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C12N 5/10 (2006.01)

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(54) Titre : ANTICORPS NEUTRALISANTS ANTI-VIRUS DE L'IMMUNODEFICIENCE HUMAINE (VIH)
(54) Title: HUMAN IMMUNODEFICIENCY VIRUS (HIV)-NEUTRALIZING ANTIBODIES

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WHAT IS CLAIMED IS:

1. An antibody, comprising a heavy chain with a CDR 1 comprising the amino acid sequence GRFWS (SEQ ID NO: 421), a CDR 2 comprising the amino acid sequence YFSDTDRSEYNPSLRS (SEQ ID NO: 422), and a CDR 3 comprising the amino acid sequence AQQGKRIYGIVSFGELFYYYMDA (SEQ ID NO: 436), and a light chain with a CDR 1 comprising the amino acid sequences of GERSRGSRAVQ (SEQ ID NO: 430), a CDR 2 comprising the amino acid sequence NNQDRPA (SEQ ID NO: 179), and a CDR 3 comprising the amino acid sequence HYWDSRSPISWI (SEQ ID NO: 431).
2. An isolated fully human monoclonal antibody comprising a heavy chain sequence comprising the amino acid sequence of SEQ ID NO: 434 and a light chain sequence comprising amino acid sequence of SEQ ID NO: 439.
3. The antibody of claim 2, wherein heavy chain variable sequence comprises the amino acid sequence of SEQ ID NO: 435 and light chain variable sequence comprises the amino acid sequence of SEQ ID NO: 440.
4. The antibody according to any one of claims 1 to 3, wherein the antibody neutralizes HIV-1 species belonging to two or more clades, wherein the clades are selected from Clade A, Clade B, Clade C, Clade D, and Clade AE.
5. A fragment of the antibody of any one of claims 1 to 4, wherein the fragment has the same binding specificity as the antibody of any one of claims 1 to 4.
6. The fragment of claim 5, which is selected from the group consisting of the Fab, Fab', F(ab')₂, Fv, single chain Fv, diabody, and domain antibody (dAb) fragments.
7. An isolated nucleic acid molecule encoding the antibody of any one of claims 1 to 3, or the fragment thereof of claim 5 or 6.

8. The nucleic acid molecule of claim 7, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO: 433 encoding a heavy chain variable sequence and the nucleotide sequence of SEQ ID NO: 438 encoding a light chain variable sequence.

9. The nucleic acid molecule of claim 8, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO: 432 encoding a heavy chain sequence and the nucleotide sequence of SEQ ID NO: 437 encoding a light chain sequence.

10. The nucleic acid molecule according to claim 7, 8 or 9, which is selected from the group consisting of cDNA, hnRNA, and mRNA.

11. A vector comprising the nucleic acid molecule of any one of claims 7 to 10.

12. A cell comprising the vector of any one of claims 7 to 10.

13. An immortalized B cell clone expressing the antibody of any one of claims 1 to 4.

14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the antibody of any one of claims 1 to 4, or the fragment of claim 5 or 6 or the nucleic acid molecule as recited in any one of claims 7 to 10.

15. Use of a therapeutically effective amount of the antibody as recited in any one of claims 1 to 4 or the fragment of claim 5 or 6 or the nucleic acid molecule as recited in any one of claims 7 to 10 for immunization against HIV or to reduce the effect of an HIV infection.

16. The use according to claim 15, additionally comprising the use of a second therapeutic agent.

17. The use according to claim 16, wherein said second therapeutic agent is an anti-viral agent.

18. Use of an effective amount of the pharmaceutical composition of claim 14 to treat an individual infected with HIV-1.

19. Use of an effective amount of an antibody according to any one of claims 1 to 4 or the fragment of claim 5 or 6 or the nucleic acid molecule as recited in any one of claims 7 to 10 as an adjuvant therapy to treat an individual infected with HIV-1.

20. The use according to claim 19, wherein the use comprises multiple doses of said antibody.

21. Use of an immunotherapeutically effective amount of the antibody according to claims 1 to 4 or the fragment of claim 5 or 6 or the nucleic acid molecule as recited in any one of claims 7 to 10 for treatment of HIV-1 infection in an individual, or post-exposure prophylaxis of an individual.

22. Use of the antibody as recited in any one of claims 1 to 4 or the fragment of claim 5 or 6 in the manufacture of a medicament for immunization against HIV or to reduce the effect of an HIV infection.

23. Use of the pharmaceutical composition of claim 14 in the manufacture of a medicament to treat an individual infected with HIV-1.

24. Use of the antibody according to any one of claims 1 to 4 or the fragment of claim 5 or 6 in the manufacture of a medicament for use as an adjuvant therapy to treat an individual infected with HIV-1.

25. Use of the antibody according to any one of claims 1 to 4 or the fragment of claim 5 or 6 in the manufacture of a medicament for treatment of HIV-1 infection in an individual, or postexposure prophylaxis of an individual.

26. Use of the antibody according to any one of claims 1 to 4 or the fragment of claim 5 or 6 or the nucleic acid molecule as recited in any one of claims 8 to 11 in the manufacture of a medicament for use as an adjuvant therapy to treat an individual against a plurality of HIV-1 species.

27. A method for producing the antibody to any one of claims 1 to 4 or the fragment according of claim 5 or 6 comprising (i) culturing an immortalized B cell clone expressing the antibody to any one of claims 1 to 4 or the fragment according of claim 5 or 6 and (ii) isolating the antibody or fragment.

FIG. 1A Heavy Chain Tree

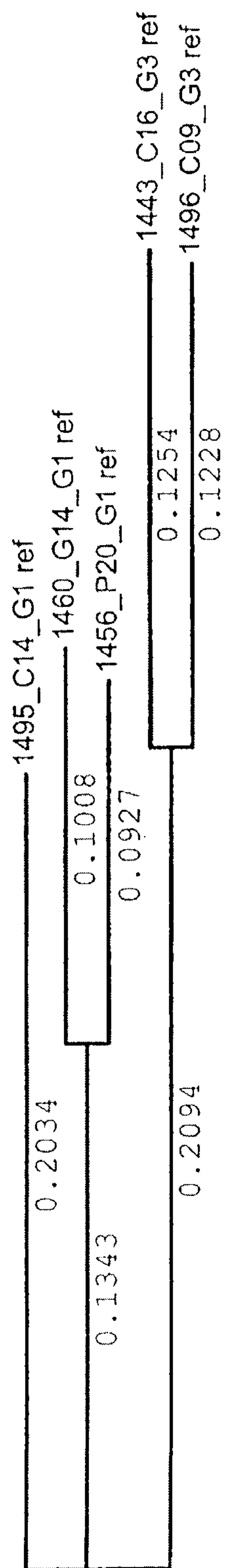


FIG. 1B Light Chain Tree

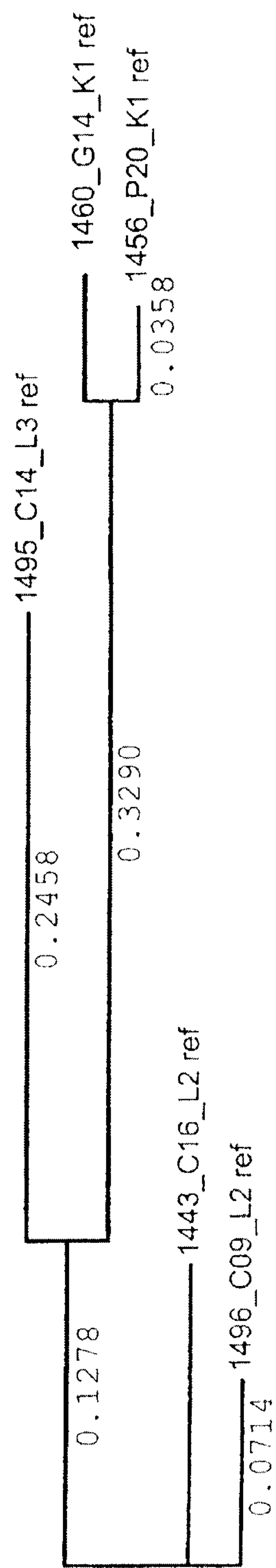


FIG. 2

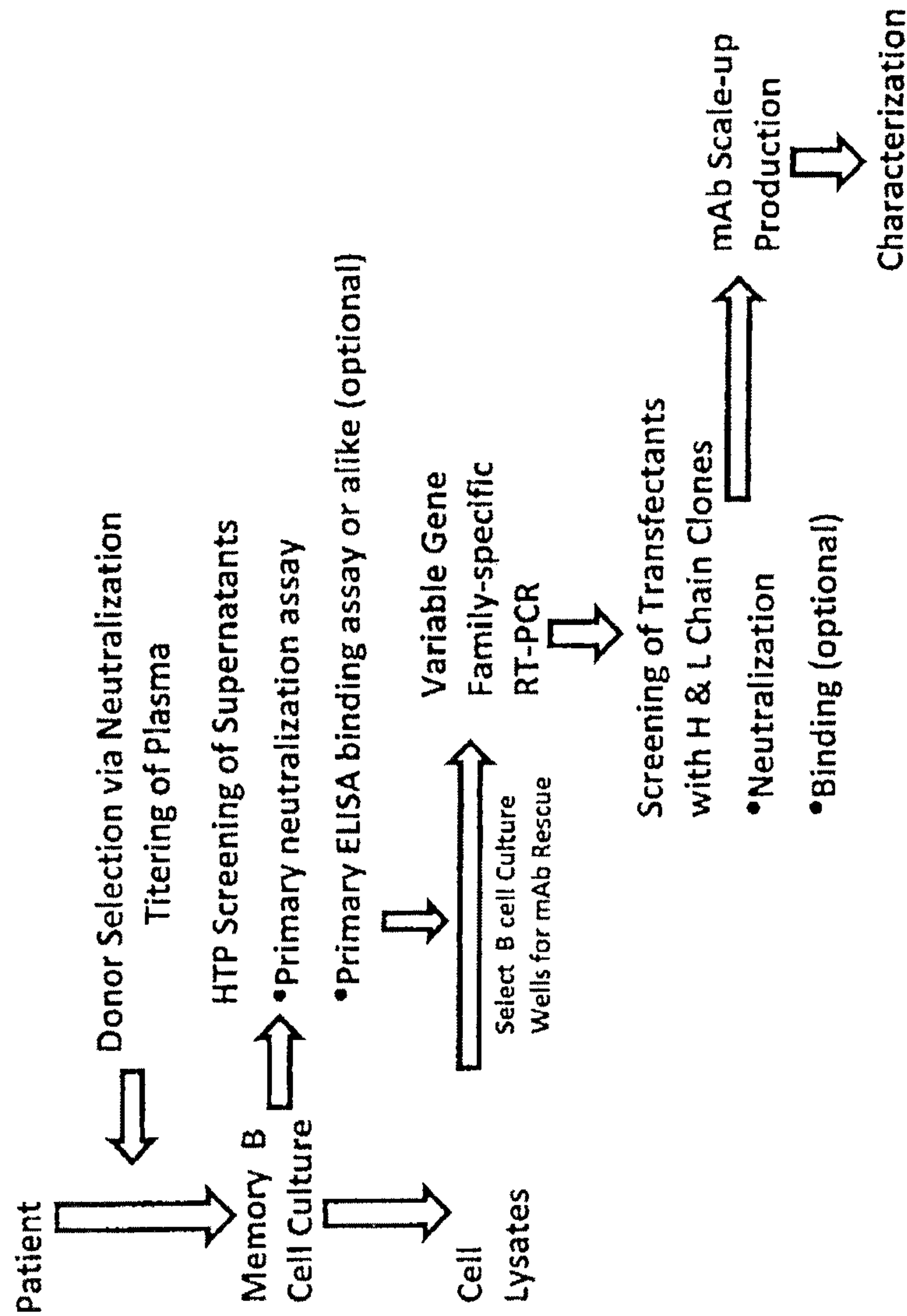
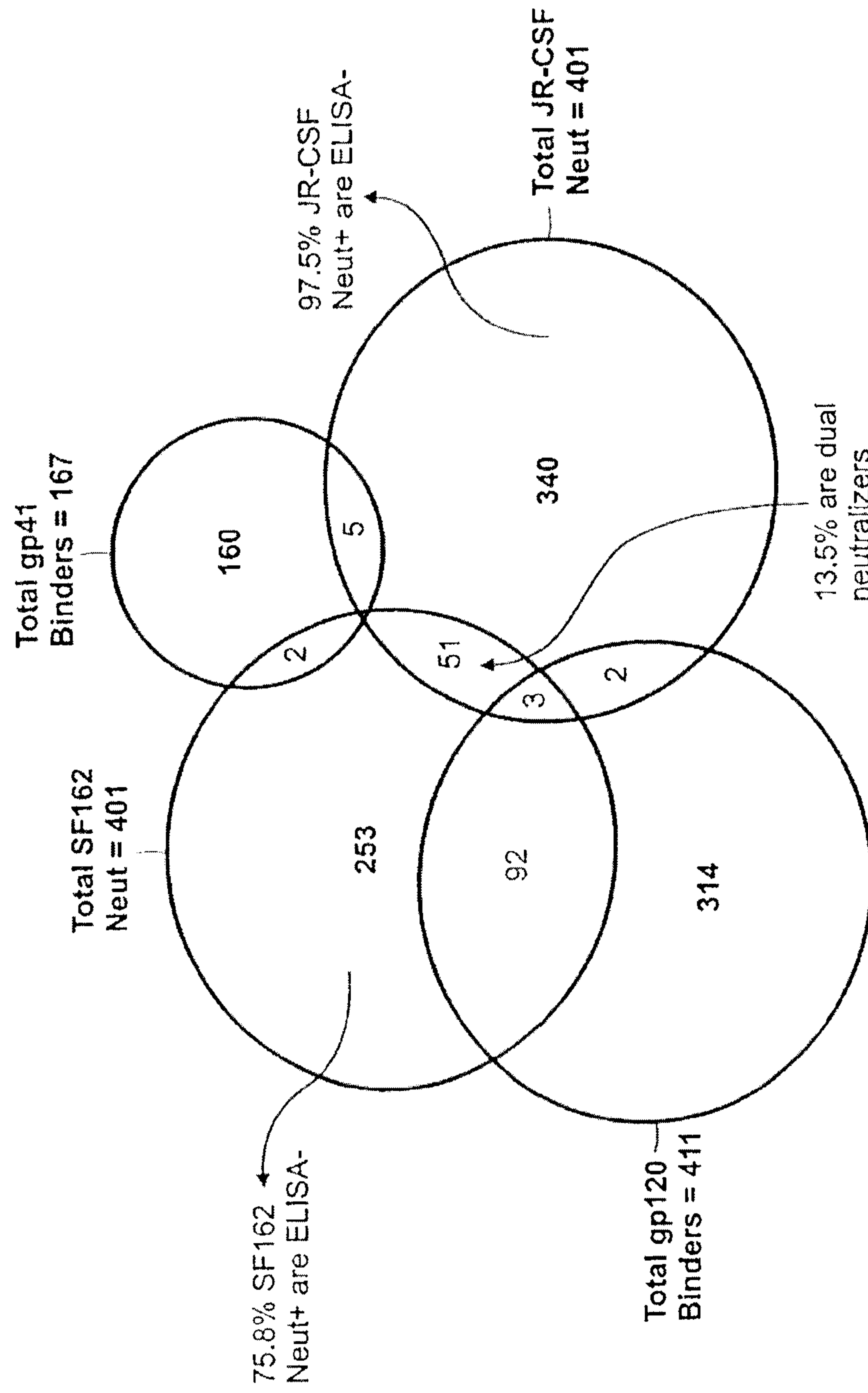


