB.syn3.1

MGARASVLSGGELDRWEKIRLRPGGKKQYRLKHIVWASRELERFAINPGLLETSDGCRQI
LGQLQPALQGTGSEELKSLFNTVATLYCVHQRIDVKDTKEALDKIEEEQNKSKKKAQQAAA
DTGNS SQVSNYPYIVQNIQGMVHQAI SPRTLNAWVKVIEEKAFSPEVIMFSALESEGAT
PQDLNNTMLNNTVGGHQAAMQMLKETINEEAAADWDRHLHPVHAGPIAPGQMREPRGSDIAGTT
STLQEQIGWMTNPPPIPVGEIYKRWIIMGLNKIVRMYS PSSILDIKQGPKEPFRDYVDRF
YKVLRAEQASQEVKNWMTETLLVQNSNPDCCKTILKALGPGATLEEMMTACQGVGGPFGHKA
RVLAEAMSQMTNSATIMMQRGNFRNQRKPVKCFNCGKEGHI AKNCRAPRKKGCWKCGREG
HQMDC-TERQANFLGKIWPSYKG-RPGNFLQNR-----EPTAP
PAESFRFGEETTPSQKQETIDKELYPLASLRSFLGSDPSSQ

>gagB.syn3.2

MGARASVLSGGQLDRWEKIRLRPGGKKKYRLKHLVWASRELERFAVNPGLLETAEGCRQI
LEQLQPSLQGTGSEELRSLFNTVAVLYCVHQRIEVKDTKEALDKVEEEQNKSKKKAQQTAA
DTGNS SQVSNYPYIVQNMQGMVHQALS PRTLNAWVKVIEEKAFSPEVIMFTALSEGAT
PQDLNNTMLNNTVGGHQAAMQMLKDTINEEAAEWDRHLHPVQAGPVAPGQIREPRGSDIAGST
STLQEQIGWMTSNPPPIPVGEIYKRWIILGLNKIVRMYS PVSILDIRQGPKEPFRDYVDRF
YKTLRAEQATQEVKNWMTETLLVQANANPDCKTILKALGPGATLEEMMTACQGVGGPFGHKA
RVLAEAMSQVTNSATIMMQRGNFRNQRKIVKCFNCGKEGHI ARNCRAPRKRGCWKCGKEG
HQMDC-NERQANFLGKIWPSHKG-RPGNFLQSRP-----EPSAP
PEESFRFGEETTPSQKQEPIDKELYPLASLRSFLGNDPSLQ

>gagB.syn3.3

MGARASVLSGGELDKWEKIRLRPGGKKKYKPKHIVWASRELERFAVNPGLLETSEGCRQI
LGQLQPSLQGTGSEELRSLYNTVATLYCVHQKIEVKDTKEALEKIEEEQNKCKKKAQQAAA
GTGNS SQVSNYPYIVQNLQGMVHQPI SPRTLNAWVKVVEEKAFSPEVIMFSALESEGAT
PQDLNNTMLNNTVGGHQAAMQMLKETINEEAAEWDRHLHPVHAGPVAPGQMRDPRGSDIAGTT
SNLQEQIGWMTNPPPIPVGDIYKRWIILGLNKIVRMYSPTSILDIRQGPKESFRDYVDRF
YKTLRAEQASQDVKNWMTETLLVQANANPDCRTILKALGPAATLEEMMTACQGVGGPFGHKA
RILAEAMSQVTNPATIMMQRGNFRNQRKTVKCFNCGKEGHLARNCRAPRKKGCWKCGKEG
HQMKEC-TERQANFLGKIWPSHKG-RPGNFLQSRP-----EPTAP
PEESFRFGEETATPPQKQEPIDKELYPLTSLRSFLGNDPSSQ

>gagB.syn4.1

MGARASVLSGGQLDRWEKIRLRPGGKKKYRLKHLVWASRELERFAVNPGLLETAEGCRQI
LEQLQPSLQGTGSEELRSLFNTVATLYCVHQRIDVKDTKEALDKIEEEQNKCKKKAQQAAA
DTGNS SQVSNYPYIVQNIQGMVHQALS PRTLNAWVKVVEEKAFSPEVIMFTALSEGAT
PQDLNNTMLNNTVGGHQAAMQMLKETINEEAAEWDRHLHPVQAGPVAPGQMREPRGSDIAGST
STLQEQIGWMTNPPPIPVGDIYKRWIILGLNKIVRMYS PVSILDIRQGPKESFRDYVDRF
YKVLRAEQASQEVKNWMTETLLVQANANPDCRTILKALGPAATLEEMMTACQGVGGPFGHKA

Fig. 9 cont'd-4

RVLAEAMSQMTNSATIMMQRGNFRNQRKTVKCFNCGKEGHIKNCRAPRKKGCWKCGKEG
HQMKEC-TERQANFLGKIWPSYKG-RPGNFLQSRP-----EPSAP
PAESFRFGREETTPSQKQETIDKELYPLTSLRSLEFGNDPSSQ

>gagB.syn4.2

MGARASVLSGGELDKWEKIRLRPGGKKKYKLKHIWASRELERFAINPGLLETSEGCRQI
LGQLQPALQTGSEELRSLYNTVATLYCVHQKIEVKDTKEALEKVEEEQNKSKQKAQQAAA
DTGNNSQVSNYPPIVQNLQGMVHQAI SPRTLNAWVKVIEEKAFSPEVIMFAALSEGAT
PQDLNTMLNTVGGHQAAMQMLKETINEEAADWDRHPVHAGPIAPGQIREPRGSDIAGTT
SNLQEQIAWMTNNPPIPVGEIYKRWIIMGLNKIVRMYSPSILDIKQGPKEPFRDYVDRF
YRTLRAEQASQDVKNWMTETLLVQANANPDCRTILKALGPGATLEEMMTACQGVGGPASHKA
RVLAEAMSQVTNPATIMMQRGNFRNQRKPVKCFNCGKEGHLAKNCRAPRKRGCWKCGKEG
HQMKDC-NERQANFLGKIWPSHKG-RPGNFLQNRP-----EPSAP
PEESFRFGREETATPSQKQEPIDKELYPLASLRSLEFGSDPSSQ

>gagB.syn4.3

MGARASILSGGELDRWEKIRLRPGGKKQYRLKHIWASRELERFAVNPGLLETSEGCKQI
LEQLQPALQTGSEELKSLYNTVAVLYCVHQRIEIKDTKEALEKIEEEQNKSKKKAQQTAA
DTGNNSQVSNYPPIVQNLQGMVHQPI SPRTLNAWVKVIEEKAFSPEVIMFSALEGAT
PQDLNTMLNTVGGHQAAMQMLKETINEEAAEWDRHPVHAGPVAPGQMRDPRGSDIAGTT
SNLQEQIGWMTSNPPIPVGEIYKRWIILGLNKIVRMYSPSILDIRQGPKEPFRDYVDRF
YKTLRAEQATQEVKNWMTETLLVQANANPDCRTILKALGPGATLEEMMTACQGVGGPASHKA
RILAEAMSQVTNSATVMMQRGNFRNQRKTIKCFNCGKEGHLARNCRAPRKKGCWKCGREG
HQMKDC-TERQANFLGKIWPSYKG-RPGNFLQNRP-----EPTAP
PAESFRFGREETTPPQKQEPIDKELYPLASLKSLEFGNDPSSQ

>gagB.syn4.4

MGARASVLSGGKLDKWEKIRLRPGGKKKYQLKHIWASRELERFALNPGLLETSDGCRQI
LGQLQPSLOTGSEELKSLFNTVAVLYCVHQRIEIKDTKEALDKVEEEQNKSKKKAQQA
GTGNSSQVSNYPPIVQNMQGMVHQALS PRTLNAWVKVIEEKAFSPEVIMFSALSEGAT
PQDLNTMLNTVGGHQAAMQMLKDTINEEAAEWDRVHPVHAGPIAPGQMRDPRGSDIAGTT
STLQEQIGWMTSNPPIPVGEIYKRWIILGLNKIVRMYSPSSILDIRQGPKEPFRDYVDRF
YKTLRAEQASQEVKNWMTETLLVQNSNPDCRTILKALGPAATLEEMMTACQGVGGPASHKA
RVLAEAMSQVTNSATIMMQRGNFRNQRKIVKCFNCGKEGHIARNCRAPRKKGCWRCGKEG
HQMKDC-TERQVNFGLKIWPSYKG-RPGNFLQSRP-----EPTAP
PEESFRFGEEKTTPSQKQEPIDKELYPLASLKSLEFGNDPSSQ

>gagB.syn6.1

MGARASILSGGELDRWEKIRLRPGGSKKYRLKHIWASRELERFAVNPGLLETAEGCRQI
LGQLQPSLOTGSEELRSLYNTIATLYCVHQRIEIKDTKEALEKIEEEQNKSKKKAQQTAA
DTGNNSQVSNYPPIVQNLQGMVHQPI SPRTLNAWVKVIEEKAFSPEVIMFSALSEGAT
PQDLNTMLNTVGGHQAAMQMLKETINEEAAEWDRHPVHAGPVAPGQIREPRGSDIAGTT
SNLQEQIGWMTSNPPIPVGEIYKRWIILGLNKIVRMYSPSILDIRQGPKEPFRDYVDRF
YRTLRAEQASQDVKNWMTETLLVQANANPDCRTILKALGPGATLEEMMTACQGVGGPGHKA
RVLAEAMSQVTNSATVMMQRGNFRNQRRTVKCFNCGKEGHIARNCRAPRKKGCWKCGQEG
HQMKDC-TERQANFLGKIWPSYKG-RPGNFLQSRP-----EPTAP
PAESFRFGREETTPPQKQEPIDKELYPLTSLKSLFNDPSSQ

>gagB.syn6.2

MGARASVLSGGKLDKWEKIRLRPGGKKKYRLKHVVWASRELERFAVNPGLLESSEGCRQI
LEQLQPSLOTGSEELRSLYNTVATLYCVHQRIDVKDTKEALDKIEEEQNKCKKKAQQA
DTGNNSQVSNYPPIVQNLQGMVHQPI SPRTLNAWVKVIEEKAFSPEVIMFAALSEGAT
PQDLNTMLNTVGGHQAAMQMLKETINEEAAEWDRVHPVHAGPIAPGQMRDPRGSDIAGST
STLQEQIGWMTNNPPIPVGDIYKRWIILGLNKIVRMYSPASILDIRQGPKEPFRDYVDRF
YKTLRAEQATQEVKNWMTETLLVQANANPDCRTILKALGPGATLEEMMTACQGVGGPGHKA
RVLAEAMSQMTNSATIMMQRGNFRNQRKTIKCFNCGKEGHIARNCKAPRKKGCWKCGREG
HQMKDC-IERQANFLGKIWPSHKG-RPGNFLQNRP-----EPTAP
PEESFRFGREETATPPQKQEPIDKELYPLASLKSLEFGSDPSSQ

Fig. 9 cont'd-5

>gagB.syn6.3

MGARASVLSGGELDRWEKIRLRPGGKKKYRLKHLVWASRELERFAVNPGLLETS DGCRQI
LGQLQPALQTGSEELKSLYNTVATLYCVHQKIDVRDTKEALDKIEEEQNKSKQKAQQA
DTGNSSQVSNYPIVQNIQGQMVHQAI SPRTLNAWVKVVEEKAFSPEVI PMFTALSEGAT
PQDLNNTMLNTVGGHQAAMQMLKETINEEAAEWDR LHPVQAGPVAPGQMRPRGSDIAGTT
STLQEQIGWMTHNPPI PVGEIYKRWIIMGLNKIVRMYS PPSI LDIRQGPKE SFRDYVDRF
YKVLRAEQASQEVKNWMTETLLVQANANPDCKTILKALGPGATLEEMMTACQGVGGP SHKA
RVLAEAMSQVTNSATIMMQRGNFRNQRKTVKCFNCGKEGHI AKNCRAPRKRGCWKCGKEG
HQMKEC-TERQANFLGKIWPSHKG-RPGNFLQSRP-----EPTAP
PEESFRFGEEKTTSPSQKQETIDKELYPLASLRS LFGNDPSSQ

>gagB.syn6.4

MGARASVLSGGELDKWEKIRLRPGGKKKYQLKHI VWASRELERFAVNPGLLETSEGCKQI
LEQLQPALQTGSEELRSLYNTIAVLYCVHQKIEIKDTKEALDKVEEEQNKSKKKAQQA
GTGNSSQVSNYPIVQNLQGQMVHQPLSPRTLNAWVKVVEEKAFSPEVI PMFTALSEGAT
PQDLNNTMLNTVGGHQAAMQMLKETINEEAAEWDR LHPVHAGPIAPGQMRPRGSDIAGST
STLQEQIGWMTHNPPI PVGDIYKRWIILGLNKIVRMYS PTSILDIKQGPKEPFRDYVDRF
YKTLRAEQATQEVKNWMTETLLVQANANPD CRTILKALGPAATLEEMMTACQGVGGP SHKA
RILAEAMSQVTNPATIMMQRGNFRNQRKPVKCFNCGKEGHI ARNCRAPRKRGCWKCGKEG
HQMKDC-TERQVNFLGKIWPSHKG-RPGNFLQNR P-----EPSAP
PAESFRFGREETTTSPSQKQEPIDKEMYPLAS LRS LFGSDPSSQ

>gagB.syn6.5

MGARASVLSGGQLDRWEKIRLRPGGKKQYRLKHI VWASRELERFAINPGLLETSEGCRQI
LGQLQPSLQTGSEELKSLFNTVAVLYCVHQRI EVKDTKEALEKVEEEQNKSKKKAQQA
DTGNSSQVSNYPIVQNLQGQMVHQALSPRTLNAWVKVIEEKAFSPEVI PMFSALSEGAT
PQDLNNTMLNTVGGHQAAMQMLKDTINEEAAEWDR LHPVHAGPVAPGQMRDPRGSDIAGTT
STLQEQIAWMTNPNPI PVGEIYKRWIILGLNKIVRMYS PTSI LDIRQGPKEPFRDYVDRF
YKVLRAEQASQDVKNWMTETLLVQANANPDCKTILKALGPAATLEEMMTACQGVGGP GHKA
RVLAEAMSQVTNSTTIMMQRGNFRNQRKIVKCFNCGKEGHL AKNCRAPRKKGCWKCGKEG
HQMKEC-TERQANFLGKIWPSHKG-RPGNFLQSR P-----EPSAP
PEESFRFGREETATPSQKQEPIDKDLYPLAS LKSLFGNDPLSQ

>gagB.syn6.6

MGARASVLSGGKLDKWEKIRLRPGGKKKYKLKHI VWASRELERFALNPGLLETSEGCRQI
LRQLQPSLQTGSEELRSLYNTVATLYCVHQKIEVKDTKEALEKIEEEQNKSKKKAQQTAA
DTGNNSQVSNYPIVQNMQGQMVHQALSPRTLNAWVKVVEEKAFSPEVI PMFSALSEGAT
PQDLNNTMLNTVGGHQAAMQMLKDTINEEAAEWDR LHPAQAGPIAPGQIREPRGSDIAGTT
SNLQEQIAWMTNPNPI PVGDIYKRWIILGLNKIVRMYS PVSILDIRQGPKEPFRDYVDRF
YKTLRAEQASQEVKNWMTETLLVQNSNPDC KTILKALGPGATLEEMMTACQGVGGP GHKA
RVLAEAMSQVTNPATIMMQGNFKNQRKTVKCFNCGKEGHL ARNCRAPRKKGCWRCGKEG
HQMKDC-NERQANFLGKIWPSHKG-RPGNFLQSR P-----EPTAP
PEESFRFGREETTPAQKQEPIDKELYPLTSLRS LFGNDPSLQ

>gagC.syn1.1

MGARASILRGGKLDKWEKIRLRPGGKKHYMLKHLVWASRELERFALNPGLLETSEGCKQI
IKQLQPALQTGTEELRSLYNTVATLYCVHEKIEVRDTKEALDKIEEEQNKSQOKTQQA
ADG---KVSQNYPIVQNLQGQMVHQAI SPRTLNAWVKVIEEKAFSPEVI PMFTALSEGAT
PQDLNNTMLNTVGGHQAAMQMLKDTINEEAAEWDR LHPVHAGPIAPGQMRPRGSDIAGTT
STLQEQIAWMTSNPPI PVGDIYKRWIILGLNKIVRMYS PVSILDIKQGPKEPFRDYVDRF
FKTLRAEQATQDVKNWMTDTLLVQANANPDCKTILRALGPGATLEEMMTACQGVGGP SHKA
RVLAEAMSQ-ANNTNIMMQRSNFKGSKRIVKCFNCGKEGHI ARNCRAPRKKGCWKCGKEG
HQMKDC-TERQANFLGKIWPSHKG-RPGNFLQSR PE-----PTAPPA-----EPTAP
PAESFRFEE--TTPAPKQEPKDRE--PLTSLKSLFGSDPLSQ

>gagC.syn3.1

MGARASVLRGEKLDKWERIRLRPGGKKHYMLKHLVWASRELERFALNPSLLETSEGCKQI
IQQLQPALKTGTEELRSLFNTVATLYCVHAGIEVRDTKEALDKIEEEQNKCQOKTQQA
ADG---KVSQNYPIVQNLQGQMVHQALSPRTLNAWVKVIEEKAFSPEVI PMFTALSEGAT

Fig. 9 cont'd-6

PSDLNTMLNTVGGHQAAMQMLKDTINEEAAEWDRLHPVQAGPVAPGQMREPRGSDIAGTT
SNLQEQIAWMTGNPPVPVVDIYKRWIILGLNKIVRMYSVPSILDIRQGPKEPFRDYVDRF
FKTLRAEQSTQEVKNWMTETLLVQANANPDCKTILRALGPAASLEEMMTACQGVGGP SHKA
RVLAEAMSQ-ANSTNIMMQRGNFNGPKRI IKCFNCGKEGHLARNCRAPRKKGCWKCGKEG
HOMKDC-IERQANFLGKIWPSNKG-RPGNFLQNRPE-----PTAPPVEPTAPPAEPTAP
PAESEKFEE--TTPAPKQEPKDRE--PLTSLRSLFGSDPLSQ

>gagC.syn3.2

MGARASILRGEKLDTWEKIRLRPFGGRKHYMLKHIVWASRELEKFA LNPG LLETSEGCKQI
MKQLQPALQTGTEELKSLYNTVATLYCVHEKIEVRDTKEAVDKIEEEQNKSQOKTQQAKA
ADE---KVSQNYPIVQNIQGMVHQPI SPRTLNAWVKVIEEKGFNPEVI PMFTALSEGAT
PQDLNTMLNTVGGHQAAMQMLKDTINDEAAEWDRLHPVHAGPIAPGQMREPRGSDIAGST
STLQEQITWMTSNPPVPVGEIYKRWIILGLNKIVRMYSVPSILDIKQGPKEPFRDYVDRF
FKVLRAEQATQDVKNWMTDTLLIQANANPDCKTILKALGPGASLEEMMTACQGVGGP GHKA
RVLAEAMSQ-ANNTNIMMQRSNFKGPKRIVKCFNCGKEGHI AKNCRAPRKKGCWKCGQEG
HOMKDC-TERQANFLGKIWPSQKG-RPGNFLQNRP-----EPSAP
PAESFRFGE--TTPAPKQELKDRE--PLTSLKSLFGSDPLSQ

>gagC.syn3.3

MGARASILRGGKLDKWEKIRLRPGGKRYMLKHLI WASRELERFALNPG LLETAEGCKQI
IKQLQPALQTGTEELRSLYNTVATLYCVHKRIDVRDTKEALDKIEEEQNKI QOKTQQAKA
ADG---KVSQNYPIVQNAQGMVHQAI SPRTLNAWVKVVEEKAFSPEI I PMFTALSEGAT
PQDLNSMLNAVGGHQAAMQMLKDTINEEAAEWDRLHPVHAGPVAPGQIREPRGSDIAGTT
STLQEQIAWMTSNPPIPVVDIYKRWIIMGLNKIVRMYSVPSILDIKQGPKE SFRDYVDRF
FKTLRAEQATQEVKNWMTDTLLVQANANPDCKTILRALGPGATLEEMMTACQGVGGP SHKA
RVLAEAMSQ-TNSA-ILMQRSNFKGSKRIVKCFNCGKEGHI ARNCRAPRKRGCWKCGKEG
HOMKEC-TERQANFLGKIWPSHKG-RPGNFLQSRP-----EPTAP
PAESFRFEE--TTPAPKQESKDRE--PLISLKS LFGNDPLSQ

>gagC.syn4.1

MGARASVLRGEKLDTWERIKLRPGGKHYMIKHLVWASRELEKFA LNPG LLETSEGCKQI
IQQLQPALKTGTEELKSLYNTVATLYCVHERIDVRDTKEALDKIEEEQNKI QOKTQQAKE
ADG---KVSQNYPIVQNAQGMVHQALS PRTLNAWVKVVEEKAFSPEI I PMFTALSEGAT
PSDLNTMLNTIGGHQAAMQMLKDTINDEAAEWDRLHPVHAGPIAPGQIREPRGSDIAGTT
STLQEQITWMTSNPPVPVGEIYKRWIILGLNKIVRMYSVPSILDIKQGPKE SFRDYVDRF
FKTLRAEQSTQEVKNWMTETLLVQANANPDCKTILKALGPGATLEEMMTACQGVGGP GHKA
RVLAEAMSQ-TNSA-ILMQRSNFKGSKRIVKCFNCGREGHI ARNCKAPRKKGCWKCGKEG
HOMKDC-IERQANFLGKIWPSHKG-RPGNFLQNRPE-----PTAPP-----EPTAP
PAESFRFGE--TTPAPKQEQKDRE--PLISLKS LFGSDPLLQ

>gagC.syn4.2

MGARASILRGEKLDKWERIRLRPGGKHYMLKHLVWASRELD R FALNPG LLETSDGCKQI
IKQLHPALQTGTEELRSLFNTVATLYCVHAGIEVRDTKEAVDKIEEEQNKSQOKTQQAKA
ADE---KVSQNYPIVQNIQGMVHQPI SPRTLNAWVKVIEEKAFSPEVI PMFTALSDGAT
PQDLNTMLNTVGGHQAAMQMLKDTINEEAAEWDRIHPVHAGPVAPGQMRDPRGSDIAGST
STLQEQIAWMTNPPVPVVDIYKRWIIMGLNKIVRMYSVPSILDIRQGPKEPFRDYVDRF
FRTLRAEQATQDVKNWMTDTLLIQANANPDCKTILRALGPGASLEEMMTACQGVGGP GHKA
RVLAEAMSQ-ANNTNIMMQKSNFKGPKRTVKCFNCGKEGHI ARNCRAPRKRGCWKCGKEG
HOMKEC-TERQANFLGKIWPSQKG-RPGNFLQSRP-----EPSAP
PAESFRFEE--TTPAPKQESKDRE--PLTSLKSLFGSDPSSQ

>gagC.syn4.3

MGARASILRGGKLDTWEKIRLRPGGKRYMLKHLI WASRELERFALNPS LLETSEGCKQI
MKQLQPALQTGTEELRSLYNTVATLYCVHKGIKVQDTKEALDKIEEEQKKSQOKTQQAEA
ADK--GVSQNYPIVQNLQGMVHQPLSPRTLNAWVKVIERKAFSPEVI PMFSALSEGAT
PQDLNSMLNAVGGHQAAMQMLKDTINEEAAEWDRLHPVHAGPIAPGQMREPRGSDIAGTT
SNLQEQIAWMTSNPPIPVVDIYKRWIVLGLNKIVRMYSVPSILDIKQGPKEPFRDYVDRF
FKTLRAEQATQEVKNWMTDTLLVQANANPDCKTILRALGPAASLEEMMTACQGVGGP GHKA

Fig. 9 cont'd-7

RVLAEAMSQ-ANS-NIMMQRGNFKGPKRIKCFNCGKEGHLARNCRAPRKKGCWKCGREG
HQMKDC-TERQANFLGKIWPSNKG-RPGNFLOSRP-----EPTAP
PAESFGFGE--TTPAPKQELKDRE--PLTSLKSLFGNDPLSQ

>gagC.syn4.4

MGARASILRGGKLDKWEKIRLRPGGGRKHYMLKHIIVASRELERFALNPGLLETAEGCKQI
IKQLQPALQGTGTEELKSLFNTVATLYCVHEKIEVRDTKEALDKIEEEQNKCQOKTQQA
ADG---KVSQNYPIVQNLQGGQMVHQAI SPRTLNAWVKVIEEKGFNPEVIMFTALSEGAA
PQDLNMTMLNTIGGHQAAMQMLKDTINEEAAEWDRLHPVQAGPVAPGQMRPRGSDIAGTT
SSLQEQIAWMTGNPPVPVVDIYKRWIILGLNKIVRMYSVPSILDIRQGPKEPFRDYVDRF
FKVLRAEQATQDVKNWMTETLLVQANANPDCKTILRALGPGATLEEMMTACQGVGGPSHKA
RVLAEAMSQ-ANNANIMMQRSNFKGPKRIVKCFNCGKEGHIKNCRAPRKKGCWKCGQEG
HQMKDC-NERQANFLGRIWPSHKG-RPGNFIQSRPEPTAPLEPTAPPA-----EPTAP
PAESFKFEE--TTPAPKQEPKDRE--PLTSLRSLFGSDPLSQ

>gagC.syn6.1

MGARASVLRGEKLDTWERIKLRPGGKHYMIKHLVWASRELEKFAALNPGLLETAEGCKQI
IRQLQPALQGTGTEELRSLYNTVATLYCVHKRIDVRDTKEALDKIEEEQNKSQOKAQQA
ADG---KVSQNYPIVQNLQGGQMVHQALS PRTLNAWVKVIERKAFSPEVIMFSALESEGAT
PQDLNMTMLNTVGGHQAAMQMLKDTINEEAAEWDRIHPVHAGPIAPGQMRPRGSDIAGTT
STLQEQITWMTSNPPVPVGEIYKRWIILGLNKIVRMYSVPSILDIRQGPKEPFRDYVDRF
FKTLRAEQSTQEVKNWMTDTLLAQNANPDCKIILRGLGPGATLEEMMTACQGVGGPGHKA
RVLAEAMSQ-ANS-NILMQRSNFKGPRRTIKCFNCGKEGHLAKNCRAPRKKGCWKCGKEG
HQMKEC-TERQANFLGKIWPSQKG-RPGNFLOSRP-----EPSAP
PAESFRFEE--TTPALKQEPKDRE--PLTSLRSLFGSDPLSQ

>gagC.syn6.2

MGASASILRGEKLDKWEKIRLRPGGKCYMLKHIIVASKELEKFAALNPGLLETSEGCKQI
MKQLQPALQGTGTEELKSLYNTVATLYCVHEKIEVRDTKEALDKIEEEQKKSQOKTQQA
ADK--GKVSQNYPIVQNAQGGQMVHQALS PRTLNAWVKVVEEKAFSPEIIMFTALSEGAA
PQDLNMTMLNTVGGHQAAMQMLKDTINEEAAEWDRLHPVHAGPIAPGQIREPRGSDIAGTT
STLQEQVAVMTSNPPVPVVDIYKRWIIVLGLNKIVRMYSVPSILDIKQGPKEPFRDYVDRF
FKTLRAEQSSQEVKNWMTDTLLVQANANPDCKTILRALGPAASLEEMMTACQGVGGPSHKA
RVLAEAMSQ-ANSTNIMMQRGNFKGPKRIVKCFNCGREGHIANCRAPRKKGCWKCGQEG
HQMKDC-IERQANFLGKIWPSHKG-RPGNFIQSRPE-----PTAPP-----EPTAP
PAESFRFGE--TTPAPKQESKDRE--PLTSLKSLFGNDPLSQ

>gagC.syn6.3

MGARASVLKGEKLDKWERIRLRPGGKKQYRLKHLVWASRELERFALNPSLLETSEGCRQI
IKQLQPALKGTGTEELRSLYNTIATLYCVHKGIKVQDTKEALDKVEEEQNKSQOKTQQA
ADE---KVSQNYPIVQNLQGGQMVHQPLSPRTLNAWVKVIEEKGFNPEVIMFTALSEGAT
PQDLNSMLNAVGGHQAAMQMLKDTINEEAAEWDRLHPVQAGPVAPGQIREPRGSDIAGTT
SSLQEQIAWMTGNPPVPVVDIYKRWIILGLNKIVRMYSVPSILDIKQGPKEPFRDYVDRF
FKTLRAEQATQDVKNWMTETLLVQANANPDCKTILRALGPGATLEEMMTACQGVGGPSHKA
RVLAEAMSQ-ANNANIMMQRSNFKGPKRTVKCFNCGKEGHIKNCRAPRKKGCWKCGREG
HQMKDC-IERQANFLGKIWPSNKG-RPGNFLOSRPE-----PTAPPA-----EPTAP
PAESFRFEE--TTPAPKQELKDRE--PLTSLKSLFGSDPLSQ

>gagC.syn6.4

MGARASILRGEKLDKWEKIRLRPGGGRKHYMLKHIIVASRELEGFALNPGLLETSEGCKQI
IKQLQPALQGTGTEELRSLFNTVATLYCVHSGIEVRDTKEAVDKIEEEQNKIQQKTQQA
ADG---KVSQNYPIVQNSQGGQMVHQAI SPRTLNAWVKVIEEKAFSPEVIMFTALSEGAT
PSDLNMTMLNTIGGHQAAMQMLKDTINDEAAEWDRLHPVHAGPIAPGQMRDPRGSDIAGST
STLQEQIAWMTNPPVPVVDIYKRWIIMGLNKIVRMYSVPSILDIKQGPKEPFRDYVDRF
FRTLRAEQATQEVKNWMTETLLVQANANPD CRTILKALGPGATLEEMMTACQGVGGPGHKA
RVLAEAMSQ-ANNINIMMQRNFKGPKRIKCFNCGKEGHIARNCKAPRKKGCWKCGKEG
HQMKDC-NERQANFLGKIWPSHKG-RPGNFLOSRP-----EPTAP
PAESFRFEE--TTPTPKQEPKDRE--PLTSLKSLFGSDPSSQ

Fig. 9 cont'd-8

>gagC.syn6.5

MGARASILRGGKLDKWEKIRLRPGGKKRYMLKHLI WASRELERFALNPGLLETS DGCKQI
IQQLQPALKTGTEELKSLFNTVAVLYCVHKGIEVRDTKEAVDKIEEEQNKIQQKMQQQKV
TDG---KVSQNYPIVQNIQGMVHQPI SPRTLNAWVKVIEEKGF SPEVIMFTALSEGAT
PSDLNTMLNTVGGHQAAMQMLKDTINEEAAEWD RTHPVHAGPVAPGQMRPRGSDIAGTT
STLQEQIGWMTNPNPPIPVGEIYKRWII LGLNKIVRMYS PVSILDIKQGPKEPFRDYVDRF
FKALRAEQATQEVKGMWTD TLLVQANANPDCKTILKALGSGATLEEMMTACQGVGGPGHKA
RVLAEAMSQ--ANNTNIMMQKSNFKGPRRI VKCFNCGREGHIAKNCRAPRKKGCWKCGQEG
HQMKDC-TERQANFLGRIWPSHKG-RPGNFLQSRPE-----PTAPL-----QP'AP
PAESFKFEE--TTPAPKQEQKDRE--PLTSLRSLFGNDPLSQ

>gagC.syn6.6

MGARASILRGGKLDTWEKIRLRPGGKKHYMLKHLVWASRELD RFALNPGLLETADGCKQI
IKQLHPALQGTGTEEIKSLFNTVATLYCVHAGIEVRDTKEALDKIEEEQNKCQOKTQOAKE
ADK---KVSQNYPIVQNLQGMVHQAI SPRTLNAWVKVIEEKAFNPEIIPMFTALSDGAT
PQDLNTMLNTVGGHQAAMQMLKDTINEEAAADWDR LHPVHAGPVAPGQLREPRGSDIAGTT
SNLQEQIAWMTSNPPIPVGDIYKRWII LGLNKIVRMYS PVSILDIKQGPKEPFRDYVDRF
FKVLRAEQATQDVKNWMTDTLLIQANANPDCKTILRALGPGASLEEMMTACQGVGGPSHKA
RVLAEAMSQ-TNSA-ILMQRSNFKGSKRIVKCFNCGKEGHLARNCRAPRKRGCWKCGKEG
HQMKDCTTERQANFLGKIWPSHKGGRPGNFLQNRPE-----PTAPL-----EPTAP
PAESFGFGE--TTPAPKQEPKDRE--PLISLKS LFGSDPLSQ .

>gagM.syn1.1

MGARASILRGGKLDKWEKIRLRPGGKKHYMLKHLVWASRELERFALNPGLLETSEGCKQI
IKQLOPALQGTGTEELRSLFNTVATLYCVHEKIEVRDTKEALDKIEEEQNKSQOKTQOAKA
ADG---KVSQNYPIVQNLQGMVHQAI SPRTLNAWVKVIEEKAFSPEVIMFTALSEGAT
PQDLNTMLNTVGGHQAAMQMLKDTINEEAAEWDRLHPVHAGPIAPGQMRPRGSDIAGTT
STLQEQIAWMTSNPPIPVGEIYKRWII LGLNKIVRMYS PVSILDIRQGPKEPFRDYVDRF
FKTLRAEQATQDVKNWMTDTLLVQANANPDCKTILRALGPGATLEEMMTACQGVGGPSHKA
RVLAEAMSQ--ANNTNIMMQRSNFKGSKRIVKCFNCGKEGHIARNCRAPRKKGCWKCGKEG
HQMKDC-TERQANFLGKIWPSHKG-RPGNFLQSRPE-----PTAPPA-----EPTAP
PAESFRFEE--TTPAPKQEPKDRE--PLTSLKSLFGSDPLSQ

>gagM.syn3.1

---RASVLSGGKLDWEKIRLRPGGKKKYKLKHI VWASRELERFAVNPGLLETSEGCRQI
LGQLQPSLQGTGSEELRSLYNTVAVLYCVHQRIEVRDTKEALEKIEEEQNKSKKKAQOAAA
DTGNSSQVSQNYPIVQNLQGMVHQAI SPRTLNAWVKVIEEKAFSPEVIMFTALSEGAT
PSDLNTMLNTIGGHQAAMQILKDTINEEAAEWDRLHPVHAGPIAPGQMRPRGSDIAGTT
STLQEQIGWMTNPNPPIPVGEIYKRWII LGLDKIVRMYSPTSILDIRQGPKEPFRDYVDRF
YKTLRAEQASQEVKNWMTETLLVQANANPDCKTILKALGPAATLEEMMTACQGVGGPSHKA
RILAEAMSQV'TNSATIMMQRGNFRNQRKT VKCFNCGKEGHIARNCRAPRKKGCWKCGKEG
HQMKDC-NERQANFLGKIWPSHKG-RPGNFLQSRP-----EPTAP
PEESFRFGEETTPSQKQEPIDKELYPLASLKS LFGNDPLSQ

>gagM.syn3.2

MGARASILRGGKLDKWEKIRLRPGGKKHYMLKHLVWASRELERFALNPGLLETAEGCKQI
IKQLQPALKTGTEELKSLYNTVATLYCVHEKIEVRDTKEALDKLEEEQNKSQOKTQOAAA
GTGSSSKVSQNYPIVQNAQGMVHQALS PRTLNAWVKVVEEKAFSPEVIMFSALAEAT
PQDLNTMLNTVGGHQAAMQMLKDTINEEAAADWDR LHPVHAGPVAPGQMRPRGSDIAGST
STLQEQIAWMTSNPPIPVGDIYKRWII LGLNKIVRMYS PVSILDIKQGPKEPFRDYVDRF
FKTLRAEQATQDVKNWMTDTLLVQANANPDCKTILRALGPGASLEEMMTACQGVGGPGHKA
RVLAEAMSQ--ANNANIMMQRGNFKGQKR- IKCFNCGKEGHLARNCRAPRKKGCWKCGREG
HQMKDC-TERQANFLGRIWPSHKG-RPGNFPQSRP-----EPSAP
PAESFGFGE--TTPAPKQELKDRE--PLTSLKSLFGSDPLSQ

>gagM.syn3.3

MGARASVLSGGELDRWEKIRLRPGGKKKYRLKHLVWASRELEK FALNPGLLETSEGCKQI
MKQLQPALQGTGTEELRSLFNTVATLYCVHQRIDVKDTKEALDKIEEEQNKIQQKTQOAKA
ADG---KVSQNYPIVQNIQGMVHQPI SPRTLNAWVKVVEEKGFNPEVIMFSALSEGAT

Fig. 9 cont'd-9

PQDLNMMMLNIVGGHQAAMQMLKETINEEAAEWDRVHPVHAGPIPPGQMREPRGSDIAGTT
SNLQEQIGWMTSNPPVPVVDIYKRWIVLGLNKIVRMYSVPSILDIRQGPKEPFRDYVDRF
FKVLRAEQATQEVKNWMTDTLLIQNANPDCKSILRALGPGATLEEMMTACQGVGGPSHKA
RVLAEAMSQ-TNSA-ILMQRSNFKGSKRIVKCFNCGKEGHIARNCRAPRKRKGCWKCGQEG
HQMKDC-TERQVNFGLKIWPSNKG-RPGNFLQNRPE-----PTAPPA-----EPTAP
PAESFRFEE--TTPAPKQEPKDRE--PLTSLRSLFGNDPSSQ

>gagM.syn4.1

MGARASVLSGGELDRWEKIRLRPGGKKKYKLVWASRELERFAVNPGLLETSEGCRQI
LGQLQPSLQGTGSEELRSLYNTVAVLYCVHQRI DVKDTKEALEKIEEEQNKSOQKTQOAKA
ADG---KVSQNYPIVQNAOQGMVHQALSPRTLNAWVKVIEEKGFSPPEVI PMF'SALAEAT
PQDLNMTMLNTIGGHQAAMQMLKDTINDEAAEWDRLHPVQAGPVAPGQIREPRGSDIAGTT
SNLQEQIGWMTSNPPIPVGDIYKRWIIMGLNKIVRMYSPTSILDIRQGPKESFRDYVDRF
FRTLRAEQASQEVKNWMTETLLVQNSNPDCKTILKALGPAATLEEMMTACQGVGGPGHKA
RVLAEAMSQ-VQOPNIMMQRGNFKGQKR- IKCFNCGREGHLARNCRAPRKKGCWKCGREG
HQMKDC-TESKANFLGKIWPSNKG-RPGNFLQSRP-----EPSAP
PAESFGFGEE-ITPSQKQEQKDKELYPLASLKSFLGNDPLSQ

>gagM.syn4.2

MGARASVLSGGKLDWEKIRLRPGGKKKYRLKHLVWASRELDRELFALNPSLLETAEGCKQI
MKQLQPALKTGTTELKSLYNTVATLYCVHEKIDVRDTKEALDKIEEEQNKIQOKTQOAKE
ADG---KVSQNYPIVQNIQOQMVHQPLSPRTLNAWVKVVEEKAFSPPEVI PMFTALSDGAT
PQDLNSMLNAVGGHQAAMQILKDTINEEAAEWDRLHPVHAGPVAPGQMREPRGSDIAGTT
STLQEQIGWMTNPPPIPVGEIYKRWIILGLNKIVRMYSVPSILDIKQGPKESFRDYVDRF
FKVLRAEQATQDVKNWMTDTLLIQNANPDCKSILRALGPGATLEEMMTACQGVGGPSHKA
RILAEAMSQVTNSATIMMQRGNFRNQRKTVKCFNCGKEGHLARNCKAPRKRKGCWKCGKEG
HQMKEC-TERQANFLGKIWPSNKG-RPGNFPQSRP-----EPTAP
PEESFRFGEETTTSPQKQEPIDKELYPLASLRSFLGNDPSSQ

>gagM.syn4.3

MGARASILRGGKLDKWEKIRLRPGGKKRYMLKHLI WASRELERFALNPGLETAEGCQQI
IEQLQSTLKTGSEELKSLFNTVATLYCVHQRIEVKDTKEALDKVEEEQNKSKKKAQOAAA
DTGNSSQVSNYPIVQNLQOQMVHQALSPRTLNAWVKVIEEKAFSPPEIIPMFTALSEGAT
PSDLNMTMLNTVGGHQAAMQMLKDTINEEAAEWDRVHPVHAGPIPPGQMREPRGSDIAGTT
SSLQEQIAWMTSNPPVPVGEIYKRWIVLGLNKIVRMYSVPSILDIRQGPKEPFRDYVDRF
FKTLRAEQASQDVKNWMTETLLVQANANPDCKTILRALGPGASLEEMMTACQGVGGPSHKA
RVLAEAMSQ-TNSA-ILMQRSNFKGSKRIVKCFNCGKEGHIARNCRAPRKRKGCWKCGQEG
HQMKDC-NERQANFLGKIWPSHKG-RPGNFLQNRPE-----PTAPP-----EPTAP
PAESFRFEE--TTPAPKQELKDRE--PLTSLKSLFGSDPLSQ

>gagM.syn4.4

MGARASVLRGEKLDKWERIRLRPGGKKHYMLKHLVWASRELEKLFALNPGLETAEGCQQI
IKQLQPALQGTTELRSLENTVATLYCVHAGIEVRDTKEALDKIEEI QNKSKQKTQOAAA
GTGSSSKVSQNYPIVQNLQOQMVHQPLSPRTLNAWVKVVEEKGFNPEVI PMFSALSEGAT
PQDLNMMMLNIVGGHQAAMQMLKETINEEAAEWDRLHPVHAGPIAPGQMREPRGSDIAGST
STLQEQIAWMTGNPPVPVVDIYKRWIILGLNKIVKMSPTSILDIKQGPKEPFRDYVDRF
YKTLRAEQATQEVKNWMTDTLLVQANANPDCKSILKALGTGATLEEMMSACQGVGGPAHKA
RVLAEAMSQ-ANNTNIMMQRSNFKGPKRI IKCFNCGKEGHIAKNCRAPRKKGCWKCGKEG
HQMKDC-TERQANFLGRIWPSNKG-RPGNFLQSRPE-----PTAPPA-----EPTAP
PAESFKFEE--TTPAPKQEPKDRE--PLTSLRSLFGSDPLLQ

>gagM.syn6.1

MGARASILSGGKLDWEKIRLRPGGRKHYMLKHLI WASRELERFALNPGLETAEGCQQI
IEQLQSTLKTGSEELKSLFNTVATLWCVHQRIEVKDTKEALDKLEEEQNKSOQKTQOAKA
ADG---KVSQNYPIVQNLQOQMVHQSI SPRTLNAWVKVIEEKAFSPPEVI PMFSALAEAT
PQDLNMTMLNTIGGHQAAMQILKDTINEEAAEWDRIHPVHAGPVAPGQMRDPRGSDIAGTT
SNLQEQIAWMTSNPPVPVGEIYKRWIILGLDKIVRMYSVPSILDIRQGPKEPFRDYVDRF
FKTLRAEQATQEVKGWMTDTLLVQANANPDCKTILKALGPGATLEEMMSACQGVGGPGHKA

Fig. 9 cont'd-10

RVLAEAMSQ-ANNTNIMMOKSNFKGPKRI IKCFNCGKEGHLARNCRAPRKKGCWKCGQEG
HOMKDC-TERQANFLGRIWPSHKG-RPGNFPQSRL-----EPTAP
PAESFGFGEE-IAPSPKQEPKEKELYPLTSLKSLFGNDPLSQ

>gagM. syn6.2

MGARASILRGGKLDKWEKIRLRPGGKKKYKLVWASRELEKFALNPGLLETSEGCRQI
LGQLQPSLOTGSEELKSLYNTVATLYCVHQRIDVKDTKEALEKIEEEQNKSQOKTQAAA
DKG----VSQNYPIVQNLQGMVHQALSPRTLNAWVKVIEEKAFSPEIIPMFTALSEGAT
PQDLTTMLNTVGGHQAAMQMLKETINDEAAEWDRLHPVHAGPVAPGQLREPRGSDIAGST
STLQEQIAWMTGNPPVPVGDYKRWIVLGLNKIVRMYSPTSILDIRQGPKEPFRDYVDRF
YKTLRAEQASQDVKNWMTETLLVQANANPDCRTILKALGPAATLEEMMTACQGVGGPAHKA
RVLAEAMSQVTNPATIMMQRGNFRNQRKTVKCFNCGKEGHLAKNCRAPRKRGCWKCGKEG
HOMKDC-NERQANFLGKIWPSNKG-RPGNFLQNR-----EPTAP
PAESFRFGEEKTPSQKQEPIDKELYPLASLRSLEFGNDPLSQ

>gagM. syn6.3

MGARASVLRGEKLDKWERIRLRPGGKKRYMLKHLI WASRELERFALNPSLLETSEGCKQI
IQQLQPALKTGTEELRSLYNTVATLYCVHEKIEVRDTKEAVDKIEEEQNKSKKKAQAAA
DTGNSSQVSNYPIVQNIQGMVHQALSPRTLNAWVKVVEEKGFNPEVIPMFSALSEGAT
PQDLNMLNIVGGHQAAMQMLKDTINEEAAEWDRLHPVQAGPVAPGOMREPRGSDIAGTT
STLQEQITWMTSNPPIPVGEIYKRWIIMGLNKIVRMYSVPSILDIKQGPKEPFRDYVDRF
FRTLRAEQASQEVKNWMTETLLIQANANPDCKTILRALGPAASLEEMMTACQGVGGPGHKA
RVLAEAMSQ-TNSA-ILMORSNFKGSKRIVKCFNCGKEGHIARNCRAPRKKGCWRCGKEG
HOMKDC-TESKANFLGKIWPSHKG-RPGNFLQNRPEPTAPPEPTAPPAEPTAPPAEPTAP
PAESFKFEE--TTPAPKQELKDRE--PLISLKSLFGSDPLLQ

>gagM. syn6.4

MGARASILRGEKLDWEKIRLRPGGKKQYRLKHLI WASRELEDRFALNPSLLETAEGCKQI
IKQLHPALQGTGTEELRSLFNTVATLYCVHAGIEVRDTKEALDKIEEEQNKIQOKTQOAKA
ADE---KVSQNYPIVQNMQGMVHQPLSPRTLNAWVKVVEEKAFSPEVIPMFAALSEGAT
PSDLNMLNIVGGHQAAMQMLKDTINDEAAEWDRLHPAQAGPIPPGQIREPRGSDIAGTT
STPQEQIGWMTNPPPIPVGEIYKRWIVLGLNKIVRMYSPTSILDIRQGPKEPFRDYVDRF
FKALRAEQATQEVKGWMTETLLVQNSNPDCKTILRALGPGASLEEMMTACQGVGGPSHKA
RILAEAMSQ-ANS-NIMMORSNFKGPKRIVKCFNCGKEGHIARNCRAPRKKGCWKCGREG
HOMKDC-IERQANFLGKIWPSQKG-RPGNFLQSRP-----EPSAP
PAESFRFGE--TTPAPKQEPKDRE--PLTSLRSLEFGSDPLSQ

>gagM. syn6.5

MGARASVLSGGELDRWEKIRLRPGGKKKYRLKHLVWASRELERFAINPGLLETSDGCKQI
IKQLQPALQGTGSEELRSLYNTIATLYCVHQKIEVKDTKEALDKIEEIQNKSKOKTQOAAA
GTGSSSKVSQNYPIVQNAQGMVHQSLSPRTLNAWVKVIEEKGFNPEVIPMFTALSEGAT
PHDLNMLNIVGGHQAAMQMLKETINEEAAEWDRVHPVHAGPIPPGQIREPRGSDIAGST
STLQEQIGWMTSNPPIPVGDYKRWIILGLNKIVRMYSPTSILDIRQGPKEPFRDYVDRF
FKCLRAEQATQEVKNWMTDTLLIQANANPDCKSILRALGPGATLEEMMTACQGVGGPGHKA
RILAEAMSQ-VQQPNIMMQRGNFKGQKR-IKCFNCGREGHIARNCKAPRKKGCWKCGKEG
HOMKDC-TERQVNFLGKIWPSYKG-RPGNFLQSRP-----EPTAP
PEESFRFGEETTPSQKQETIDKELYPLASLKSLFGNDPSSQ

>gagM. syn6.6

MGARASVLSGGKLDWAWERIRLRPGGKKHYMLKHLVWASRELERFAVNPGLLETSEGCKQI
MKQLQPALQGTGTEELKSLYNTVAVLYCVHQRIETKDTKEALDKIEEIQNKCOOKTQOAKE
ADG---KVSQNYPIVQNLQGMVHQPI SPRTLNAWVKVIEEKGFSPPEVIPMFTALSDGAT
PQDLNSMLNAVGGHQAAMQMLKDTINEEAAEWDRLHPVHAGPIAPGOMREPRGSDIAGTT
SSLQEQIAWMTNPPVPVGEIYRRWII LGLNKIVKMYSPTSILDIKQGPKEPFRDYVDRF
FKVLRAEQATQDVKNWMTDTLLVQANANPDCKSILKALGTGATLEEMMTACQGVGGPSHKA
RVLAEAMSQVTNSATIMMOKGNFRNQRKIVKCFNCGREGHLARNCKAPRKRGCWKCGKEG
HOMKEC-TERQANFLGKIWPSKSG-RPGNFPQSRP-----EPTAP
PAESFRFEE--TTPAPKQESKDRE--PLTSLKSLFGSDPSSQ

Fig. 10

>ENV-B.syn1.1
 MRVTGIRKKNYQHLWRWGTMLLWRWGTMLLGLMLMICSATEKLWVTVYYGVPVWKEATTTLF
 CASDAKAYDTEVHNVWATHACVPTDPNPQEVVLENTENFNMMWKNMVEQMHEDIISLWD
 QSLKPCVKLTPLCVTLNCTDDVRNVT--NNATNTNSSW--GEPMEKGEIKNCSFNITTSIRD
 KVQKEYALFYKLDVVP--DNDSNNTN-----YRLISCNTSVITQACPKVSFEPIPIH
 YCAPAGFAILKCNCKKFNGTGPTNVSTVQCTHGIRPVVSTQLLNGSLAEEVVIRSEN
 FTNNAKTIMVQLNVSVEINCTRPNNNTRKSIHIGPGRAFYTTGDIIGDIRQAHCNISRAQ
 WNNLTKHIVEKLGKQFGNNTIIVFNHSSGGDPEIVMHSFNCGGEFFYCNSTKLFNSTWTR
 N-NGTWTRN---DTERSINSTE---EHITLPCRICKQIINMWQEVGKAMYAPPPIRGQIRCSS
 NITGLLLTRDGGNDT-----SGTEIFRPGGGDMRDNRSELYKYKVVKIEPLGVAPTAK
 RRVVQREKRAVG--IGAVFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEA
 QQHLLQLTVWGIKQLQARVLAVERYLRDQQLLGIWGCSSGKLICTTAVPWNASWSNKSLE
 IWNMTWMEWEKEIDNYTNLIYNLLEESQNOQEKNEQELLELDKWASLWNWFDISNWLWY
 IKIFIMIVGGLVGLRIVEFAVLSIVNRVRQGYSPFSFQTRLPAPRGPDRPEGIEEEGGGERD
 RDRSVRLVDGFLALIWDLRSCLFLSYHRLRDLLLIVTRIVELLG-----RRGWEALK
 YWWNLLQYWSQELKNSAVSLLNATAIAVAEGTDRVIEALQRACRAILHIPRRIROGLERA
 LL-

>ENV-B.syn3.1
 MRVKETRKNYQHLWKWGTML-----LGMLMICSATEKLWVTVYYGVPVWRDANATLF
 CASDAKAYDTEAHNVWATHACVPTDPNPQEVVELKNVTENFNMMWKNMVEQMHEDIINLWD
 QSLKPCVELTPLCVTLNCTDYVKNIT--NNATSTNSSW--GKPMKGEIKFCSFNITTSIRN
 KVQKQYALFYKLDIVPI--DNDNTS-----YRLISCNTSTITQACPKVTFEPIPIH
 YCAPAGFAILKCNKTFNGTGPTNVSTVQCTHGIRPVIISTQLLNGSLAEEVVIRSEN
 FTNNAKTIMVQLNVSVEINCTRPNNNTRRSIPIGPRVFTTEDIIGDIRQAHCNISRAQ
 WNNLTKHIVEKLGKQFGNNTIIVFNHSSGGDPEIVMHSFNCRGGEFFYCKSTKLFNSTWTR
 N-NGTWTRN---DTERSINSTE---EHITLPCRICKQIINMWQEVGKAMYAPPIKGOISCS
 NITGLLLTRDGGNDT-----SGTEIFRPGGGDMRDNRSELYKYKVVRIEPLGVAPTAK
 RRVVQREKRAVG--IGAVFLGFLGAAGSTMGAASMTLTVQARLLLSGIVQQQSNLLRAIEA
 QQHMLQLTVWGIKQLQARLLAVERYLRDQQLLGLWGCSSGKLICTTTPWNTSWSNKSLE
 IWDNMTWQWEREIDNYTGLIYNLLEKSQNOQEKNEQELLELDKWASLWNWFDITNWLWY
 IKIFIMIVGGLVGLRIVFTVLSIVNRVRKGYSPFSFQTRLPTRGPDRPGGIEEEGGEQD
 RDRSGPLVNGFLALIWDLRSCLFLSYHRLRDLLLIVARIVELLG-----RRGWEILK
 YWWNLLLYWSQELKNSAVSLLNATAIAVAEGTDRVIEVVQRAFRAILHIPRRIROGFERA
 LL-

>ENV-B.syn3.2
 MRVTGIRKKNYQHLWRWGTMLLWRWGTMLLGLMLMICSAAAGKLWVTVYYGVPVWKEANTTLF
 CASDAKAYDTEVHNVWATHACVPIIDPNPQEVVLENTENFNMMWKNMVEQMHEDIISLWD
 ESLKPCVKLTPICVTLNCTDDVRNVT--NNATNTNSSW--GEPMEKGEIKNCSFNITTSIRD
 KVQKQYALFYKLDVVP--DNDSNNTN-----YRLISCNTSVITQACPKISFEPIPIH
 FCAPAGFAILKCNCKKFNGTGPTNVSTVQCTHGIRPVVSTQLLNGSLAEEIVIRSEN
 FTDNAKTIVQLNESVVINCTRPNNNTRKSIHIGPGRAFYATGETIIGDIRQAHCNLSRAK
 WNDTLKQIVIKLREQFG--NKTIVFNQSSGGDPEIVMHSFNCGGEFFYCNSTQLFNSTWTW
 N-NSTW--N---NTRKSNSTE---EITLPCRICKQIINMWQKVGKAMYAPPPIRGQIRCSS
 NITGILLTRDGGNNNET---NRTETFRPGGGNMKDNWRSELYKYKVVKIEPLGIAPTAK
 RRVVQREKRAVGTIGAMFLGFLGAAGSTMGAASLTLTVQARQLLPGIVQQQNNLLKAIEA
 QQHLLRLTVWGIKQLQARVLAVERYLRDQQLLGIWGCSSGKIICTTAVPWNASWSNKSLE
 IWDNMTWMEWEKEIDNYTNLIYNLLEESQNOQEKNELELELDKWANLWNWFDISNWLWY
 IKIFIMIIGGLVGLRIVFAVLSIVNRVRQGYSPFSFQTRLPAPRGPDRPEGIEEEGGGERD
 RDRSVRLVDGFLALIWDLRSCLFLYHRLRDLLLIAARIVELLG-----RRGWEALK
 YWWNLLQYWSQELKNSAISLLNATAVAVAEGTDRVIEALQRACRAILHIPRRIROGLERL
 LL-

>ENV-B.syn3.3
 MRVKGIRKNCQHLWRWGTML-----LGMLMICSAAEQWVTVYYGVPVWKEATTTLF
 CASDAKAYDKEVHNVWATHASVPTDPNPQEVVLENTENFNMMWKNMVDQMHEDIISLWD
 QSLKPCVKLTPLCVTLNCTD--LRNATNGNDTNTTSSS--REMMGGGEMKNCSFNVTTSIRD
 KVQKEYALFYKLDVPI--DSRNNSNNTN-----YNSYRLINCNTSVITQACPKVSFEPIPIH

Fig. 10 cont'd-1

YCTPAGFAILKCKDKKFNGTGPCTKVSTVQCTHGIRPVVSTQLLNGSLAE EEEVIIRSEN
FTNNAKTIIVQLKEAVEINCTRPSNNTRKSIPIGPGRAFYT TGDII GDIRKAHCNISRA N
WNN'LRQIVEKLG EQFGNNKTIIFKQSSGGDPEIVTHSFNCGGGEFFYCNSTQLFNSTWNF
--NGTWNKN---FNNTWNNTEGTNDTITLPCRIKQIINRWQEVGKAMYAPPISGQIRCSS
NITGLILTRDGGNNGNET--NGTEIFRPGGGMRDNRSELYRYKVVKIEPLGVAPTKAK
RRVVQREKRAVG-IGALFLGFLGAAGSTMGAASITLTVQARQLLSGIVQQONNLLRAIEA
QQHLLQLT VWGIKQLQARILAVERYLKDQQLLGIWGCSGKLICTTAVFWNTSWSNRSLNE
IWNNTWMEWEREIDNYTSLIYTLIEESQOQEKNEQELLELDKWASLWNWF SITNWLWY
IRIFIMIVGGLIGLRIVFAVLSVVRVROGYSPLSFQTHLPAQRGPDRPEGTEEEGGERD
RDRSGRLVDGFLAIIWVDLRSCLFSYHRLRDL LLIVTRIVELLG-----RRGWEVLK
YWWNLLQYWIQELKNSAVSLFNATAIAVAEGTDRIIEVVQRAYRAILHIPTIRQGLERA
LL-

>ENV-B.syn4.1

MRVTGIRKNYQHLWRWGTMLLWRWGTMLLGIILMICSAAAGKLWVTVYYGVPVWKDATTLEF
CASDAKAYDTEVHNVWATHASVPTDPNPQEVVLENTEDFNMWKNNMVDQM HEDII SLWD
QSLKPCVELTPLCVTLNCTDDVRNVT-NNATNTNSSW-GEPMEKGEIKFCSFNITTSIRN
KVQKQYALFYKLDV VPI-DNDSNNTN-----YRLISCNTSVITQACPKVTFEPIPIH
YCAPAGFAILKCNKTFNGTGPCTKVSTVQCTHGIRPVVSTHLLLNGSLAE EEEVIIRSEN
FTDNTKTIIVQLKEAVEINCTRPNNTRKGIHIGPGRAFYT TGEIIGDIRQAHCNLSRAK
WNDTLKQIVIKLREQFG-NKTIIFNQSSGGDPEIVMHTFNCGGGEFFYCNSTQLFNSTW--
-----QN---ETSGSINITDIGENITLPCRIKQIVNMWQKVGKAMYAPPIKQOISCSS
NITGLLLTRDGGNNGNET--NGTEIFRPGGGMKDNWRSELYRYKVVKIEPLGVAPTRAK
RRVVQREKRAVT-LGAMFLGFLGAAGSTMGAASMTLTVQARLLLSGIVQQQSNLLRAIEA
QQHLLRLTVWGIKQLQARILAVERYLQDQQLLGIWGCSGKLICTTAVPWNASWSNKSQDE
IWNNTWMEWEREIDNYTGLIYTLLEESQIQEKNEQELLELDKWASLWNWF'DITNWLWY
IKIFIMIVGGLIGLRIVFTVLSIVNRVRKGYSP LSFQTHLPAPRGPDRPGGIEEEGGEQD
RDRSGPLVNGFLALI IWVDLRSCLFSYHRLRDL LLIVARIVELLG-----RRGWEVLK
YWWNLLQYWSQELKNSAISLLNATAVAVAEGTDRVIEALQACRAILHIPRRIRQGLERL
LL-

>ENV-B.syn4.2

MRVKGIRKNCQHLWRWGILL-----LGMLMICSAAEQWLWVTVYYGVPVWRDANATLEF
CASDAKAYDTEAHNVWATHACVPTDPNPQEVVLEKNTENFNMWKNNMVEQM QEDIISLWD
QSLKPCVKLTPICVTLNCTDYVKNIT-NNATSTNSSW-GKPM EKGEIKNCSFNVTTSIRD
KVQKEYALFYRLDV VPI-DNDSNNDSTNTNYTNYRLISCNTSTITQACPKVSEFQPIPIH
YCAPAGFALLKCNKDFNGTGPCKNVSTVQCTHGSIKPVVSTQLLNGSLAE EEEIVIRSEN
FTNNAKTIIVQLNESVVINCTRPNNTRKSIHIGPGRAFYATGDII GDIRKAHCNISRA N
WNN'LRQIVEKLG EQFG-NKTIVFNQSSGGDVEIVMHSFNCGGGEFFYCNSTQLFNSTWNF
--NGTWNKN---FNNTWNNTEGTNDTITLPCRIKQIINMWQGVGKAMYAPPISGQIRCSS
NITGLILTRDGGNN-NET--NRTETFRPGGDMRDNRSELYKYKVVKIEPLGIAPT KAR
RRVVQREKRAVGTIGAMFLGFLGTAGSTMGAASLTLTVQARLLLSGIVQQONNLLKAIEA
QQHLLQLT VWGIKQLQARLLAVERYLGDQQLLGLWGCSGKLICTTVPWNASWSNKS LDK
IWDNMTWMEWEREIDNYTGLIYNLLEKSQOQEKNELELLELDKWANLWNWF'DITKWLWY
IKIFIMIIGGLIGLRIVFAVLSVVRVROGYSPLSLQTRLPTQRGPDRPEGIAEEGGERD
RDRSGPLVDGFLAIIWVDLRSCLFSYHHLRDL LLIVTRIVELLG-----RRGWEALK
YWWNLLLYWSQELKNSAVNLLNTTAIAVAEGTDRIIEVLQRIYRAFLHIPRRIRQGFERA
LL-

>ENV-B.syn4.3

MRVKEIRKNYQHLWKWGTML-----LGMLMICSAAAGNLWVTVYYGVPVWKEANTTLEF
CASDAKAYETE VHNWATHACVPI DPNPQEVV LGNV TENFNMGKNNMVEQM HEDII SLWD
ESLKPCVKLTPLCVTLNCTDELKNATFRSNTT TNSSW--EKMEKGEIKNCSFNITTNMRD
KMQKEYALFYKLDV IPI-DSRNNSSNSTE--YNSYRLINCNTSVITQACPKISFEPIPIH
YCTPAGFAILKCKDKKFNGKGPCTNVSTVQCTHGIRPVVSTQLLNGSLAE KEVVIRSDN
FTNNAKTIMVQLNVSVEINCTRPNNTRRSIPIGPGRVFYTTEDIIGDIRQAHCNISRAQ
WNN'TLKHIVEKLGKQFGNNKTIIVFNHSSGGDPEIVMHSFNCRGGEFFYCKSTKLENSTWTR

Fig. 10 cont'd-2

N-NGTWTRN---DTERSNSSTE---EHITLPCRIKQIINMWQEVGKAMYAPPPIRGQIRCSS
NITGILLTRDGGNDT-----SGTEIFRPGGGDMKDNWRSELYKYKVVRIEPLGVAPTEAK
RRVVQREKRAVG-IGAVFLGFLGAAGSTMGAAVTLTVQARLLLSGIVQQQNNLLRAIEA
QORLLQLTVWGIKQLQARVLAVERYLRDQQLLGIWGC SGKI ICTTAVPWNTSWSNRS LNE
IWNMTWMEWEKEIDNYTNLIYNLLEESQNQQEKNEQELLALDKWANLWNWFDISNWLWY
IKIFIIVGGLVGLRIVFAVLSIVNRVRQGYSPLSFQTRLPA PRGPDRPEGIEEEGGGERD
RDRSVRLVDGFLALIWDLLRSLCLFSYHRLRDL LLI-----VELLG-----RRGWEILK
YWWNLLQYWGQELKNSAVSLLNATAIAVAEGTDRVIEVVQRAYRAI LHIPTRIROGLERA
LL-

>ENV-B.syn4.4

MRVKETRKNYQHLWRWGIML-----LGMLMICSATEKLWVTVYYGVPVWKEATTTLF
CASDAKAYDKEVHNWVATHACVPTDPSPQEVVLENTENFNMMWKNMVEQM HEDIINLWD
QSLKPCVRLTPLCVTLNCTN-VNVTNLKNETNTKSSSGG EKMEEGEMKNCSFNITTSIRD
KVQKQYALFYKLDVVPI-DNDNTS-----YRLISCNTSVIKQACPKVSFEPIPIE
FCAPAGFAILKCNDDKFNGTGPCTNVSTVQCTHGIRPVI STQLLLNGSLAEEEVVIRSEN
FTDNAKTIIIVQLNETVEINCTRPSNNTRKSIPIGPGR AFYTTGDIIGDIRQAYCNISRAK
WNNTLKQIVTKLREQFGNNKTIIFKQSSGGDPEIVTHSFNCGGEFFYCNSTKLFNSTWTW
N-NSTW--N---NTRKRSNDTE---EIITLPCRIKQIINRWQEVGKAMYAPPIEGQIRCLS
NITGLLLTRDGGTNNT---NTNETFRPGGGNMRDNWRSELYKYKVVQIEPLGVAPTKAK
RRVVQREKRAVG-IGALFLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQNNLLRAIEA
QQHMLQLTVWGIKQLRARVLAVERYLKDQQLLGIWGC SGRLICTTNVPWNTSWSNKS LNE
IWDNMTWMEWEREIDNYTSLIYTLIEESQNQQEKNEQD LLDKWA SLWNWFSITNWLWY
IRIFIMIVGGLVGLRIVFTVISIVTRVRQGYSPLSFQTRLPTPRGPDRPEGTEEEGGGERD
RDRSGRLVDGFLALFWDDLRSCLFLYHRLRDL LLI AARIVEL LG-----RRGWELLK
YWWNLLQYWIQELKNSAVSLENAIAIAVAEGTDWVIEISQRAFR AVLHIPPVRIROGLERA
LQ-

>ENV-B.syn6.1

MRVTGIRKNYQHLWRWGTM LLLWRWGTM L LGILMICS AAGKLWVTVYYGVPVWKDATTTLF
CASDAKAYDTEAHNVWATHACVPI DPNPQEVVLENTENFN AWKNNMVEQM HEDMISLWD
QSLQPCVRLTPLCVTLNCTDDVRN-----ATSTNSSW-GKPM EKGEIKNCSFNITTSIRD
KVQKQYALFYKLDVVPI-DNDSNNTN-----YRLISCNTS IITQACPKITFEPIPIH
YCTPAGFALLKCNDDKFNGTGPCTKVSTVQCTHGIRPVVSTH LLLNGSLAEEEVVIRSEN
FTNNAKTIMVQLNVSVEINCTRPSNNTRKSIHIGPGR AFYTTGDIIGDIRKAHCNISRAN
WNNTLRQIVEKLGEQFGNNKTIIVFNHSSGGDLEIVTHSFICGGEFFYCNSTKLFNSTWTW
N-NSTW--N---NTRKRSNDTE---EIITLPCRIKQIINMWQEVGKAMYAPPPIRGKIRCSS
NITGLLLTRDGGTNNT---NTNETFRPGGGDMRDNWRNELYKYKVVRIEPLGIAPTEAK
RRVVQREKRAVG-IGAMFLGFLGTAGSTMGAASVALTVQARQLLP GIVQQQNNLLRAIDA
QQHLLQLTVWGIKQLQARILAVERYLKDQQLLGFWGC SGKLICTTNVPWNTSWSNKSYSQ
IWENMTWMEWEREINNYTGLIYNLLEKSQNQQEKNEQEL LELDKWASLWSWFDISNWLWY
IKIFIIVGGLVGLRIVFAVLSIINRVRQGYSPLSFQTHLPAPRGPDRPEGIAEEGGGERD
RDRSGRLVNGFLALIWDLRSLCLFSYHHLRDL LLI-----VELLG-----RRGWEVLK
YWWNLLLYWSQELKNSAISLLNATAVAVAEGTDRVIEALQRACRAI LHI PRRIROGLERL
LL-

>ENV-B.syn6.2

MRVKETRKNYQHLWKWGTM L-----LGILMICSATENLWVTVYYGVPVWKEATTTLF
CASDAKAYDKEVHNWVATHACVPTDPNPQEVVELKNVTENFNMMWKNNMVEQM QEDIISLWD
QSLKPCVRLTPLCVTLNCTD-LRNATNGNDTNTTSSS-REMMGGGEMKNCSFNITTNIRD
KVQKEYALFYKLDIVPI-DNDNTN-----YRLISCNTSVVTQACPKVSFEPIPIH
FCAPAGFAILKCNDDKFNKG PCTNVSTVQCTHGIRPVI STQLLLNGSLAEEEVVIRSEN

Fig. 10 cont'd-3

FTNNVKTIIIVQLNETVEINCTRPNNNTRRSIPIGPGRVFYTTEDIIGDIRQAHCNLSRTQ
WNNLTKQIVTKLREQFG-NKTIIIFNQSSGGDPEIVMHTFNCGGEFFYCNTTKLFNSTW--
--NDTTINR----TEGSNNTR----NITLPCRIKQIINLWQEVGKAMYAPPIQGQISCS
NITGLLLLTRDGGNN-NET--NRTETFRPGGNNMRDNWRSELYKYKVVKIEPLGVAPTKAK
RRVVQREKRAVG-IGALFLGFLGAAGSTMGAASVTLTVQARQLLSGIVQQRNLLRAIEA
QQRMLQLTVWGIKQLRARVLAVERYLKDQQLMGIWGCSGKLICTTTPVWNASWSNKSLE
IWDNMTWMEWEREIDNYTSLIYTLIEESQNOQEKNELELLELDKWASLWNWFSITNWLWY
IRLFIMIVGGLVGLRIVFTVISIVTRVRQGYSPLSFQTRLPTPRGPDPRGGIEEEGGEQD
RDRSIRLVDGFLALIWDLLRSLCLFSYHRLRDLWI----VELLG-----RRGWEALK
YLWNLQYWSQELKKSASVSLFNATAIAVAEGTDWVIEVIQRAFRAFIHIPTRVROGLERA
LQ-

>ENV-B.syn6.3

MRVKGIRKNCQHLWRWGILL-----LGMLMICSATEKLWVTVYYGVPVWKETTTTLF
CASDAKAYVAEKHNWATHACVPTDPNPREVVMGNVTEEFNIWNNSMVEQMHEDIISLWE
QSLKPCVKLTPLCVSLKCTDL-----KNDTNTNSSSGRMIMEKGEIKNCSFNITTGIRG
KVQ-EYSLFYKLDVVQM-DEDNTS-----YRLINCNTSVITQACPKVSFQPIPIH
YCAPAGFAILKCKDKKFNGTGCKNVSTVQCTHGIRPVISTQLLNGSLAEGEVVIRSEN
FTDNAKTIIIVQLKDFKINCTRPNNNTRKSIPIGPGRAFATGDIIGDIRQAHCNISTTK
WNKTLGQVVKLREQFK-NKTIVFKQSSGGDPEVVMHSFNCGGEFFYCNTSOLFNSTW--
-----N---STSLFNSTN---GTITLQCRIKQIINRWQEVGKAMYAPPIEGQIRCLS
NITGLLLVRDGGINVTNN--TGTEVERPGGGDMRDNRSELYKYKVIKIEPLGVAPTRAK
RRVVQREKRAVG-LGAMFLGFLGAAGSTMGAASITLTVQARQLLSGIVQQRNLLRAIEA
QQHMLQLTVWGIKQLQARVLAVERYLQDQQLLGIWGCSSGKLICTTTPVWNASWSNKSLE
IWDNMTWMEWEREIDNYTGLIYTLLEESQNOQEKNEHELLELDKWASLWNWFSITNWLWY
IKIFIMIIGGLIGLRIVFAVLSIVNRVRQGYSPISFQTRLPAAPRGPDRPDGIEEEGGDRD
RDRSGRLVDGFLALIWDLLRSLCLFSYRRLRDLLLIAARIVELG-----HRGWEALK
YWWNLQYWIQELKNSAVNLNNTAIAVAEGTDRVIEVVQRAYRAILNIPTRIROGFERA
LL-