FIG. 3A



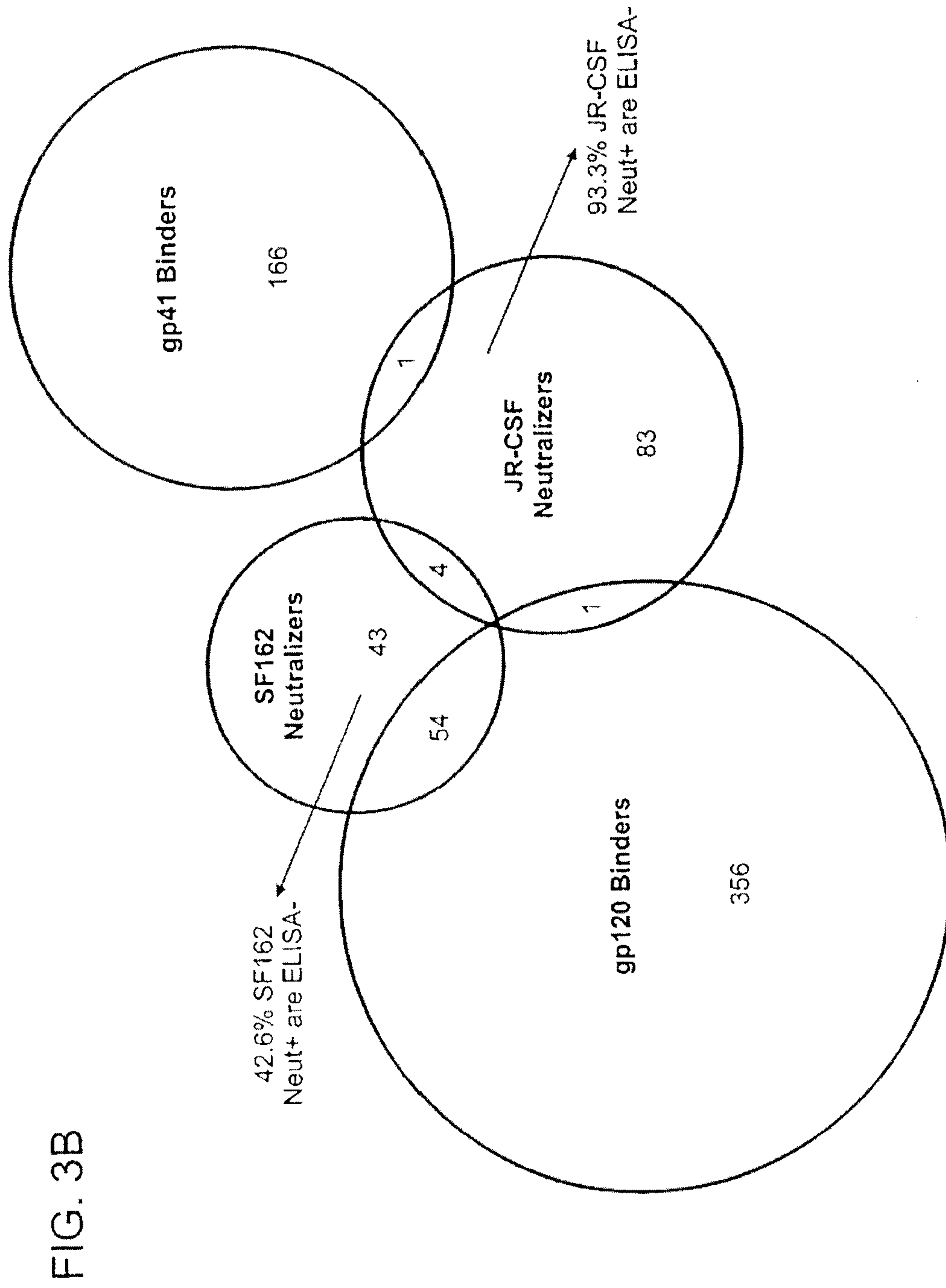


FIG. 4 PGK9 and PGK16 Neutralization Assays

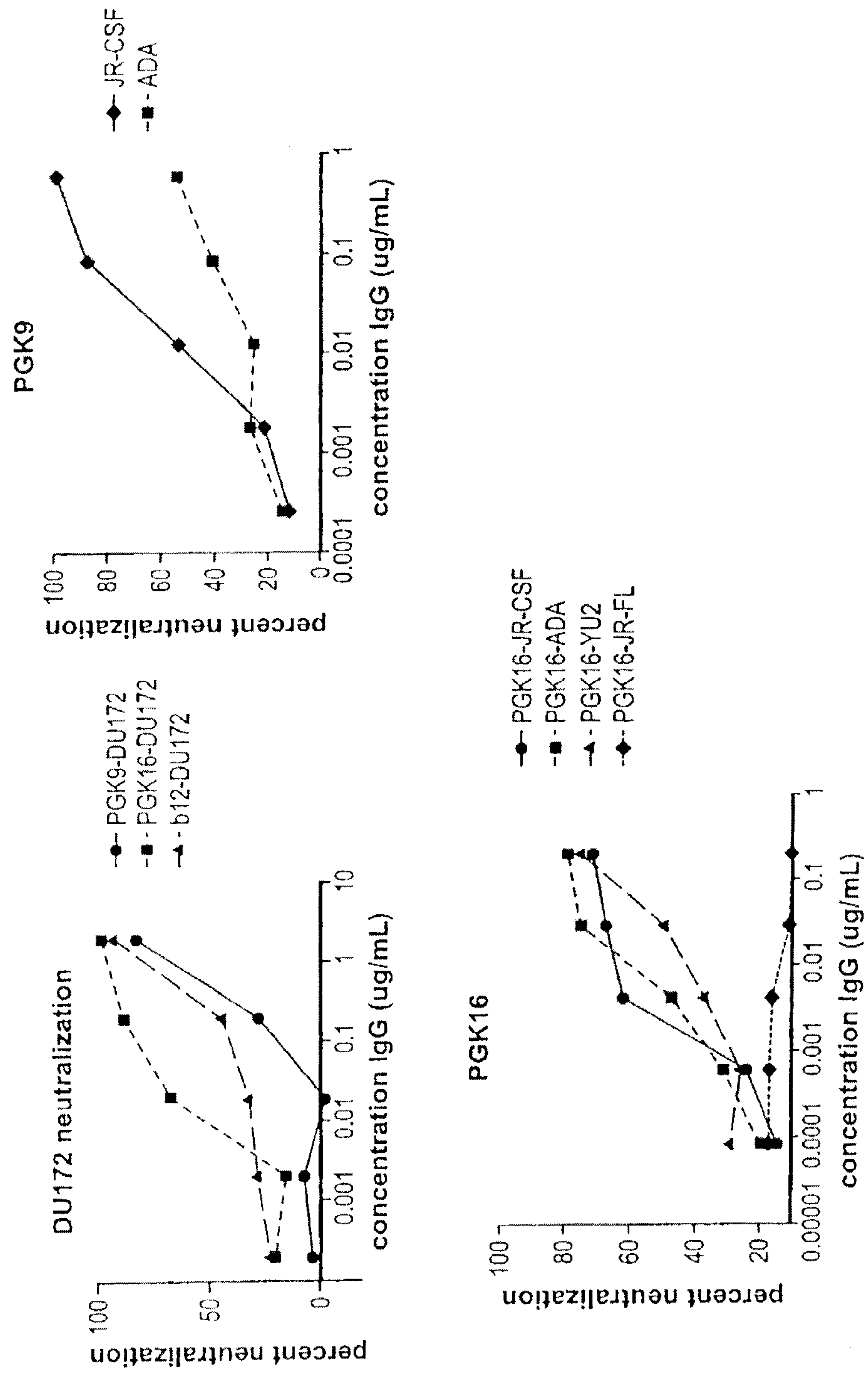
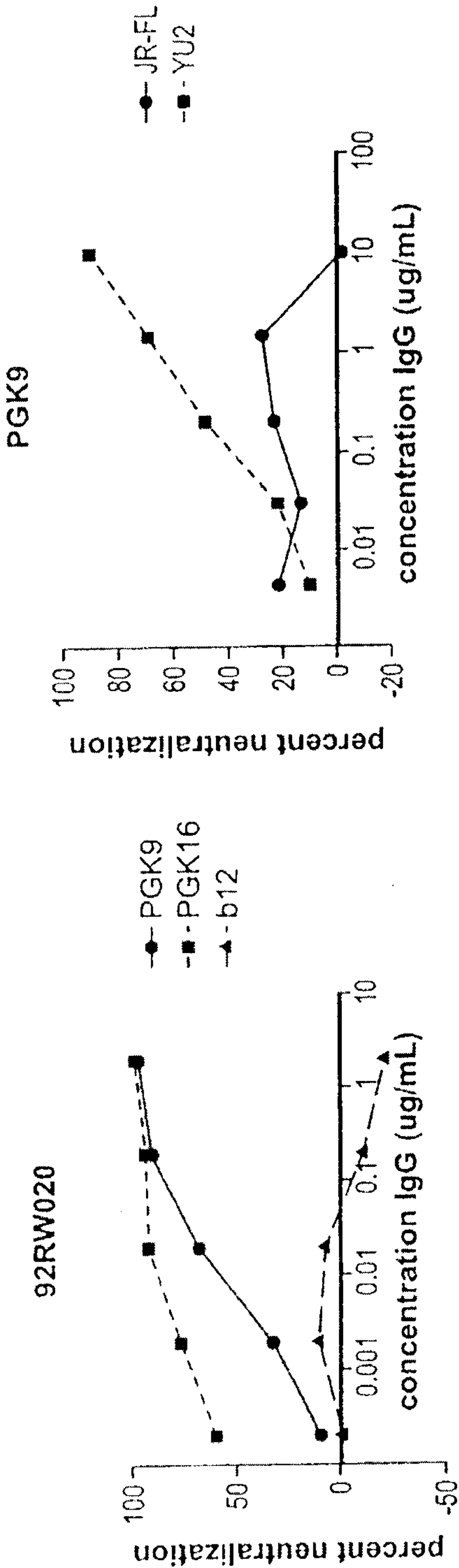


FIG. 4 (continued)



Virus Strain						
	clade B			clade C		clade A
	YU2	JR -FL	JR -CSF	ADA	DU172	ZM214
PGK9	0.4	>10	0.004	0.4	0.6	>2
PGK16	<0.1	>10	0.002	<0.1	0.008	>2

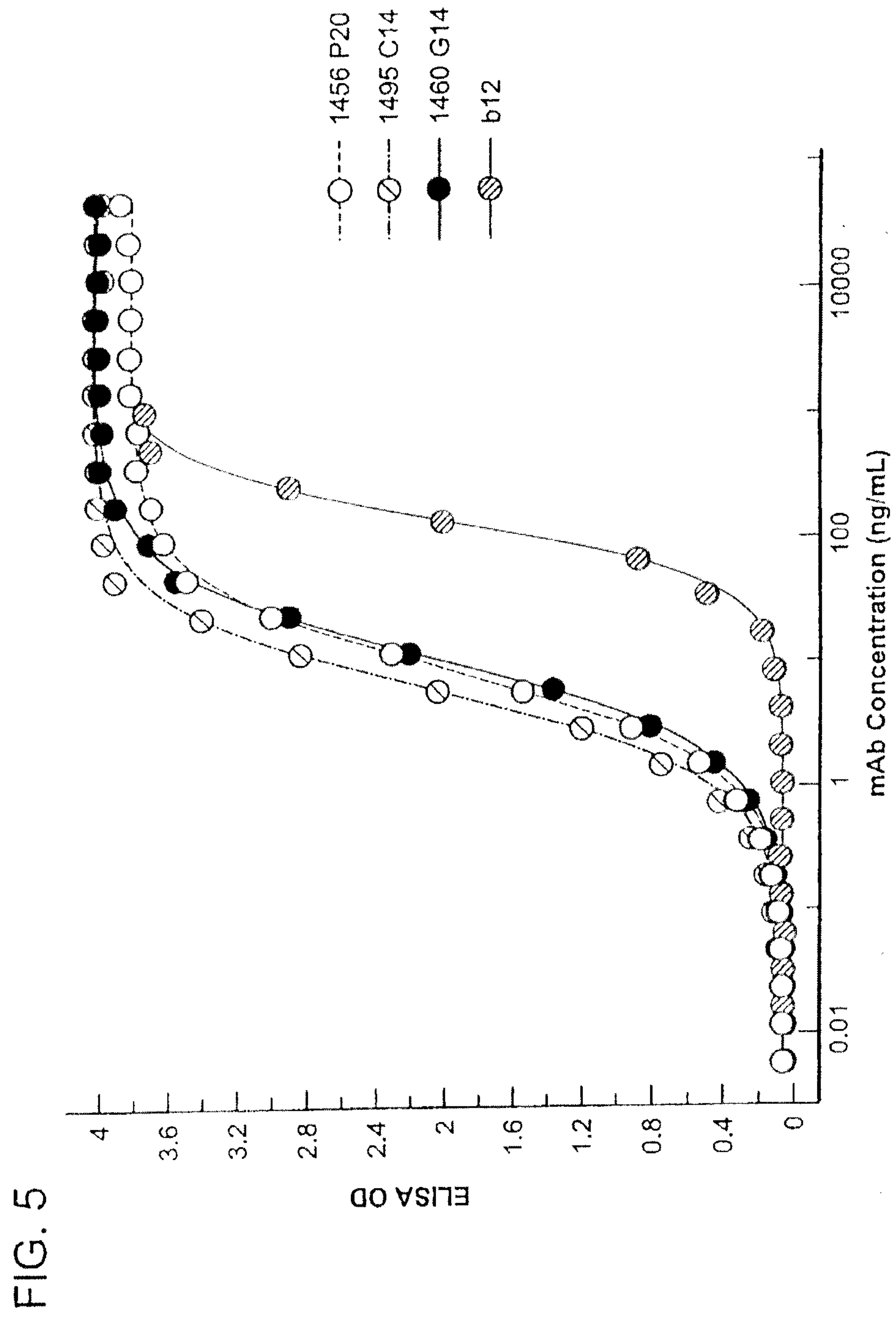


FIG. 6

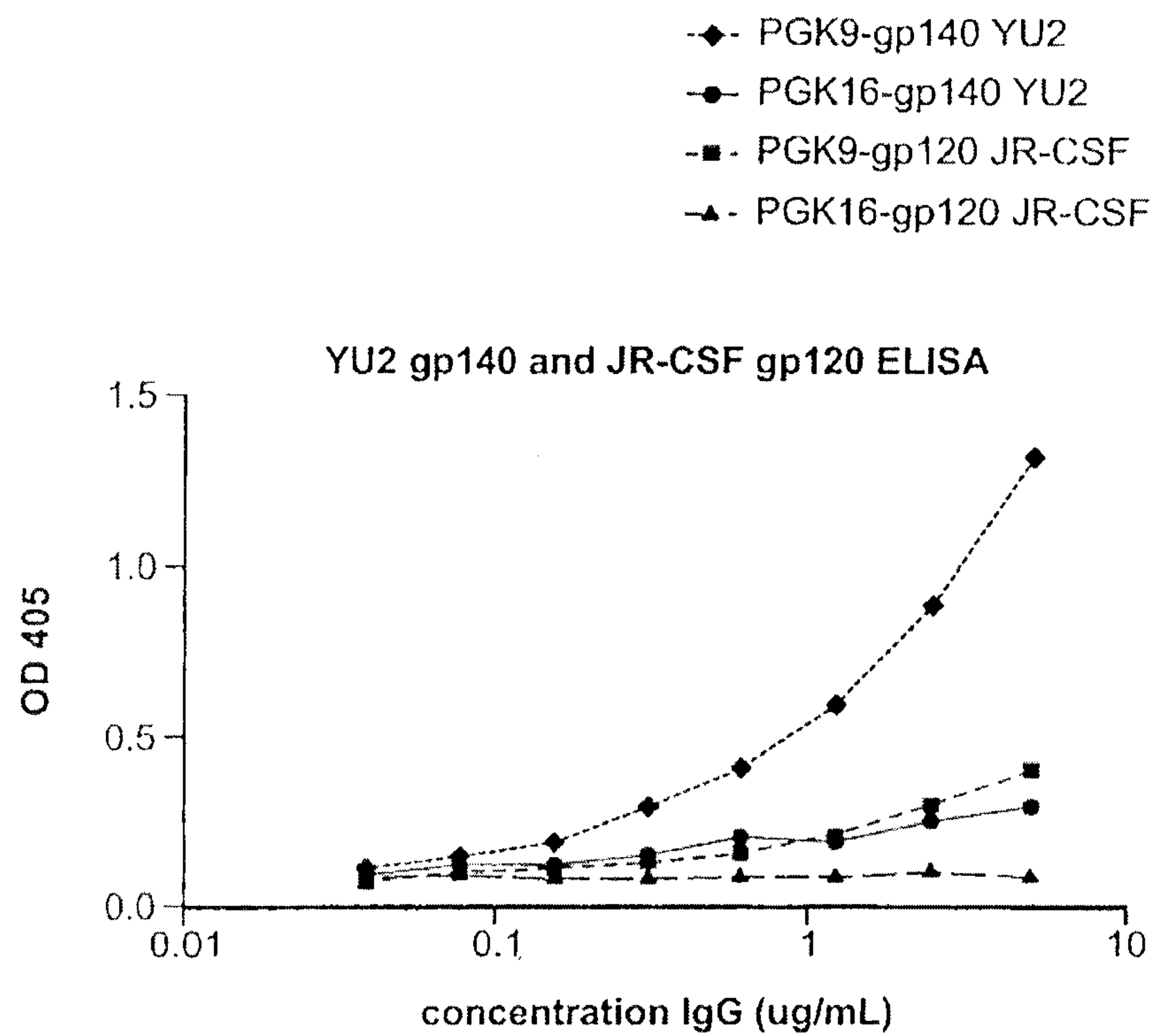


FIG. 6 (continued)

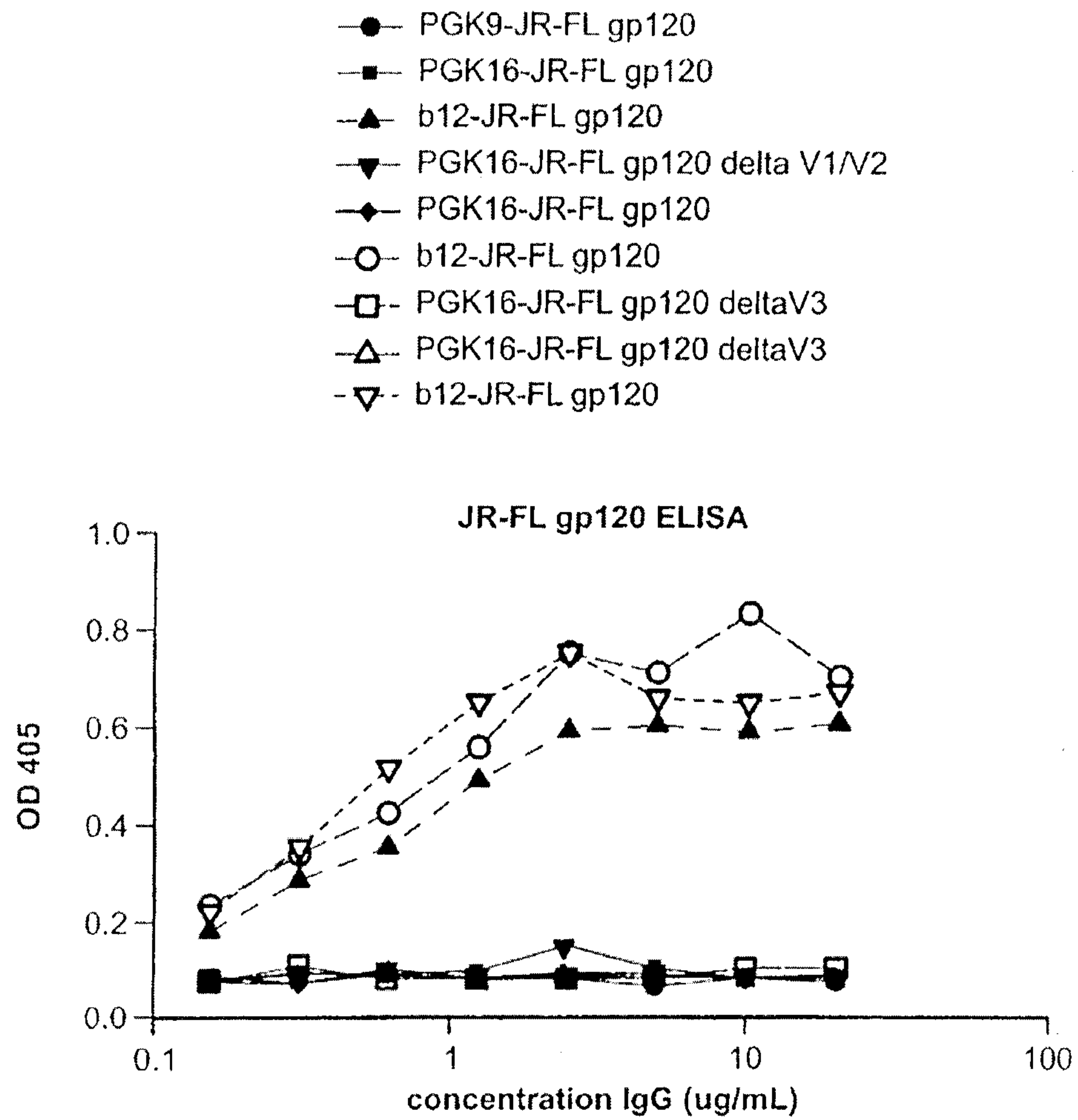


FIG. 6 (continued)