>ENV-B.syn6.4

MRVKEIRKNCQRLWRWGTM-----LGMLMICSAAEQWLWVTVYYGVPVWRDANATLE
CASDAKAYDTEVHNWATHASVPTDPNPQEVVLGNVTENFNMMWKNMVEQMHEDEVISLWD
QSLKPCVKLTPICVTLNCTDYVKNIT--NNATSTNSSW--GEPMEKGEIKNCSFNITTSMD
KVQKYALFYKLDVVPI-DNDSNNNDSTNTNYTNYRLISCNTSVIKQACPKVSFDPIPIH
YCTPAGFAILKCRDKKFNGTGCKNVSTVQCTHGIRPVVPTQLLLNGSLAEEDVIRSEN
FSDNAKTIIIVHLNESVEINCTRLNNNTRKSIHMGPGRAFATGEIIGDIRQAHCNISRAK
WNNLTKQIAIKLREQFGNKTIIIFKQSSGGDPEIVTHSFNCGGEFFYCNTSOLFNSTWNF
--NGTWNKN---FNNTWNTEGTNDTITLPCRIKQIINMWQKVGKAMYAPPIISGQIRCTS
NITGLLLTRDGGN---DT--SGTEIFRPGGNNMKDNWRSELYKYKVVQIEPLGVAPTEAK
RRVVQREKRAVG-IGAVFLGFLGAAGSTMGAAAVTLTVQARLLLSGIVQQRNLLKAIEA
QQHLLRLTVWGIKQLQARLLAVERYLGDQQLLGLWGCSSGKLICTTAVPWNTSWSNRSLE
IWNMTWMEWEREIDNYTNLIYNLLEESQNOQEKNEKELLELDKWANLWNWFDISNWLWY
IRIFIMIVGGLIGLRIVFIVLSVNRVRQGYSPLSLQTRLPTQRPDRPEGTEEEGGDRD
RDTSGRLVDGFLALIWDLLRSLCLFSYRRLRDLLLIVTRIVELG-----RRGWEALK
YWWNLQYWGQELKNSAVSLLNATAITVAEGTDRVIEVLQRAYRAILNIPTRIROGLERI
LL-

>ENV-B.syn6.5

MRVKGIRRNQHLWRWGIML-----LGMLMICSATEQLWVTVYYGVPVWKEANTTLF
CASDAKAYKTEAHNVWATHASVPTDPNPQEVVLGNVTENFNMMWKNMMAEQMHEDIINLWD
QSLKPCVELTFLCVTLNCTDELKNATFRSNTTNSW--EKMEKGEIKNCSFNVTTSIRD
KMQKEYALFYRLDVVPI-DNDNTS-----YRLISCNTSVITQACPKISFEPIPIH
YCVFAGFAILKCNKTFNGTGCTNVSTVQCTHGIRPVVSTQLLLNGSLAEEDVIRSEN
FTDNKTIIIVQLKEAVEINCTRPNNNTRKGIHIGPGRAFATGDIIGDIRQAHCNLSRAK
WNDTLKQIVIKLREQFG-NKTIVFNQSSGGDVEIVMHSFNCGGEFFYCNTSOLFNSTW--
--NANDIRN---VTRGSNRTTGGNDTLLPCRIKQIVNMWQEVGKAMYAPPIKQIKCSS

Fig. 10 cont'd-4

NITGLLLTRDGGNNGNET--NGTEIFRPGGGDMRNNWRSELYKYKVVRIEPLGVAPT KAR
RRVVQREKRAVT-LGAMFLGFLGAAGSTMGAASMTLTVQARLLLSGIVQQQS NLLRAIEA
QORLLQLTVWGIKQLQARILAIERYLKDQQLLGIWGC SGKI ICTTAVPWNASWSNKSQDE
IWNMTWMQWEREIDNYTGLIYNLIEESQNOQEKNEQELLALDKWANLWNWF DITKWLWY
IKIFIMIVGGLIGLRIVFTVLSIVNRVRKGYSPLSFQTRLPAQRGPDRPEGIEEGGERD
RDRSGPLVDGFLAIFWVDLRSFLFSYRHLRDL LLI VARIVELLG-----RRGWELLK
YWWNLLQYWSQELKSSAVSLLNATAI A VAEGTDRI LEVLQRAYRAILHIPVRIROGLERA
LL-

>ENV-B.syn6.6

MRVKGIRKNYQHLWRWGMML-----FGMLMICSAAGNLWVTVYYGVPVWREATTLE
CASDAKAYETE VHNWATHACVPTDPS PQEVVLE NVTEDFNMWKNNMVDQM HEDIISLWD
ESLKPCVKLTPLCVTLNCTDDVRNVT-NNATNTNSSW-GEPM EKGEIKFC SFNITTSIRN
KVQKQYALFYKLDVIPI-DSRNN SNNSTE--YNSYRLINCNSSTITQACPKVTFEPIPIH
YCAPAGFAILKCNK KFNGTGPCNNVSTVQCTHGIRPVVSTQ LLLNGSLAEKEVVIRSDN
FTNNAKTII VQLNESVVINCTRPNNNTRKRISMGPGRVYYTTGEIIGDIRRAHCNISRAQ
WNNTLKHIVEKLGKQFGNNTI-FNHSSGGDPEIVMHSFNCRGEFFYCKSTKLFNSTWTR
N-NGTWTRN---DTERS NSTE---EHITLPCR IKQI INMWQGVGKAMYAPP IRGQIRCSS
NITGLILTRDGGNNDT----RGTEIFRPGGGDMKDNWRSELYRYKVVKIEPLGIAPTKAK
RRVVQREKRAVGTIGAMFLGFLGTAGSTMGAASLT LTVQARLLLSGIVQQQNNLLRAIEA
QQHLLQLTVWGIKQLQAKVLAVERYLRDQQLLGIWGC SGR LICTTNVPWNASWSNKS LDK
IWNMTWMEWDREINNYTSLIYSLIEESQNOQEKNEQDLLALDKWASLWNWF DITNWLWY
IKIFIMVVGGLVGLRIIFAVLSIVNKVRQGYSPLSLQTHLPARRGPDRPEGIEEGGERD
RDRSVRLVDGFLALFWDDLRSCLFLYHRLRDL LLI VTRV ELLG-----RRGWEALK
YCWNLLQYWSQELKNSAVSLFNAIAI A VAEGTDRIIEVVQRICRAIRHIPRRIROGF ERA
LL-

>ENV-C.syn1.1

MRVRGIQRNWPQWWIWGILG-----FWMLMICNVVGNLWVTVYYGVPVWKEAKTTLE
CASDAKAYEKEVHNWATHACVPTDNPQEI VLE NVTENFNMWKNDMVDQM HEDIISLWD
QSLKPCVKLTPLCVTLNCTDVKNATSNGT TTYNNSI-DS--MNGEIKNCSFNITTEIRD
KKKQVYALFYRLDIVPL-DNNSSE-----YRLINCNTSTITQACPKVSFDPIPIH
YCAPAGYAILKCNKTFNGTGPCNNVSTVQCTHG IKPVVSTQ LLLNGSLAE E E I I IRSEN
LTNNAKTII VHLNESVEIVCTRPNNNTRKSIRIGPGQTFYATGDIIGDIRQAHCNISEKQ
WDQTLYRVSEKLEHFP-NKTIKFAPSSGGDLEITTHSFNCRGEFFYCNTSKLFNSTY--
--NSTQMHN---DTGS--NST-----ITLPCR IKQI INMWQEVGRAMYAPPIAGNITCKS
NITGLLLTRDGGTNN-----NNTETFRPGGGDMRDNWRSELYKYKVVVEIKPLGIAPTKAK
RRVVEREKRAVG-IGAVFLGFLGAAGSTMGAASIT LTVQARQLLSGIVQQQS NLLRAIEA
QQHMLQLTVWGIKQLQTRVLA IERYLKDQQLLGIWGC SGKLICTTAVPWNSSWSNKSQTD
IWDNMTWMQWDREISNYTDTIYRLL EDSQNOQEKNEKDLLALDSWKNLWNWF DITNWLWY
IKIFIMIVGGLIGLRIIFAVLSIVNRVRQGYSPLSFQTLTPNPRGPDR LGRIEEGGEQD
RDRSIRLVSGFLALAWDDLRSCLFLSYHRLRDFILVTARAVELLGRSSLRGLQRGWEALK
YLGSLVQYWGLELKKS AISLLDPIAIAVAEGTDRIIE LIQRICRAIRNIPRRIROGF EAA
LL-

>ENV-C.syn3.1

MRVMGIQRNCQQWWIWGSLG-----FWMLMIYNVMGNLWVTVYYGVPVWKEAKTTLE
CASDAKAYDTEVHNWATYACVPTDNPQEMVLE NVTENFNMWKNNMVDQM HEDIISLWD
QSLKPCVKMTPLCVTLNCSNAK D-----NTTI-DNE-MKGEIKNCSFNITTELRD
KKKQVYALFYKLDIVPL-NSNSSE-----YRLINCNTSAITQACPKVSFDPIPIH
YCAPAGYAILKCNNETFNGTGPCNNVSTVQCTHGIRPVVSTQ LLLNGSLAEKEI I IRSEN
LTDNVKTI I VHLNESVEINCTRPNNNTRRSIRIGPGQAFYATGEIIGDIRQAYCNISGEK
WNETLQRVGGKLEHFP-NKTIKFAPSSGGDLEITTHSFNCRREFFYCNTSGLFN GTY--
--NGNGTYN---GTGTDNST-----ITIPCR IKQI INMWQEVGRAMYAPPIEGNITCKS
NITGLLLVRDGGTENNTET-NNTETFRPGGGDMRDNWRSELYRYRVVEIKPLGIAPTKAK
RRVVERGKRAVG-IGAVFLGFLGVAGSTMGAASIT LTVQARQVLSGIVQQQS NLLRAIEA
QQHLLQLTVWGIKQLQTRVLA IERYLKDQQLLGIWGYSGKLICTTAVPWNSSWSNRSQED

Fig. 10 cont'd-5

IWNNMTWMQWDREINNYTNTIYRLLEDSONQOEKNEQDLLALDSWKNLWNWFEDITNWLWY
IRIFIMIVGGLIGLRIIFAVLSIVNVRVQGYSPLSLQTLTPNPRELDRLGRIEEGGGEQD
RDRSIRLVSGFLALAWDDLRSCLCFSYHRLRDFILIAARAAELLGRSSLKGLQRCWEILK
YLGSLIQYWGLELKKSAINLLDTIAIVVAEGTDRIIEFIQRICRAICNI PRIRIQGFEAA
LQ-

>ENV-C.syn3.2

MRVRGILRNWQQWIIWGILG-----FWMLMICNVVGNLWVTVYYGVPVWREAKTTLF
CASDAKAYEREVHNWATHACVPTDPNFQELVLENTENFNMMWKNMVDQMHQDIISLWD
ESLKPCVKLTPLCVTLKCVNVTKNS--NATVNSNATV--NNNTMGEEIKNCSEFNATTEIRD
KKQNVYALFYRLDIVPL--NENNDNSS-----YRLINCNTSTITQACPKVTFDPIPIH
YCTPAGYAILKCNKTFNGTGPCHNVSTVQCTHGKIPVISTQLLNGSLABEEIIRSEN
LTNNVKTIIVHLNKSVEIVCTRPGNNTKRSVRIGPGQTFYATGDIIGDIRQAHCNISRTA
WNKTLQEVGKLAHFHFP--NKTIEFKPSSGGDLEVTTHSFNCRGEGFFYCNTSKLFNSTYNS
TYNSTYNSN---STNSNSNST-----ITLQCRIKQI INMWQKVGRAIYAPPIAGNITCRS
NITGLLLLTRDGGNNDTGNNDTEIFRPGGGDMKDNWRNELYKYKVVVEVKPLGIAPTGA
RRVVEREKRAVG--LGAVFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQNNLLRAIEA
QQHMWQVTVWGIKQLQARVLALERYLKDQQLLGLWGCSGKLICTTNVPWNSSWSNKS LTD
IWENMTWMQWDKEISNYTDTIYRLLEVSQNOQEKNEKDLLALDSWNNLWNWFSITKWLWY
IKIFIMIVGGLIGLRIIFGVLSIVKRVVQGYSPLSFQTLTPNPRGPDRLGRIEEGGGEQD
KDRSIRLVNGFLALAWDDLRLNLCCLFSYHQLRDFILIVARAVELLGHSSLRGLQRCWEALK
YLGSLVQYWGLELKRSAISLLDTIAIIVAEGTDRIIEVIQRICRAIRNIPTIRIQGFEAA
LLQ

>ENV-C.syn3.3

MRVRGIQRNWPQWIIWGILG-----FWMIIICRVVGNLWVTVYYGVPVWTEAKATLF
CASDAKAYEKEVHNWATHSCVPTDPNPQEIIVLGNVTENFNMWENDMVDQMHEDVISLWD
QSLKPCVKLTPLCVTLNCT-----NANVTVNATSDGS--IKEEIKNCSEFNTTTEIRD
KKQKVYALFYRPDIVPLSGSNSSE-----YILINCNTSTVTQACPKVSFEPIPIH
YCAPASYAILKCNKTFNGTGPCQNVSTVQCTHGKIPVVSTQLLNGSLAEGEIIRSEN
LTNNAKTIIVHLNESIEIVCTRPNNTKRSIRIGPGQTFATGDIIGNIRQAHCNISEEK
WNKTLQEVSRKLEHFP--NKTIIFNSSSGDLEITTHSFNCGGEGFFYCNTTKLFNDS---
-----ALSAFNKTS--NETITLPCRIKQI INMWQGVGRAMYAPPIAGNITCNS
SITGLLLLTRDGGT-----NTEIFRPGGGNMKDNWRSELYKYKVVVEIKPLGVAPTEAK
RRVVEREKRAVG--IGAVLLGFLGAAGSTMGAASITLTAQARQLLSGIVQQSNLLKAIEA
QQHMLQTVWGIKQLQARVLAIERYLQDQQLLGIWGCSSGKLICTTTVPWNSSWSNKSQTD
IWDNMTWMQWDREISNYTNTIYRLLEESQNOQEQNEKDLLALDKWQNLWSWFSITNWLWY
IKIFIIVGGLIGLRIILGVLSIVRRVVRQGYSPLSFQTLIPNPRGPDRLGGIEEGGEQD
RDRSVRLVSGFLSLAWDDLRSCLCFCYHRLRDFILVTARAVELLGRSSLRGLQKWEALK
YLGSLVQYWGLELKRSAISLLDTIAIIVAEGTDRIIEFIQRICRAIRNIPTIRIQGLEAA
LQ-

>ENV-C.syn4.1

MRVRGILRNYQQWIIWGSLG-----FWMLMIYNVGGNLWVTVYYGVPVWKEAKTTLF
CASDAKAYDTEVHNWATHACVPTDPDPQEIIVLGNVTENFNMWENDMVDQMHEDIISLWD
ESLKPCVKLTPLCVTLKCTNVTST---GNTRGNNTS--EN---REEMKNCSFNNTTTEIRD
KKQKVYALFYKPDVVPL--KENSSE-----YILINCNTSTVTQACPKVSFDPIPIH
YCAPAGFAILKCNKTFNGTGPCNNVSTVQCTHGKIPVVSTQLLNGSLAEIIRSEN
LTDNAKTIIVHLNESIEIVCTRPGNNTKRSIRIGPGQAFYATGDIIGDIRQAYCNISKAT
WNKTLQEVGKELAKHFP--NKTINFNSSSGDLEITTHSFNCGGEGFFYCNTTKLFNNSL--
-----LNNTADNST---STITLQCRIKQI INMWQGVGQAMYAPPIAGNITCKS
NITGLLLLTRDGGDTST---NGTEIFRPGGGNMKDNWRSELYKYKVVVEVKPLGIAPTGA
RRVVEREKRAVG--IGAVLLGFLGAAGSTMGAASITLTAQARQVLSGTVQQSNLLRAVEA
QQHMLQTVWGIKQLQTRVLAIERYLKDQQLLGIWGCSSGKLICTTNVPWNSSWSNKSQEE
IWENMTWMQWDREISNYTGTIYRLLEESQNOQEKNEQDLLALDSWKNLWNWFDISNWLWY
IKIFIIVGGLIGLRIIFGVLSIVKRVVQGYSPLSFQTLIPNPRGPDRLERIEEGGEQD
RGRSIRLVSGFLAIAWDDLRSCLCFSYHQLRDFILIAVRAVELLGHSSLRGLQRCWEALK
YLGSLVQYWGLELKRSAISLLDTIAIIVAEGTDRIIEFIQRICRAIRNIPTIRIQGFEAA
LQ-

Fig. 10 cont'd-6

>ENV-C.syn4.2

MRVMGIQRNCQQWWIWGILG-----FWILMICNVMGNLWVTVYYGVPVWKEAKATLF
CASDAKAYEKEVHNIWATHACVPTDPNPQELVLENTENFNMWDMNDMVDQMHDIIISLWD
QSLKPCVKLAPLCVTLNCTNATVTA TRNGSDIMNTTS-ND----GEMKNCSFNVTTEL RD
KKKKEYALFYRLDIVPL-NEGSGNANQNNSNYSDYRLINCNTSAITQACPKVTFDPIPIH
YCTPAGYAILKCN DKT FN GTGPCHNVSTVQCTH GIRPVVSTQ LLLNGSLAEGEIMIRSEN
LTNNAKTIIVHLNKSVEIVCTRPNNNTRKSVRIGPGQTFYATNDIIGDIRQAHCNI SEEK
WNKTLQQVGGKLAHFPP-NKTIEFKPSSGGDLEVTTHSFNCRGEFFYCNTSGLFN GTF--
--DGT-----ESNSTSNAT-----ITIPCRIKQIINMWQKVGRAIYAPPIAGNITCRS
NITGLLLVRDGGNDNKT---NDTETFRPGGGDMRDNRSELYKYKVVEVKPLGVAPT KAK
RRVVQREKRAVG-IGAVFLGFLGVAGSTMGAASMTLVQARQVLSGIVQQQSNLLRAIEA
QQHLLQLTVWGIKQLQARVLALERYLRDQQLLGMWGC SGKLICTTAVPWNSSWSNKSQED
IWGNMTWMQWDKEISNYTNTIYRLLEDSQNQQERNEKDLLALDSWKNLWSWEDITNWLWY
IKIFIMIIGGLIGLRIFAVLSIVNRVRQGYSPLSLQTLTPNPRGPDRLGRIEEEGGEQD
KDRSIRLVNGFLALAWDDLRLNLCFSYHRLRDFILIVARAVELLGRNSLRGLQRGWETLK
YLGSLIQYWGLELKKSAISLLDTTAVAEAGTDRIIELIQRICRAICNI PRRIROGLEAA
LQ-

>ENV-C.syn4.3

MRVRGIQRNWPQWWIWGILG-----FWMIICRVVGNLWVTVYYGVPVWREAKTTLF
CASNAKAYEKEVHNWVATHACVPTDPNPQELVLENTENFNMWKNDMVDQMHDV IISLWD
QSLKPCVKMTPLCVTLNCTDVKNATSNGTTTYNNSI-DS--MNGEIKNCSFN TTTTEL RD
KKQKAYALFYRPDIVPLPGKDNSKDNSSEYEE--YILINCNSSTITQACPKVSFEPIPIH
YCAPASYAILKCN NETFN GTGPCKNVSTVQCTHGIKPVISTQ LLLNGSLAEKEIIRSEN
LTNNVKTIIIVHLKESVEINCTRPNNNTRKSI RIGPGQTFYATGDIIGNIRQAHCNISREK
WNTTLKRVKEKLEHFP-NKTIKFAPSSGGDLEITHTFNCRGEFFYCNTSKLENSTYV-
--NRTDMND---D--TGNNST-----ITLPCR I KQIINMWQEVGRAMYAPPIAGNITCNS
SITGLLLTRDGGNNT-----ENTETFRPGGGNMKDNWRNELYKYKVVEIKPLGVAPTEAK
RRVVEREKRAVG-LGAVFLGFLGAAGSTMGAASITLVQARQLLSGIVQQQNNLLRAIEA
QQHMLQLAVWGIKQLQARVLAIERYLQDQQLLGIWGC SGKLICTTSPVWNSSWSNRSQED
IWNMTWMQWDREISNYTDTIYRLLEVSQNQQEQNEKDLLALDKWQNLWSWFSITNWLWY
IRIFIMIVGGLIGLRIFAVLSLVNRVRQGYSPLSFQTLTPSPRGPDR LGGIEEGGEQD
RDRSIRLVSGFLSLAWDDLRLSLCLFSYHRLRDFILIAARAAELLGRSSLRGLQRGWEILK
YLGSLAQYWGLELKKSAINLLDTTAVAEAGTDRIIEVIQRICRAIYNI PRRIROGFEAS
LL-

>ENV-C.syn4.4

MRVRGIPRNWQQWWIWGILG-----FWMLMICNVVGNLWVTVYYGVPVWTEAKTTLF
CASDAKAYEREVHNWVATYACVPTDPNPQEMVLENTENFNMWKNDMVEQM HEDIISLWD
QGLKPCVKLTPLCVTLNCSNAKKD-----NTTI-DNE-MRGEIKNCSFNITTEL RD
KKQQVYALFYKLDIVPL-NSNSSE-----YRLINCNTSTITQACPKVNFDP IPIH
YCAPAGYAILKCN NKT FN GTGPQNVSTVQCTHRIKPVVSTQ LLLNGSLAEGEIIRSEN
LTDNVKTIIIVHLNESVEIVCTRPNNNTRKSMRIGPGQTFYATGEIIGDIRQAHCNISKEK
WNNTLQEVREKLEHFP-NKTIKFAPHS GG DPEITTHSFNCRGEFFYCNTS QLENSTY--
--NSTQMHN---DTGS--NST-----ITLPCR I KQIINMWQGVGRAMYAPPIEGNITCTS
NITGLLLTRDGGT-----NNTETFRPGGGDMRNNWRSELYKYKVVEIKPLGIAPT KAK
RRVVERGKRAVG-IGAVFLGFLGAAGSTMGAASIALTAQARQLLSGIVQQQSNLLK AIEA
QQHMWQVTVWGIKQLQARVLAMERYLKDQQLLGLWGC SGKLICTTTPVWNSSWSNKSQTD
IWDNMTWMQWDREINNYTNTIYKLLLEDSQNQQEKNEKDLLALDSWNNLWNWFSITKWLWY
IKIFIMIVGGLIGLRILGVLSIVRRVRQGYSPLSFQTLTPNPRELDRLGRIEEGGGEQD
RDRSVRLVSGFLALAWDDLRLSLCLFCYHRLRDFILVTARAVELLGRSSLKGLQRGWEALK
YLGSLVQYWGLELKKSAISLFDTTAVAEAGTDRIIELVQRICRAIRNI PRRIROGFEAA
LL-

>ENV-C.syn6.1

MRVRGIQRNWPQWWIWGILG-----FWIIIMCRVMGNMWVTVYYGVPVWREAKTTLF
CASDAKGYEKEVHNAWATHACVPTGPNPQEMVLENTENFNMWKNNMVDQM HEDIINLWD
QSLKPCVRLTPLCVTLKCVNVTKNS--NATVNSNATV--NNNTMGEEIKNCSFNATTEIRD
KKQKAYALFYRPDIVPL-NENSSSENNSSE----YILINCNTSTITQACPKVSFDPIPIH
YCAPASYAILKCN NETFN GTGPQNVSTVQCTHGIKPVISTQ LLLNGSLAEEDIIRSEN

Fig. 10 cont'd-7

LTNNAKTIIVHLNQSVEIVCTRPGNNTRKSMRIGPGQTFYATNDIIGNIRQAHCNISEGK
WNETLLRVKKLEEHFP-NKTIKFEPPSSGGDLEITHTFNCRGEEFFYCDTSTLFNHTY--
--VSAYMNTDVSADRKNDTQ-SNSTITLPCRIRQIINMWQEVGRAIYAPPIAGNITCRS
NITGLLLVRDGGNTT-----NSTETFRPEGGNMKDNWRSELYKYKVVEIRPLGIAPTGA
RRVVEREKRAVG-IGAVFLGFLGVAGSTMGAASMTLTVQARQVLSGVVQQQSNLLQAIEA
QQHLLQLTVWGIKQLQTRVLALERYLRDQQLLGIWGC SGKI ICTTAVPWNTSWSNKSQED
IWNNTWMOQWDREINNYTNTIYKLLSESONQOEKNEQD LLDLSDWNSLWNWFSITKWLWY
IRIFIIIVGSLIGLRIIFGVLSIVKRVRQGYSP LLSQTLTPNPREPDRLGRIEEGGGEQD
RDRSVRLVNGFLALVWDDLRLSLCLFCYHRLRDFILVTARVV ELLGRSSLRGLQKGWEALK
YLGSLVQYWGLELKKSAINLLDTIAIAVGEGETDRIIEVIQRICRAIYNI PRRIROGF EAS
LL-

>ENV-C.syn6.2

MRVRGBILRNYQQWWIWGSLG-----FWMLMIYNVGGNLWVTVYYGVPVWTDKATTLF
CASDAKAYDKEVHNVWATHACVPTDPNPQELVLENTENFNMWKNDMVNQMHEDIISLWD
ESLKPCVKLTPLCVTLNCTNATVTATRNGSDIMNTTS-ND----GEMKNCSFNITTEL RD
KKRKEYALFYRLDIVPL-DENNSSEKSSSENSSEYRLINCNTSAITQACPKVTFDPIPLH
YCAPAGYAILKCKDKTFNGTGPCSNVSTVQCTHGIKPVVSTRLLNGSLAEGEIIIRSEN
LTNNVKTIIIVHLKEPVEINCTRPNNTRESIRIGPGQTFYATGDIIGDIRQAHCNISREK
WNKTLQEVGKKLAEHFP-NKTIKFAPHSGGDLEITMHSFNCRGEEFFYCN TSGLENGTY--
--MPTYMPN---GTESNSNST-----ITIPCRIKQIINMWQEVGRAMYAPPIEGNITCNS
NITGLLLVRDGGINKT-----NNTETFRPGGGDMRNNWRSELYKYKVVEIKPLGVAPTEAK
RRVVEREKRA-A-LGAMFLGFLGAAGSNMGAASITLTAQARQLLSGIVQQRSNLLRAIEA
QQHLLQLTVWGVKQLQARVLAMERYLKDQQLLGLWGC SGKLICTTSVPWNSSWSNRSQEE
IWNNTWMEWDREISNYTNTIYRLLEDSQNQOEKNEKDLLALDSWKNLWSWFDITNWLWY
IKIFIMIIGGLIGLRIVFAVLSIVNRVRQGYSP LSFQTLTPSPRGPDRLGRIEEEGGEQD
KDRSVRLVSGFLSLAWDDLRLSLCLFSYHRLRDLILIAARAV ELLGHSSLRGLQRGWEILK
YLGSLAQYWGLELKRSAISLLDTIAITVAEGTDRIIEI IQRICRAICNI PRRIROGFETA
LL-

>ENV-C.syn6.3

MRVMGILRNCQQWWIWGVLG-----FWMLMICNVVGNLWVTVYYGVPVWKEAKATTLF
CASNAKAYEREVHNIWATHACVPTDPNPQEMVLKNVTENFNMWKNDMVDQM HEDVISLWD
QSLKPCVKLAPLVCVTLNCTNVTVNDTLHQNF-----DMKNCSFNVTTEL RD
KKQKVYALFYRLDVVPL-GDNSS-----YRLINCNTSTIAQACPKVNFDP IPIH
YCTPAGYAILKCNDKTFNGTGPCKNVSTVQCTHEIKPVVSTQ LLLNGSLAEEGIIRSEN
LTDNAKTIIVHLNESVEINCTRPGNNTRQSIRIGPGQAFYATGAIIGDIRQAHCNISKDE
WEKTLKRVSEKLEHFP-NKTIEFKPSSGGDLEVTTHSFNCRREFFYCN TSKLFNSTY--
--NSTQMHN---DTGS--NST-----ITLPCIKQIINMWQGVGQAMYAPPIKGNITCKS
NITGILLTRDGGNLT-----NGTETFRPGGGDMKDNWRSELYRYRVVEIKPLGIAPT KAK
RRVVQREKRAVG-IGALFLGFLGTAGSTMGAASLTLTVQARQLLS SIVQQQSNLLRAIEA
QQHMLQLTIWGIKQLQTRVLAVERYLKDQQLLGMWGC SGKLICTTAVPWNASWSNKSQEE
IWGNMTWMOQWDREISNYTDIIYRLLEESQNQOERNEKDLLALDSWNNLWNWFNITNWLWY
IKIFIMIVGGVIGLRIIFAVLSLVNRVRQGYSP LSFQTLTPNPRELDRLGRIEEEGGEQD
RDRSIRLVNGFLAIAWDDLRLSLCLFSYRRLRDFILIAARAE LLLGRSSLRGLQRGWETLK
YLGSLIQYWGLELKKSAISLFDTIAIAVAEGTDRIIEI IQRICRAIRNI PRRIROGLEEA
LQ-

>ENV-C.syn6.4

MRVMGIQRNCQQWWIWGILG-----FWMLMIYNVVG NLWVTIYYGVPVWKEAKATLF
CASDAKAYDTEVHNVWATHACVPTDPDPQEMVLGNVTENFNMWKNDMADQM HEDIISLWD
QGLKPCVKLTPLCVTLHCTN-----TNITNENRTI-GDKLNE-EMKNCSFNITTEL RD
KKQQVYALFYKPDVVPL-NGGEHNETGE-----YILINCNSSTITQACPKVSFEPIPIH
YCAPAGFAILKCNKTFNGTGPCHNVSTVQCTHGIKPVVSTQ LLLNGSLAEEIIRSEN
LTDNVKTIIIVHLNKSVEIVCTRPNNTTRKSIRIGPGQTFYATNDIIGDIRQAYCNISAEK
WNKTLERVEEKLKEHFP-NKTIKFNSSSGGDLEITTHSFNCRGEEFFYCN TSNLENGTY--
--HGTQSTN---ST---NST-----ITLQCRIKQIINMWQKVGRAMYAPPIAGNITCKS
NITGLLLRLDGGTEN-----NDTETFRPGGGNM RDNWRSELYKYKVVEVKPLGIAPTTAK
RRVVERDKRAVG-IGAVLLGFLGAAGSTMGAASMLTVQARQLLSGIVQQQSNLLRAVEA

Fig. 10 cont'd-8

QQHMLQLTWVGKIQQLQARVLALERYLKDQQLLGIWGC SGRLICTTAVPWNSSWSNKTQGE
IWENMTWMQWDKEINNYTNTIYRLLEESQTQQEQNEKDLLALDSWKNLWNWFDTKWLWY
IKIFIMVVGGLIGLRIIFAVLSIVNSVRQGYSPLSLQTLTPNPRGPDRLERIEEGGEQD
RNRSIRLVNGFLALAWDDLRLSLCLFSYHHLRDFILVTARAVELLGRSSLKGLQRGWEALK
YLGNLVQYWGLELKKSAISLLDTTAVAEAGTDRIIELVQRICRAILNIPTRIRQGFEEA
LQ-

>ENV-C. syn6.5

MRVRGIPRNWPQWWTWGILG-----FWMIIICRVVGNLWVTVVYGVVPVWTEAKTTLF
CASDAKAYEREVHNVWATHSCVPTDNPQEIIVLGNVTENEFNMWENDMVDQMHQDIISLWD
QSLKPCVKMTPLCVTLNCSNAKGD-----NTTI-DNE-MKGEIKNCSFNITTEIRD
KKQKVHALFYRLDIVPL-NEGSGNANQNSNSYDYRLINCNTSTVTQACPKVTFDPIPIH
YCAPARYAILKCNNTFNGTGPCNNVSTVQCTHGKIPVSTQLLLSGSLAEIIIIVIRSEN
LTNNAKIIIVHLNESVEIVCTRPNNNTRRSIRIGPGQTFYATGEIIGDIRQAHCNISAKQ
WNTTLERVKEKLRHFP-NKTIKFEPSGGDFEITTHSFNCGGEFFYCNTSOLFENSTY--
--NSTYMSN---NTGENSNET-----ITLPCRKQIINMWQVGRAMYAPPIAGNITCNS
SITGLLLTRDGGNNNDTGNNDTEEFRPGGGDMRDNRSELYKYKVVVELKPLGIAPTEAK
RRVVKREKRAVG-IGAVLFGFLGAAGSTMGAASIALTAQARQVLSGIVQQQNNLLRAIEA
QQHVLQLTWVGKIQQLQTRVLAIERYLKDQQLLSLWGC SGKLICTTVPWNS SWSNKS LTD
IWDNMTWMQWDREISNYTGTIYRLLEDSQSQQEKNEKDLLELDKWNLWNWFDISNWLWY
IKIFIIVGGLIGLRIIFAVLSIINRVQGYSPLLFQTLTPNPRGLDRLGRIIEEGGEQD
KDRSIRLVNGFLALAWEDLRLSLCLFSYHQLRDFILIVARAVELLG-----RRGWEALK
YLGNLVLYWGLELKKSAVSLLDTIAIIVAGGTDRIEVVQRICRAIRNIPTRIRQGLEAA
LL-

>ENV-C. syn6.6

MRVRGILRNWQQWVIWGILG-----FWMVMICNVMGNLWVTVVYGVVPVWQEAKTTLF
CASDAKAYEKEVHNVWATHACVPTDPSQEIIVLENVTENEFNMWKNMVEQMHEDIISIWD
QSLKPCVTLTPLCVTLNCTDVKNVATSNGTTTYNNISI-DS--MNGEIKNCSFNITTEIRD
KKKQVYALFYKLDIVPL-NSNSSE-----YRLINCNTSAVTQACPKVSWDPIPIH
YCAPAGYAILKCNKTFNGTGPCNTVSTVQCTHRIKPVVTTQLLNGSLAEKEIIIRSEN
LTNNIKTIIIVHLNESIEIVCTRPNNNTRKSVRIGPGQTFATGDIIGDIRKAHCNISSEDK
WNETLQRVGKKLVEHFP-NKTIKFASSGGDLEVTTHSFNCKGGEFFYCNTTKLFD-----
-----DSERINTT-----TTIILPCRKQFINMWQVGRAMYAPPIAGNITCTS
NITGLLLTRDGGT-----NNTTEIFRPGGGNMKDNWRNELYKYKVVVEVKPLGVAPTAK
RRVVEREKRAVG-LGAVFLGFLGAAGSTMGAASITLTVQARQLLEFGIVQQQSNLLKAIEA
QQHMWQVTVWVGKIQQLQARVLAIERYLQDQQLLGIWGC SGKLICTTNPWNS SWSNKS QTD
IWDNMTWMQWDKEISNYTDTIYRLLEVSQNOQEQNEKDLLALDKWQNLWNWF SITNWLWY
IRIFIMIVGGLIGLRIILGVLSIVRRVRQGYSPLSFQTLIPNPRGPDRLGGIEEGGEQD
RDRSIRLVSGFLALAWDDLRLNCLFSYHRLRDFILIVVRAVELLGRNSLRGLQRGWEALK
YLGSLGQYWGLEIKKSAISLLDTIAIIVVAEGTDRIIEFIQRFCAIRNLPRRIRQGFEEA
LL-

>ENV-M. syn1.1

MRVTGIRKNYQHLWRWGTMLLWRWGTMLLGLMLICSAAGNLWVTVVYGVVPVWKEATTLF
CASDAKAYDTEVHNVWATHACVPTDNPQEVVLENVTENEFNMWKNMVEQMHEDIISLWD
QSLKPCVKLTPLCVTLNCTDDVRNVT-NNATNTNS SW-GEPMKGEIKNCSFNITTSIRD
KVQKEYALFYKLDVVPIDNDSNNTN-----YRLISCNTSVITQACPKVSFEPPIPIH
YCAPAGFAILKCNDDKFNGTGPCNTVSTVQCTHGKIPVSTQLLNGSLAEIIIIVIRSEN
FTNNAKTIIVQLNESVEINCTRPNNNTRKSVRIGPGQTFYATGDIIGDIRQAHCNISRAQ
WNNTLKHIVEKLGKQFGNKTIVFNHSSGGDFEIVMHSFNCGGEFFYCNTTKLFNSTWTR
N-NGTWTRN---DTERSNSTE---EHITLPCRKQIINMWQEVGKAMYAPPIRGQIRCSS
NITGLLLTRDGGNDT-----SGTEIFRPGGGDMRDNRSELYKYKVVKIEPLGVAPTAK
RRVQREKRAVG-IGAVFLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQNNLLRAIEA
QQHLLQLTWVGKIQQLQARVLAVERYLKDQQLLGIWGC SGKLICTTAVPWNS SWSNKS LNE
IWNMTWMEWEREIDNYTGLIYTLIEESQNOQEQNEKDLLELDKWA SLWNWF DISNWLWY
IKIFIMIVGGLIGLRIVFAVLSIVNRVRQGYSPLSFQTRLPA PRGPD RPEGIEEGGERD
RDRSIRLVSGFLALAWDDLRLSLCLFSYHRLRDL LLIVTRIVELLG-----RRGWEALK