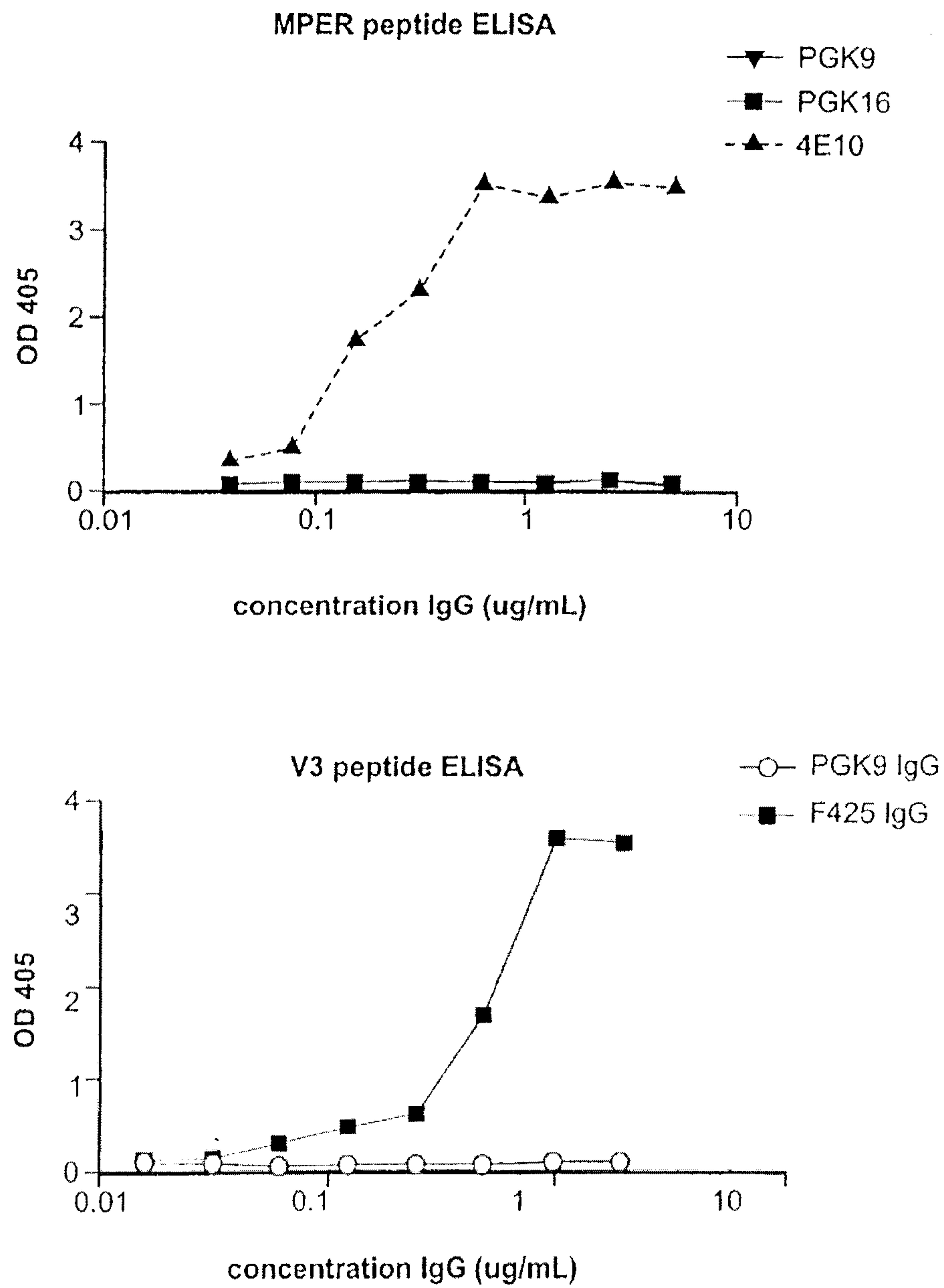


FIG. 7
Binding of PG16 and PG9 to HIV-1YU2 gp160 expressed on Cell Surface
in the presence and absence of sCD4

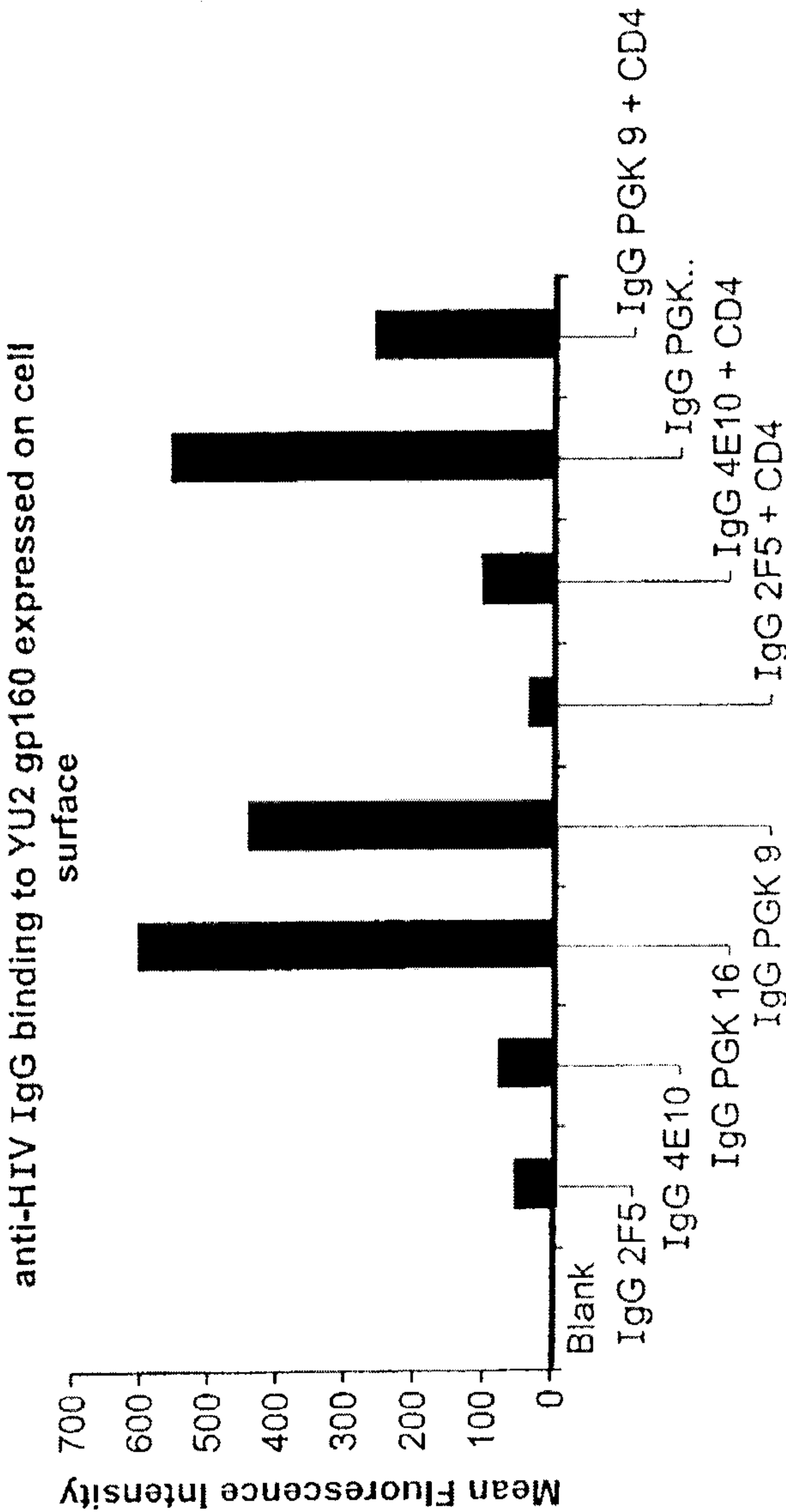


FIG. 8

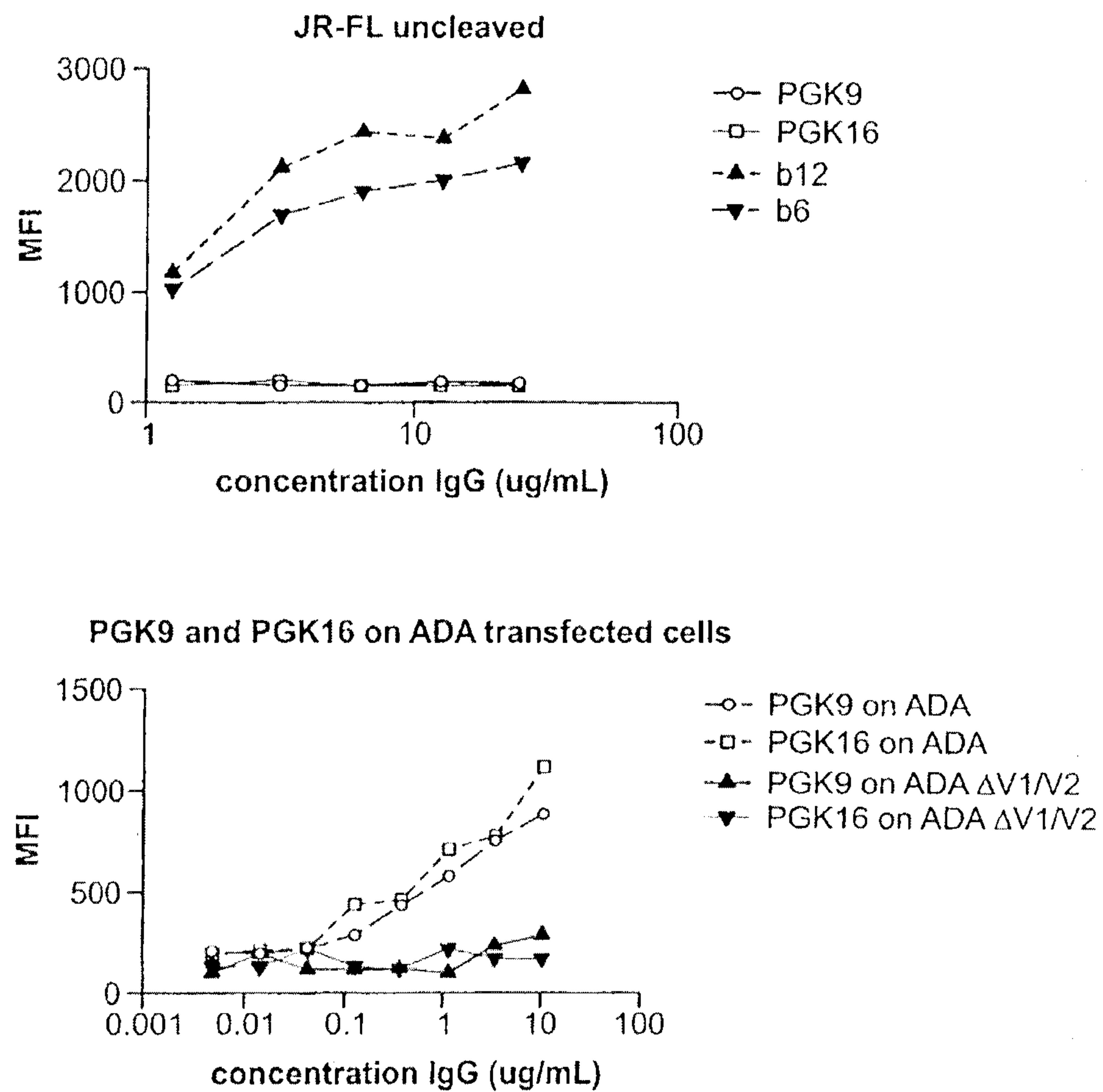
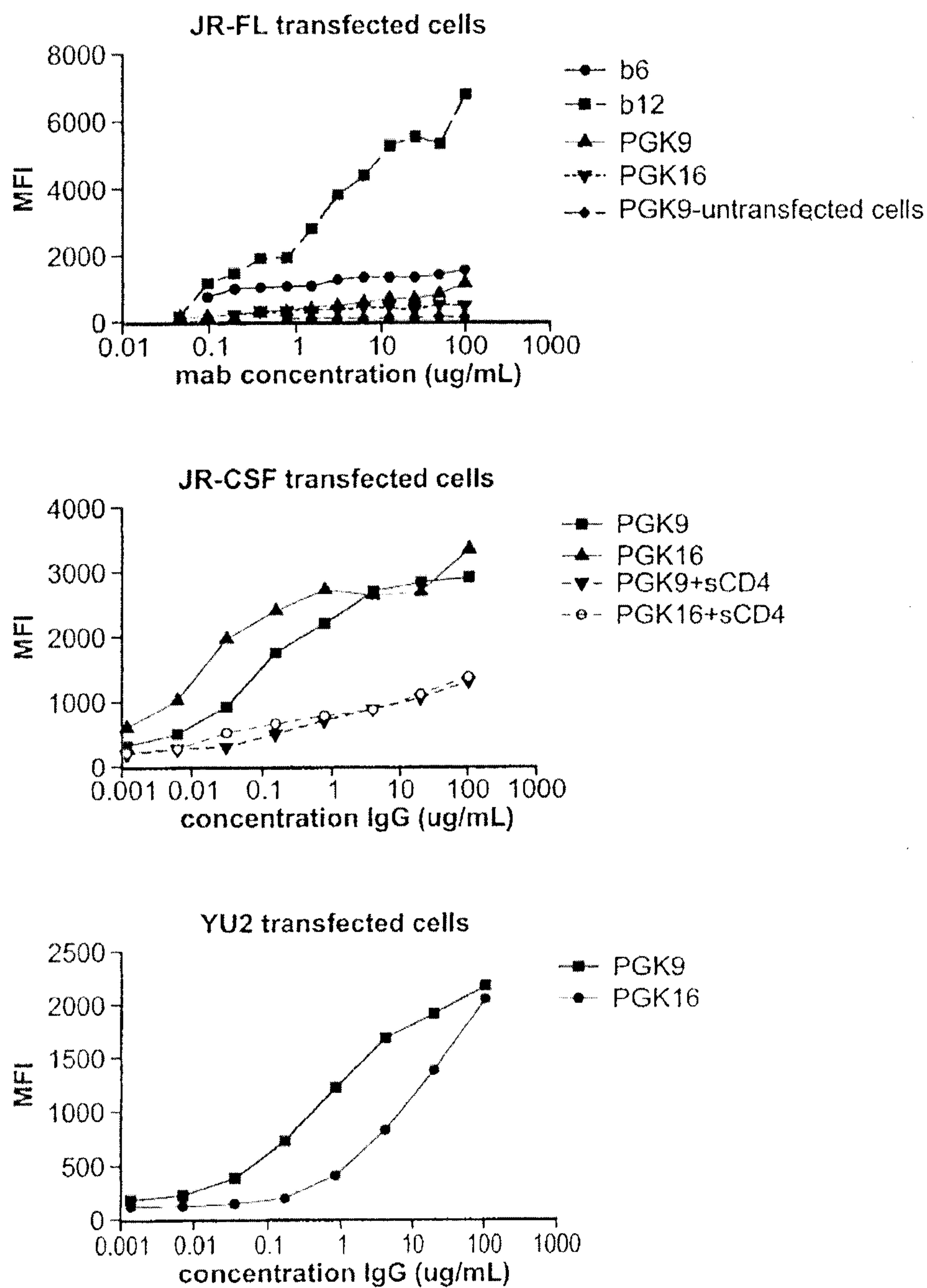


FIG. 8 (continued)