Fig. 10 cont'd-9

YWWNLLQYWSQELKNSAVSLLNATAIAVAEGTDRVIEALQRACRAILHIPRRIROGLERA
LL-

>ENV-M.syn3.1

MRVRGIQRNWPQWWIWGILG-----FWMLMICNVVGNLWVTVYYGVPVWKEAKTTLF
CASDAKAYEKEVHNVWATYACVPTDPNPQEIHLNVTEEFNMWKNMVDQMHEDEIISLWD
QSLKPCVQLTPLCVTLNCTN-VNVTNLKNETNTKSSSGGKMEEGEMKNCSFNITTSIRD
KVQKEYALFYKLDVVPIDNDSNNTN-----YRLISCNTSVITQACPKVTFEPIPIH
YCTPAGFAILKCKDKKFNGTGPKNVSTVQCTHGKIPVISTQLLNGSLAEDEIIRSEN
ITNNAKTIIVQLNESVEINCTRPNNTRKSVRIGPGQTFYATGEIIGDIRQAHCNLSRAK
WNDTLKQIVIKLREQFG-NKTIVFNQSSGGDPEIVMHSFNCGGEFFYCNTTQLFNSTW--
-----N---STSLFNSTN---GTITLQCRIKQIINMWQEVGKAMYAPPIEGNITCKS
NITGLLLVRDGGT---EP--NDTETFRPGGGNMKDNWRSELYKYKVVKIEPLGVAPTKAK
RRVVQREKRAVGTIGAMFLGFLGAAGSTMGAASMTLTVQARLLLSGIVQQQNNLLRAIEA
QQHLLQLTVWGIKQLQARILAVERYLKDQQLLGLWGCSGKLICTTAVPWNTSWSNKSQTD
IWDNMTWMEWEREIDNYTGLIYTLIEESQNOQEKNEQELLELDKWASLWNWFDITKWLWY
IKIFIMIVGGLVGLRIVFAVLSIVNRVRKGYSPLSFQTLTPNPRGPDRLGRIEEEGGEQD
RDRSIRLVSGFLALAWDDLRSCLFSYHQLRDFILIVARAVELLGRSSLRGLQRGWEALK
YLGSLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEVIQRICRAIRNIPRRIROGFERA
LL-

>ENV-M.syn3.2

MRVTGIRKNYQHLWRWGTMLLWRWGTMLLGIILMICSAAAGKLWVTVYYGVPVWRDAETTLF
CASDAKAHETEVEHNIWATHACVPTDPNPQEVVLGNVTENFNMWKNMVEQMHEDEIISLWD
ESLKPCVKLTPICVTLNCTDDVRNVT--NATNTNSSW-GEPMEKGEIKNCSFNMTTELRO
KKQKVHALFYKLDIVPL-NSNSSE-----YRLINCNTSAITQACPKVSFEPIPIH
YCAPAGFAILKCNKDFNGTGPCNTVSTVQCTHGIRPVVSTQLLNGSLAEDEEVVIRSEN
FTNNAKTIMVQLNVSVEINCTRPNNTRKSIHIGPGRAFYTGDIIIGDIRQAHCNISRAQ
WNNTLKHIVEKLGKQFGNKTIVFNHSSGGDPEITTHSFNCGGEFFYCNSTKLFNSTWTR
N-NGTWTRN---DTERSNSSTE---EHITLPCRIKQIVNMWQRVGQAMYAPPIRGQIRCSS
NITGLLLTRDGGNDT-----SGTEIFRPGGGDMRNNWRNELYKYKVVRIEPLGVAPTRAK
RRVVEREKRAVG-LGAVFLGFLGAAGSTMGAASLTLTVQARQVLSGIVQQQSNLLKAIEA
QQHLLKLTWGIKQLQARVLAVERYLRDQQLLGIWGCSGKLICTTTVPWNASWSNKSLE
IWNMTWMEWEKEIDNYTNLIYNLLEESQNOQEKNEQDLLALDKWANLWNWFDISNWLWY
IKIFIIIVGGLIGLRIVFAVLSIINRVROGYSPLSLQTLIPNPRGPDRPGGIEEEEGGEQG
RDRSIRLVNGFLALAWDDLRLNCLFSYHRLRDLILLIVTRIVELLG-----RRGWEALK
YWWNLLQYWSQELKNSAISLLNATAVAVAEGTDRVIEALQRACRAILHIPRRIROGLERL
LL-

>ENV-M.syn3.3

MRVKETRKNYQHLWKWGTML-----LGMLMICSAAEQWLWVTVYYGVPVWKEATTTLF
CASDAKAYDTEVHNVWATHACVPTDPSQEVVLENVTENFNMWKNMVEQMHTDEIISLWD
QSLKPCVKLTPICVTLNCTDYVKNIT--NATSTNSSW-GKPMKGEIKNCSFNITTSIRN
KVQKQYALFYKLDIVPI--DNDNTS-----YRLINCNTSTITQACPKVSFDPIPIH
YCAPAGYAILKCNKTFNGTGPCNNVSTVQCTHGKIPVVSTQLLNGSLAEDEIIRSEN
LTNNAKTIIVHLNKSVEINCTRPNNTRKSIHIGPQAFYATGDIIIGDIRKAHCNISGK
WNHTLEQVMEELKKHFP-NKTIKFNSSSGGDLEITTHSFNCRGEFFYCNTSGLFNSTW--
--NDTTINR----TEGSNNTR----NITLPCRIKQIINMWQGVGRAMYAPPIAGNITCKS
NITGILLTRDGGNNN-----STNETFRPGGGDMRDNWRSELYKYKVVVEIKPLGIAPTKAK
RRVVEREKRAVG-IGAVFLGFLGTAGSTMGAASITLTVQARQLLSGIVQQQSNLLRAIEA
QQHMLQLTVWGIKQLQTRVLAERYLKDQQLLGIWGCSGKLICTTNVPWNSSWSNKSQSE
IWDNMTWMMQWDREISNYTDTIYRLLEDSONQOQEKNEKDLLALDSWKNLWNWFDITNWLWY
IRIFIMIVGGLIGLRIFAVLSIVNRVRQGYSPLSFQTRLPAAPRGPDRPEGIEEEEGGERD
RDRSVRLVDGFLALIWDLLRSCLFSYHRLRDFILIAARTVELLGHSSLKGLRLGWGLK
YLWNLLQYWIQELKNSAVSLLNATAIAVAEGTDRVIEVVQRAYRAILHIPTRIROGLERA
LL-

Fig. 10 cont'd-10

>ENV-M.syn4.1
 MRVKETRKNYQHLWKWGTML-----LGMLMICSAAEQWVTVVYGVVWKEATTTLF
 CASDAKAHETEVEHNIWATHACVPTDPNPQEVVLENTENFNMWKNMVEQMHTDIISLWD
 QSLKPCVELTFLCVTLHCTDL-----GNATNT-----MEKGEIKNCSFNMTTELDR
 KKQKVYALFYRLDIVPI-DNDNTS-----YRLINCNTSVIKQACPKVTFEPIPIH
 YCTPAGFAILKCNCKNFNGTGPCKNVSTVQCTHGIRPVVSTQLLLNGSLAEKEIIRSEN
 LTDNAKTIIVHLNKSVEINCTRPSNNTRKSVRIGPGQTFYATGDIIGDIRQAHCNISRK
 WNNTLTKQIVTKLREQFK-NKTIVFNQSSGGDLEITTHSFNCRGEEFFYCNTTQLENSTW--
 -----KN---DTEVSNNTK-GNDTITLPCRKQIVNMWQEVGRAMYAPPIEGNITCNS
 NITGILLTRDGGNNGNET--NGTEIFRPGGGNMRDMWRNELYKYKVVVEIKPLGVAPTEAK
 RRVVEREKRAVG-IGAVFLGFLGAAGSTMGAASITLTVQARQLLTGIVQQQSNLLRAIEA
 QQHMLQLTVWGIKQLQTRVLAIERYLKQDQQLLGLWGCSGKLICTTAVPWNSWSNKTynd
 IWDNMTWMOVDREISNYTDTIYRLLEDSQNOQEKNEKDLLALDSWKNLWNWFDITNWLWY
 IKIFIMIVGGLIGLRIFAVLSIVNRVRQGYSPLSFQTLTPNPRGPDRPGGIEEEGGEGG
 RDRSIRLVNGFLALAWDDLRLNLCFSYHQLRDFILIVARAVELLGRSSLRGLQRGWEALK
 YLGSVQYWGLELKKSAISLLDTIAIAVAEGTDRVIEVVQRAYRAILHIPTRIRQGLERL
 LL-

>ENV-M.syn4.2
 MRVIRGIQRNWPQWIIWGIIG-----FWMLMICNVVGNLWVTVVYGVVWKEAKTTLF
 CASDAKAYEKEVEHNVWATHACVPTDPSPEVLENTENFDMWKNMVEQMVEDVISLWD
 QSLKPCVKLAPLCVTLNCTDYVKNIT-NNATSTNSSW-GKPMKGEIKFCSEFNITTSIRM
 KVQKQYALFYKLDVVQM-DEDNTS-----YRLISCNTSTITQACPKVTFDPIPIH
 YCAPAGFAILKCNKNTFNGTGPCNTVSTVQCTHGIRPVVSTQLLLNGSLAEKEIIRSEN
 LTNNAKTIIVHLNESVEIVCTRPNNNTRKSIHIGPGRFYATGEIIGDIRQAHCNLSRAK
 WNDTLKQIVIKLREQFG-NKTIIFNQSSGGDPEITTHSFNCGGEEFFYCNS'TQLENSTWNF
 --NGTWNKN---FNNTWNTEGTNDTITLPCCKIKQIINMWQVGOAMYAPPISGQIRCSS
 NITGLILTRDGGN---DT--SGTEIFRPGGGDMRDNRSELYKYKVVKIEPLGVAPTKAK
 RRVVQREKRAVG-IGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQSNLLKAIEA
 QQHLLQLTVWGIKQLQARILAVERYLKDQQLLGIWGCSSGKLICTTTPWNASWSNKSLE
 IWDNMTWMEWEREIDNYTGLIYNLIEESQTQOQEKNEQELLELDKASLWNWFDITKWLWY
 IKIFIMIIGGLIGLRIVFTVLSIVNRVRKGYSPLSFQTLTHHQREPDRPERIEEGGEGQD
 RDRSGRLVDGFLAIWVDLRSCLFSYHRLRDLILLIVPRIVELLG-----RRGWEVLK
 YWWNLLQYWSQELKNSAVSLLNATAIAVAEGTDRIIEVIQRICRAIRNIPRIRQGLERA
 LL-

>ENV-M.syn4.3
 MRVKETQMNWPNLWKWGTLI-----LGLVIICSASDNLWVTVVYGVVWKAETTTLF
 CASDAKAYDTEVHNWATYACVPTDPNPQEIHLNVTENFNMWKNMVDQMHEDIISLWD
 ESLKPCVKLTPLCVTLNCTDEVRNVT-NNATNTNSSW-GEPMEKGEIKNCSFNITTSIRD
 KVQKEYALFYKLDVPI-DNDSNNTN-----YRLISCNTSVITQACPKVSFEPIPIH
 YCAPAGYAILKCNCKNFNGTGPCNNVSTVQCTHGIRPVVTTQLLLNGSLAEKEIIRSEN
 ITNNAKTIIVQLNESVVINCTRPNNNTRKSIIRIGPGQAFYATGDIIGNIRQAHCNISRAN
 WNNTLRQIVEKLGEQFGNNKTIVFNHSSGGDPEIVTHSFNCAGEFFYCNTTKLENSTWTR
 N-NGTWTRN---DTERSNSTE---EHITLPCRKQIINMWQEVGKAMYAPPIRGQIRCSS
 NITGLLLLTRDGGNNN-----STNETFRPGGGNMKDNWRSELYKYKVVQIEPLGIAPTKAK
 RRVVEREKRAVG-LGAVFLGFLGTAGSTMGAASLTLTVQARQVLSGIVQQQSNLLRAIEA
 QQHLLKLTWGIKQLQARVLAIERYLQDQQLLGMWGCSSGKLICTTNVPWNSWSNKSQTD
 IWDNMTWLQWDKEISNYTSLIYTLIEESQNOQEKNEQDLLALDKWASLWSWFDISNWLWY
 IKIFIIIVGGLIGLRIVFAVLSIINRVRQGYSPLSLQTLIPNPRGPDRLGRIEEEGGEGQD
 RDRSIRLVSGFLALAWDDLRLSLCIFSYHRLRDFILIAARTVELLGHSSLKGLRLGWEGLK
 YLGNLLLYWGQELKNSAINLLDTIAIAVAGWTDRIEIGQRAGRAILNIPRIRQGFERA
 LL-

>ENV-M.syn4.4
 MRVTGIRKNYQHLWRWGTMLLWRWGTMLLGLMICSAAAGKLWVTVVYGVVWRDADTTLF
 CASDAKAYDTEAHNVWATEASVPTDPNPQEIIVLENTENFNMWKNMVEQMHEDIISLWD
 QSLKPCVQLTPLCVTLNCTN-VNVTNLKNETNTKSSSGGKMEEGEMKNCSFNITTEIRD
 KKQKVHALFYKLDIVPL-NSNSSE-----YRLINCNTSAITQACPKVSFDPIPIH

Fig. 10 cont'd-11

YCTPAGYAILKCNKFKNGTGPCKNVSSVQCTHGIKPVISTQLLNGSLAE EEEVIRSEN
FTNNAKTIMVQLNVSVEINCTRPNNNTRRSIPIGPGRAFYTTGDIIGDIRKAHCNISRAQ
WNNTLKHIVEKLGKQFGNNKTIIFKPSSGGDPEIVMHSFNCGGEFFYCNTSGLFNSTW--
-----N---STSLFNSTN---GTITLQCRIKQIINMWQGVGRAMYAPPIAGNITCKS
NITGLLLVRDGGT---EP--NDTETFRPGGGDMKDNWRSELYKYKVVRIEPLGVAPTRAK
RRVVEREKRAIG-LGAMFLGFLGAAGSTMGAASVTLTVQARLLLSGIVQQONLLRAIEA
QQHLRLTVWGIKQLQARVLAVERYLRDQQLLGIWGC SGKI ICTTAVPWNTSWSNRS LNE
IWNMTWMEWEKEIDNYTNLIYNLLEESQNQQEKNEQEL LALDKWANLWNWEDISNWLWY
IRIFIMIVGGLVGLRIVFAVLSIVKRV RQGYSPLSFQTRLPAPRGPDRPEGIEEEGGERD
RDRSVRLVDGFLALIWDLLRSLCLFSYHHLRDL LLIIVARIVELLG-----RRGWEALK
YWWNLLQYWIQELKNSAISLLNATAVAVAEGTDRVIEALQRACRAILHIPRRIROGFEAA
LL-

>ENV-M. syn6.1

MRVMGIQRNCQQWWIWGILG-----FWMLMICNVMGNLWVTVYYGVPVWKEANTTLF
CASDAKAYEREVHNWATHASVPTDPNPQEVVLENTEDFNMMWKNMVEQM QEDVISLWD
QSLQPCVKLTPLCVTLNCTD-LRNATNGNDTNTTSSS-REMMGGGEMKNCSFNITTEIRD
KKQKVYALFYKLDVVP I-DNDSNNTN-----YRLISCNTSAVTQACPKVTFDPIPIH
YCTPAGFAILKCRDKKFN GTGPCKNVSTVQCTHGIKPVVTTQLLNGSLAE EEEIVIRSEN
FTDNAKTIIVQLKEAVEINCTRPNNNTRKGIHIGPGRAFYATGEIIGDIRQAHCNVSRSF
WNKTLQQVATQLRKHF--NKTIIFNSSSGDLEITTHSFNCRGGEFFYCNTSGLFNSTW--
--NDTTINR----TEGSNNTR----NITLPCRIKQFINMWQEVGRAMYAPPIAGNITCRS
NITGLLLTRDGGNNGNET--NGTEIFRPGGGDMRNNWRSELYKYKVV EIKPLGIAPTKAR
RRVVQREKRAVG-IGAVFLGFLSAAGSTMGAASITLTVQARQLLTGIVQQOSNLLKAIEA
QQHMLQLTVWGVKQLQARVLAVERYLRDQQLLGIWGC SGRLICTTAVPWNTSWSNKS LNE
IWDNMTWMEWEREIDNYTSLIYTLIEESQNQQEKNEQELLELDKWANLWNWFSITNWLWY
IRIFIMIVGGLIGLRIIFGVLSIVKRV RQGYSPLSFQTRLPAPRGPDRPEGIEEEGGERD
RDRSGRLVDGFLALIWDLLRSLCLFSYHRLRDL LILIAARIVELLGHSSLKGLRLGWEALK
YLWNLLLYWGQELKNSAISLLNTTAIVVAEGTDRVIEVLQ RAGRAILNIPRRIROGFEAA
LL-

>ENV-M. syn6.2

MRVTGIRKNYQHLWRWGTMLLWRWGTMLL GILMICSAAAGKLWVTVYYGVPVWREAKTTLF
CASDAKAYEKEVHNWATYACVPTDPNPQEMVLENTENFNMMWKNMVDQM HEDIISLWD
ESLKPCVKLTPLCVTLHCTDL-----GNATNT-----MEKGEIKNCSFNITTEIRD
KKQKVHALFYRLDVVPI-DNDNTS-----YTLINCNTSVITQACPKVTFEPIPIH
YCAPAGFAILKCNKFKNGTGPCTNVSTVQCTHGIKPVVSTQLLNGSLAE GEIIRSEN
LTDNAKTIIVHLNESVEIVCTRPNNNTRKSVRIGPGQTFYATGAIIGDIRQAYCNISRAK
WNNTLKQIVTKLREQFGNNKTIIFKPSSGGDLEITMHHFNCRGGEFFYCNTTQLFNSTWNF
--NGTWNKN---FNNTWNNTEGTNDTITLPCRIKQIINMWQGVGRAMYAPPIISGQIRCSS
NITGLLLTRDGGT-----NNT EIFRPGGGNMRDNWRSELYKYKVVKIEPLGVAPTKAK
RRVVQREKRAVG-IGALFLGFLGAAGSTMGAASMTLTVQARQVLSGIVQQORNLLRAIEA
QQHLLQLTVWGIKQLQARILAVERYLKDQKFLGLWGC SGKI ICTTAVPWNASWSNKS LDD
IWNMTWMOWEREIDNYTGLIYSLIEESQTQQEKNEQELLQLDKWASLWNWFDITNWLWY
IRLFIMIVGGLVGLRIVFTVLSIVNRV RKGYSPLSFQTLTHHQREPDRPERIEEGGGEQG
RDRSVRLVSGFLALEWDDLRSCLFCYHRLRDF LILIAARTVELLGHSSLKGLRRGWEGLK
YLWNLLQYWIQELKNSAISLLNATAVAVAEGTDRVIEALQRACRAILHIPRRIROGLERL
LL-

>ENV-M. syn6.3

MRVRGIQRNWPQWWIWGILG-----FWMIICRVVGNLWVTVYYGVPVWKDAETTLF
CASDAKSYETEAHNIWATHACVPTDPS PQEVVLGNVTENFNMMWKNDMVEQM HEDIISLWD
QSLKPCVELTPLCVILNCTDDVRNVT-NNATNTNSSW-GEPMEKGEIKNCSFNITTSIRN
KVQKQYALFYKLDVQI-DDNNTSNTS-----YRLINCNTSAITQACPKVSFDPIPIH
YCAPAGYAILKCNKTFNGTGPCHNVSTVQCTHGIKPVISTQLLNGSLAE EEEVIRSEN
FTNNAKTIMVQLNVSVEINCTRPNNNTRKSIHIGPGRAFYTTGDIIGDIRQAHCNISRAQ
WNNTLKHIVEKLGKQFGNNKTIIFKPSSGGDPEIVMHSFNCRGGEFFYCNTSKLFNSTWTR
N-NGTWTRN---DTERSNS TE---EHITLPCRIKQIINMWQRVGQAMYAPPIAGNITCNS
SITGLLLTRDGGN---DT--SGTEIFRPGGGNIKDNWRSELYKYKVVQIEPLGVAPTRAK

Fig. 10 cont'd-12

RRVVEREKRAVG--IGAMIFGFLGAAGSTMGAASMLTVQARQLLSGIVQQSNLLMAIEA
QOHLKLTVWGIKQLRARVLAVERYLKDQQLLGIWGC SGKHICTTNVPWNSSWSNKSLE
IWNMTWIEWEREINNYTGLIYNLLEKSONQOEKNEQDLLALDKWASLWSWFDISNWLWY
IKIFIIIVGGLIGLRIVFAVLSLVNRVRQGYSPLSLQTLPTFRGPDRPEGTEEEGGEQG
RDRSIRLVSGFLALAWDDLRLSCLFSYHRLRDFILIVARTVELLGRSSLKGLRLGWGLK
YLGNNLLYWGQELKISALSLLDTTATAVAGWTDRIEIQRLCRAIRNIPRIRQGAERA
LQ-

>ENV-M.syn6.4

MRVKETQMNWPNLWKWGTLI-----LGLVIICSASDNLWVTVYYGVPVWRDADTTLF
CASDAKAHETEVEHNVWATHACVPTDPNPQEIHLNVTEEFNMWKNMVEQMHTDIIISLWD
QSLKPCVRLTPLCVTLNCTDELKNATFRSNTTNSW--EKMERGEIKNCSFNITTSIRD
KVQKEYALFYKLDIVPL-NSNSSE-----YRLINCNTSVIKQACPKISFDPPIPIH
YCAPAGFAILKCKDKKFNGTGPCQNVSTVQCTHRIKPVVSTQFLLNGSLAEEDIIIRSEN
ITNNAKTIIVQLNESVVINCTRPNNNTRRSIPIGPGRVFTTEDIIGDIRQAHCNLSRAK
WNTDLKQIVIKLREQFG-NKTIVFNQSSGGDLEIVMHSFNCGGEFFYCNSTQLFNSTWF-
--NSTW-----STEGSNTE-GSDTITLPCRIKQIVNMWQGVGKAMYAPPIRQIRCSS
NITGILLTRDGGTNGT----NETETFRPGGGMKDNWRSELYRYKVKIEPLGIAPTAK
RRVVEREKRAIG-LGAMFLGFLGTAGSTMGAASLTLTVQARQLMSGIVQQNNLLRAIEA
QOHLKLTVWGIKQLQARVLALERYLKDQQLLGLWGC SGKLICTTTPWNSSWSNKSQTD
IWDNMTWMQWDREISNYTNTIYRLLEDSONQOEKNEKDLLALDSWKNLWNWFDITKWLWY
IKIFIMIVGGLIGLKIIVFAVLSIINVRVQGYSPLSFQTLIPNPRGPDRPGGIEEGGEQD
RDRSIRLVNGFLALIWVDLRLSCLFSYHRLRDLIIIVTRIVELLG-----RRGWEALK
YWWNLLQYWSQELKNSAINLLDTTATAVAEGTDRIIEVIQRICRAIRNIPTRIRQGLERA
LL-

>ENV-M.syn6.5

MRVKGIRKNYQHLWKWGTM-----LGMLMICSATEKLWVTVYYGVPVWKEATTTLF
CASDAKAYDTEVHNVWATYACVPTDPNPQELVLENTENFDMWKNMVEQMHEIDIINLWD
QSLKPCVKLTPICVTLNCTDYVKNIT-NNATSTNSW-GKPMKGEIKNCSFNMTTEL RD
KKQKVYSLFYKLDVVQM-DEDNTS-----YRLISCNTSVITQACPKISFEPIPIH
YCTPAGYAILKCNKFNNGTGPCKNVSSVQCTHGKIPVISTQLLLNGSLAEEDIIIRSEN
LTNNVKTIIIVHLNKSVEINCTRPNSNTRTSIRIGPGQAFYATGDIIGDIRKAHCNISRAK
WNNTLRQIVEKLGEQFGNKTIVFNHSSGGDPEITTHSFNCGGEFFYCNTTKLFNSTWTW
N-NSTW--N---NKRSDTE---EITLPCRIKQIINMWQEVGKAMYAPPIQGVIRCES
NITGLIILTRDGGNNN-----STNETFRPGGDMRDNWRSELYKYKVVRIEPLGVAPTEAK
RRVVQREKRAVGTIGAMFLGFLGAAGSTMGAASVTLTVQARLLLSGIVQQNNLLKAIEA
QOHLRLTVWGIKQLQARVLAIERYLQDQQLLGIWGC SGKLICTTNVPWNSSWSNRSLNE
IWNMTWMEWEKEIDNYTNTLIYNLLEESQIQOEKNEQELLALDKWANLWNWFDISNWLWY
IRIFIIIVGGLVGLRIVFAVLSIVNKVRQGYSPLSFQTHLPAQRGPDRPEGIEEGGEQD
RDRSVRLVDGFLAIWVDLRLSCLFSYHRLRDLIIIVARIVELLG-----RRGWEVLK
YWWNLLKYWSQELKNSAVSLLNATAVAEGTDRIIEVIQRICRAICNIPRIRQGFERA
LL-

>ENV-M.syn6.6

MRVKETRKNYQHLWRWGIML-----LGMLMICSAAEQWVTVYYGVPVWKEAKTTLF
CASNAKAYDTEAHNVWATHACIPTDPNPQEIIVLENTESFNMWKNMVDQMHEIDVISLWD
QSLKPCVQLTPLCVTLNCTN-VNVTLKNETNTKSSSGGKMEEGEMKNCSEFNVTTEL RD
KKKKEYALFYRLDIVPL-NEGNNSNSSY-----YRLINCNTSTITQACPKVSFEPIPIH
FCAPAGFAILKCNKFNNGTGPCKNVSTVQCTHGKIPVISTQLLLNGSLAEKEIIIRSEN
LTNNAKIIIVQLNESVEINCTRPNNTRKSIRIGPGQTFYATGDIIGNIRQAHCNISRTQ
WNNTLKQIAIKLREQFG-NKTIIIFNQSSGGDPEIVTHSFNCGGEFFYCKSTKLFNSTW--
-----N---STSLFNSTN---GTITLQCRKQIINRWQEVGKAMYAPPIEGNITCKS
NITGLLLVRDGGINVTNN--TGTEVFRPGGDMKDNWRNELYKYKVVVEIKPLGVAPTRAR
RRVVEREKRAVG-LGAVFLGFLGAAGSTMGAASVTLTVQARQLLFGIVQQSNLLRAIEA
QQRMLQLTVWGIKQLQTRVLAIERYLKDQQLLGMWGC SGKLICTTAVPWNSSWSNKTYND
IWDNMTWLQWDKEISNYTDTIYRLLEESQNERNEKDLLELDKWASLWNWFNITNLWY
IKIFIMIIGGLIGLRIIFAVLSIVNRVRQGYSPLSFQTLTPNPRGPDRLGRIEEEGGEQD
KDRSIRLVNGFSALIWDDLRLNCLFSYHQLRDFILVTARAVELLGRSSIRGLQRGWEALK
YLGSLVQYWGLELKKSAISLLDTTATAVANWTDRIEIVVQRAYRAILHIPTRIRQGFEEA
LQ-

Fig. 10 cont'd-13

>POL-B.syn1.1

FFRENLAFFPQKAREFSSEQTRANSPTRR-----ELQVWGRDNNSLSEAGA
DR----QGTVS-FSFPQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMNLPGRWKPK
MIGGIGGFIVRQYDQIPIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTLNFPISPIE
TVPVKLKPMDGPKVKQWPLTEEKIKALVEICTEMEKEGKISKIGPENPYNTPVFAIKKK
DSTKWRKLVDFRELNRRTQDFWEVQLGIPHPAGLKKKKSVTVLDVGDAYFSVPLDKDFRK
YTAFTIPSTNNETPGIRYQYNVLPQGWKGSFAIFQS SMTKILEPFRKQNPDIYIYQYMD
LYVGSDELIGQHRTKIEELRQHLLRWGFTTPDKKHQKEPPFLWMGYELHPDKWTVQPIVL
PEKDSWTVNDIQKLVGKLNWASQIYAGIKVKQLCKLLRGTALTEVIPLTEEALELAEN
REILKEPVHGVYDPSKDLIAEIQKQGGQWYQIYQEPFKNLKTGKYARMRGAHTNDVK
QLTEAVQKIATESIVIWGKTPKFKLPIQKETWETWWTEYQATWIPEWEFVNTPPLVKLW
YQLEKEPIVGAETFYVDGAANRETCLGKAGYVDRGRQKVVSLDITTNQKTELQAIHLAL
QDSGLEVNIVTDSQYALGIIQAQPKSESELVSQIEQLIKKEKVYLAWVPAHKGIGGNE
QVDKLVSAGIRKVLFLDGDIDKAQEEHEKYHSNWRAMASDFNLPPVVAKEIVASCDKCQLK
GEAMHGQVDCSPGIWQLDCTHLEGKIIILVAVHVASGYIEAEVI PAETGQETAYFLLKLAG
RWPVKTIHTDNGSNFTSTTVKAACWWAGIKQEFGI PYNPQSQGVVESMNKELKKIIGQVR
DQAEHLKTAVQMAVFIHNFKRKGGIGGYSAGERIVDIIATDIQTKELQKQITKIQNFRVY
YRDSRDPLWKGPAKLLWKGEGAVVIQDNSDIKVVPRRKAKIIRDYGKQ MAGDDCVASRQD
ED-

>POL-B.syn3.1

FFRENLAFFPQKAREFPSEQTRANSPTR-----ELQVWGGDNNSLSEAGD
DR----QGTVS-FSFPQITLWQRPIVTIKIGGQKKEALLDTGADDTVLEEMNLPGRWKPK
IIGGIGGFIVKQYDQILIEICGHKAIGTVLVGPTPANIIGRNLLTQIGCTLNFPISPIE
TVPVRLKPGMDGPKVKQWPLTEEKIKALIEICTELENEGKISKIGPENPYNTPVFAIKKK
DGTKWRKLVDFRELNRRTQDFWEVQLGIPHPAGLKKKKSVTVLDVGDAYFSVPLDKDFRK
YTAFTIPSTNNETPGIRYQYNVLPQGWKGSFSIFQSSMTKILEPFRKQNPDIYIYQYMD
LYVGSDELIEQHRTKIEELRQHLLRWGFTTPDKKHQKEPPFLWMGYELHPDKWTVQPIVL
PEKDSWTVNDIQKLVGKLNWASQIYAGIKVKQLCRLLRGTALTEVVPLTEEALELAEN
REILKEPVHGVYDPSKDLVAEIQKQGLGQWYQIYQEPYKNLKTGKYAKMRGAHTNDVK
QLTEAVQKIATESIVIWGKTPKFKLPIQKETWEAWWMEYQATWIPEWEFVNTPPLVKLW
YQLEKEPIVGAETFYVDGAANRDTKLGKAGYVDRGRQKVVSLDITTNQKTELQAIHLAL
QDSGLEVNIVTDSQYALGIIQAQPKSESELVSQIEQLIKKEKVYLAWVPAHKGIGGNE
QVDKLVSSGIRKVLFLDGDIDKAQEDHEKYHSNWKAMASDFNLPPVVAKEIVACCDKCQLK
GEAMHGQVDCSPGIWQLDCTHLEGKVIILVAVHVASGYIEAEVI PAETGQETAYFILKLAG
RWPVTTIHTDNGSNFTSTAVKAACWWAGIKQEFGI PYNPQSQGVVESINKELKKIIGQVR
DQAEHLKTAVQMAVFIHNFKRKGGIGGYSAGERMIDIATDIQTTELQKQITKLQNFRVY
FRDSRDPLWKGPAKLLWKGEGAVVIQDNSEIKVVPRRKAKIIRDYGKQ MAGDDCVASRQD
ED-

>POL-B.syn3.2

FFREDLAFLQKAREFSSEQTRANSPTRG-----ELQVWGRDNNSLSEAGA
DR----QGTVS-LSFPQITLWQRPLVTVKIGGQLKEALLDTGADDTVLEEMSLPGRWKPK
MIGGIGGFIVRQYDQILVEICGHKAIGTVLVGPTPVNIIGRDLLTQIGCTLNFPISPID
TVPVKLKPMDGPKVKQWPLTEEKIKALVEICTEMEKEGKISKIGPENPYNTPIFAIAIKKK
DSTKWRKLVDFRELNRRTQDFWEVQLGIPHPAGLKKKKSVTVLDVGDAYFSVPLDEDFRK
YTAFTIPSTNNETPGIRYQYNVLPQGWKGSFAIFQSSMTRILEPFRKQNPDLVIYQYMD
LYVGSDELIGQHRTKIEELREHLLRWGFTTPDKKHQKEPPFLWMGYELHPDKWTVQPIML
PEKDSWTVNDIQKLVGKLNWASQIYPGIKVKQLCKLLRGAKALTEVIPLTKEALELAEN
REILKEPVHGAYYDPSKDLIAEIQKQGGQWYQIYQDPFKNLKTGKYARMRGAHTNDVR
QLTEAVQKITTESIVIWGKIPKFKLPIQKETWETWWTEYQATWIPEWEFVNTPPLVKLW
YQLEKEPIIGAETFYVDGAANRETCLGKAGYVTNKGROKVVSIITDTTNQKTELQAILLAL
QDSGLEVNIVTDSQYALGIIQAQPKSESELVSQIEELIKKEKVYLTWVPAHKGIGGNE
QIDKLVSAGIRKVLFLDGDIDQAQEEHEKYHSNWRAMASDFNI PPVVAKEIVASCDKCQLK
GEAIIHGQVDCSPGIWQLDCTHLEGKIIILVAVHVASGYIEAEI IPTETGQETAYFLLKLAG
RWPVKTVHTDNGSNFTSTTVKAACWWAGVKQEFGI PYNPQSQGVVESMNNELKKIIGQIR
DQAEHLKTAVQMAVFIHNFKRKGGIGGYSAGERIVDIIATDIQTKELQKQITKIQNFRVY
YRDNRDPLWKGPAKLLWKGEGAVVIQENS DIKVVPRRKVKIIRDYGKQ MAGDDCVASGQD
ED-

Fig. 10 cont'd-14

>POL-B.syn3.3

FFREDLAF PQGEAREFSSEQTRANSPTRR-----ELQVWGRDSNSLSEAGA
DR----QGTVS-FNEFPQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEDMNLP GKWKPK
MIGGIGGF IKVRQYDQIPIEICGHKAVGTVLVGPTFVNIIGRNLLTQLGCTLNFPISPIE
TVPVKLKP GMDGPKVKQWPLTEEKIKALVEICTELEKEGKISKIGPENPYNTPVF AIKKK
DSTKWRKVVD FRELNKKTQDFWEVQLGIPHP SGLKKKKS VTVLDVGDAYFSVPLDKDFRK
YTAFTIPSVNNETPGVRYQYNVLPQG WKGSPAIFQCSMTKILEPFRKQNP DIVIYQYMDD
LYVGS DLEIGQHRAKIEELRQHLLRWGFTTPDKKHQNEPPFLW MGYELHPDKWTVQPIEL
PEKDSWTVNDIQKLVGKLNWASQIYPGIKVRQLCKLLRGTKALTEVIPLTEEA ELELAEN
REILREP VHG VYYDPTKDLIAEIQKQEQGQWTYQIYQEPFKNLKTGKYARTRGAHTNDVK
QLTEAVQKVATESI VIW GKT PKFKLP IQKETWEAWWTEY WQATWIPEW E FVNT PPLVKLW
YQLEKEPIEGAETFYVDGASNRET KL GKAGYVTNRGRQKV VPLTDTTNQKTELQAIYLAL
QDSGSEVNI VTD S QYALGI IQAQPDKSESELVNQIIEQLIKKEKIYLA WVP AHKGIGGNE
QVDKLV SAGIRKILFLDGI DKAQEEHEKYHNNWRAMASDFNL PPIVAKEIVASCDKCQLK
GEA IHGQVDCSPGIWQLDCTHLEGKVILVAVHVASGYIEAEVI PAETGOETAYFILKLAG
RWPVKTIHTDNGSNFTSATVKAACWWAGIKQEFGI PYNPQSOGV VESMNKELKKIIGQVR
DQAEHLKTAVQMAVFIHNFKRKGGIGEYSAGERIIDIIATDIQTRELQKQITKI QNFRVY
YRDSRDPLWKGP AKLLWKGEGAVVIQDNSDIKV VPRRKAKIIRDY GKQMAGDDCVAGRQD
ED-