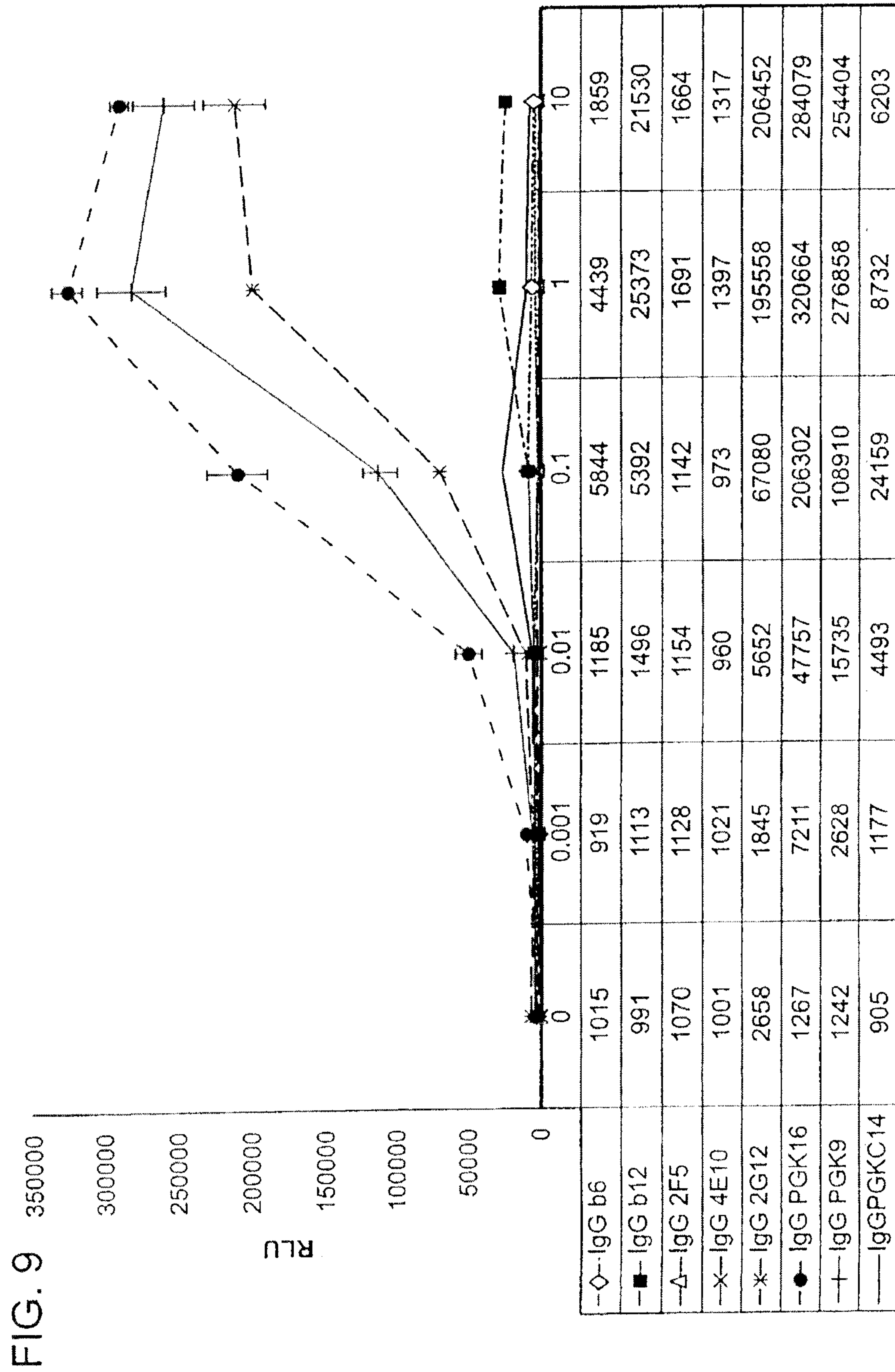


FIG. 10A

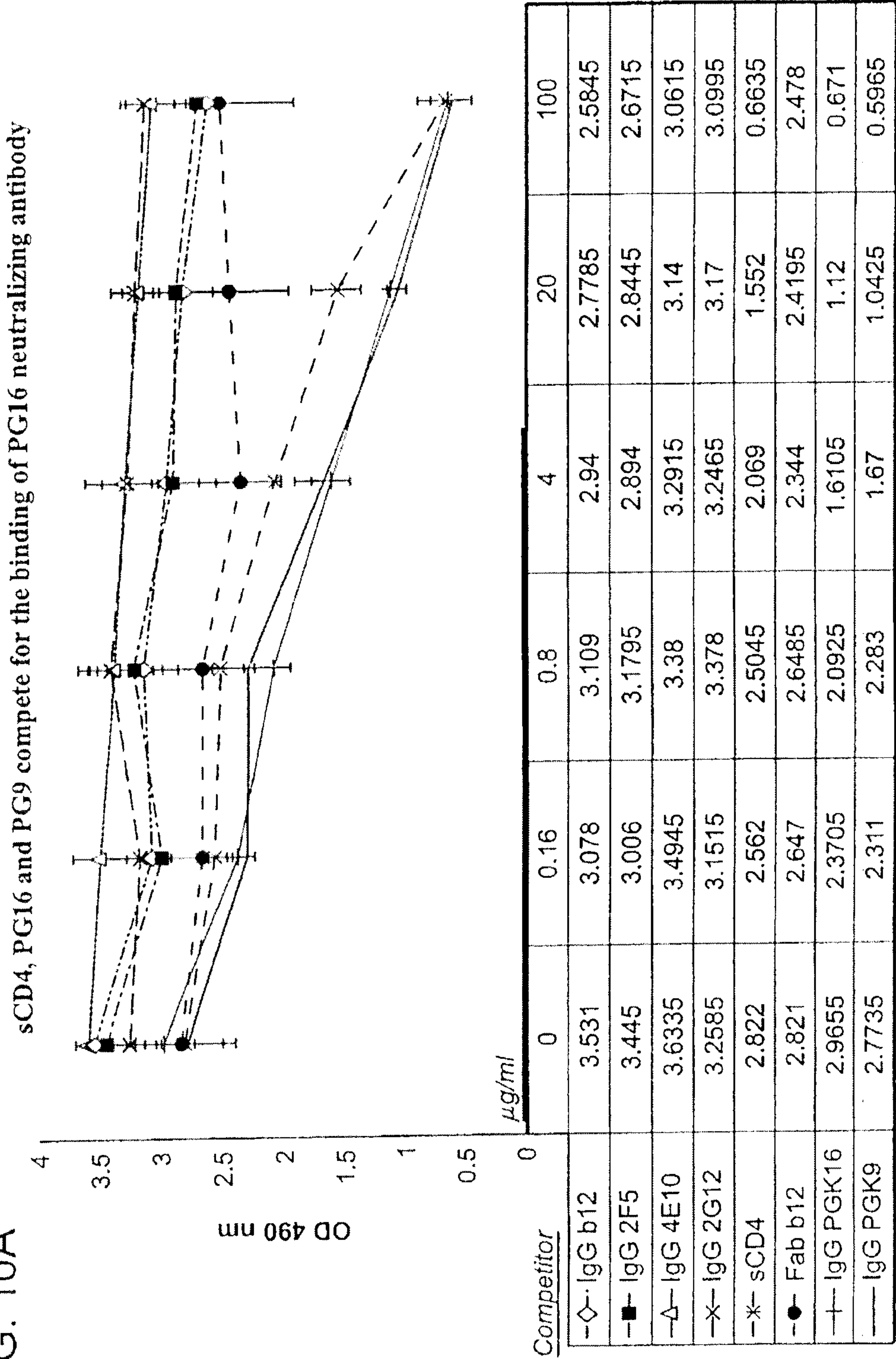


FIG. 10B

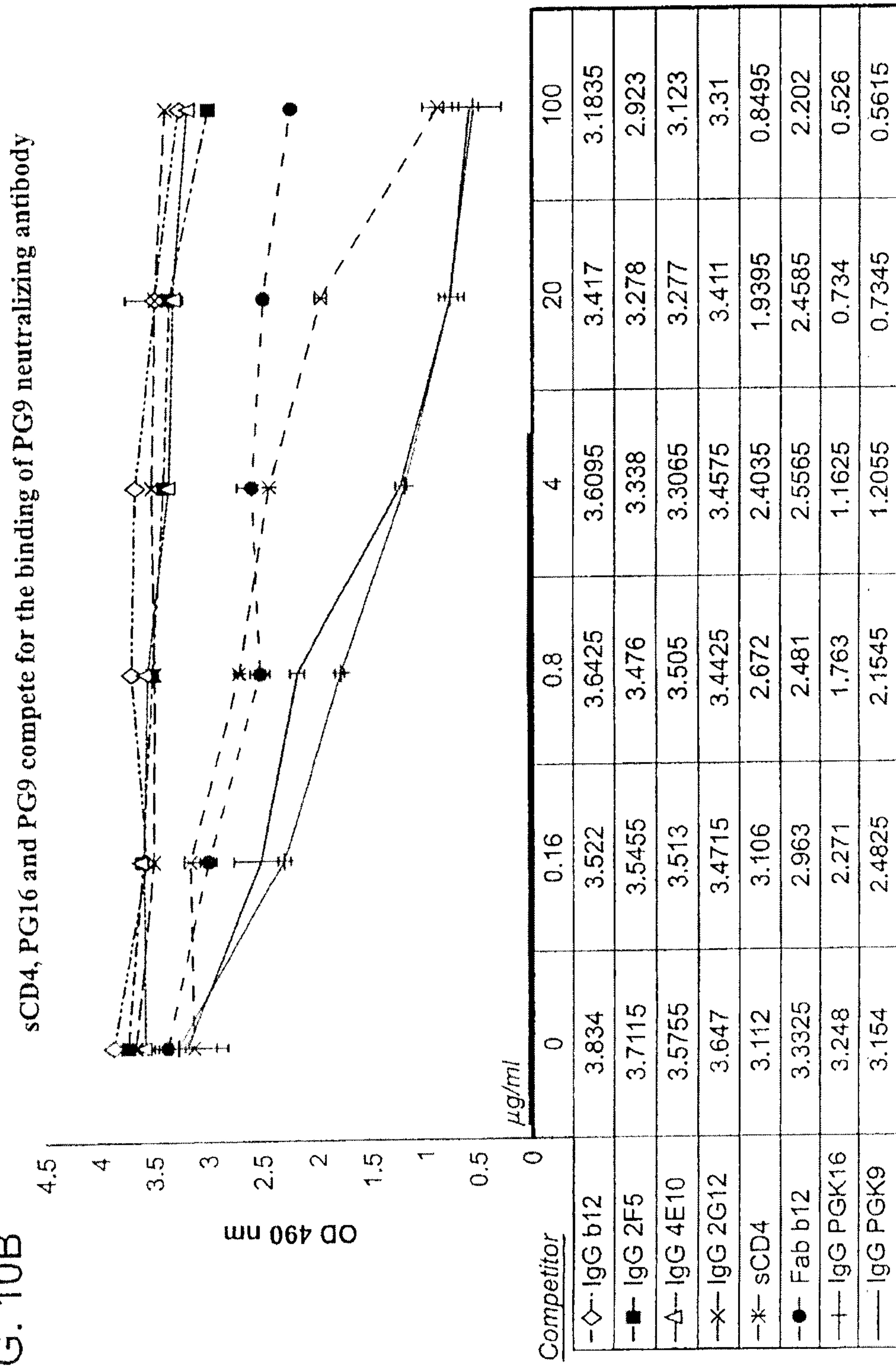


FIG. 11A

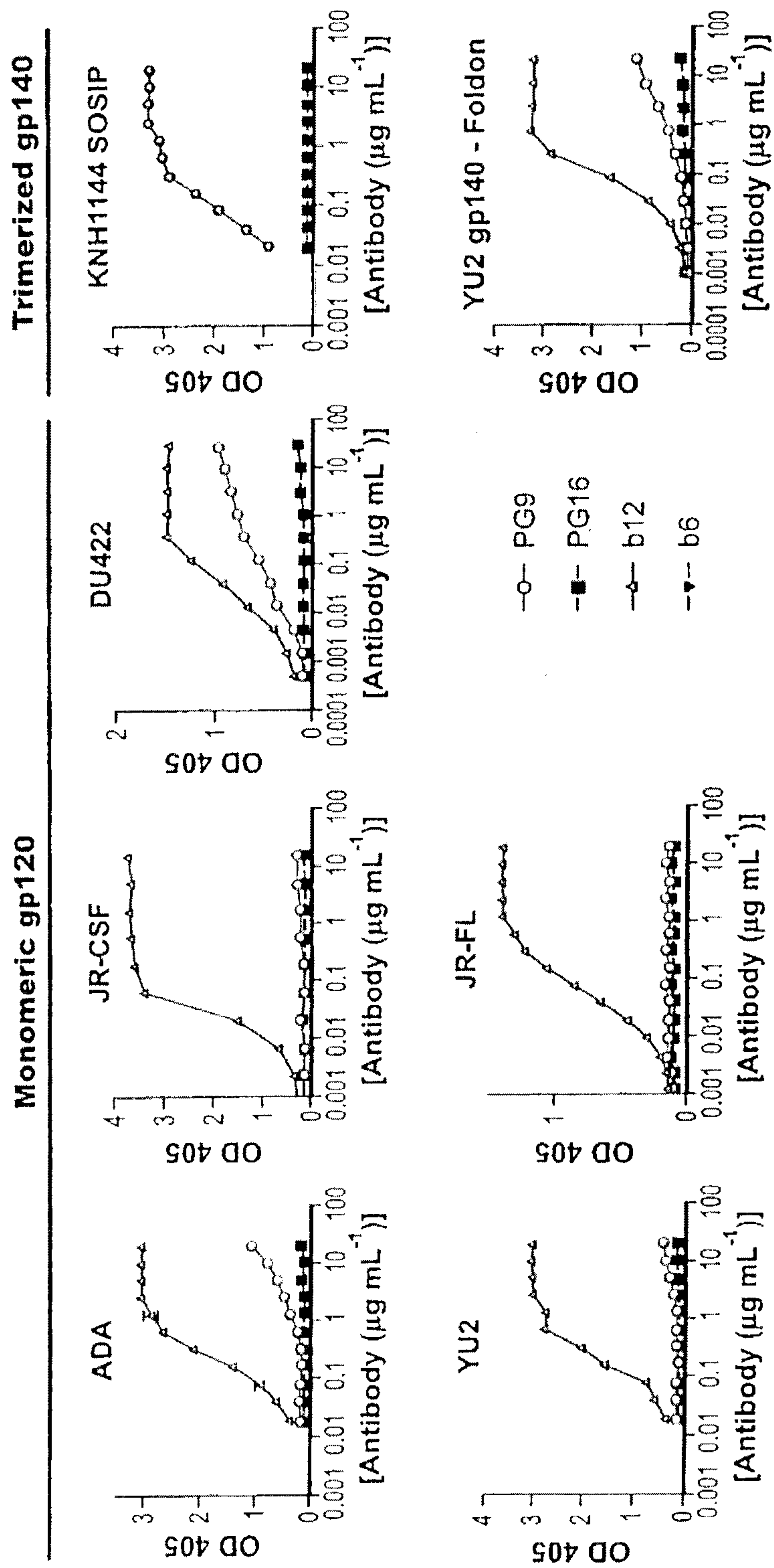


FIG. 11B

Cell surface Env

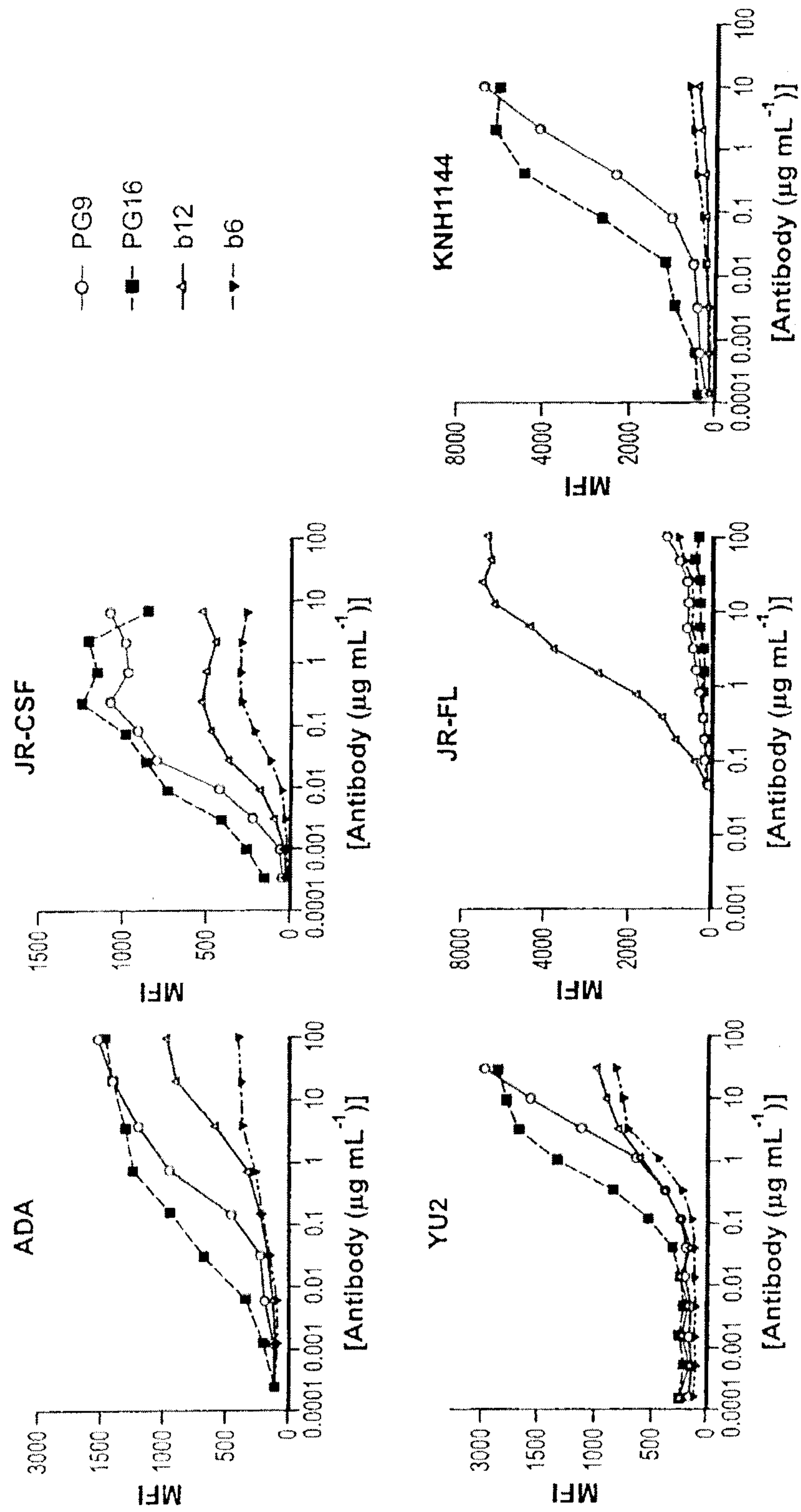


FIG. 12

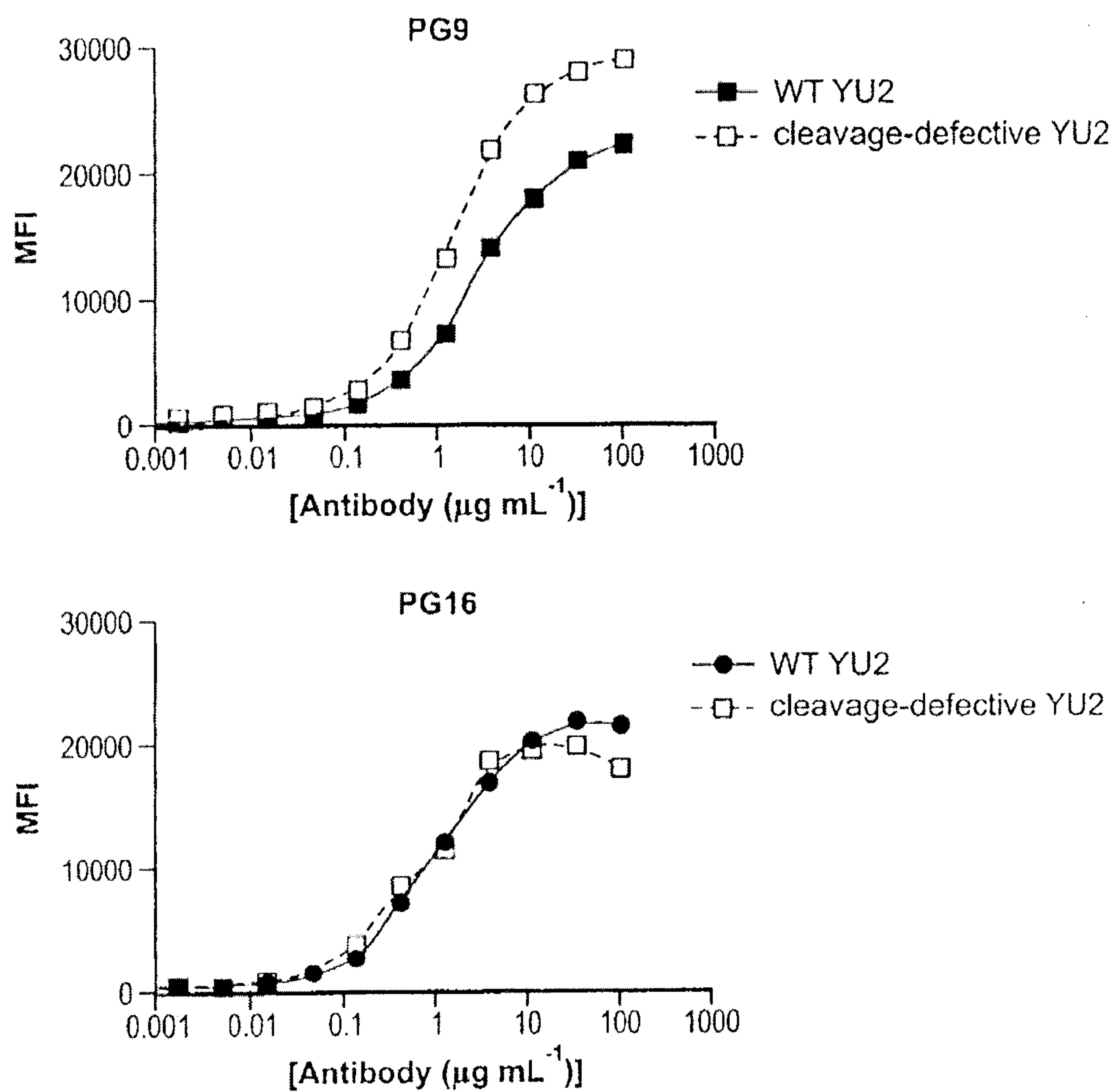


FIG. 13A

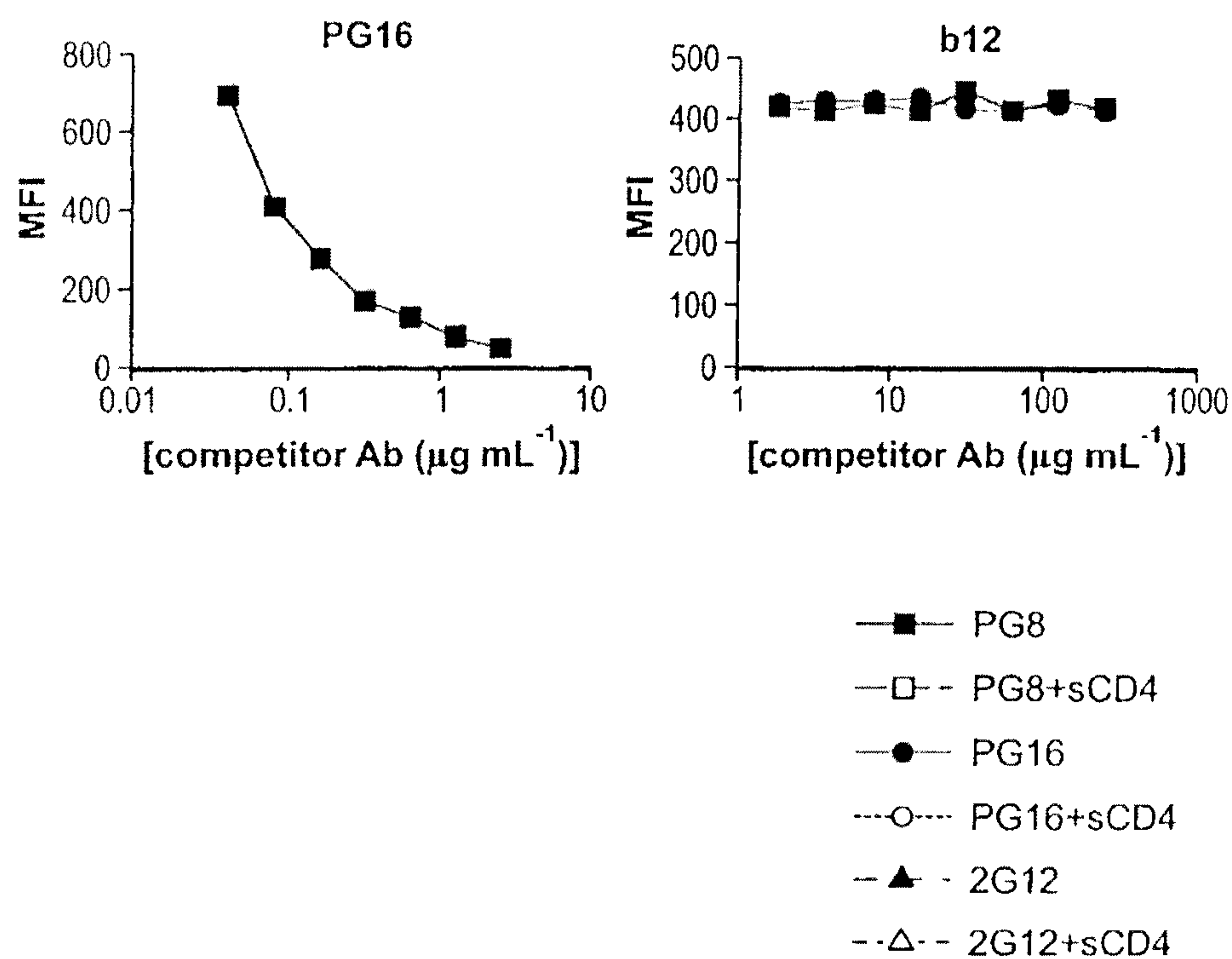


FIG. 13B

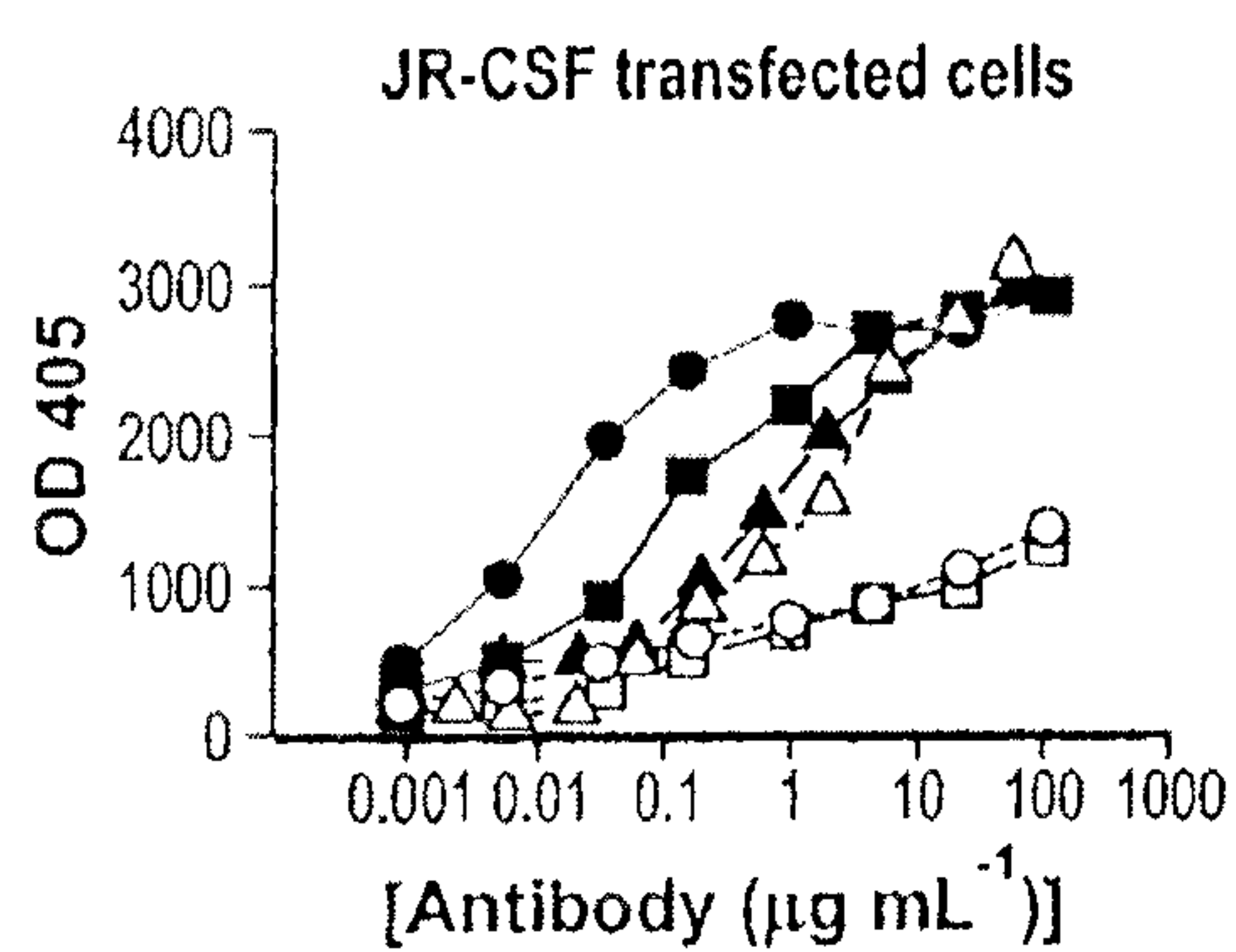