>POL-B.syn4.1

FFRENLA FPQGEAREFSSEQNRANSPTRR-----ELQVWGGDNNSLSEAGA
DR----QGTVS-LSFPQITLWQRPLVTIRIGGQLKEALLDTGADDTVLEEMSLPGRWKPK
MIGGIGGF IKVRQYDQILIEICGHKAIGTVLIGPTPVNIIGRNLLTQLGCTLNFPISPID
TVPVKLKP GMDGPKVKQWPLTEEKIKALVEICTEMEKEGKISKIGPENPYNTPIFAIKKK
DSTKWRKLVDFREJNRRTQDFWEVQLGIPHP SGLKKKKS VTVLDVGDAYFSVPLDKDFRK
YTAFTIP SINNETPGVRYQYNVLPQG WKGSPAIFQSSMTKILEPFRKQNPDMVIYQYMDD
LYVGS DLEIGQHRTKIEELRQHLLRWGLTTPDKKHQKEPPFLW MGYELHPDKWTVQPIKL
PEKDSWTVNDIQKLVGKLNWASQIYAGIKVRQLCKLLRGAKALTEVIPLTAEAELELAEN
REILREP VHG VYYDPSKDLIAEIQKQGGQWTYQIYQDPFKNLKTGKYAKMRGAHTNDVK
QLTEAVQKVATESI VIW GKT PKFERLP IQKETWEAWWTEY WQATWIPEW E FVNT PPLVKLW
YQLEKEPIEGAETFYVDGAANRDTKL GKAGYVTD RGRQKV VSLTDTTNQKTELQAIHLAL
QDSGLEVNI VTD S QYALGI IQAQPDKSESELVSQIIEELIKKEKVYLA WVP AHKGIGGNE
QIDKLV SAGIRRVLF DGI DQAQEEHEKYHSNWRAMASDFNL PPIVAKEIVASCDKCQLK
GEA IHGQVDCSPGIWQLDCTHLEGKILLVAVHVASGYIEAEVI PAETGOETAYFLLKLAG
RWPVKTIHTDNGSNFTSTTVKAACWWAGIKQEFGI PYNPQSOGV VESMNKELKKIIEQVR
DQAEHLKTAVQMAVFIHNFKRKGGIGEYSAGERIIDIIATDIQTRELQKQITKI QNFRVY
YRDNRDPLWKGP AKLLWKGEGAVVIQDNSDIKV VPRRKAKIIRDY GKQMAGDDCVAGRQD
ED-

>POL-B.syn4.2

FFRENLA FPQ GKAREFPSEQTRANSPTSR-----ELQVWGRDNNSLSEAGD
DR----CGTVS-FSFPQITLWQRPLVTVKIGGQLKEALLDTGADDTVLEEMNLPGRWKPK
MIGGIGGF IKVRQYDQIPIEICGHKAVGTVLVGPTPVNIIGRDLLTQIGCTLNFPISPIE
TVPVKLKP GMDGPKVKQWPLTEEKIKALIEICTELENEGKISKIGPENPYNTPVF AIKKK
DGTKWRKLVDFRELNKRTQDFWEVQLGIPHPAGLKQKKS VTVLDVGDAYFSVPLDKEFRK
YTAFTIPSTNNETPGIRYQYNVLPQG WKGSPAIFQCSMTKILEPFRKQNPDLVIYQYMDD
LYVGS DLEIEQHRTKIEELREHLLKWGFTTPDKKHQNEPPFLW MGYELHPDKWTVQPIML
PEKDSWTVNDIQKLVGKLNWASQIYAGIKVKQLCKLLRGTKALTEVVPLTEEA ELELAEN
REILKVPVHG VYYDPSKDLVAEIQKQGLGQWTYQIYQEPFKNLKTGKYARTRGAHTNDVR
QLTEAVQKIATESI VIW GKT PKFKLP IQKETWEAWWMEY WQATWIPEW E FVNT PPLVKLW
YQLEKEPIVGAETFYVDGAANRET KL GKAGYVTDKGRQKV VPLTDTTNQKTELQAINLAL
QDSGSEVNI VTD S QYAIGI IQAQPDRSESELVSQIIEQLINKEKVYLA WVP AHKGIGGNE
QVDKLV SSGIRKVLFLDGI DKAQEDHEKYHSNWRAMAGDFNL P PVVAKEIVACCDKCQLK
GEAMHGQVDCSPGIWQLDCTHLEGKVILVAVHVASGYIEAEVI PAETGOETAYFILKLAG
RWPVKTVHTDNGSNFISTTVKAACWWAGVKQEFGI PYNPQSOGV VESMNNELKKIIGQVR
DQAEHLKTAVQMAV FVHNFKRKGGIGGYTAGERIVDIIASDIQTKELQKQITKI QNFRVY

Fig. 10 cont'd-15

YRDSRDPLWKGPAKLLWKGEGAVVIQDNSEIKVVPRRKAKIIRDYGKQ MAGDDCVASRQ
ED-

>POL-B.syn4.3

FFREDLAF LQ GKAREFSSEQTRANSPTRR-----ELQVWGRDNNSPSEAGA
DR----QGTVS-FNFPQITLWQRPIVVIKIGGQLKEALLDTGADDTVLED MNLPGKWKPK
MIGGIGGF I KVRQYDQILVEICGHKAIGTVLVGPTPANI IGRNLLTQIGCTLNFPISPIE
TVPVKL KSGMDGPKVKQWPLTEEKIKALIEICTEMEKEGKISKIGPENPYNTPVFAIKKK
DSTKWRKLVDFRELNRKRTQDFWEVQLGIPHPSGLKKKKS VTVLDVGDAYFSVPLDEDFRK
YTAFTI PSVNNETPGIRYQYNVLPQGWKGS PAIFQSSMTRILEPFRKQNPDI VIYQYMD
LYVGS DLEIGQHRAKIEELRQHLLRWGFTTPDKKHQKEP PFLWMGYELHPDKWTVQPIEL
PEKDSWTVNDIQKLVGKLNWASQIYPGIKVRQLCKLLRGTKALTEVIPLTEEALELAEN
REILKEPVHGVYDPSKELIAEIQKQEQGQWTYQIYQEPFKNLKTGKYARMRGTHTNDVK
QLTEAVQKITTESIVIWGRTPKFKLPIQKETWESWTEYWQATWIPEWEFVNT PPLVKLW
YQLEREPIAGAETFYVDGASNRETKLGKAGYVTNRGRQKVVS LPTDTNOKTELQAIYLAL
QDSGLEVNIVTDSQYAIIGI IQAQPDKSESELVNOIIEQLIKKEKIYLAWVPAHKGIGGNE
QVDKLVSNGRKI LFLDGDIDKAQDEHEKYHSNWKAMASDFNLPPVAKEIVACCDKCQLK
GEAMHGQVDCSPGIWQLDCTHLEGKIILVAVHVASGYIEAEVI PAETGQETAYFLLKLAG
RWPVKI IHTDNGSNFTSTAVKAACWWAGIKQEFGI PYNPQSOGVVESINKELKKI IKQVR
DQAEHLKTAVQMAVFIHNFKRKGGIGGYSAGERMIDI IATDIQTTELQKQITKLQNERVY
FRDSRDPLWKGPAKLLWKGEGAVVIQDNNDIKVVPRRKVKIIRDYGKQ MAGDDCVASGQD
ED-

>POL-B.syn4.4

FFREDLAF PQGKARELSSEQTRANSPTRG-----ELQVWGRD S NSLSEAGA
DR----PGTVS-FSFPQITLWQRPLVTIKIGGQKEALLDTGADDTVLEE INLPGRWKPK
IIGGIGGF I KVQYDQIPIEICGHKVIGTVLVGPTPANI IGRNLLTQIGCTLNFPISPIE
TVPVRLKPGMDGPKVKQWPLTEEKIKALVEICTELEKEGKISKIGPENPYNTPVFAIKKK
DSTKWRKVVDRELNRKKTQDFWEVQLGIPHAGLKKKKS VTVLDVGDAYFSVPLDENFRK
YTAFTI PSINNETPGIRYQYNVLPQGWKGS PSI FQSSMTKILEPFRKQNP EIVIYQYMD
LYVGS DLELGQHRTKIEELRQHLLKWFYTPDKKHQKEP PFLWMGYELHPDKWTVQPIVL
PEKDSWTVNDIQKLVGKLNWASQIYPGIKVKQLCRLLRGAKALTEVIPLTKEAELELAEN
REILKEPVHGVYDPTKDLIAEIQKQEGEQWTYQIYQEPYKNLKTGKYARMRGAHTNDVK
QLTETVQKITTESIVIWGKIPKEKLPKIQKETWETWWTEYWQATWIPEWEFVNT PPLVKLW
YQLEKEPIIGAETFYVDGAASRETKLGKAGYVTNKG RQKVVSITDTNOKTELQAILLAL
QDSGLEVNIVTDSQYAIIGI IQAQPDKSESEIVSQIIEQLIKKEKVYLTWVPAHKGIGGNE
QVDKLVSAGIRKVLFLDGDIDKAQEEHEKYHNNWRAMASDFNI PPVAKEIVASCDKCQLK
GEAMHGQVDCSPGIWQLDCTHLEGKVILVAVHVASGYIEAEI IPTETGQETAYFILKLAG
RWPVTTIHTDNGSNFTSATVKAACWWAGVKQEFGI PYNPQSOGVIESMNKELKKIIGQIR
DQAEHLKTAVQMAVFIHNFKRKGGIGGYSAGERIVDI IATDIQTKELQNKQITKIQNERVY
YRDSRDPLWKGPAKLLWKGEGAVVIQENS DIKVVPRRKVKIIRDYGKQ MAGDDCVASRQD
ED-

>POL-B.syn6.1

FFREDLAF PQGEAREFCSEQTRANSPATR-----ELQVWGRDNTSLSEAGA
DR----PGTVS-FSFPQITLWQRPIVTVKIEGQLKEALLDTGADDTVLEEMNLP GKWKPK
MIGGIGGF I KVRQYDQVSI EICGHKAIGTVLVGPTPANI IGRNLLTQIGCTLNFPISPIE
TVPVKL KPGMDGPKVKQWPLTEEKIKALVEICTELEKEGKISKIGPENPYNTPVFAIKKK
DSTKWRKVVDRELNRKRTQDFWEVQLGIPHPSGLKKKKS VTVLDVGDAYFSVPLDENFRK
YTAFTI PSINNETPGIRYQYNVLPQGWKGS PAIFQSSMTKILEPFRKQNPDI IYQYMD
LYVGS DLEIGQHRAKIEELRQHLLKWFYTPDKKHQKEP PFLWMGYELHPDKWTVQPIEL
PEKDSWTVNDIQKLVGKLNWASQIYAGIKVKELCKLLRGTKALTEVVPLTEEALELAEN
REILKEPVHGVYDPSKDLIAELQKQGGQWTYQIYQEPYKNLKTGKYARTRGAHTNDVR
QLTEAVQKIATEGIVIWGKTPKFKLPIQKETWEAWWTEYWQATWIPEWEFVNT PPLVKLW
YQLEKEPIILGAETFYVDGASNRETKLGKAGYVTD RGRQKVVS LPTDTNOKTELQAINLAL
QDSGLEVNIVTDSQYALGIIQAQ PDRSESELVSQIIEQLINKEKVYLA WVPAHKGIGGNE
QVDKLVSTGIRRVFLDGDIDKAQEEHEKYHSNWRAMASDFNL PPIVAKEIVASCDKCQLK
GEAIHGQVDCSPGIWQLDCTHLEGKVILVAVHVASGYIEAEVI PAETGQETAYFILKLAG

Fig. 10 cont'd-16

RWPVKTIHTDNGSNFTSTTVKAACWWAGIKQEFGI PYNPQS QGVV ESMNKELKKIIEQVR
DQAEHLKTAVQMAV FVHNFKRKG GIGEYSAGERI VDI IATDI QTKELQKHITKI QNFRVY
YRDSRDELWKGP AKLLWKGE GAVVIQDNSEIKV VPRRKAKI IRDYGKQ MAGDDCVASRQD
ED-

>POL-B.syn6.2

FFREDLAFPQ GKARELS SEQTRANSPTS PTRG-----ELQVWGRDSNSLSEAGA
DR----QGPVS--FSFPQITLWQRPIVTIKIGGQLKEALLDTGADDTVLEDMNLPGRWKPK
MIGGIGGFIVKQYDEILVEICGHKAIGTVLIGPTPVNIIGRNLLTQLGCTLNFPISPIE
TVPVKLKS GMDGPKVKQWPLTEEKIKALVEICTELEKEGKISKIGPENPYNTPIFAIAKKK
DSTKWRKLVDFRELNRKTQDFWEVQLGIPHPAGLKKKSVTVLDVGDAYFSVPLDKDFRK
YTAFTI P SVNNETPGIRYQYNVLPQGWKGS PAIFQCSMTKILEPFRKQNPDMVIYQYMDD
LYVGS DLEIGQHRIKIEELREHLLKWF TTPDKKHQNEPPFLW MGYELHPDKWTVQPIVL
PEKDSWTVNDIQKLVGKLNWASQIYPGIKVRQLCKLLRGTKALTEVIPLTEAELELAEN
REILREP VHG VYYDPTKDLIAEIQKQGQWTYQIYQEPFKNLKTGKYARMRGAHTNDVK
QLTEAVQKITTESIVIWGKIPKFRLP IQKETWEAWWIEYWQATWIPEWEFVNT PPLVKLW
YQLE REPIAGAE TFYVDGAANRETKLGKAGYVTNRGRQKVVSITDTTNQKTELQAILLAL
QDSGLEVNIVTDSQYALGI IQAQPKSESELVNIIEQLIKKEKIYLA WVP AHKGIGGNE
QIDKLV SAGIRKVLFLDGI DKAQDEHEKYHSNWRAMAGDFNLPPVVAKEIVACCDKCQLK
GEAMHGQVDCSPGIWQLDCTHLEGKII LVAHVHVASGYIEAEVIPAETGQETAYFLLKLAG
RWPVTTIHTDNGSNFTSATVKAACWWAGVKQEFGI PYNPQS QGVV ESMNKELKKIIEQVR
DQAEHLKTAVQMAVFIHNFKRKG GIGEYSAGERI IIDI IATDI QTKELQKHITKI QNFRVY
YRDSRDP IWKGP AKLLWKGE GAVVIQDNSEIKV VPRRKAKI IRDYGKQ MAGDDCVAGRQD
ED-

>POL-B.syn6.3

FFRENLAFFPQGEAREFSSEQTRANSPTRG-----ELQVWGRDSNSLSEAGD
DR----QGTVS--FSFPQITLWQRPLVTIKIGGQKKEALLDTGADDTVLEEMNLPGRWKPK
IIGGIGGFIVKQYDQIPIEICGHKAVGTVLVGP TPVNIIGRDLLTQIGCTLNFPISPIE
TVPVKLKS GMDGPKVKQWPLTEEKIKALIEICTEMEKEGKISKIGPENPYNTPVFAIAKKK
DGTKWRKLVDFRELNRKTQDFWEVQLGIPHPAGLKKKSVTVLDVGDAYFSVPLDREFRK
YTAFTI PSLNNETPGIRYQYNVLPQGWKGS P SIFQSSMTKILEPFRKQNPDLVIYQYMDD
LYVGS DLELGQHRTKIEELRQHLLKWFYTPDKKHQKEPPFLW MGYELHPDKWTVQPIKL
PEKDSWTVNDIQKLVGKLNWASQIYPGIKVKQLCRLLRGAKALTEVVPLTKEAELELAEN
REILKEPVH GAYYDPTKDLIAEVQKQELGQWTYQIYQEPFKNLKTGKYARMRGAHTNDVK
QLTETVQKITTESIVIWGKTPKFRLP IQKETWESWWT EYWQATWIPEWEFVNT PPLVKLW
YQLEKEPI TGAET FYVDGAANRETKIGKAGYVTDKGRQKVVS L P DTTNQKTELQAIHLAL
QDSGSEVNIVTDSQYAIGI IQAQPDRSESEVNIIEQLIKKEKVYLA WVP AHKGIGGNE
QVDKLV SNGIRKILFLDGI DKAQEEH ERYHSNWKAMASDFNLPPVVAKEIVACCDKCQLK
GEA IHGQVDCSPGIWQLDCTHLEGKVI LVAHVHVASGYIEAEVIPAETGQETAYFILKLAG
RWPVKI IHTDNGSNFTSTAVKAACWWAGIKQEFGI PYNPQS QGVV ESMNKELKKIIEQVR
DQAEHLKTAVQMAVFIHNFKRKG GIGGYSAGERI IIDI IASDI QTKELQKHITKI QNFRVY
YRDSRDP VWKGP AKLLWKGE GAVVIQDNSEIKV VPRRKAKI IRDYGKQ MAGDDCVASRQD
ED-

>POL-B.syn6.4

FFRENLAFFPQRKAREFSSEQTRANSPTRR-----ELQVWGGDNNSLSEAGA
DR----QGTVS--LSFPQITLWQRPLVTIKVGGQLKEALLDTGADDTVLEEINLPGRWKPK
MIGGIGGFIVRQYDQILVEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTLNFPISPIE
TVPVKLKP GMDGPKVKQWPLTEEKIKALVEICTEMEKEGKISKIGPENPYNTPIFAIAKKK
DSTKWRKLVDFRELNRRTQDFWEVQLGIPHPAGLKKKSVTVLDVGDAYFSVPLDEDFRK
YTAFTI P S INNETPGVRYQYNVLPQGWKGS PAIFQASMTKILEPFRKQNPDIVIYQYMDD
LYVGS DLEIGQHRIKIEELRQHLLRWGLTTPDKKHQKEPPFLW MGYELHPDKWTVQPIML
PEKDSWTVNDIQKLVGKLNWASQIYAGIKVRQLCKLLRGAKALTEVIPLTAEAELELAEN
REILKVPVHG VYYDFSKELIAEIQKQEQGQWTYQIYQDPFKNLKTGKYARMRGHTNDVR
QLTEAVQKITTESIVIWGKIPKFKLP IQKETWETWWT EYWQATWIPEWEFVNT PPLVKLW
YQLEKEPI IGAET FYVDGAASRETKLGKAGYVTDGRQKVVISLDTTNQKTELQAIHLAL
QDSGVEVNIVTDSQYALGI IQAQPKSESEIVSQIIEQLIKKEKVYLTWVPAHKGIGGNE

Fig. 10 cont'd-17

QVDKLVSTGIRKVLFLDGDQAQEEHEKYHSNWRMTMASDFNLPPIVAKEIVASCDKCQLK
GEAMHGQVDCSPGIWQLDCTHLEGKVILVAVHVASGYIEAEVIPAETGQETAYFLLKLAG
RWPVKTHTDNGPNEISTTVKAACWWAGIKQEFGI PYNPQSOGVVE SMNNELKKIIGQVR
EQAEHLKTAVQMAVFIHNFKRKGGIGGYSAGERMIDI IATDIQTTELQKQITKLNFRVY
FRDSRDPLWKGP AKLLWKGEGAVVIQENSDIKVVP RRKAKI IRDYGKQ MAGDDCVAGRQD
ED-

>POL-B.syn6.5

FFRENLAFFPQ GKAREFPSEQTRANSPTS R-----ELQVWGRDNNLS EAGA
NR----QGTVS-FSFPQITLWQRPLVTVKIGGQLKEALLDTGADDTVLEMDLPGRWKPK
MIGGIGGFIVRQYDQIPIEICGHKVI GTVLVGP TPANI IGRNLLTQIGCTLNFPISP I E
TVPVRLKPGMDGPKVKQWPLTEEKIKALVEICTELEKEGKISKIGPENPYNTPVFAIKKK
DSTKWRKLVDFRELNKKTQDFWEVQLGIPHPSGLKKKKS VTVLDVGDAYFSVPLDKEFRK
YTAFTIPSTNNETPGIRYQYNVLPQGWKGS PAIFQASMTKILEPFRKQNP EIVYQYMDD
LYVGS DLEIEQHRTKIEELRQHLLRWGFTTPDKKHQKEPPFLWMGYELHPDKWTVQPIVL
PDKDSWTVNDIQKLVGKLNWASQIYPGIKIRQLCKLLRGAKALTEVIPLTKEAELELAEN
REILKEPVHGVYDPSKDLIAEIQKQGGQWTYQIYQEPFKNLKTGKYAKMRGAHTNDVK
QLTEAVQKVATESIVIWGKTPKFKLPIQKETWEAWWMEYWQATWIPEWEFVNT PPLVKLW
YQLEKEPIEGAETFYVDGAANRDTKLGKAGYVTKGRQKVVTLTDTTNQKTELQAIHLAL
QDSGLEVNIVTDSQYALGIIQAQPKSESEIVNQIIEQLIKKEKVYLAWVPAHKGIGGNE
QVDKLVSSGIRKVLFLDGDKAQEDHEKYHSNWRAMANDENLPPVVAKEIVACCDKCQLK
GEAMHGQVDCSPGIWQLDCTHLEGKVILVAVHVASGYIEAEVIPAETGQETAYFILKLAG
RWPVKT VHTDNGSNFTSNTVKAACWWAGIKQEFGI PYNPQSOGVVE SMNKQLKQIIGQVR
DQAEHLKTAVQMAVFIHNFKRKGGIGGYSAGERIVDI IATDIQTRELQKQITKI QNFRVY
YRDSREPLWKGP AKLLWKGEGAVVIQDNSDIKVVPRRKAKI IRDYGKQ MAGDDCVASGQD
ED-

>POL-B.syn6.6

FFREDLAFLO GKAREFSSEQTRAISPTRR-----ELQVWGRDNNSPSEAGA
DR----QGTVS-FNFPQITLWQRPLVTIRIGGQLKEALLDTGADDTVLEEMSLPGRWKPK
MIGGIGGFIVRQYDQILIEICGHKAVGTVLIGPTPVNI IGRNLLTQIGCTLNFPISP ID
TVPVKL KPGMDGPKVKQWPLTEEKIKALIEICTELENEGKISKIGPENPYNTPIFAIKKK
DSTKWRKLVDFRELNKR TQDFWEVQLGIPHPSGLKKKKS VTVLDVGDAYFSIPLDEDFRK
YTAFTIPSINNETPGTRYQYNVLPQGWKGS PAIFQS SMTRILEPFRKQNP DIVIYQYVDD
LYVGS DLEIGQHRTKIEELREHLLRWGFTTPDKKHQKEPPFLWMGYELHPDKWTVQPI TL
PEKDSWTVNDIQKLVGKLNWASQIYAGIKVKQLCKLLRGTKSLTEVVPLTAEAELELAEN
REILKEPVHGAYYDPSKDLVAEIQKQGLGQWTYQIYQEPFKNLKTGKYAKMRGTHTNDVK
QLTEAVQKIATESIVIWGRTPKFKLPIQKETWDAWWTEYWQATWIPEWEFVNT PPLVKLW
YQLEKEPIVGAETFYVDGAANRETRLGKAGYVTDGRQKVVPLTDTTNQKTELQAIYLAL
QDSGLEVNIVTDSQYALGIIQAQPKSESELVSQIIEELIKKEKVYLAWVPAHKGIGGNE
QVDKLVSAGIRRVLFLDGDKAQEEHEKYHNNWRAMASDFNI PPVVAKEIVASCDKCQLK
GEA IHGQVDCSPGIWQLDCTHLEGKII L VAVHVASGYIEAEI IPTETGQETAYFLLKLAG
RWPVKTHTDNGRNFTS NSVKAACWWAGIKQEFGI PYNPQSOGVVE SMNRELKKIIGQIR
DQAEHLKTAVQMAVFIHNFKRKGGIGGYSAGERIVDI IASDIQTKELQKQITKI QNFRVY
YRDNRDPLWKGP AKLLWKGEGAVVIQDNNDIKVVP RRKVKI IRDYGKQ MAGDDCVASRQD
ED-

>POL-C.syn1.1

FFRENLAFFPQGEAREFPSEQTRANSPTS RANSPTS R-----ELQV--RGDNPRSEAGA
ER----QGT---LNFPQITLWQRPLVSIKVGGOIKEALLDTGADDTVLEEINLPGKWKPK
MIGGIGGFIVRQYDQILIEICGKKAIGTVLVGP TPVNI IGRNMLTQLGCTLNFPISP I E
TVPVKL KPGMDGPKVKQWPLTEEKIKALTAICEEMEKEGKITKIGPENPYNTPVFAIKKK
DSTKWRKLVDFRELNKR TQDFWEVQLGIPHAGLKKKKS VTVLDVGDAYFSVPLDEGFRK
YTAFTIPSINNETPGIRYQYNVLPQGWKGS PAIFQSSMTKILEPFRAQNP EIVYQYMDD
LYVGS DLEIGQHRAKIEELREHLLKWGFTTPDKKHQKEPPFLWMGYELHPDKWTVQPIQL
PEKDSWTVNDIQKLVGKLNWASQIYPGIKVRQLCKLLRGAKALTDIVPLTEEALELAEN
REILKEPVHGVYDPSKDLIAEIQKQGHQWTYQIYQEPFKNLKTGKYAKMRTAHTNDVK

Fig. 10 cont'd-18

QLTEAVQKIAMESIIVIWGKTPKFRLLPIQKETWETWWTDYWQATWIPWEFVNTPPPLVKLW
YOLEKEPIAGAETFYVDGAANRETKIGKAGYVTDGRGRQKIVSLTETTNOKTELQAIQLAL
QDSGSEVNIIVTDSQYALGIIQAQPKSESELVNQIIEQLIKKERVYLSWVPAHKGIGGNE
QVDKLVSSGIRKVLFLDGDIDKAQEEHEKYHSNWRAMASEFNLPPIVAKEIVASCDKQCQLK
GEAIHGQVDCSPGIWQLDCTHLEGKIILVAVHVASGYIEAEVI PAETGQETAYYILKLAG
RWPVKVIHTDNGSNFTSAAVKAACWWAGIQQEFGIPYNPQSOGVVE SMNKELKKIIGQVR
DQAEHLKTAVQMAVFIHNFKRKGGIGGYSAGERIIDIIATDIQTKELQKQITKIQNFRVY
YRDSRDPIWKGPAPKLLWKGEAVVIQDNSDIKVVPRRKVKI IKDYGKQ MAGADCVAGRQD
EDQ

>POL-C.syn3.1

FFRENLAFPQGEAREFPPEQTRANSPT-RANSPTS-----KLQV--RGDNPCSEAGA
ER----QGT---FNFPQITLWQRPLVTIKVGGQVKEALLDTGADDTVLEEINLPGKWKPK
MIGGIGGFIVRQYDQIVIEICGKKAIGTVLIGTPVNIIGRNMLTQLGCTLNFPISPIE
TVPVKLPGMDGPKIKQWPLTEEKIKALTAICDEMEKEGKIEKIGPENPYNTPIFAIKKK
DSTKWRKLVDFKELNKRTQDFWEVQLGIPHPAGLKKKRSVTVLDVGDAYFSVPLDESFRK
YTAFTIPSINNETPGIRYQYNVLPQGWKGSFAIFQSSMTRILEPFRAKNPEIIVYQYMDD
LYIGSDLEIGQHRAKVEELREHLLRWGFTTPDKKHQKEPPFLWMGYELHDPKWTVQPIQL
PEKDSWTVNDIQRLVGLNWSAQIYPGIKVRQLCKLLRGTALTDIVPLTEEALELAEN
REILKEPVHGVYDPSKDLIAEIQKQGGDQWTYQIYQESFKNLKTGKYAKMRSHTNDVK
QLTEAVQKIALESIVIWGKAPKFRLLPIQKETWEIWWTDYWQATWIPDWEFVNTPPPLVKLW
YOLEKEPIAGAETFYVDGAANRETKIGKAGYVTDGRGRQKVVTLTETTNOKTELQAIQLAL
QDSGLEVNIIVTDSQYALGIIQAQPKSESELVNQIIEELIKKERVYLSWVPAHKGIGENE
QVDKLVSSNGIRKVLFLDGDIDKAQEEHEKYHSNWRAMANEFNLPVVAKEIVASCDKQCQLK
GEAIHGQVDCSPGMWQLDCTHLEGKIVLAVHVASGYVEAEVI PAETGQETAYFILKLAG
RWPVKI IHTDNGSNFTSNAVKAACWWAGIQQEFGIPYNPQSOGVVE SMNKELKKIIGQVR
EQAEHLKTAVQMAVFIHNFKRKGGIGGYSAGERIIDIIASDIQTKELQKQITKIQNFRVY
YRDSRDPVWKGPAPKLLWKGEAVVIQDNGDIKVVPRRKAKI IKDYGKQ MAGDDCVAGRQD
EDQ

>POL-C.syn3.2

FFRENLAFOQGEAREFPSEQTRANSPTSRSNSPTSRELOV--RGDNPRSEAGV
ER----QGT---LNFPQITLWQRPLVSIKVGGOIKEALLDTGADDTVLEDINLPGKWKPR
MIGGIGGFIVRQYDQIPIEICGKKAIGTVLVGTPVNIIRRNLMLTQLRCTLNFPISPIK
TVPVKLPGMDGPKVKQWPLTEEKIKALTEICEEMEKEGKITKIGPENPYNTPVFAIKKK
DSTKWRKLVDFRELNKRTQDFWEVQLGIPHPAGLKKKRSVTVLDVEDAYFSVPLDEGFRK
YTAFTIPSTNNETPGIRYQYNVLPQGWKGSFAIFQCSMTKILEPFRTQNPDIVIYQYMDD
LYVGSLEIGQHRAKIEELRAHLLKWGLTTPDKKHQKEPPFLWMGYELHDPKWTVQPIKL
PEKDSWTVNDIQKIVGKLNWSAQIYPGIKVKQLCKLLRGAKALTDIIPLTEEALELAEN
REILKEPVHGAYDPSKDLVAEIQKQGHQWTYQIYQEPYKNLKTGKYAKMRTAHTNDVR
QLTEAVQKIAQESIVIWGKTPKFRLLPIQKETWETWWTDYWQATWIPWEFINTPPPLVKLW
YOLEKEPIVGAETFYVDGAANRETKMGKAGYVTDKGRQKIVSLTETTNOKTELQAIQLAL
QDSGPEVNIIVTDSQYALGIIQAQPKDRSESELVNQIIEQLINKERIYLSWVPAHKGIGGNE
QVDKLVSSGIRKVLFLDGDIDKAQEDHEKYHNNWRAMASDFNLPPIVAREIVASCDKQCQLK
GEAMHGQVDCSPGVWQLDCTHLEGKIILVAVHVASGYMEAEVI PAETGQETAYYILKLAG
RWPVKVIHTDNGSNFTSTAVKAACWWAGIKQEFGIPYNPQSOGVVEAMNKELKKIIEQVR
DQAEHLKTAVQMAVLIHNFKRKGGIGGYSAGERIVDIIATDIQTRRELQKQIIQIQNFRVY
YRDSRDPVWKGPAPKLLWKGEAVVIQDNSDIKVVPRRKVKI IKDYGKQ MAGADCVASRQD
ED-

>POL-C.syn3.3

FFRENLAFPQKAREFPSEQARANSPTSRSNSPTS-----ELQV--RRDNPRSEAGA
ER----QGT---LNCQITLWQRPLVSIKIGGQTRREALLDGADDTVLEEISLPGKWKPK
MIGGIGGFIVRQYDQILIEICGKKAIGSVLVGTPVNIIGRNLLTQLGCTLNFPISPIE
TIPVKLPGMDGPRVKQWPLTEEKIKALTAICEEMEKEGKISKIGPENPYNTPIFAIKKK
DSTKWRKLVDFRELNKRTQDFWEIQLGIPHPAGLKKKRSVTVLDVGDAYFSVPLDEDFRK
YTAFTIPSINNATPGIRYQYNVLPQGWKGSPSIFQSSMTKILEPFRAQNPEIIVYQYMDD
LYVGSLEIEQHRAKIEELREHLLKWGFTTPDKKHQKEPPFLWMGCELHDPKWTVQPIQL

Fig. 10 cont'd-19

PEKESWTVNDIQKLVGKLNWASQIYAGIKVKQLCRLLRGAKALTDIVPLTAEAELELAEN
REILREFVHGVYYDPSKELIAEIQKQGQDQWTYQIYQEPFKNLKTGKYAKRRTAHTNDVK
QLAEAVQKIAMESIVIWGKIPKFRLP IQKETWEAWWTDYWQATWIPWEFVNT PPLVKLW
YQLEKDP IAGVETFYVDGAANRETKLGKAGYVTDGRGRQKIVSLSETTNQKTELHAIQLAL
QDSGSEVNIIVTDSQYALRI IQAQPKSESEIVNQIIEQLIKKERVYLAWVPAHKGIGENE
QVDKLVSKGIRKVLFLDGIEKAQEEHERYHSNWRAMASEFNLPPIVAKEIVASCDKCQLK
GEATHGQVDCSPGIWQLDCTHLEGKVIIVAVHVASGYIEAEVI PAETGQETAYFLKLAG
RWPVKTIHTDNGSNFTSAAVKAACWWAGIHQEFGI PYNPQSOGVVE SMNKELKKIIGQVR
DQAEHLKTAVLMAVFIHNFKRKGGIGDYSAGERIIDIIATDIQTKELQKQI I KIQNERVY
YRDNRPDIWKGP AKLLWKGEGAVVLQDNSDIKVI PRRKAKIIRDY GKQ MAGADCVAGRQD
ENQ

>POL-C.syn4.1

FFRENLAFFPQ GKAREFPSEQARANSPTS RANSPTS R-----ELQV--RRDNPRSEAGA
ER----QGT---LNL P QITLWQRPLVSIKVG GQIKEALLDTGADDTVLEDINLPGKWKPK
MIGGIGGF I KVRQYDQIPIEICGKKAIGTVLVGPTPVNII GRNMLTQLGCTLNFPISPIE
TIPVKLKPGMDGPKVKQWPLTEEKIKALTEICKEMEKEGKIEKIGPENPYNTPVFALKKK
DSTKWRKLVDFRELNKRTQDFWEVQLGIPHPSGLKKKKS VTVL DVEDAYFSVPLDENFRK
YTAFTIPSVNNETPGIRYQYNVLPQGWKGS PAIFQC SMTKILEPFRTQNP EIVYQYMDD
LYVGS DLEIGQHRAKIEKLRHLLKWGFTT PDKKHQKEPPFLWMGYELHPDKWTVQPIKL
PEKDSWTVNDIQRLV G KLNWASQIYAGIKVRQLCKLLRGAKALTDIVPLTKEAELELAEN
REILKEPFVHGVYYDPSKELIAEIQKQGQDQWTYQIYQEPFKNLKTGKYAKRRTAHTNDVK
QLAEAVQKITMESIVIWRTPKFRLP IQKETWEAWWTDYWQATWIPWEFVNT PPLVKLW
YQLEKEPIAEAEETFYVDGAANRETKMGKAGYVTDKGRQKIVSLTETTNNQKTELHAIQLAL
QDSGPEVNIIVTDSQYALGI IQAQPKSESESELVSQIIEQLINKERIYLSWVPAHKGIGNE
QVDKLVSKGIRKVLFLDGIDKAQEEHERYHSNWRAMANEFNLPPIVAREIVASCDKCQLK
GEATHGQVDCSPGVWQLDCTHLEGKIIIVAVHVASGYVEAEVI PAETGQETAYFLKLAG
RWPVKTIHTDNGSNFTSAAVKAACWWAGVQQEFGI PYNPQSOGVVE SMNKELKKIIGQIR
DQAEHLKTAVQMAVFIHNFKRKGGIGDYSAGERIIDIIATDIQTR ELQKQI I QIQNERVY
YRDSRDPVWKGP AKLLWKGEGAVVLQDNSDIKVVPRRKVKI IKDY GKQ MAGADCVAGRQD
ENQ

>POL-C.syn4.2

FFRENLAFFPEGEAREFPSEQTRANSPT-RANSPTS R-----KLQV--RGDNPRSEAGV
ER----QGT---LNF P QITLWQRPLVSIKIGGQTR EALLDTGADDTVLEEIKLPGNWKPK
MIGGIGGF I KVRQYDQILIEICGKKAIGTVLIGPTPVNII GRNLLTQLGCTLNFPISPIK
TVPVKLKPGMDGPKVKQWPLSEEKIKALTEICEEMEKEGKISKIGPENPYNTPVFALKKK
DSTKWRKLVDFRELNKRTQDFWEIQLGIPHAGLKKKKS VTVL DVGDAYFSVPLDEDFRK
YTAFTIP S INNATPGIRYQYNVLPQGWKGS PSIFQSSMTKILEPFRAKNPEIVYQYMDD
LYVGS DLEIGQHRAKVEELREHLLKWGLTTPDKKHQKEPPFLWMGYELHPDKWTVQPIQL
PDKDSWTVNDIQKLV G KLNWASQIYPGIKVKQLCKLLRGTKALTDIVPLTAEAELELAEN
REILREFVHGVYYDPSKDLVAEIQKQGNDQWTYQIYQEPYKNLKTGKYAKMRS AHTNDVK
QLTEAVQKIALESIVIWGKAPKFRLP IQKETWEIWWTDYWQATWIPDWEFVNT PPLVKLW
YQLEKDP IAGVETFYVDGAANRETKLGKAGYVTDGRGRQKIVSLSETTNQKTELQAIQLAL
QDSGLEVNIIVTDSQYALGI IQAQPKSESESELVNQIIEELIKKEKVYLSWVPAHKGIGENE
QVDKLVSSGIRKVLFLDGIEKAQEEHEKYHNNWRAMASEFNLPPIVAKEIVASCDKCQLK
GEATHGQVDCSPGMWQLDCTHLEGKIIIVAVHVASGYLEAEVI PAETGQDTAYYILKLAG
RWPVKVIHTDNGTNFTSAAVKAACWWAGIQQEFGI PYNPQSOGVVE SMNKELKKIIGQVR
EQAEHLKTAVLMAVFIHNFKRKGGIGEYSAGERIIDMIATDIQTKELQNQITKIQNERVY
YRDSRDPDIWKGP AKLLWKGEGAVVIQDNGDIKVVPRRKVKIIRDY GKQ MAGDDCVAGRQD
EDQ

>POL-C.syn4.3

FFRENLAFFPQGEAREFPPEQTRANSPTSRTNSPTS R-----ELQV--RGDNPHSEAGA
ERQGTLOGT---LNC P QITLWQRPLVSI R VGGQIKEALLDTGADDTVLEEISLPGKWKPK
MIGGIGGF I KVRQYDQIVIEICGKKAIGSVLVGPTPVNII RRNMLTQLRCTLNFPIS SIE
TVPVKLKPGMDGPRVKQWPLTEEKIKALTAICEEMEKEGKITKIGPDNPNYNTPVFALKKK

Fig. 10 cont'd-20

DSTKWRKLVDFKELNKR... YTAFTIPS'TNNETPGIRYQYNVLPQGWKGS... LYIGSDLEIEQHRAKIEELRAHLLKWGFTT... PEKESWTVNDIQRLVGKLNWASQIYSGIKVRQLCKLLRGVKALTDIVPLTEEALELELAEN... REILKETVHGAYYDPSKDLIAEIQKQGHQDQWYQIYQEPFKNLKTGKYAKMRTAHTNDIK... QLTEAVQKIAMESIVIWGKTPKFRLLPIQKETWETWWTWTDYQATWIPEWEFINTPPLVKLW... YQLEKEPIVGAETFYVDGAANRDTKLGKAGYITDRGRQKVVTLTETTNQKAEIQAIQLAL... QDSGSKVNIIVTDSQYALGIIQAQPDSESELVNCIIEQLIKKERVYLSWVPAHKGIGGNE... QIDKLVSSGIRRVFLDGDIDKAQEDHEKYHSNWRAMASDFNLPPIVAKEIIASCDKCQLK... GEAMHGQVDCSPGIWQLDCTHLEGKVIIVAVHVASGYIEAEVI PAETGQETAYYILKLAG... RWPVKI IHTDNGSNFTSNAVKAACWWAGIHQEFGIPYNPQSQGVVEAMNKELKKIIGQVR... DQAEHLKTAVLMAVFIHNFKRGGGIGGYSAGERIIDIIASDIQTKELQKQITKIQNFRVY... YRDSRDFIWKGPAKLLWKGEGAVVIQDNSDIKVI PRRKAKI IKDYGKQ MAGADCVAGGQD... EN-

>POL-C.syn4.4

FFRENLAFFQGEAREFPSEQTRAISPTSR-----ELQV--RGDNPCEAGA... ER----QGT---FNFPQITLWQRPLVTIKVGGQVKEALLDTGADDTVLEEINLPGKWKPR... MIGGIGGFIVRQYEQILIEICGKRAIGTVLVGPTPINII GRNMLTQIGCTLNFPISSIE... TVPVKLPKGMGPKIKQWPLTEEKIKALTAICDEMEKEGKITKIGPENPYNTPIFAIKKK... DSTKWRKLVDFRELNKR... YTAFTIPSINNETPGIRYQYNVLPQGWKGS... LYVGS... PEKDSWTVNDIQKIVGKLNWASQIYPGIKVRQLCRLLRGAKALTDIIPLTEEALELELAEN... REILKEPVHGAYYDPSKDLIAEIQKQGDQWYQIYQESFKNLKTGKYAKMRTAHTNDVR... QLTEAVQKIAQESIVIWGKIPKFRLLPIQKDTWETWWTWTDYQATWIPDWEFVNTPPLVKLW... YQLEKEPIAGAETFYVDGAANRETKIGKAGYVTDGRGRQKVI TLTETTNQKTELQAIHLAL... QDSGSEVNIIVTDSQYALRI IQAOPDKSESEIVNQTIEQLINKERVYLSWVPAHKGIGGNE... QVDKLYSNGIRKVLFLDGDIDKAQEEHEKYHSNWRAMASEFNLPVVAKEIVASCDKCQOK... GEAIHGQVDCSPRIWQLDCTHLEGKVIILVAVHVASGYMEAEVI PAETGQETAYFILKLAG... RWPVKVIHTDNGSNFTSTAVKAACWWAGIKQEFGIPYNPQSQGVVESMNKELKKIIEQVR... DQAEHLKTAVQMAVLIHNFKRGGGIGGYSAGERIVDIIATDIQTKELQKQIILKIQNFRVY... YRDNRPDIWKGPAKLLWKGEGAVVIQDNSEIKVVPRRKAKI IRDYGKQ MAGADCVASRQD... ED-

>POL-C.syn6.1

FFRENLAFFQGEAREFPSEQTRAISPTSR-----ELQV--RGNNPRSEAGA... ER----QGT---LNLFPQITLWQRPLVSIKIGGQTTREALLDTGADDTVLEEIKLPGNWKPK... MIGGIGGFIVRQYDQILIEICGKRAIGTVLVGPTPVNII GRNMLTQIGCTLNFPISSIE... TVPVKLPKGMGPKVKQWPLTEEKIKALTEICEEMEKEGKITKIGPDNPYNTPVFAIKKK... DSTKWRKLVDFKELNKR... YTAFTIPSINNETPGIRYQYNVLPQGWKGS... LYVGS... PEKDSWTVNDIQKLVGKLNWASQIYSGIKVRQLCKLLRGVKALTDIVPLTKEAELELELAEN... REILREPVG... QLTEAVQKIATESIVIWGKIPKFRLLPIQKDTWETWWTWTDYQATWIPDWEFVNTPPLVKLW... YQLEKEPIAEAEETFYVDGAASRETKMGKAGYVTDGRGRQKVITLTETTNQKTELQAIKLAL... QDSGSEVNVVTVDSQYALGIIQAQPDKSESEIVNQTIEQLINKERVYLSWVPAHKGIGGNE... QVDKLVSRGIRKVLFLDGDIDKAQDEHEKYHSNWRAMASEFNLPPIVAREIVASCDKCQLK... GEATHGQVDCSPGIWQLDCTHLEGKIIILVAVHVASGYIEAEVIPTETGQETAYYILKLAG... RWPVKI IHTDNGSNFTSSAVKAACWWAGIQEFGIPYNPQSQGVVESMNKELKKIIGQVG... DQAEHLKTAVQMAVFIHNFKRGGGIGGYSAGERIIDIIATDIQTRRELQKQIILKIQNFRVY... YRDSRDFIWKGPAKLLWKGEGAVVIQDNSEIKVVPRRKVKI IKDYGKQ MAGADCMASRQD... ED-

>POL-C.syn6.2

FFRENLAFFQGEARELPSEQTRANGPTSR-----ELQV--RGDNPCEAGA... ER----QGT---FNFPQITLWQRPLVTIKVGGQVKEALLDTGADDTVLEEINLPGKWKPK

Fig. 10 cont'd-21

MIGGIGGFVKVRQYDQIPIEICGKRAIGTVLVGPTPINIIGRNMLTQLGCTLNFPISPIE
TVPVQLKPGMDGPRVKQWPLTEEKIKALTEICKEMEKEGKISKIGPENPYNTPIFAIKKK
DSTKWRKLVDFRELNKRTQDFWEVQLGIPHPAGLKKKRSVTVLDVGDAYFSVPLDEDFRK
YTAFTIP SINNETPGVRYQYNVLPQGWKGSPIFQSSMTKILEPFRTQNP EIVIYQYMDD
LYIGSDLEIGQHREKIEELREHLLKWGFTT PDKKHQKEPPFLWMGYELHPDKWTVQPIKL
PEKDSWTVNDIQRLVGKLNWASQIYAGIKVRQLCKLLKGAKALTDIVTLTEEALELELAEN
REILKEPVYGVYDPSKDLVAEIQKQGNDQWTYQIYQESFKNLKTGKYAKMRTAHTNDIK
QLTEAVQKIAQESIVIWGKTPKFRLP IQKETWEAWWTDYWQATWIPDWEFVNT PPLVKLW
YQLEKEPMAGVETFYVDGAANRET KIGKAGYVTDGRGRQKVVTITETTNOKTELQAIYLAL
QDSGSKVNIIVTDSQYALGIIQAQPKSESELVSIIEQLINKEKIYLSWVPAHKGIGGNE
QVDKLVSSGIRKVLFLDGDIDKAQEDHERYHSNWRAMASDFNLPPTIVAKEIVASCDQCQLK
GEAMHGQVDCSPGMWQLDCTHLEGKIIIVAVHVASGYIEAEVISAETGQETAYYILKLAG
RWPVKVHTDNGSNFTSAAVKAACWWAGVQOEFGI PYNPQSOGVVE SMNKELKRIIGQVR
DQAEHLKTAVQMAVFIHNFKRKGGIGGYSAGERIIDMIATDIQTKELQKQI IQIQNFRVY
YRDSRDP IWKGPAKLLWKGEGAVVIQDKGDIKVVPRRKAKI IRDYGKQ MAGADCMAGRQD
EDQ

>POL-C.syn6.3

FFREDLAFPQGEARKFPPEQTRANSPTS RANSPTS R-----KLQV--RGDNPRSEAGV
ER----CGT---LNFPQITLWQRPLVSIKVGGOIREALLDTGADDTVLEEMSLPGKWKPK
MIGGIGGFVKVKQYEQILIEICGKKAIGSVLVGPTPVNIIGRNLLTQLGCTLNFPISPIE
TVPVKLPGMDGPKVKQWPLTEEKIKALTAICDEMEKEGKITKIGPENPYNTPVFAIKKK
DSTKWRKLVDFKELNKRTQDFWEVQLGIPHPAGLKKKRSVTVLDVGDAYFSVPLDENFRK
YTAFTIPSRNNETPGIRYQYNVLPQGWKGS PAIFQASMTKILEPFRAKNPEIVIYQYMDD
LYVGS DLEIGQHRAKIEELRDHLLKWGFTT PDKKHQKEPPFLWMGYELHPDKWTVQPIEL
PEKDSWTVNDIQKLVGKLNWASQIYPGIQVKQLCKLLRGAKALTDVVPLTEEALELELAEN
REILKEPVHGAYYDPSKDLIAEIQKQGHQWTYQIYQEPYKNLKTGKYAKRRAAHTNDVK
QLTEAVQKIAMESIVIWGKTPKFRLP IQKETWETWWTEYWQATWIPEWEFVNT PPLVKLW
YQLEKEPIAGAETFYVDGAANRET KMKGAGYITDRGRQKIISLTETTNOKTELHAIQLAL
QDSGSEANIVTDSQYALGIIQAQFDRSESELVNQIIEQLIKKERVYLA WVPAHKGIGENE
QVDKLVSSGIRKILFLDGDIDKAQEEHEKYHSNWKAMASEFNLPV VAREIVASCDKCQLK
GEAMHGQVDCSPRIWQLDCTHLERKVIIVAVHVASGYMEAEVIPAETGQETAYFILKLAG
RWPVKVIHTDNGSNFTSNAVKAACWWAGIHQOEFGI PYNPQSOGVVE SMNKELKKIIEQVR
DQAEHLKTAVQMAVLIHNFKRKGGIGGYTAGERIIDI IATDIQTKELQNKIITKIQNFRVY
YRDNRPDIWKGPAKLLWKGEGAVVLQDNSDIKVVPRRKVKI IRDYGKQ MAGADCVAGRQD
ED-

>POL-C.syn6.4

FFRKNLAFPQGEAREFPPEQTRANSPTS R-----ELQV--RGDNPLSEAGA
ERQGT LQGT---LNCPQITLWQRPLVSIKVGGOIKEALLDTGADDTVLEEISLPGKWKPK
MIGGIGGFVKVRQYDQIVIEICGKKAIGAVLVGPTPVNI IRRNMLTQLRCTLNFPISPIK
TVPVKLPGMDGPKVKQWPLSEEKIKALTAICEDMEKEGKITKIGPENPYNTPIFAIKKK
DSTKWRKLVDFRELNKRTQDFWEVQLGIPHPAGLKKKRSVTVLDVEDAYFSVPLDEGFRK
YTAFTIP SINNATPGIRYQYNVLPQGWKGS PAIFQSSMTKILEPFRTKNPDIVIYQYMDD
LYVGS DLEIGQHRAKIEKLREHLLRWGLTTPDKKHQKEPPFLWMGYELHPDKWTVQPIQL
PDKDSWTVNDIQKLVGKLNWASQIYAGIKVKQLCRLLRGAKALTDIIP LTEEALELELAEN
REILKEPVHGAYYDPSKDLIAEIQKQGGQWTYQIYQEPYKNLKTGKYAKMRTAHTNDVK
QLAEAVQKITMESIVIWGRTPKFRLP IQKETWETWWTDYWQATWIPEWEFINT PPLVKLW
YQLEKEPIVGAETFYVDGAANRET KLGKAGYVTDKGRQKIVSLTETTNOKTELQAIHLAL
QDSGSEVNIVTDSQYALRIIQAQPKSESELVNQIIEQLINKERIYLSWVPAHKGIGGNE
QVDKLVSNIRKVLFLDGDIEKAQEEHERYHSNWRAMANEFNLPPIVAREIVASCDKCQIK
GEAMHGQVDCSPGVWQLDCTHLEGKVIIVAVHVASGYVEAEVIPAETGQEAAYFILKLAG
RWPVKTIHTDNGSNFTSTAVKAACWWAGIKOEFGI PYNPQSOGVVE SMNKELKKIIGQVR
DQAEHLKTAVQMAVLIHNFKRKGGIGDYSAGERIIDIIATDMQTKELQKQI IKVQNFRVY
YRDSRDP IWKGPAKLLWKGEGAVVIQDNGDIKVVPRRKVKI IKDYGRQ MAGADCVASRQD
ED-

Fig. 10 cont'd-22

>POL-C.syn6.5
FFRENLAFFPEGEAREFFPSEQARANSPTSR-----ELQV--RRDNPRSEAGA
EG----QGT---LNFPQITLWQRPLVSIRVGGQIKEALLDTGADDTVLEEINLPGRWKPK
MIGGIGGFIVRQYDQITIEICGKKAIGTVLVGPTPINTIGRNMLTQIGCTLNFPISPIE
TVPVKLKPMDGPKIKQWPLTEEKIKALKAI CEEMEKEGKIEKIGPENPYNTPVFAIKKK
DSTKWRKLVDFRELNKRTQDFWEIQLGIPHPAGLKRKKSVTVLDVGDAYFSVPLYEDERK
YTAFTIPSVNNETPGIRYQYNVLPQGWKGS PAIFQCSMTKILEPFRAQNPEI VIYQYMDD
LYVGS DLEIGQHRAKVEELREHLLKWGLTTPDKKHQKEPPFLWMGYELHDPKWTVQPIQL
PEKESWTVNDIQKIVGKLNWASQIYPGIKVRQLCRLLRGAKALTDIVPLTAEAELELAEN
REILKEPVHGVYYDPSKELIAEIQKQGDQWYQIYQEPFKNLKTGKYAKMRS AHTNDVK
QLTEAVQKIALESIVIWGKAPKFR LPIQKETWEIWWTDYWQATWIPEWEFVNT PPLVKLW
YQLEKEPIAGVETFYVDGAANRDTKIGKAGYVTD RGRQKIVSLSETTNQKTELQAIQLAL
QDSGLEVNIVTDSQYALGIIQAQPDNSESELVNQIIEELIKKERVYLSWVPAHKGIGGNE
QVDKLVSKGIRKVLFLDGIDKAQEEHEKYHNNWRAMASDFNLPPVVAKEIVACCDKQCQLK
GEA IHGQVDCSPGIWQLDCTHLEGKVIIVAVHVASGYLEAEVI PAETGQETAYFLLKLAG
RWPVKVIHTDNGPNFTSAAVKAACWWAGINQEFGI PYNPQSQGVVESMNKELKKIIGQVR
EQAEHLKTAVQMAVFIHNFKRKGGIGGYSAGERIVDI IATDIQTKELQNQI I KIQNFRVY
YRDSRDP IWKGP AKLLWKGE GAVVIQENS DIKVVPRRKAKI IKDYGKQ MAGDDCVAGRQD
EDQ

>POL-C.syn6.6
FFRENLAFFQGEAREFFPSEQTRANSPT-RANSPTSRTNSPTSRELQV--RGDNPHSEAGA
ER----QGS---LNFPQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEDINLPGKWKPR
MIGGIGGFIVRQYEQIPIEICGKKAIGTVLIGPTPVNIIGRNLLTQIGCTLNFPISPIE
TIPVKLKPMDGPKVKQWPLTEEKIKALTAI CEEMEKEGKITKIGPDNPYNT PVFAIKKK
DSTKWRKLVDFRELNKRTQDFWEVQLGIPHPAGLKKKKSVTVLDVGDAYFSVPLDKDFRK
YTAFTIPSTNNETPGIRYQYNVLPQGWKGS PAIFQSSMIKILEPFRAKNPELVIYQYMDD
LYVGS DLEIMQHRAKIEELRAHLLKWGFTTPDKKHQKEPPFLWMGYELHDPKWTVQPIVL
PEKDSWTVNDIQKLVGKLNWASQIYPGIKVKQLCKLLRGTALTDIVPLTEEAELELAEN
REILKETVHGAYYDPSKDLIAEIQKQGYDQWYQIYQEPFKNLKTGKYAKKRTAHTNDVR
QLTEAVQKIAIESIVIWGKTPKFR LPIQKETWETWWADYWQATWIPEWEFVNT PPLVKLW
YQLEKDP IAGAETFYVDGAANRET KKKGKAGYVTDKGRQKVVTLETETNQAELQAIQLAL
QDSGPEVNIVTDSQYALRIIQAQPDKSESEGLVNQIIEQLIKKEKVYLSWVPAHKGIGGNE
QIDKLVSSGIRRVFLFLDGIDKAQEDHEKYHSNWRAMAGEFNLPVVAKEIVASCDKCCQK
GEA IHGQVDCSPGIWQLDCTHLEGKIIIVAVHVASGYIEAEVI PAETGQDTAYYILKLAG
RWPVKVIHTDNGTNETSAAVKAACWWASIQQEFGI PYNPQSQGVVEAMN KELKKIIGQIR
DQAEHLKTAVLMAVFIHNFKRKGGIGGEYSAGERI IDI IASDIQTKELQKQITKIQNFRVY
YRDSRDPVWKGP AKLLWKGE GAVVIQDNS DIKVI PRRKAKI IRDYGKQ MAGADCVAGGQD
ED-

>POL-M.syn1.1
FFRENLAFFPQGEAREFFPSEQTRANSPTS RANSPTS R-----ELQV--RGDNPRSEAGA
ER----QGT---LNFPQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEDINLPGKWKPK
MIGGIGGFIVRQYDQILIEICGKKAIGTVLVGPTPVNIIGRNMLTQIGCTLNFPISPIE
TVPVKLKPMDGPKVKQWPLTEEKIKALTEICTEMEKEGKISKIGPENPYNTPVFAIKKK
DSTKWRKLVDFRELNKRTQDFWEVQLGIPHPAGLKKKKSVTVLDVGDAYFSVPLDESFRK
YTAFTIP SINNETPGIRYQYNVLPQGWKGS PAIFQSSMTKILEPFRKQNPDI VIYQYMDD
LYVGS DLEIGQHRAKIEELREHLLKWGFTTPDKKHQKEPPFLWMGYELHDPKWTVQPIQL
PEKDSWTVNDIQKLVGKLNWASQIYPGIKVKQLCKLLRGAKALTDIVPLTEEAELELAEN
REILKEPVHGVYYDPSKDLIAEIQKQGDQWYQIYQEPFKNLKTGKYAKMRTAHTNDVK
QLTEAVQKIATESIVIWGKTPKFR LPIQKETWETWWTDYWQATWIPEWEFVNT PPLVKLW
YQLEKEPIVGAETFYVDGAANRET KLGKAGYVTD RGRQKVVSLETETTNQKTELQAIQLAL
QDSGSEVNIVTDSQYALGIIQAQPDKSESELVNQIIEQLIKKEKVYLSWVPAHKGIGGNE
QVDKLVSSGIRKVLFLDGIDKAQEEHEKYHSNWRAMASDFNLPPIVAKEIVASCDKQCQLK
GEAMHGQVDCSPGIWQLDCTHLEGKVIIVAVHVASGYIEAEVI PAETGQETAYFILKLAG
RWPVKVIHTDNGSNFTSAAVKAACWWAGIQQEFGI PYNPQSQGVVESMNKELKKIIGQVR
DQAEHLKTAVQMAVFIHNFKRKGGIGGYSAGERI IDI IATDIQTKELQKQITKIQNFRVY

Fig. 10 cont'd-23

YRDSRDPiWKGPakLLWkGEGAVVIQDNsDIKVVPRRkAKIIRDYgKQMaGDDCVaGRQD
EDQ

>POL-M.syn3.1

FFRENLAfPQGEAREfPSEQTRAnsPTrAnsPTr-----ELQV--RGDNPRSEAGA
ER----QGT---LNFPQITLWQRPLVSIKVGgQIKeALLDTGADDTVLEeINLPGKWKPK
MIGGIGGFikVRQYDQIPiEiCGKRAIGTVLVGPTPINIIGRNMLTQLGCTLNFPiSPIK
TVPVklKPGMDGPKVKQWPLTEEKIKALTAICEEMEKEGKITKIGPENPYNTPVFAIKKK
DGTkWRKLVDFRELnkRTQDFWEVQLGIPHPsGLKkkKsvSVLDVGDAYfSVPLDESFRK
YTAFTiPSINNETPGIRYCYNVLPQGWKGS PAIFQCSMTKILEPFRAQNPEIVIYQYMDD
LYIGSDLEIGQRRAKIEELREHLLRWGFTTPDKKHQKEPFLWMGCELHPDKWTVQPIQL
PEKDSWTVNDIQKIVGKLNWASQIYPGIKVRQLCKLLRGAKALTDIVPLTEEAELELAEN
REILREPvHGvYDPSKDLVAEIQKQGQDQWTYQIYQEPFKNLKTGKYAKMRTAHTNDVK
QLTEAVQKIALESIVIWGKIPKfRLPIQKETWEAWWMEYWOATWIPeWefINTPPLVKLW
YQLEKEPIAGAETfYVDGAANRETKIGKAGYVTDGRGRQKIVSLTETTNQKAELOAIQLAL
QDSGPEVNIvTDSQYALGIIQAHPDKSESELVNQIIEQLIKKERVYLSWVPAHKGI GENE
QVDKLVsNGIRKILFLDGIDKAQEEHEKYHSNWRAMASEFNLPPIVAKeIVASCNKCQLK
GEALHGQVDCSPGMWQLDCTHLEGKVIIVAVHVASGYMEAEVIPAETGQETAYYTLKLAG
RWPVKVvHTDNGSNFTSTAVKAACWWAGIQEFGIPYNPQSQGVIESMNKELKKIIGQIR
DQAEHLKTAVQMAVfIHNFKRKGGIGeYSAGERIIDLIATDIQTRELQKQIKIQNFRVY
YRDSRDPiWKGPakLLWkGEGAVVLQDNsDIKVVPRRkVKIKDYgKQMaGADCVaGRQD
ENQ

>POL-M.syn3.2

FFRENLAfQGEARKfSSEQTGAnsPTr-----ELRV--RRGDNPLSEAGA
ER----RGTVPsLSfPQITLWQRPLVTVKIGGQLIEALLDTGADDTVLEdINLPGKWKPR
MIGGIGGFikVKQYDQILiEiCGKKAIGTVLVGPTPVNIIGRNMLTQIGCTLNFPiSPID
TVPVTLKPGMDGPKIKQWPLTEEKIKALTEICTEMEKEGKISRIGPENPYNTPIFAIKKK
DSTkWRKLVDFRELnkKTQDFWEVQLGIPHPAGLKKKRSVTVLDVGDAYfSVPLDKDFRK
YTAFTiPSTNNETPGIRYQYNVLPQGWKGS PSiFQSSMTRI LEPFRAKNPEIVIYQYMDD
LYVGSdLEIEQHRTKIEELRQHLLRWGLTTPDKKHQKEPFLWMGYELHPDRWTVQPIEL
PEKESWTVNDIQKLVGKLNWASQIYAGIKVKQLCKLLRGTKALTEVVPLTEEAELALEEN
REILKDPVHGAYYDPSKDLIAEIQKQGHQDQWTYQIYQEQYKNLKTGKYARKRSAHTNDVR
QLTEAVQKIATESIVIWGKTPKfRLPIQRETWETWWTDYWOATWIPeWefVNTPPLVKLW
YQLEKDPiAGVETfYVDGASNRETKKGGKAGYVTDKGRQKVSLTETTNQKTELHAIHLAL
QDSGSEVNIvTDSQYALGIIQAQPDRSESELVNQIIEELIKKEKVYLSWVPAHKGIGGNE
QVDKLVSSGIRKVLFLDRIDKAQEEHeryHSNWRtMASDFNLPPIVAKeIVANCDKQCQLK
GEAMHGQVDCSPGIWQIDCTHLEGKVIIVAVHVASGYIEAEVIPAETGQETAYFLKLAG
RWPVKVIHTDNGSNFTSAAVKAACWWANVTQEFGI PYNPQSQGVVESMNKELKKIIGQVR
EQAEHLKTAVQMAVLIHNFKRKGGIGGYSAGERIIDIIASDIQTKELQKQIKVQNFRVY
YRDSRDPVWKGPakLLWkGEGAVVIQDNsDIKVVPRRkVKIIRDYgKQMaGDDCVaGRQD
EDQ

>POL-M.syn3.3

FFREDLAfPQgKAREfSSEQTRAnsPTr-----ELQVWGRDNNSLSEAGA
DR----QGTvS-fSFPQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMNLPGRWKPK
MIGGIGGFikVRQYDQILiEiCGHKAIGTVLIGPTPVNIIGRNLLTQIGCTLNFPiSPIE
TVPVklKPGMDGPRVKQWPLTEEKIKALVEICTEMEKEGKISKIGPENPYNTPVFAIKKK
DSTRWRKLVDFRELnkRTQDFWEIQLGI PHPAGLKKKsvTVLDVGDAYfSVPLDEGFRK
YTAFTiPSVNNETPGVRYQYNVLPQGWKGS PAIFQSSMTKILEPFRKQNPDIVIYQYMDD
LYVGSdLEIGQHRTKIEELREHLLKwGFTTPDKKHQNEPFLWMGYELHPDKWTVQPIVL
PEKDSWTVNDLQKLVGKLNWASQIYPGIKVKQLCRLLRGAKALTEVIPLTKEAELELAEN
REILKEPvHGvYDPSKELIAEIQKQGQDQWTYQIYQEPYKNLKTGKYARMrgAHTNDVK
QLTEVVQKIAMESIVIWGKTPKfKLPiQKETWETWWTeyWOATWIPdWefVNTPPLVKLW
YQLEKEPIVGAETfYVDGAANRETKLGKAGYVTDGRGRQKVSLTDTTNQKTELQAIHLAL
QDSGLEVNIvTDSQYAIgIIQAQPDKSESELVSQIIEQLIKKEKVYLAWVPAHKGIGGNE
QVDKLVsAGIRKVLFLDGIDKAQEDHEKYHNNWRAMASDFNLPPVVAKeIVASCDKQCQLK

Fig. 10 cont'd-24

GEA IHGQVDCSPGIWQLDCTHLEGKIILVAVHVASGYLEAEVIPAETGQETAYFILKLAG
RWPVKTIHTDNGSNFTSTTVKAACWWAGIKQEFGI PYNPQS QGVVESINKELKKIIGQVR
DQAEHLKTAVLMAVFIHNFKRRGGIGGYSAGERIVDI IATDIQTKELQKQITKI QNERVY
YRDSRDPLWKGP AKLLWKGEGAVVIQDNSEIKV VPRRKAKI IRDYGKQ MAGDDCVASRQD
ED-

>POL-M.syn4.1

FFRENLAFPQQGEARKFSSEQTRANSPTRG-----ELQVWGRDNNPLSEAGA
ER----RGTVP SLSFPQITLWQRPLVTVKIGGQLIEALLDTGADDTVLEDINLPGKWKPK
MIGGIGGFIVKQYDQILIEICGKKAIGTVLVGPTPVNI IGRNMLTQIGCTLNFPISPID
TVPVTLKPGMDGPRIKQWPLTEEEKIKALTEICKEMEEEGKISKIGPENPYNTPIFAIKKK
NSTRWRKLVDFRELNKKTQDFWEVQLGIPHPAGLKRKKS SVTVLDVEDAYFSVPLDESFRK
YTAFTIIP SINNETPGVRYQYNVLPQGWKGS PAIFQCSMTKILEPFR IKNPEMVIYQYMDD
LYVGS DLEIGQHRIKIEELRAHLLSWGFTTPDKKHQKDP PFLWMGYELHPDRWTVQPIEL
PEKDSWTVNDIQKLVKLNWASQIYSGIKVRQLCRLLRGAKALTDIVPLTEEALELAEN
REILKEPVHGAYYDPSKDLVAEIQKQGDQWTYQIYQEPFKNLKTGKYARKRSAHTNDVK
QLTEVVQKIATESIVIWGKTPKFRLP IQRETWETWWTEYWQATWIPEWEFVNTPPLVKLV
YQLEKDP IAGVETFYVDGAASRETKLGKAGYVTD RGRQKVVSLTETTNOKTELHAIHLAL
QDSGSEVNI VTD SQYVLGIIQAQPD RSESELVNQIIEELIKKEKVYLSWVPAHKGIGGNE
QVDKLVSSGIRKVLFLNGIDKAQEEHERYHSNWRTMASDFNLPPIVAKEIVANCDKCQLK
GEAMHGQVDCSPGVWQLDCTHLEGKVIIVAVHVASGYIEAEVIPAETGQEAAYFILKLAG
RWPVKVHTDNGSNFTSA AVKAACWWANVRQEFGI PYNPQS QGVVESMNNELKKIIGQIR
DQAEHLKTAVLMAVFIHNFKRRGGIGEYSAGERIIDI IATDIQTR ELQKQITKI QNERVY
FRDSRDPIWKGP AKLLWKGEGAVVIQDNSEIKV VPRRKVKI IRDYGKQ MAGDDCVAGRQD
EN-

>POL-M.syn4.2

FFRENLAFPQGEAREFPSEQARANSPTS RANSPTS R-----DLWDGGRDNL P--SEAGA
ER----QGT---LNFPQITLWQRPLVTVRIGGQLREALLD TGADDTVLEDIDLPGKWKPK
IIGGIGGFIVRQYEQIPIEICGHKAIGTVLVGPTPINI IGRNMLTQLGCTLNFPISPIK
TVPVVKLPGMDGPRVKQWPLTEEEKIKALTAICEEMEKEGKITKIGPENPYNTPVFAIKKK
DSTRWRKLVDFRELNRRTQDFWEVQLGIPHPAGLKKKRS SVTVLDVGDAYFSVPLDEGFRK
YTAFTIIP SVNNETPGIRYQYNVLPQGWKGS PSI FQSSMTRILEPFR AKNPEIVIYQYIDD
LYVRS DLEIGQHRAKIEELREHLLRWGFTTPDKKHQKEP PFLWMGCELHPDKWTVQPIQL
PEKDSWTINDIQKLVGKLNWASQIYPGIKVRQLCKLLRGTKALTDIVTLTEEALELAEN
REILKDPVHG VYYDPSKELIAEIQKQGDQWTYQIYQEQYKNLKTGKYAKRRTAHTNDVR
QLTEAVQKIALESIVIWGKIPKFRLP IQKETWEAWMEYWQATWIPEWEYVNTPPLVKLV
YQLEKEPIIGAE TFYVDGAANRETKLGKAGYV TNRGRQKVVSLTDTTNQKTELQAIQLAL
QDSGSEVNVVTD SQYALGIIQAHPDKSESELVNQIIEQLIKKERVYLSWVPAHKGIGGNE
QVDKLVSAGIRKVLFLDGDIDKAQEDHERYHSNWRAMASDFNLPPVVAKEIVASCNKCQLK
GEA IHGQVDCSPGIWQLDCTHLEGKIIIVAVHVASGYMEAEVIPAETGQETAYFILKLAG
RWPVKI IHTDNGSNFTSATVKAACWWANVTQEFGI PYNPQS QGVVESINKELKKIIGQVR
DQAEHLRTAVQMAVFIHNFKRRGGIGGYSAGERIVDI IATDIQTKELQKQITKI QKFRVY
YRDSRDPLWKGP AKLLWKGEGAVVIQDNSDIKVI PRRKAKI IKDYGKQ MAGADCVAGRQD
EDQ

>POL-M.syn4.3

FFRENLAFPQ GKAREFPSEQTRANSPTS RANSPTS R-----ELQV--RGDNPRSEAGA
ER----QGT---FNFPQITLWQRPLVSIKVG GQIKEALLDTGADDTVLEEINLPGKWKPR
MIGGIGGFIVRQYDQILIEICGKRAIGTVLVGPTPANI IGRNLLTQLGCTLNFPISPIE
TVPVVKLPGMDGPKIKQWPLTEEEKIKALTEICTEMEKEGKISKIGPENPYNTPIFAIKKK
DSTKWRKLVDFKELNKR TQDFWEVQLGIPHPSGLK KKS SVTVLDVGDAYFSVPLDEDFRK
YTAFTIIP STNNETPGIRYQYNVLPQGWKGS PAIFQASMTKILEPFR AQNPEIVIYQYMDD
LYVGS DLEIEQRRAKVEELREHLLKWGFTTPDKKHQNEP PFLWMGYELHPDKWTVQPIKL
PEKESWTVNDIQKLVGKLNWASQIYPGIKVKQLCRLLRGTKALTEVIPLTKEAELELAEN
REILREP VHG VYYDPTKDLIAEIQKQGHQWTYQIYQEPHKNLKTGKYAKMRTAHTNDVK
QLAEAVQKIAMESIVIWGKIPKFKLPIQKETWETWWTDYWQATWIPDWEFVNTPPLVKLV

Fig. 10 cont'd-25

YQLEKEPIAGAETFYVDGAANRETKIGKAGYVTDGRGRQKIVSLTETTNOKAELQAIQLAL
QDSGPEVNIIVTDSQYALGIIQAQPKSESEIVNQIIEKLEKDKVYLSWVPAHKGIGGNE
QIDKLVSNNGIRKVLFLDGIKAQEEHEKYHSNWRAMASEFNLPPIVAKEIVASCDKCOLK
GEATHGQVDCSPGMWQLDCTHLEGKIIILVAVHVASGYIEAEVIPTETGQETAYYILKLAG
RWPVKVIHTDNGSNFTSTAVKAACWWAGIQQEFGIYPYNPQGGVVE SMNKELKKIIGQVR
EQAEHLKTAVQMAVLIHNFKRKGGIGGYSAGERIIDIIASDIQTKELQKQI IKVQNFVY
YRDSRDP IWKGP AKLLWK GEGAVVLQD NSDIKVVPRRKVKI IKDY GKQ MAGADCVASRQD
EN-

>POL-M.syn4.4

FFREDLAFPQ GKAREFSSEQTRANSPTRR-----ELQVWGRDNNSLSEAGA
DR----QGTVS-FSFPQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMNLPGRWKPK
MIGGIGGF I KVRQYDQIPIEICGKKAIGTVLIGPTPVNII GRNLLTQIGCTLNFPISPIE
TIPVVKLPGMDGPKVKQWPLTEEKIKALVEICTEMEKEGKISRIGPENPYNTPVF AIKKK
DGTKWRKLVDFRELNKRTQDFWEIQLGIPHPAGLKKKKS SVSVLDVGDAYFSVPLDKDFRK
YTAFTIP SINNETPGIRYCYNVLPQGWKGS PAIFQSSMTKILEPFRKQNPDI VIYQYMD
LYIGSDLEIGQHRTKIEELRQHLLRWGLTTPDKKHQNEPPFLWMGYELHHPDKWTVQPIVL
PEKDSWTVNDLQKLVGKLNWASQIYAGIKVKQLCKLLRGAKALTEVVPLTEAELELEEN
REILKEPVHGVYYDPSKDLIAEIQKQGQGWTYQIYQEPYKNLKTGKYARMRGAHTNDVK
QLTEAVQKIAQECIVIWGKTPKFKLPIQKETWETWWMQATWIPEWEFINTPPLVKLW
YQLEKEPIVGAETFYVDGASNRETKK GKAGYVTDKGRQKVVTLTETTNOKTELQAIHLAL
QDSGLEVNIIVTDSQYAIGIIQAQPKSESELVSQIIEQLIKKEKVYLAWVPAHKGIGGNE
QVDKLVSNNGIRKILFLDGI DKAQEEHEKYHNNWRAMASDFNI PPVVAKEIVACCDKCOLK
GEALHGQVDCSPRIWQLDCTHLEGKVILVAVHVASGYLEAEVI PAETGQETAYFLLKLAG
RWPVKTIHTDNGSNFTSTTVKAACWWAGIKQEFGIYPYNPQSQGVIESM NKELKKIIEQVR
DQAEHLKTAVQMAV FVHNFKRKGGIGDYSAGERIIDII STDIQTRELOKQI IKIQNFVY
YRDSRDPVWKGP AKLLWK GEGAVVIQDNNEIKVVPRRKAKI IRDY GKQ MAGDDCVASRQD
ED-

>POL-M.syn6.1

FFREDLAFPQGEARKFPSEQTRANSPTRG-----ELQVWGRDNNSLSEAGD
DR----QGTVS-FNLPQITLWQRPLVTVRIGGQLIEALLDTGADDTVLEDMNLP GKWKPK
MIGGIGGF I KVRQYEQIPIEICGHKAIGTVLIGPTPVNII GRNLLTQIGCTLNFPISPID
TVPVTLKPGMDGPKIKQWPLTEEKIKALTEICTEMEKEGKISRIGPENPYNTPVF AIKKK
NSTRWRKLVDFRELNKRTQDFCEVQLGIPHPAGLKKKRSVTVLDVGDAYFSVPLDENFRK
YTAFTIP SINNETPGVRYQYNVLPQGWKGS PAIFQASMTKILEPFRTKNPELVIYQYMD
LYVGS DLEIEQHRTKIEELRAHLLSWGFTTPDKKHQKEPPFLWMGYELHHPDKWTVQPIEL
PEKDSWTVNDIQKIVGKLNWASQIYPGIKVRQLCRLLRGFKALTDIVPLTAEAELELAEN
REILREP VHG VYYDPSKELIAEIQKQGHQWTYQIYQDPFKNLKTGKYARKRSAHTNDVR
QLTEAVQKITTESIVIWGKTPKFR LPIQRETWEAWWMEYWQATWIPEWEFINTPPLVKLW
YQLEKDP I VGAETFYVDGAASRETKLGKAGYVTNKGROKVVSLNETTNQKTELHAIHLAL
QDSGSEANIVTDSQYALGIIQAQPKDRSESEVVNQIIEELIKKEKVYLSWVPAHKGIGGNE
QVDKLVSSGIRKVLFLDGI DKAQEDHERYHSNWRMTASDFNLPPIVAREIVASCDKCOQK
GEAMHGQVDCGPGIWQLDCTHLERKVILVAVHVASGYIEAEVI PAETGQETAYFVLKLAG
RWPVKVIHTDNGSNFTSAAVKAACWWANVTQEFGIYPYNPQSQGVVE SMNNE LKKIIGQVR
EQAEHLKTAVLMAVFIHNFKRKRGIGGYSAGERIVDIIASDIQTKELQKQITKI QNFVY
FRDSRDP IWKGP AKLLWK GEGAVVIQDNNDIKVVPRRKVKI IRDY GKQ MAGDDCVAGRQD
EN-

>POL-M.syn6.2

FFREDLAFPQGEARKFSSEQTRANSPTSR-----ELRVWG-GDNTLSETGA
ER----QGT---LNFQITLWQRPLVTIKVGGQIKEALLDTGADDTVLEDINLP GKWKPK
MIGGIGGF I KVRQYDQIPIEICGKKAIGSVLVGPTPVNII GRNMLTQLGCTLNFPISPIK
TVPVVKLPGMDGPKVKQWPLSEEKIKALTAICDEMEKEGKITKIGPDNPYNTPVF AIKKK
DGTKWRKLVDFKELNKRTQDFWEIQLGIPHPAGLKKKKS SVSVLDVGDAYFSVPLDESFRK
YTAFTIP SLNNETPGIRYCYNVLPQGWKGS PAIFQSSMTKILEPFRAQNF EIVIYQYIDD
LYVRS DLEIGQHRAKIEELREHLLKWGLTTPDKKHQKEPPFLWMGYELHHPDRWTVQPIQL

Fig. 10 cont'd-26

PKDSWTVNDLQKLVGKLNWASQIYPGIRVKQLCKLLKGAKALTDIVTLTEEALELAEN
REILKNPVHGVYDPAKDLIAEIQKQNDQWTYQIYQEPHKNLKTGKYAKMRTAHTNDVK
QLTEVVQKIAMESIVIWGKVPKFRLPQKETWETWWTDYWQATWIPDWEFVNTPLVVKLW
YQLEKEPIAGAETFYVDGAANRETKMGKAGYVTDGRGRQKVVSLETTNQTTELQAIQLAL
QDSGPEVNIVTDSQYAIGI IQAQPDKSESEIVNQIIEQLIKKERVYLSWVPAHKGIGENE
QVDKLVSTGIRRVFLDGI DKAQEEHERYHSNWRAMASEFNLPPIVAKEIVASCDQCQLK
GEAMHGQVDCSPGVWQLDCTHLEGKIIIVAVHVASGYMEAEVI PAETGQETAYFILKLA
RWPVKVIHTDNGPNFTSATVKAACWWANITQEFGI PYNPQGGQGVVESMNKELKKI IKQVR
DQAEHLKTAVQMAVLIHNFKRKGGIGGYSAGERIIDIIASDIQTKELQKQI IKIQNFQVY
YRDSRDPIWKGPAKLLWKGEGAVVLQDNSDIKVVPRRKVKI IKDYGKQ MAGADCVAGGQD
ED-

>POL-M. syn6.3

FFRENLAFFPQKAREFFSEQTRAISPTSR-----ELQVWGGDNNLSLSEAGA
ER----QGTVS-FSFPQITLWQRPIVTIKIGGQLREALDGTGADDTVLEEMNLPGRWPK
MIGGIGGFIVKQYDNILIEICGHKAVSTVLVGPFPANI IGRNLLTQLGCTLNFPISPIE
TVPVKLKP GIDGPKVKQWPLTEEKIKALVEICTEMEKEGKISKIGPENPYNTPIFAIKK
DSTRWRKLVDFRELNRRRTQDFWEVQLGIPHPAGLKRKKSVTVLDVGDAYFSVPLDKEFRK
YTAFTIPSINNETPGIRYQYNVLPQGWKGPSIFQSSMTKILEPFRKKNPEMVIYQYMD
LYIGSDLEIGQHRIKIEELREHLLKWGF TTPDKKHQKEPPFLWMGCELHPDKWTVQPIML
PEKDSWTVNDIQKLVGKLNWASQIYAGIKVRQLCKLLRGTALTEVVPLTEEALELAEN
REILKEPVHGVYDPSKDLIAEVQKQGDQWTYQIYQEPFKNLKTGKYAKKRSHTNDVK
QLTEAVQKIALESIVIWGKAPKFRLPQKETWEAWWTEYWQATWVPEWEFVNTPLVVKLW
YQLETEPIAGAETYYVDGAANRETKLKGAGYVTDNRGRQKVVSLETTNQTTELQAIHLAL
QDSGLEVNIVTDSQYALGI IHAQPDKSESELVNQIIEQLINKERIYLSWVPAHKGIGENE
QVDKLVSKGIRKVLFLDGI EKAQEEHEKYHSNWKAMASEFNLPVVAKEIVACCDKQK
GEALHGQVDCSPGMWQLDCTHLEGKIIIVAVHVASGYIEAEVIPTETGQETAYFLLKLAG
RWPVKTIHTDNGSNFTSTTVKAACWWAGIKQEFGI PYNPQSQGVVESINKELKKI IGQIR
DQAEHLKTAVLMAVFIHNFKRKGGIGGYTAGERIVDIIATDIQTKELQKQITKVQNFVY
YRDSREPLWKGPAKLLWKGEGAVVIQDNNEIKVVPRRKAKILRDYGKQ MAGADCVASRD
EN-

>POL-M. syn6.4

FFRENLAFFQGEAREFSSEQTRTNSPTSR-----ELWDGGRDNLPS-SEAGA
ER----RGTVPSLSFPQITLWQRPLVTIKIGGQLKEALLDGTGADDTVLEEINLPGKWKPK
LIGGIGGFIVKQYDQILIEICGKKAIGTVLVGPTPINI IGRNMLTQIGCTLNFPISPIE
TIPVKLKP GMDGPRVKQWPLTEEKIKALIEICTEMEKEGKISRVPENPYNTPIFAIKK
NSNRWRKLVDFRELNKRTQDFWEVQLGIPHPGGLK KKKSVTILDVGDAYFSVPLDEDFRK
YTAFTIPSINNATPGIRYQYNVLPQGWKGPSAIFQCSMTKILEPFRKQNP EII IYQYMD
LYVRSLEIGQHRTKIEELRQHLLKWGFYTPDKKHQKEPPFLWMGYELHPDKWTVQPIKL
PEKESWTVNDIQKLVKLNWASQIYPGIRKVKQLCRLLRGAKALTEVIPLTEEALELEEN
REILKDPVHGVYDPTKDLIAEIQKQDDQWTYQIYQEPYKNLKTGKYAKRRTAHTNDVR
QLTEVVQKVATESIVIWGKIPKFKLPQKETWEIWWTDYWQATWIPWEFVNTPHLVVKLW
YQLEKEPIIGAETFYVDGASNRETKKKGAGYVTDGRGRQKIVSLETTNQTTELQAIQLAL
QDSGSEVNIVTDSQYALGI IQAHPDKSESELVSQIIEQLIKKEKVYLAWVPAHKGIGNE
QIDKLVSNKIRKILFLDGI DKAQEEHEKYHNNWRAMASDFNLPPVVAKEIVASCNKQK
GEA IHGQVDCSPRIWQLDCTHLEGKVIIVAVHVASGYVEAEVI PAETGQDTAYFILKLAG
RWPVKVVHTDNGSNFTSAAFKAACWWANVQOEFGI PYNPQSQGVVEAMNKELKKI IEQVR
DQAEHLKTAVQMAVVFVHNFKRKGGIGDY SAGERIIDIIATDIQTR ELQKQI IKIQNFVY
YRDNRPDIWKGPAKLLWKGEGAVVIQDNSDIKVI PRRKAKI IRDYGKQ MAGDDCMAGROD
EDQ

>POL-M. syn6.5

FFREDLAFLOQKAREFSSEQTRANSPTR-----ELQVWGRDSNSLSEAGA
DR----QGTVS-FNFPQITLWQRPLVTIKIGGQLKEALLDGTGADDTVLEDIDLPGKWKPK
IIGGIGGFIVKQYDQILIEICGKRAIGTVLVGPTPVNI IGRNILTQIGCTLNFPISPID
TVPVKLKP GMDGPRIKQWPLTEEKIKALTEICKEMEEEGKISKIGPENPYNTPVFAIKK

Fig. 10 cont'd-27

DSTKWRKVVDRELNKGTQDFWEVQLGIPHPAGLKQKKSVTVLDVEDAYFSVPLDKDFRK
YTAFTIPSVNNETPGIRYQYNVLPQGWKGS PAIFQS SMTRILEPFRKQNPDIYQYMDD
LYVGS DLEIGQHRTKVEELRQHLLRWGFTTPDKKHQKDPFLWMGYELHPDKWTVQPIVL
PEKDSWTINDIQKLVGKLNWASQIYSGIKVRQLCKCLRGTALTEVIPLTKEAELELAEN
KEILKEPVHGVYDPSKDLVAEIQKQGQGWYQIYQEQYKNLKTGKYARMRGAHTNDVK
QLAEAVQKIATESIVIWGKIPKFRLP IQRETWETWWTEYWQATWIPEWEYVNT PPLVKLW
YQLEKEPIVGAETFYVDGAANRDTKLGKAGYVTDGRGRQKVPLTDTTNQKTELQAINLAL
QDSGSKVNIIVTDSQYVLGT IQAQ PDRSESEIVNQIIEKLIKDKVYLSWVPAHKGIGGNE
QVDKLV SAGIRKVLFLDGDIDKAQDEHEKYHSNWRAMASDFNLPPIVAKEIVASCDKCQLK
GEATHGQVDCSPGIWQLDCTHLEGKVIIVAVHVASGYIEAEVISAETGQETAYYILKLAG
RWPVKI IHTDNGSNFTSTAVKAACWWAGIQQEFGI PYS PQSQGVVESMNKQLKQIIGQVR
DQAEQLKTAVQMAVFIHNFKRKGGIGEYSAGERIIDII STDIQTRELOKQITKIQNFRVY
YRDSRDPVWKGP AKLLWK GEGAVVIQDNSEIKVVP RRKAKI IRHYGKQ MAGDDCVASRQD
EDQ

>POL-M.syn6.6

FFRENLAFPQGEAREFPSEQARANSPTS SRANSPTS R-----ELQV--RGDNPRSEAGA
ERQGT LQGT---LNC PQITLWQRPLVSIKVGQVKEALLDTGADDTVLEEMSLPGKWKPK
MVGIGGFIKVRQYDQILVEICGHKAIGTVLVGPTPVNI IRRNMLTQLRCTLNFPISPIE
TVPVTLKPGMDGPKVRQWPLTEEKIKALTAICEEMEKEGKITKIGPENPYNTPVFAIRKK
DSTKWRKLVDFRELNKKTQDFWEVQLGIPHPAGLKKKSVTVLDVGDAYFSVPLDEGFRK
YTAFTIPSTNNETPGIRYQYNVLPQGWKGS PAIFQSSMIKILEPFRKNPEIYIYQYMDD
LYVGS DLEIGQHRAKVEELREHLRWGFTTPDKKHQNEPPFLWMGYELHPDKWTVQPIQL
PEKDSWTVNDIQRLVGKLNWASQIYAGIKVKQLCKLLRGAKALTDIVPLTEEAELELAEN
REILKTPVHGVYDPSKDLIAEIQKQGQDQWSYQIYQEPFKNLKTGKYARTRGAHTNDVR
QLTEAVQKIAQECIVIWGKTPKFKLPIQKDTWETWWMDYWQATWIPKWEFVNT PPLVKLW
YQLEKDPIAGVETFYVDGAANRETKIGKAGYVTDKGRQKVVTLET TNQKTELHAIYLAL
QDSGSEVNVVTD SQYALGI IQAQ PDRSESELVNQIIEKLI GKDKVYLSWVPAHKGIGENE
QVDKLV SNGIRKVLFLDGDIDKAQEDHEKYHSNWRAMANEFNLPPIVAKEIVANCDKCQLK
GEAMHGQVDCSPGIWQIDCTHLEGKVIIVAVHVASGYLEAEVIPAETGQEAAYF I LKLAG
RWPVKTVHTDNGSNFTSNAVKAACWWANVRQEFGI PYNPQSQGVIESMNKELKKIIGQVR
DQAEHLRTAVQMAVFIHNFKRKGGIGGYSAGERMIDI IATDIQTTELOKQITKIQKFRVY
YRDSRDPVWKGP AKLLWK GEGAVVIQENS DIKVVPRRKAKI IKDYGKQVAGADCVAGRQD
EDQ

POLYVALENT VACCINE

[0001] This application is a continuation of U.S. application Ser. No. 11/990,222, filed Apr. 20, 2009, which is the U.S. national phase International Application No. PCT/US2006/032907, filed Aug. 23, 2006, which designated the U.S. and claims priority from U.S. Provisional Application No. 60/710,154, filed Aug. 23, 2005, and U.S. Provisional Application No. 60/739,413, filed Nov. 25, 2005, the entire contents of which are incorporated herein by reference.

[0002] This invention was made with Government support under Contract No. DE-AC52-06NA25396 awarded by the U.S. Department of Energy. The Government has certain rights in the invention.

[0003] The content of the ASCII text file submitted with this application on Dec. 3, 2010 named Sequence_Listing.txt created Dec. 3, 2010, which is 870 KB, is also incorporated herein by reference.

[0004] The Sequence Listing filed Apr. 20, 2009 in U.S. application Ser. No. 11/990,222 is incorporated herein by reference.

TECHNICAL FIELD

[0005] The present invention relates, in general, to an immunogenic composition (e.g., a vaccine) and, in particular, to a polyvalent immunogenic composition, such as a polyvalent HIV vaccine, and to methods of using same. The invention further relates to methods that use a genetic algorithm to create sets of polyvalent antigens suitable for use, for example, in vaccination strategies.

BACKGROUND

[0006] Designing an effective HIV vaccine is a many-faceted challenge. The vaccine preferably elicits an immune response capable of either preventing infection or, minimally, controlling viral replication if infection occurs, despite the failure of immune responses to natural infection to eliminate the virus (Nabel, *Vaccine* 20:1945-1947 (2002)) or to protect from superinfection (Altfeld et al, *Nature* 420:434-439 (2002)). Potent vaccines are needed, with optimized vectors, immunization protocols, and adjuvants (Nabel, *Vaccine* 20:1945-1947 (2002)), combined with antigens that can stimulate cross-reactive responses against the diverse spectrum of circulating viruses (Gaschen et al, *Science* 296:2354-2360 (2002), Korber et al, *Br. Med. Bull.* 58:19-42 (2001)). The problems that influenza vaccinologists have confronted for decades highlight the challenge posed by HIV-1: human influenza strains undergoing antigenic drift diverge from one another by around 1-2% per year, yet vaccine antigens often fail to elicit cross-reactive B-cell responses from one year to the next, requiring that contemporary strains be continuously monitored and vaccines be updated every few years (Korber et al, *Br. Med. Bull.* 58:19-42 (2001)). In contrast, co-circulating individual HIV-1 strains can differ from one another by 20% or more in relatively conserved proteins, and up to 35% in the Envelope protein (Gaschen et al, *Science* 296:2354-2360 (2002), Korber et al, *Br. Med. Bull.* 58:19-42 (2001)).

[0007] Different degrees of viral diversity in regional HIV-1 epidemics provide a potentially useful hierarchy for vaccine design strategies. Some geographic regions recapitulate global diversity, with a majority of known HIV-1 subtypes, or clades, co-circulating (e.g., the Democratic Repub-

lic of the Congo (Mokili & Korber, *J. Neurovirol* 11(Suppl. 1):66-75 (2005)); others are dominated by two subtypes and their recombinants (e.g., Uganda (Barugahare et al, *J. Virol.* 79:4132-4139 (2005)), and others by a single subtype (e.g., South Africa (Williamson et al, *AIDS Res. Hum. Retroviruses* 19:133-144 (2003)). Even areas with predominantly single-subtype epidemics must address extensive within-clade diversity (Williamson et al, *AIDS Res. Hum. Retroviruses* 19:133-44 (2003)) but, since international travel can be expected to further blur geographic distinctions, all nations would benefit from a global vaccine.

[0008] Presented herein is the design of polyvalent vaccine antigen sets focusing on T lymphocyte responses, optimized for either the common B and C subtypes, or all HIV-1 variants in global circulation [the HIV-1 Main (M) group]. Cytotoxic T-lymphocytes (CTL) directly kill infected, virus-producing host cells, recognizing them via viral protein fragments (epitopes) presented on infected cell surfaces by human leukocyte antigen (HLA) molecules. Helper T-cell responses control varied aspects of the immune response through the release of cytokines. Both are likely to be crucial for an HIV-1 vaccine: CTL responses have been implicated in slowing disease progression (Oxenius et al, *J. Infect. Dis.* 189:1199-208 (2004)); vaccine-elicited cellular immune responses in nonhuman primates help control pathogenic SIV or SHIV, reducing the likelihood of disease after challenge (Barouch et al, *Science* 290:486-92 (2000)); and experimental depletion of CD8+ T-cells results in increased viremia in SIV infected rhesus macaques Schmitz et al, *Science* 283:857-60 (1999)). Furthermore, CTL escape mutations are associated with disease progression (Barouch et al, *J. Virol.* 77:7367-75 (2003)), thus vaccine-stimulated memory responses that block potential escape routes may be valuable.

[0009] The highly variable Env protein is the primary target for neutralizing antibodies against HIV; since immune protection will likely require both B-cell and T-cell responses (Moore and Burton, *Nat. Med.* 10:769-71 (2004)), Env vaccine antigens will also need to be optimized separately to elicit antibody responses. T-cell-directed vaccine components, in contrast, can target the more conserved proteins, but even the most conserved HIV-1 proteins are diverse enough that variation is an issue. Artificial central-sequence vaccine approaches (e.g., consensus sequences, in which every amino acid is found in a plurality of sequences, or maximum likelihood reconstructions of ancestral sequences (Gaschen et al, *Science* 296:2354-60 (2002), Gao et al, *J. Virol.* 79:1154-63 (2005), Doria-Rose et al, *J. Virol.* 79:11214-24 (2005), Weaver et al, *J. Virol.*, in press)) are promising; nevertheless, even centralized strains provide limited coverage of HIV-1 variants, and consensus-based reagents fail to detect many autologous T-cell responses (Altfeld et al, *J. Virol.* 77:7330-40 (2003)).

[0010] Single amino acid changes can allow an epitope to escape T-cell surveillance; since many T-cell epitopes differ between HIV-1 strains at one or more positions, potential responses to any single vaccine antigen are limited. Whether a particular mutation results in escape depends upon the specific epitope/T-cell combination, although some changes broadly affect between-subtype cross-reactivity (Norris et al, *AIDS Res. Hum. Retroviruses* 20:315-25 (2004)). Including multiple variants in a polyvalent vaccine could enable responses to a broader range of circulating variants, and could also prime the immune system against common escape mutants (Jones et al, *J. Exp. Med.* 200:1243-56 (2004)).

Escape from one T-cell receptor may create a variant that is susceptible to another (Allen et al, *J. Virol.*, 79:12952-60 (2005), Feeney et al, *J. Immunol.* 174:7524-30 (2005)), so stimulating polyclonal responses to epitope variants may be beneficial (Killian et al, *Aids* 19:887-96 (2005)). Escape mutations that inhibit processing (Milicic et al, *J. Immunol.* 175:4618-26 (2005)) or HLA binding (Ammaranond et al, *AIDS Res. Hum. Retroviruses* 21:395-7 (2005)) cannot be directly countered by a T-cell with a different specificity, but responses to overlapping epitopes may block even some of these escape routes.

[0011] The present invention relates to a polyvalent vaccine comprising several “mosaic” proteins (or genes encoding these proteins). The candidate vaccine antigens can be cocktails of k composite proteins (k being the number of sequence variants in the cocktail), optimized to include the maximum number of potential T-cell epitopes in an input set of viral proteins. The mosaics are generated from natural sequences: they resemble natural proteins and include the most common forms of potential epitopes. Since CD8+ epitopes are contiguous and typically nine amino-acids long, sets of mosaics can be scored by “coverage” of nonamers (9-mers) in the natural sequences (fragments of similar lengths are also well represented). 9-Mers not found at least three times can be excluded. This strategy provides the level of diversity coverage achieved by a massively polyvalent multiple-peptide vaccine but with important advantages: it allows vaccine delivery as intact proteins or genes, excludes low-frequency or unnatural epitopes that are not relevant to circulating strains, and its intact protein antigens are more likely to be processed as in a natural infection.

SUMMARY OF THE INVENTION

[0012] In general, the present invention relates to an immunogenic composition. More specifically, the invention relates to a polyvalent immunogenic composition (e.g., an HIV vaccine), and to methods of using same. The invention further relates to methods that involve the use of a genetic algorithm to design sets of polyvalent antigens suitable for use as vaccines.

[0013] Objects and advantages of the present invention will be clear from the description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] FIGS. 1A-1F. The upper bound of potential epitope coverage of the HIV-1 M group. The upper bound for population coverage of 9-mers for increasing numbers of variants is shown, for $k=1-8$ variants. A sliding window of length nine was applied across aligned sequences, moving down by one position. Different colors denote results for different numbers of sequences. At each window, the coverage given by the k most common 9-mers is plotted for Gag (FIGS. 1A and 1B), Nef (FIGS. 1C and 1D) and Env gp120 (FIGS. 1E and 1F). Gaps inserted to maintain the alignment are treated as characters. The diminishing returns of adding more variants are evident, since, as k increases, increasingly rare forms are added. In FIGS. 1A, 1C and 1E, the scores for each consecutive 9-mer are plotted in their natural order to show how diversity varies in different protein regions; both p24 in the center of Gag and the central region of Nef are particularly highly conserved. In FIGS. 1B, 1D and 1F, the scores for each 9-mer are reordered by coverage (a strategy also used in FIG. 4), to provide a sense of the overall population coverage of a given protein. Coverage of gp120, even with 8 variant 9-mers, is particularly poor (FIGS. 1E and 1F).

[0015] FIGS. 2A-2C. Mosaic initialization, scoring, and optimization. FIG. 2A) A set of k populations is generated by random 2-point recombination of natural sequences (1-6 populations of 50-500 sequences each have been tested). One sequence from each population is chosen (initially at random) for the mosaic cocktail, which is subsequently optimized. The cocktail sequences are scored by computing coverage (defined as the mean fraction of natural-sequence 9-mers included in the cocktail, averaged over all natural sequences in the input data set). Any new sequence that covers more epitopes will increase the score of the whole cocktail. FIG. 2B) The fitness score of any individual sequence is the coverage of a cocktail containing that sequence plus the current representatives from other populations. FIG. 2C) Optimization: 1) two “parents” are chosen: the higher-scoring of a randomly chosen pair of recombined sequences, and either (with 50% probability) the higher-scoring sequence of a second random pair, or a randomly chosen natural sequence. 2) Two-point recombination between the two parents is used to generate a “child” sequence. If the child contains unnatural or rare 9-mers, it is immediately rejected, otherwise it is scored (Gaschen et al, *Science* 296:2354-2360 (2002)). If the score is higher than that of any of four randomly-selected population members, the child is inserted in the population in place of the weakest of the four, thus evolving an improved population; 4) if its score is a new high score, the new child replaces the current cocktail member from its population. Ten cycles of child generation are repeated for each population in turn, and the process iterates until improvement stalls.

[0016] FIG. 3. Mosaic strain coverage for all HIV proteins. The level of 9-mer coverage achieved by sets of four mosaic proteins for each HIV protein is shown, with mosaics optimized using either the M group or the C subtype. The fraction of C subtype sequence 9-mers covered by mosaics optimized on the C subtype (within-clade optimization) is shown in gray. Coverage of 9-mers found in non-C subtype M-group sequences by subtype-C-optimized mosaics (between-clade coverage) is shown in white. Coverage of subtype C sequences by M-group optimized mosaics is shown in black. B clade comparisons gave comparable results (data not shown).

[0017] FIGS. 4A-4F. Coverage of M group sequences by different vaccine candidates, nine-mer by nine-mer. Each plot presents site-by-site coverage (i.e., for each nine-mer) of an M-group natural-sequence alignment by a single tri-valent vaccine candidate. Bars along the x-axis represent the proportion of sequences matched by the vaccine candidate for a given alignment position: 9/9 matches (in red), 8/9 (yellow), 7/9 (blue). Aligned 9-mers are sorted along the x-axis by exact-match coverage value. 656 positions include both the complete Gag and the central region of Nef. For each alignment position, the maximum possible matching value (i.e. the proportion of aligned sequences without gaps in that nine-mer) is shown in gray. FIG. 4A) Non-optimal natural sequences selected from among strains being used in vaccine studies (Kong et al, *J. Virol.* 77:12764-72 (2003)) including an individual clade A, B, and C viral sequences (Gag: GenBank accession numbers AF004885, K03455, and U52953; Nef core: AF069670, K02083, and U52953). FIG. 4B) Optimum set of natural sequences [isolates US2 (subtype B, USA), 70177 (subtype C, India), and 99TH.R2399 (subtype CRF15_01B, Thailand); accession numbers AY173953, AF533131, and AF530576] selected by choosing the single sequence with maximum coverage, followed by the sequence

that had the best coverage when combined with the first (i.e. the best complement), and so on, selected for M group coverage FIG. 4C) Consensus sequence cocktail (M group, B- and C-subtypes). FIG. 4D) 3 mosaic sequences, FIG. 4E) 4 mosaic sequences, FIG. 4F) 6 mosaic sequences. FIGS. 4D-4F were all optimized for M group coverage.

[0018] FIGS. 5A and 5B. Overall coverage of vaccine candidates: coverage of 9-mers in C clade sequences using different input data sets for mosaic optimization, allowing different numbers of antigens, and comparing to different candidate vaccines. Exact (blue), 8/9 (one-off; red), and 7/9 (two-off; yellow) coverage was computed for mono- and polyvalent vaccine candidates for Gag (FIG. 5A) and Nef (core) (FIG. 5B) for four test situations: within-clade (C-clade-optimized candidates scored for C-clade coverage), between-clade (B-clade-optimized candidates scored for C-clade coverage), global-against-single-subtype (M-group-optimized candidates scored for C-clade coverage), global-against-global (M-group-optimized candidates scored for global coverage). Within each set of results, vaccine candidates are grouped by number of sequences in the cocktail (1-6); mosaic sequences are plotted with darker colors. “Non-opt” refers to one set of sequences moving into vaccine trials (Kong et al, *J. Virol.* 77:12764-72 (2003)); “mosaic” denotes sequences generated by the genetic algorithm; “opt. natural” denotes intact natural sequences selected for maximum 9-mer coverage; “MBC consensus” denotes a cocktail of 3 consensus sequences, for M-group, B-subtype, and C-subtype. For ease of comparison, a dashed line marks the coverage of a 4-sequence set of M-group mosaics (73.7-75.6%). Over 150 combinations of mosaic-number, virus subset, protein region, and optimization and test sets were tested. The C clade/B clade/M group comparisons illustrated in this figure are generally representative of within-clade, between-clade, and M group coverage. In particular, levels of mosaic coverage for B and C clade were very similar, despite there being many more C clade sequences in the Gag collection, and many more B clade sequences in the Nef collection (see FIG. 6 for a full B and C clade comparison). There were relatively few A and G clade sequences in the alignments (24 Gag, 75 Nef), and while 9-mer coverage by M-group optimized mosaics was not as high as for subtypes for B and C clades (4-mosaic coverage for A and G subtypes was 63% for Gag, 74% for Nef), it was much better than a non-optimal cocktail (52% Gag, 52% for Nef).

[0019] FIGS. 6A and 6B. Overall coverage of vaccine candidates: coverage of 9-mers in B-clade, C-clade, and M-group sequences using different input data sets for mosaic, optimization, allowing different numbers of antigens, and comparing to different candidate vaccines. Exact (blue), 8/9 (one-off; red), and 7/9 (two-off; yellow) coverage was computed for mono- and polyvalent vaccine candidates for Gag (FIG. 6A) and Nef (core) (FIG. 6B) for seven test situations: within-clade (B- or C-clade-optimized candidates scored against the same clade), between-clade (B- or C-clade-optimized candidates scored against the other clade), global vaccine against single subtype (M-group-optimized candidates scored against B- or C-clade), global vaccine against global viruses (M-group-optimized candidates scored against all M-group sequences). Within each set of results, vaccine candidates are grouped by number of sequences in the cocktail (1-6); mosaic sequences are plotted with darker colors. “Non-opt” refers to a particular set of natural sequences previously proposed for a vaccine (Kong, W. P. et al. *J Virol* 77, 12764-72 (2003)); “mosaic” denotes sequences generated by the genetic algorithm; “opt. natural” denotes intact natural sequences selected for maximum 9-mer coverage; “MBC consensus”

denotes a cocktail of 3 consensus sequences, for M-group, B-subtype, and C-subtype. A dashed line is shown at the level of exact-match M-group coverage for a 4-valent mosaic set optimized on the M-group.

[0020] FIGS. 7A and 7B. The distribution of 9-mers by frequency of occurrence in natural, consensus, and mosaic sequences. Occurrence counts (y-axis) for different 9-mer frequencies (x-axis) for vaccine cocktails produced by several methods. FIG. 7A: frequencies from 0-60% (for 9-mer frequencies >60%, the distributions are equivalent for all methods). FIG. 7B: Details of low-frequency 9-mers. Natural sequences have large numbers of rare or unique-to-isolate 9-mers (bottom right, FIGS. 7A and 7B); these are unlikely to induce useful vaccine responses. Selecting optimal natural sequences does select for more common 9-mers, but rare and unique 9-mers are still included (top right, FIGS. 7A and 7B). Consensus cocktails, in contrast, under-represent uncommon 9-mers, especially below 20% frequency (bottom left, FIGS. 7A and 7B). For mosaic sequences, the number of lower-frequency 9-mers monotonically increases with the number of sequences (top left, each panel), but unique-to-isolate 9-mers are completely excluded (top left of right panel: * marks the absence of 9-mers with frequencies <0.005).

[0021] FIGS. 8A-8D. HLA binding potential of vaccine candidates. FIGS. 8A and 8B) HLA binding motif counts. FIGS. 8C and 8D) number of unfavorable amino acids. In all graphs: natural sequences are marked with black circles (λ); consensus sequences with blue triangles (σ); inferred ancestral sequences with green squares (ν); and mosaic sequences with red diamonds (\heartsuit). Left panel (FIGS. 8A and 8C) shows HLA-binding-motif counts (FIG. 8A) and counts of unfavorable amino acids (FIG. 8C) calculated for individual sequences; Right panel (FIGS. 8B and 8D) shows HLA binding motifs counts (FIG. 8B) and counts of unfavorable amino acids (FIG. 8D) calculated for sequence cocktails. The top portion of each graph (box-and-whiskers graph) shows the distribution of respective counts (motif counts or counts of unfavorable amino acids) based either on alignment of M group sequences (for individual sequences, FIGS. 8A and 8C) or on 100 randomly composed cocktails of three sequences, one from each A, B and C subtypes (for sequence cocktails, FIGS. 8B and 8D). The alignment was downloaded from the Los Alamos HIV database. The box extends from the 25 percentile to the 75 percentile, with the line at the median. The whiskers extending outside the box show the highest and lowest values. Amino acids that are very rarely found as C-terminal anchor residues are G, S, T, P, N, Q, D, E, and H, and tend to be small, polar, or negatively charged (Yusim et al, *J. Virol.* 76:8757-8768 (2002)). Results are shown for Gag, but the same qualitative results hold for Nef core and complete Nef. The same procedure was done for supertype motifs with results qualitatively similar to the results for HLA binding motifs (data not shown).

[0022] FIG. 9. Mosaic protein sets limited to 4 sequences (k=4), spanning Gag and the central region of Nef: optimized for subtype B, subtype C, and the M group. Figure discloses SEQ ID NOS 1-84, respectively, in order of appearance.

[0023] FIG. 10. Mosaic sets for Env and Pol. Figure discloses SEQ ID NOS 85-168, respectively, in order of appearance.

DETAILED DESCRIPTION OF THE INVENTION

[0024] The present invention results from the realization that a polyvalent set of antigens comprising synthetic viral proteins, the sequences of which provide maximum coverage of non-rare short stretches of circulating viral sequences, constitutes a good vaccine candidate. The invention provides

a “genetic algorithm” strategy to create such sets of polyvalent antigens as mosaic blends of fragments of an arbitrary set of natural protein sequences provided as inputs. In the context of HIV, the proteins Gag and the inner core (but not the whole) of Nef are ideal candidates for such antigens. The invention further provides optimized sets for these proteins.

[0025] The genetic algorithm strategy of the invention uses unaligned protein sequences from the general population as an input data set, and thus has the virtue of being “alignment independent”. It creates artificial mosaic proteins that resemble proteins found in nature—the success of the consensus antigens in small animals models suggest this works well. 9 Mers are the focus of the in studies described herein, however, different length peptides can be selected depending on the intended target. In accordance with the present approach, 9 mers (for example) that do not exist in nature or that are very rare can be excluded—this is an improvement relative to consensus sequences since the latter can contain some 9 mers (for example) that have not been found in nature, and relative to natural strains that almost invariably contain some 9 mers (for example) that are unique to that strain. The definition of fitness used for the genetic algorithm is that the most “fit” polyvalent cocktail is the combination of mosaic strains that gives the best coverage (highest fraction of perfect matches) of all of the 9 mers in the population and is subject to the constraint that no 9 mer is absent or rare in the population.

[0026] The mosaics protein sets of the invention can be optimized with respect to different input data sets—this allows use of current data to assess virtues of a subtype or region specific vaccines from a T cell perspective. By way of example, options that have been compared include:

[0027] 1) Optimal polyvalent mosaic sets based on M group, B clade and C clade. The question presented was how much better is intra-clade coverage than inter-clade or global.

[0028] 2) Different numbers of antigens: 1, 3, 4, 6

[0029] 3) Natural strains currently in use for vaccine protocols just to exemplify “typical” strains (Merck, VRC)

[0030] 4) Natural strains selected to give the best coverage of 9-mers in a population

[0031] 5) Sets of consensus: A+B+C.

[0032] 6) Optimized cocktails that include one “given” strain in a polyvalent antigen, one ancestral+3 mosaic strains, one consensus+3 mosaic strains.

[0033] 7) Coverage of 9 mers that were perfectly matched was compared with those that match 8/9, 7/9, and 6/9 or less.

This is a computationally difficult problem, as the best set to cover one 9-mer may not be the best set to cover overlapping 9-mers.

[0034] It will be appreciated from a reading of this disclosure that the approach described herein can be used to design peptide reagents to test HIV immune responses, and be applied to other variable pathogens as well. For example, the present approach can be adapted to the highly variable virus Hepatitis C.

[0035] The proteins/polypeptides/peptides (“immunogens”) of the invention can be formulated into compositions with a pharmaceutically acceptable carrier and/or adjuvant using techniques well known in the art. Suitable routes of administration include systemic (e.g. intramuscular or subcutaneous), oral, intravaginal, intrarectal and intranasal.

[0036] The immunogens of the invention can be chemically synthesized and purified using methods which are well known to the ordinarily skilled artisan. The immunogens can also be synthesized by well-known recombinant DNA techniques.

[0037] Nucleic acids encoding the immunogens of the invention can be used as components of, for example, a DNA vaccine wherein the encoding sequence is administered as naked DNA or, for example, a minigene encoding the immunogen can be present in a viral vector. The encoding sequences can be expressed, for example, in mycobacterium, in a recombinant chimeric adenovirus, or in a recombinant attenuated vesicular stomatitis virus. The encoding sequence can also be present, for example, in a replicating or non-replicating adenoviral vector, an adeno-associated virus vector, an attenuated mycobacterium tuberculosis vector, a Bacillus Calmette Guerin (BCG) vector, a vaccinia or Modified Vaccinia Ankara (MVA) vector, another pox virus vector, recombinant polio and other enteric virus vector, Salmonella species bacterial vector, Shigella species bacterial vector, Venezuelan Equine Encephalitis Virus (VEE) vector, a Semliki Forest Virus vector, or a Tobacco Mosaic Virus vector. The encoding sequence, can also be expressed as a DNA plasmid with, for example, an active promoter such as a CMV promoter. Other live vectors can also be used to express the sequences of the invention. Expression of the immunogen of the invention can be induced in a patient’s own cells, by introduction into those cells of nucleic acids that encode the immunogen, preferably using codons and promoters that optimize expression in human cells. Examples of methods of making and using DNA vaccines are disclosed in U.S. Pat. Nos. 5,580,859, 5,589,466, and 5,703,055.

[0038] It will be appreciated that adjuvants can be included in the compositions of the invention (or otherwise administered to enhance the immunogenic effect). Examples of suitable adjuvants include TRL-9 agonists, TRL-4 agonists, and TRL-7, 8 and 9 agonist combinations (as well as alum). Adjuvants can take the form of oil and water emulsions. Squalene adjuvants can also be used.

[0039] The composition of the invention comprises an immunologically effective amount of the immunogen of this invention, or nucleic acid sequence encoding same, in a pharmaceutically acceptable delivery system. The compositions can be used for prevention and/or treatment of virus infection (e.g. HIV infection). As indicated above, the compositions of the invention can be formulated using adjuvants, emulsifiers, pharmaceutically-acceptable carriers or other ingredients routinely provided in vaccine compositions. Optimum formulations can be readily designed by one of ordinary skill in the art and can include formulations for immediate release and/or for sustained release, and for induction of systemic immunity and/or induction of localized mucosal immunity (e.g. the formulation can be designed for intranasal, intravaginal or intrarectal administration). As noted above, the present compositions can be administered by any convenient route including subcutaneous, intranasal, oral, intramuscular, or other parenteral or enteral route. The immunogens can be administered as a single dose or multiple doses. Optimum immunization schedules can be readily determined by the ordinarily skilled artisan and can vary with the patient, the composition and the effect sought.

[0040] The invention contemplates the direct use of both the immunogen of the invention and/or nucleic acids encoding same and/or the immunogen expressed as as indicated above. For example, a minigene encoding the immunogen can be used as a prime and/or boost.

[0041] The invention includes any and all amino acid sequences disclosed herein, as well as nucleic acid sequences encoding same (and nucleic acids complementary to such encoding sequences).

[0042] Specifically disclosed herein are vaccine antigen sets optimized for single B or C subtypes, targeting regional epidemics, as well as for all HIV-1 variants in global circulation [the HIV-1 Main (M) group]. In the study described in the Example that follows, the focus is on designing polyvalent vaccines specifically for T-cell responses. HIV-1 specific T-cells are likely to be crucial to an HIV-1-specific vaccine response: CTL responses are correlated with slow disease progression in humans (Oxenius et al, *J. Infect. Dis.* 189: 1199-1208 (2004)), and the importance of CTL responses in non-human primate vaccination models is well-established. Vaccine elicited cellular immune responses help control pathogenic SIV or SHIV, and reduce the likelihood of disease after challenge with pathogenic virus (Barouch et al, *Science* 290:486-492 (2000)). Temporary depletion of CD8+ T cells results in increased viremia in SIV-infected rhesus macaques (Schmitz et al, *Science* 283:857-860 (1999)). Furthermore, the evolution of escape mutations has been associated with disease progression, indicating that CTL responses help constrain viral replication in vivo (Barouch et al, *J. Virol.* 77:7367-7375 (2003)), and so vaccine-stimulated memory responses that could block potential escape routes may be of value. While the highly variable Envelope (Env) is the primary target for neutralizing antibodies against HIV, and vaccine antigens will also need to be tailored to elicit these antibody responses (Moore & Burton, *Nat. Med.* 10:769-771 (2004)), T-cell vaccine components can target more conserved proteins to trigger responses that are more likely to cross-react. But even the most conserved HIV-1 proteins are diverse enough that variation will be an issue. Artificial central-sequence vaccine approaches, consensus and ancestral sequences (Gaschen et al, *Science* 296:2354-2360 (2002), Gao et al, *J. Virol.* 79:1154-1163 (2005), Doria-Rose et al, *J. Virol.* 79:11214-11224 (2005)), which essentially “split the differences” between strains, show promise, stimulating responses with enhanced cross-reactivity compared to natural strain vaccines (Gao et al, *J. Virol.* 79:1154-1163 (2005)) (Liao et al. and Weaver et al., submitted.) Nevertheless, even central strains cover the spectrum of HIV diversity to a very limited extent, and consensus-based peptide reagents fail to detect many autologous CD8+ T-cell responses (Altfeld et al, *J. Virol.* 77:7330-7340 (2003)).

[0043] A single amino acid substitution can mediate T-cell escape, and as one or more amino acids in many T-cell epitopes differ between HIV-1 strains, the potential effectiveness of responses to any one vaccine antigen is limited. Whether a particular mutation will diminish T-cell cross-reactivity is epitope- and T-cell-specific, although some changes can broadly affect between-clade cross-reactivity (Norris et al, *AIDS Res. Hum. Retroviruses* 20:315-325 (2004)). Including more variants in a polyvalent vaccine could enable responses to a broader range of circulating variants. It could also prime the immune system against common escape variants (Jones et al, *J. Exp. Med.* 200:1243-1256 (2004)); escape from one T-cell receptor might create a variant that is susceptible to another (Lee et al, *J. Exp. Med.* 200:1455-1466 (2004)), thus stimulating polyclonal responses to epitope variants may be beneficial (Killian et al, *AIDS* 19:887-896 (2005)). Immune escape involving avenues that inhibit processing (Milicic et al, *J. Immunol.* 175:4618-4626 (2005)) or HLA binding (Ammaranond et al, *AIDS Res. Hum. Retroviruses* 21:395-397 (2005)) prevent epitope presentation, and in such cases the escape variant

could not be countered by a T-cell with a different specificity. However, it is possible the presence of T-cells that recognize overlapping epitopes may in some cases block these even escape routes.

[0044] Certain aspects of the invention can be described in greater detail in the non-limiting Example that follows.

EXAMPLE

Experimental Details

[0045] HIV-1 sequence data. The reference alignments from the 2005 HIV sequence database (<http://hiv.lanl.gov>), which contain one sequence per person, were used, supplemented by additional recently available C subtype Gag and Nef sequences from Durban, South Africa (GenBank accession numbers AY856956-AY857186) (Kiepiela et al, *Nature* 432:769-75 (2004)). This set contained 551 Gag and 1,131 NefM group sequences from throughout the globe; recombinant sequences were included as well as pure subtype sequences for exploring M group diversity. The subsets of these alignments that contained 18 A, 102 B, 228 C, and 6 G subtype (Gag), and 62 A, 454 B, 284 C, and 13 G subtype (Nef) sequences were used for within- and between-single-clade optimizations and comparisons.

[0046] The genetic algorithm. GAs are computational analogues of biological processes (evolution, populations, selection, recombination) used to find solutions to problems that are difficult to solve analytically (Holland, *Adaptation in Natural and Artificial Systems: An Introductory Analysis with Applications to Biology, Control, and Artificial Intelligence*, (M.I.T. Press, Cambridge, Mass. (1992))). Solutions for a given input are “evolved” through a process of random modification and selection according to a “fitness” (optimality) criterion. GAs come in many flavors; a “steady-state co-evolutionary multi-population” GA was implemented. “Steady-state” refers to generating one new candidate solution at a time, rather than a whole new population at once; and “co-evolutionary” refers to simultaneously evolving several distinct populations that work together to form a complete solution. The input is an unaligned set of natural sequences; a candidate solution is a set of k pseudo-natural “mosaic” sequences, each of which is formed by concatenating sections of natural sequences. The fitness criterion is population coverage, defined as the proportion of all 9-amino-acid sequence fragments (potential epitopes) in the input sequences that are found in the cocktail.

[0047] To initialize the GA (FIG. 2), k populations of n initial candidate sequences are generated by 2-point recombination between randomly selected natural sequences. Because the input natural sequences are not aligned, “homologous” crossover is used: crossover points in each sequence are selected by searching for short matching strings in both sequences; strings of $c-1=8$, were used where a typical epitope length is $c=9$. This ensures that the recombined sequences resemble natural proteins: the boundaries between sections of sequence derived from different strains are seamless, the local sequences spanning the boundaries are always found in nature, and the mosaics are prevented from acquiring large insertions/deletions or unnatural combinations of amino acids. Mosaic sequence lengths fall within the distribution of natural sequence lengths as a consequence of mosaic construction: recombination is only allowed at identical regions, reinforced by an explicit software prohibition against excessive lengths to prevent reduplication of repeat regions. (Such “in frame” insertion of reduplicated epitopes could provide another way of increasing coverage without generating unnatural 9-mers, but their inclusion would create “unnatu-

ral” proteins.) Initially, the cocktail contains one randomly chosen “winner” from each population. The fitness score for any individual sequence in a population is the coverage value for the cocktail consisting of that sequence plus the current winners from the other populations. The individual fitness of any sequence in a population therefore depends dynamically upon the best sequences found in the other populations.

[0048] Optimization proceeds one population at a time. For each iteration, two “parent” sequences are chosen. The first parent is chosen using “2-tournament” selection: two sequences are picked at random from the current population, scored, and the better one is chosen. This selects parents with a probability inversely proportional to their fitness rank within the population, without the need to actually compute the fitness of all individuals. The second parent is chosen in the same way (50% of the time), or is selected at random from the set of natural sequences. 2-point homologous crossover between the parents is then used to generate a “child” sequence. Any child containing a 9-mer that was very rare in the natural population (found less than 3 times) is rejected immediately. Otherwise, the new sequence is scored, and its fitness is compared with the fitnesses of four randomly chosen sequences from the same population. If any of the four randomly chosen sequences has a score lower than that of the new sequence, it is replaced in the population by the new sequence. Whenever a sequence is encountered that yields a better score than the current population “winner”, that sequence becomes the winner for the current population and so is subsequently used in the cocktail to evaluate sequences in other populations. A few such optimization cycles (typically 10) are applied to each population in turn, and this process continues cycling through the populations until evolution stalls (i.e., no improvement has been made for a defined number of generations). At this point, the entire procedure is restarted using newly generated random starting populations, and the restarts are continued until no further improvement is seen. The GA was run on each data set with $n=50$ or 500 ; each run was continued until no further improvement occurred for 12-24 hours on a 2 GHz Pentium processor. Cocktails were generated having $k=1, 3, 4,$ or 6 mosaic sequences.

[0049] The GA also enables optional inclusion of one or more fixed sequences of interest (for example, a consensus) in the cocktail and will evolve the other elements of the cocktail in order to optimally complement that fixed strain. As these solutions were suboptimal, they are not included here. An additional program selects from the input file the k best natural strains that in combination provide the best population coverage.

[0050] Comparison with other polyvalent vaccine candidates. Population coverage scores were computed for other potential mono- or polyvalent vaccines to make direct comparisons with the mosaic-sequence vaccines, tracking identities with population 9-mers, as well as similarities of 8/9 and 7/9 amino acids. Potential vaccine candidates based on natural strains include single strains (for example, a single C strain for a vaccine for southern Africa (Williamson et al, AIDS Res. Hum. Retroviruses 19:133-44 (2003))) or combinations of natural strains (for example, one each of subtype A, B, and C (Kong et al, J. Virol. 77:12764-72 (2003))). To date, natural-strain vaccine candidates have not been systematically selected to maximize potential T-cell epitope coverage; vaccine candidates were picked from the literature to be representative of what could be expected from unselected vaccine candidates. An upper bound for coverage was also determined using only intact natural strains: optimal natural-sequence cocktails were generated by selecting the single sequence with the best coverage of the dataset, and then

successively adding the most complementary sequences up to a given k . The comparisons included optimal natural-sequence cocktails of various sizes, as well as consensus sequences, alone or in combination (Gaschen et al, Science 296:2354-60 (2002)), to represent the concept of central, synthetic vaccines. Finally, using the fixed-sequence option in the GA, consensus-plus-mosaic combinations in the comparisons; these scores were essentially equivalent to all-mosaic combinations were included for a given k (data not shown). The code used for performing these analyses are available at: <ftp://ftp-t10/pub/btk/mosaics>.

Results

[0051] Protein Variation. In conserved HIV-1 proteins, most positions are essentially invariant, and most variable positions have only two to three amino acids that occur at appreciable frequencies, and variable positions are generally well dispersed between conserved positions. Therefore, within the boundaries of a CD8+ T-cell epitope (8-12 amino acids, typically nine), most of the population diversity can be covered with very few variants. FIG. 1 shows an upper bound for population coverage of 9-mers (stretches of nine contiguous amino acids) comparing Gag, Nef, and Env for increasing numbers of variants, sequentially adding variants that provide the best coverage. In conserved regions, a high degree of population coverage is achieved with 2-4 variants. By contrast, in variable regions like Env, limited population coverage is possible even with eight variants. Since each new addition is rarer, the relative benefits of each addition diminish as the number of variants increases.

[0052] Vaccine design optimization strategies. FIG. 1 shows an idealized level of 9-mer coverage. In reality, high-frequency 9-mers often conflict: because of local co-variation, the optimal amino acid for one 9-mer may differ from that for an overlapping 9-mer. To design mosaic protein sets that optimize population coverage, the relative benefits of each amino acid must be evaluated in combination with nearby variants. For example, Alanine (Ala) and Glutamate (Glu) might each frequently occur in adjacent positions, but if the Ala-Glu combination is never observed in nature, it should be excluded from the vaccine. Several optimization strategies were investigated: a greedy algorithm, a semi-automated compatible-9mer assembly strategy, an alignment-based genetic algorithm (GA), and an alignment-independent GA.

[0053] The alignment-independent GA generated mosaics with the best population coverage. This GA generates a user-specified number of mosaic sequences from a set of unaligned protein sequences, explicitly excluding rare or unnatural epitope-length fragments (potentially introduced at recombination breakpoints) that could induce non-protective vaccine-antigen-specific responses. These candidate vaccine sequences resemble natural proteins, but are assembled from frequency-weighted fragments of database sequences recombined at homologous breakpoints (FIG. 2); they approach maximal coverage of 9-mers for the input population.

[0054] Selecting HIV protein regions for an initial mosaic vaccine. The initial design focused on protein regions meeting specific criteria: i) relatively low variability, ii) high levels of recognition in natural infection, iii) a high density of known epitopes and iv) either early responses upon infection or CD8+ T-cell responses associated with good outcomes in infected patients. First, an assessment was made of the level of 9-mer coverage achieved by mosaics for different HIV proteins (FIG. 3). For each protein, a set of four mosaics was generated using either the M group or the B- and C-subtypes alone; coverage was scored on the C subtype. Several results are notable: i) within-subtype optimization provides the best

within-subtype coverage, but substantially poorer between-subtype coverage—nevertheless, B-subtype-optimized mosaics provide better C-subtype coverage than a single natural B subtype protein (Kong et al, *J. Virol.* 77:12764-72 (2003)); ii) Pal and Gag have the most potential to elicit broadly cross-reactive responses, whereas Rev, Tat, and Vpu have even fewer conserved 9-mers than the highly variable Env protein, iii) within-subtype coverage of M-group-optimized mosaic sets approached coverage of within-subtype optimized sets, particularly for more conserved proteins.

[0055] Gag and the central region of Nef meet the four criteria listed above. Nef is the HIV protein most frequently recognized by T-cells (Frahm et al, *J. Virol.* 78:2187-200 (2004)) and the target for the earliest response in natural infection (Lichterfeld et al, *Aids* 18:1383-92 (2004)). While overall it is variable (FIG. 3), its central region is as conserved as Gag (FIG. 1). It is not yet clear what optimum proteins for inclusion in a vaccine might be, and mosaics could be designed to maximize the potential coverage of even the most variable proteins (FIG. 3), but the prospects for global coverage are better for conserved proteins. Improved vaccine protection in macaques has been demonstrated by adding Rev, Tat, and Nef to a vaccine containing Gag, Pol, and Env (Hel et al, *J. Immunol.* 176:85-96 (2006)), but this was in the context of homologous challenge, where variability was not an issue. The extreme variability of regulatory proteins in circulating virus populations may preclude cross-reactive responses; in terms of conservation, Pol, Gag (particularly p24) and the central region of Nef (HXB2 positions 65-149) are promising potential immunogens (FIGS. 1,3). Pol, however, is infrequently recognized during natural infection (Frahm et al, *J. Virol.* 78:2187-200 (2004)), so it was not included in the initial immunogen design. The conserved portion of Nef that were included contains the most highly recognized peptides in HIV-1 (Frahm et al, *J. Virol.* 78:2187-200 (2004)), but as a protein fragment, would not allow Nef's immune inhibitory functions (e.g. HLA class I down-regulation (Blagoveshchenskaya, *Cell* 111:853-66 (2002))). Both Gag and Nef are densely packed with overlapping well-characterized CD8+ and CD4+ T-cell epitopes, presented by many different HLA molecules (<http://www.hiv.lanl.gov/content/immunology/maps/maps.html>), and Gag-specific CD8+ (Masemola et al, *J. Virol.* 78:3233-43 (2004)) and CD4+ (Oxenius et al, *J. Infect. Dis.* 189:1199-208 (2004)) T-cell responses have been associated with low viral set points in infected individuals (Masemola et al, *J. Virol.* 78:3233-43 (2004)).

[0056] To examine the potential impact of geographic variation and input sample size, a limited test was done using published subtype C sequences. The subtype C Gag data were divided into three sets of comparable size—two South African sets (Kiepiela et al, *Nature* 432:769-75 (2004)), and one non-South-African subtype C set. Mosaics were optimized independently on each of the sets, and the resulting mosaics were tested against all three sets. The coverage of 9-mers was slightly better for identical training and test sets (77-79% 9/9 coverage), but essentially equivalent when the training and test sets were the two different South African data sets (73-75%), or either of the South African sets and the non-South African C subtype sequences (74-76%). Thus between- and within-country coverage approximated within-clade coverage, and in this case no advantage to a country-specific C subtype mosaic design was found.

[0057] Designing mosaics for Gag and Nef and comparing vaccine strategies. To evaluate within- and between-subtype cross-reactivity for various vaccine design strategies, a calculation was made of the coverage they provided for natural

M-Group sequences. The fraction of all 9-mers in the natural sequences that were perfectly matched by 9-mers in the vaccine antigens were computed, as well as those having 8/9 or 7/9 matching amino acids, since single (and sometimes double) substitutions within epitopes may retain cross-reactivity. FIG. 4 shows M group coverage per 9-mer in Gag and the central region of Nef for cocktails designed by various strategies: a) three non-optimal natural strains from the A, B, and C subtypes that have been used as vaccine antigens (Kong et al, *J. Virol.* 77:12764-72 (2003)); b) three natural strains that were computationally selected to give the best M group coverage; c) M group, B subtype, and C subtype consensus sequences; and, d,e,f) three, four and six mosaic proteins. For cocktails of multiple strains, sets of k=3, k=4, and k=6, the mosaics clearly perform the best, and coverage approaches the upper bound for k strains. They are followed by optimally selected natural strains, the consensus protein cocktail, and finally, non-optimal natural strains. Allowing more antigens provides greater coverage, but gains for each addition are reduced as k increases (FIGS. 1 and 4).

[0058] FIG. 5 summarizes total coverage for the different vaccine design strategies, from single proteins through combinations of mosaic proteins, and compares within-subtype optimization to M group optimization. The performance of a single mosaic is comparable to the best single natural strain or a consensus sequence. Although a single consensus sequence out-performs a single best natural strain, the optimized natural-sequence cocktail does better than the consensus cocktail: the consensus sequences are more similar to each other than are natural strains, and are therefore somewhat redundant. Including even just two mosaic variants, however, markedly increases coverage, and four and six mosaic proteins give progressively better coverage than polyvalent cocktails of natural or consensus strains. Within-subtype optimized mosaics perform best—with four mosaic antigens 80-85% of the 9-mers are perfectly matched—but between-subtype coverage of these sets falls off dramatically, to 50-60%. In contrast, mosaic proteins optimized using the full M group give coverage of approximately 75-80% for individual subtypes, comparable to the coverage of the M group as a whole (FIGS. 5 and 6). If imperfect 8/9 matches are allowed, both M group optimized and within-subtype optimized mosaics approach 90% coverage.

[0059] Since coverage is increased by adding progressively rarer 9-mers, and rare epitopes may be problematic (e.g., by inducing vaccine-specific immunodominant responses), an investigation was made of the frequency distribution of 9-mers in the vaccine constructs relative to the natural sequences from which they were generated. Most additional epitopes in a cocktail compared to a k=4 cocktail are low-frequency (<0.1, FIG. 7). Despite enhancing coverage, these epitopes are relatively rare, and thus responses they induce might draw away from vaccine responses to more common, thus more useful, epitopes. Natural-sequence cocktails actually have fewer occurrences of moderately low-frequency epitopes than mosaics, which accrue some lower frequency 9-mers as coverage is optimized. On the other hand, the mosaics exclude unique or very rare 9-mers, while natural strains generally contain 9-mers present in no other sequence. For example, natural M group Gag sequences had a median of 35 (range 0-148) unique 9-mers per sequence. Retention of HLA-anchor motifs was also explored, and anchor motif frequencies were found to be comparable between four mosaics and three natural strains. Natural antigens did exhibit an increase in number of motifs per antigen, possibly due to inclusion of strain-specific motifs (FIG. 8).

[0060] The increase in ever-rarer epitopes with increasing k , coupled with concerns about vaccination-point dilution and reagent development costs, resulted in the initial production of mosaic protein sets limited to 4 sequences ($k=4$), spanning Gag and the central region of Nef, optimized for subtype B, subtype C, and the M group (these sequences are included in FIG. 9; mosaic sets for Env and Pol are set forth in FIG. 10). Synthesis of various four-sequence Gag-Nef mosaics and initial antigenicity studies are underway. In the initial mosaic vaccine, targeted are just Gag and the center of the Nef protein, which are conserved enough to provide excellent global population coverage, and have the desirable properties described above in terms of natural responses (Bansal et al, *Aids* 19:241-50 (2005)). Additionally, including B subtype p24 variants in Elispot peptide mixtures to detect natural CTL responses to infection significantly enhanced both the number and the magnitude of responses detected supporting the idea that including variants of even the most conserved proteins will be useful. Finally, cocktails of proteins in a polyvalent HIV-1 vaccine given to rhesus macaques did not interfere with the development of robust responses to each antigen (Seaman et al, *J. Virol.* 79:2956-63 (2005)), and antigen cocktails did not produce antagonistic responses in murine models (Singh et al, *J. Immunol.* 169:6779-86 (2002)), indicating that antigenic mixtures are appropriate for T-cell vaccines.

[0061] Even with mosaics, variable proteins like Env have limited coverage of 9-mers, although mosaics improve coverage relative to natural strains. For example three M group natural proteins, one each selected from the A, B, and C clades, and currently under study for vaccine design (Seaman et al, *J. Virol.* 79:2956-63 (2005)) perfectly match only 39% of the 9-mers in M group proteins, and 65% have at least 8/9 matches. In contrast, three M group Env mosaics match 47% of 9-mers perfectly, and 70% have at least an 8/9 match. The code written to design polyvalent mosaic antigens is available, and could readily be applied to any input set of variable proteins, optimized for any desired number of antigens. The code also allows selection of optimal combinations of k natural strains, enabling rational selection of natural antigens for polyvalent vaccines. Included in Table 1 are the best natural strains for Gag and Nef population coverage of current database alignments.

TABLE 1

Natural sequence cocktails having the best available 9-mer coverage for different genes, subtype sets, and numbers of sequences
Gag, B-subtype, 1 natural sequence
B.US.86.AD87_AF004394 Gag, B-subtype, 3 natural sequences
B.US.86.AD87_AF004394 B.US.97.Ac_06_AY247251 B.US.88.WR27_AF286365 Gag, B-subtype, 4 natural sequences
B.US.86.AD87_AF004394 B.US.97.Ac_06_AY247251 B.US._R3_PDC1_AY206652 B.US.88.WR27_AF286365 Gag, B-subtype, 6 natural sequences
B.CN._CNHN24_AY180905 B.US.86.AD87_AF004394 B.US.97.Ac_06_AY247251 B.US._P2_AY206654 B.US._R3_PDC1_AY206652 B.US.88.WR27_AF286365

TABLE 1-continued

Natural sequence cocktails having the best available 9-mer coverage for different genes, subtype sets, and numbers of sequences
Gag, C-subtype, 1 natural sequence
C.IN._70177_AF533131 Gag, C-subtype, 3 natural sequences
C.ZA.97.97ZA012 C.ZA.x.04ZASK161B1 C.IN.-.70177_AF533131 Gag, C-subtype, 4 natural sequences
C.ZA.97.97ZA012 C.ZA.x.04ZASK142B1 C.ZA.x.04ZASK161B1 C.IN._70177_AF533131 Gag, C-subtype, 6 natural sequences
C.ZA.97.97ZA012 C.ZA.x.04ZASK142B1 C.ZA.x.04ZASK161B1 C.BW.99.99BWMC168_AF443087 C.IN._70177_AF533131 C.IN._MYA1_AF533139 Gag, M-group, 1 natural sequence
C.IN._70177_AF533131 Gag, M-group, 3 natural sequences
B.US.90.US2_AY173953 C.IN.-.70177_AF533131 15_01B.TH.99.99TH_R2399_AF530576 Gag, M-group, 4 natural sequences
B.US.90.US2_AY173953 C.IN._70177_AF533131 C.IN.93.93IN999_AF067154 15_01B.TH.99.99TH_R2399_AF530576 Gag, M-group, 6 natural sequences
C.ZA.x.04ZASK138B1 B.US.90.US2_AY173953 B.US._WT1_PDC1_AY206656 C.IN._70177_AF533131 C.IN.93.93IN999_AF067154 15_01B.TH.99.99TH_R2399_AF530576 Nef (central region), B-subtype, 1 natural sequence
B.GB.94.028jh_94_1_NP_AF129346 Nef (central region), B-subtype, 3 natural sequences
B.GB.94.028jh_94_1_NP_AF129346 B.KR.96.96KCS4_AY121471 B.FR.83.HXB2_K03455 Nef (central region), B-subtype, 4 natural sequences
B.GB.94.028jh_94_1_NP_AF129346 B.KR.96.96KCS4_AY121471 B.US.90.E90NEF_U43108 B.FR.83.HXB2_K03455 Nef (central region), B-subtype, 6 natural sequences
B.GB.94.028jh_94_1_NP_AF129346 B.KR.02.02HYJ3_AY121454 B.KR.96.96KCS4_AY121471 B.CN._RL42_U71182 B.US.90.E90NEF_U43108 B.FR.83.HXB2_K03455 Nef (central region), C-subtype, 1 natural sequence
C.ZA.04.04ZASK139B1 Nef (central region), C-subtype, 3 natural sequences
C.ZA.04.04ZASK180B1 C.ZA.04.04ZASK139B1 C.ZA._ZASW15_AF397568

TABLE 1-continued

Natural sequence cocktails having the best available 9-mer coverage for different genes, subtype sets, and numbers of sequences
Nef (central region), C-subtype, 4 natural sequences
C.ZA.97.ZA97004_AF529682 C.ZA.04.04ZASK180B1 C.ZA.04.04ZASK139B1 C.ZA._ZASW15_AF397568
Nef (central region), C-subtype, 6 natural sequences
C.ZA.97.ZA97004_AF529682 C.ZA.00.1192M3M C.ZA.04.04ZASK180B1 C.ZA.04.04ZASK139B1 C.04ZASK184B1 C.ZA._ZASW15_AF397568
Nef (central region), M-group, 1 natural sequence
B.GB.94.028jh_94_1_NP_AF129346
Nef (central region), M-group, 3 natural sequences
02_AG.CM._98CM1390_AY265107 C.ZA.03.03ZASK020B2 B.GB.94.028jh_94_1_NP_AF129346
Nef (central region), M-group, 4 natural sequences
02_AG.CM._98CM1390_AY265107 01A1.MM.99.mCSW105_AB097872 C.ZA.03.03ZASK020B2 B.GB.94.028jh_94_1_NP_AF129346
Nef (central region), M-group, 6 natural sequences
02_AG.CM._98CM1390_AY265107 01A1.MM.99.mCSW105_AB097872 C.ZA.03.03ZASK020B2 C.03ZASK111B1 B.GB.94.028jh_94_1_NP_AF129346 B.KR.01.01CWS2_AF462757

[0063] A centralized (consensus or ancestral) gene and protein strategy has been proposed previously to address HIV diversity (Gaschen et al, Science 296:2354-2360 (2002)). Proof-of-concept for the use of artificial genes as immunogens has been demonstrated by the induction of both T and B cell responses to wild-type HIV-1 strains by group M consensus immunogens (Gaschen et al, Science 296:2354-2360 (2002), Gao et al, J. Virol. 79:1154-63 (2005), Doria-Rose et al, J. Virol. 79:11214-24 (2005), Weaver et al, J. Virol., in press)). The mosaic protein design improves on consensus or natural immunogen design by co-optimizing reagents for a polyclonal vaccine, excluding rare CD8+ T-cell epitopes, and incorporating variants that, by virtue of their frequency at the population level, are likely to be involved in escape pathways.

[0064] The mosaic antigens maximize the number of epitope-length variants that are present in a small, practical number of vaccine antigens. The decision was made to use multiple antigens that resemble native proteins, rather than linking sets of concatenated epitopes in a poly-epitope pseudo-protein (Hanke et al, Vaccine 16:426-35 (1998)), reasoning that in vivo processing of native-like vaccine antigens will more closely resemble processing in natural infection, and will also allow expanded coverage of overlapping epitopes. T-cell mosaic antigens would be best employed in the context of a strong polyvalent immune response; improvements in other areas of vaccine design and a combination of the best strategies, incorporating mosaic antigens to cover diversity, may ultimately enable an effective cross-reactive vaccine-induced immune response against HIV-1.

[0065] All documents and other information sources cited above are hereby incorporated in their entirety by reference.

SEQUENCE LISTING

The patent application contains a lengthy "Sequence Listing" section. A copy of the "Sequence Listing" is available in electronic form from the USPTO web site (<http://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US20110150915A1>). An electronic copy of the "Sequence Listing" will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

[0062] Summarizing, the above-described study focuses on the design of T-cell vaccine components to counter HIV diversity at the moment of infection, and to block viral escape routes and thereby minimize disease progression in infected individuals. The polyvalent mosaic protein strategy developed here for HIV-1 vaccine design could be applied to any variable protein, to other pathogens, and to other immunological problems. For example, incorporating a minimal number of variant peptides into T-cell response assays could markedly increase sensitivity without excessive cost: a set of k mosaic proteins provides the maximum coverage possible for k antigens.

1. A polypeptide or protein comprising at least one sequence of amino acids set forth in FIG. 9 or FIG. 10.

2. The polypeptide or protein according to claim 1 wherein said polypeptide or protein comprises at least one sequence of amino acids set forth in FIG. 9.

3. The polypeptide or protein according to claim 1 wherein said polypeptide or protein comprises at least one sequence of amino acids set forth in FIG. 10.

4. A nucleic acid comprising a nucleotide sequence that encodes the polypeptide or protein according to claim 1.

5. The nucleic acid according to claim 4 wherein said nucleic acid encodes at least one sequence of amino acids set forth in FIG. 9.

6. The nucleic acid according to claim 4 wherein said nucleic acid encodes at least one sequence of amino acids set forth in FIG. 10.

7. A vector comprising the nucleic acid according to claim 4.

8. The vector according to claim 7 wherein said vector is a viral vector.

9. A composition comprising at least one polypeptide or protein according to claim 1 and a carrier.

10. A composition comprising at least one nucleic acid according to claim 4 and a carrier.

11. A method of inducing an immune response in a mammal comprising administering to said mammal an amount of at least one polypeptide or protein according to claim 1 sufficient to effect said induction.

12. A method of inducing an immune response in a mammal comprising administering to said mammal an amount of at least one nucleic acid according to claim 4 sufficient to effect said induction.

13. A polyvalent vaccine comprising a multiplicity of HIV-1 polypeptides, each of said polypeptides comprising a computationally-designed homologous recombinant mosaic blend of epitopes of natural HIV Gag, Nef, Env or Pol protein sequences,

wherein the length of each of said epitopes is about 9 amino acids,

wherein the length of each of said polypeptides is within the range of natural HIV protein lengths,

wherein the epitopes are linked within each polypeptide via homologous crossover so the unnatural combinations of amino acids are not present,

wherein said epitopes are natural, commonly occurring T-cell epitopes, and

wherein about 3 to about 6 different types of polypeptides are present in said vaccine.

* * * * *