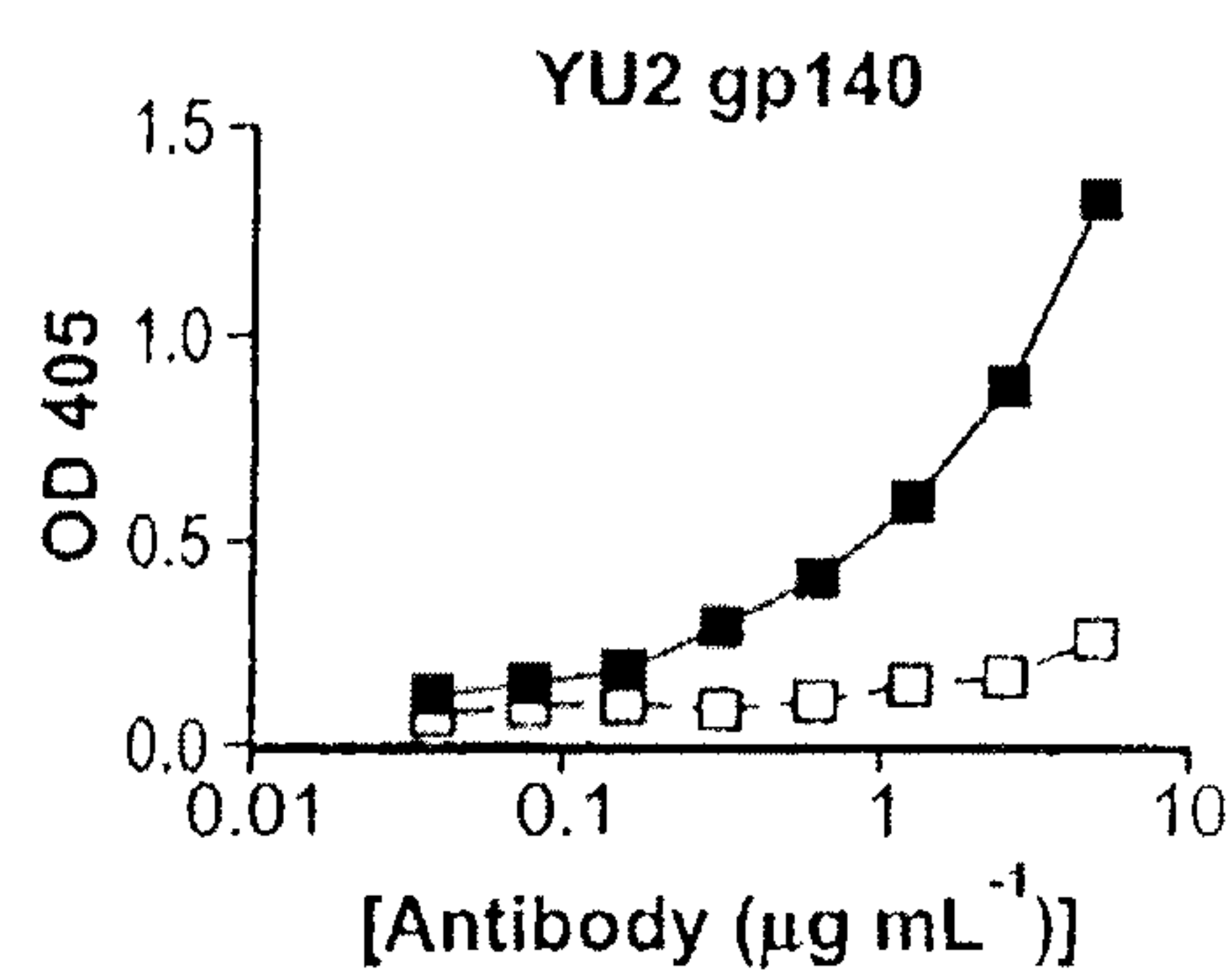
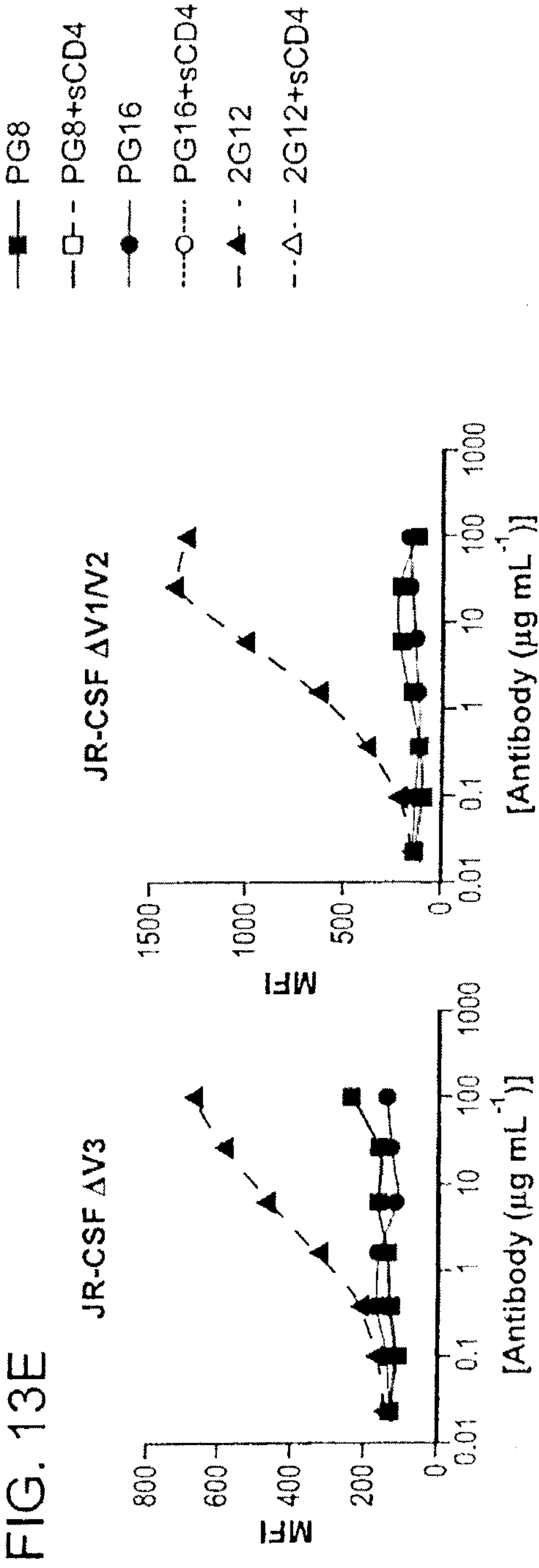
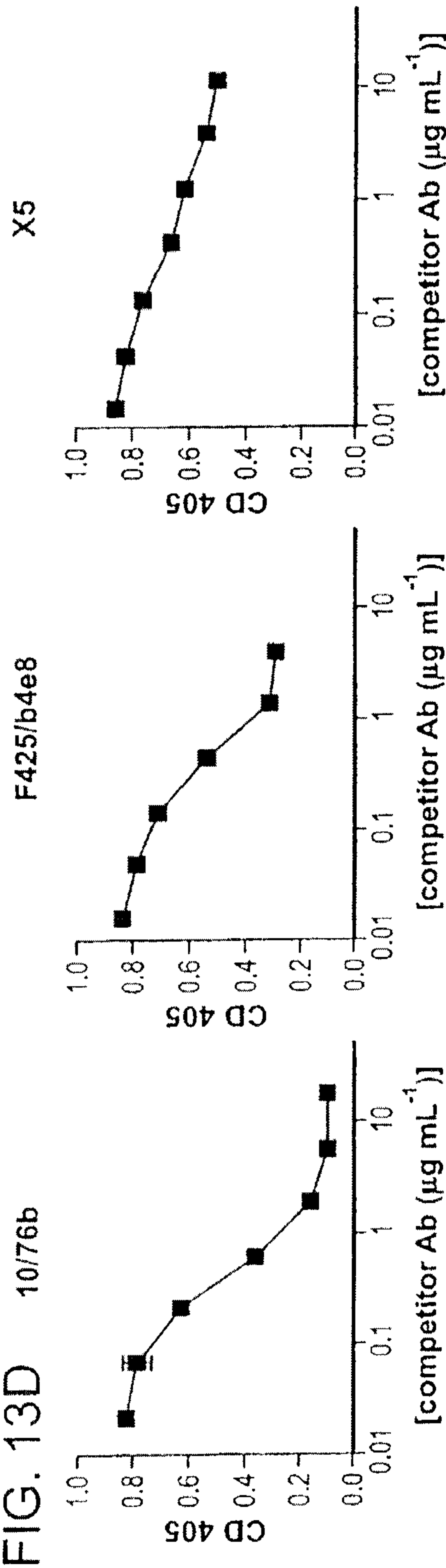


FIG. 13C





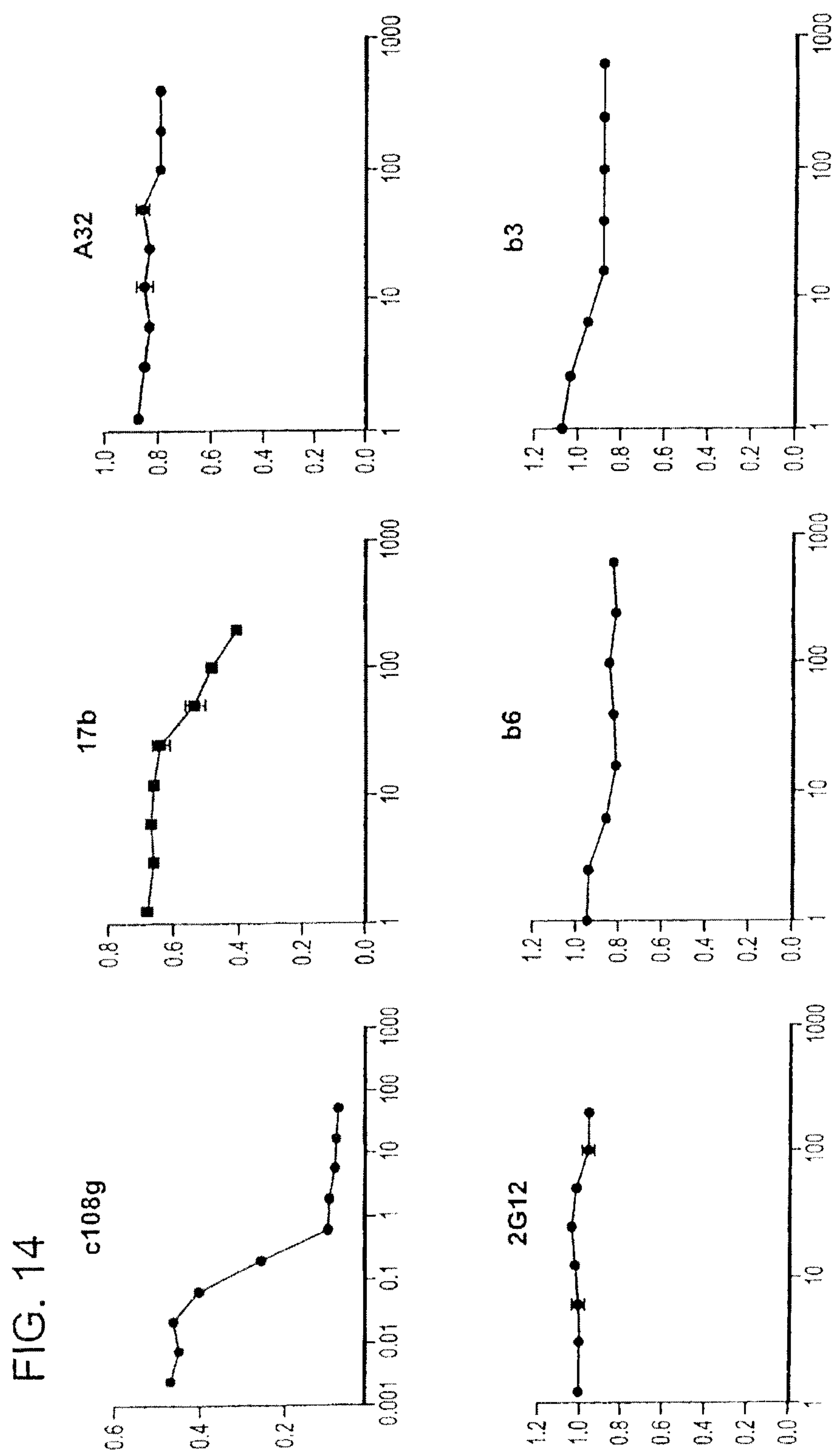


FIG. 15

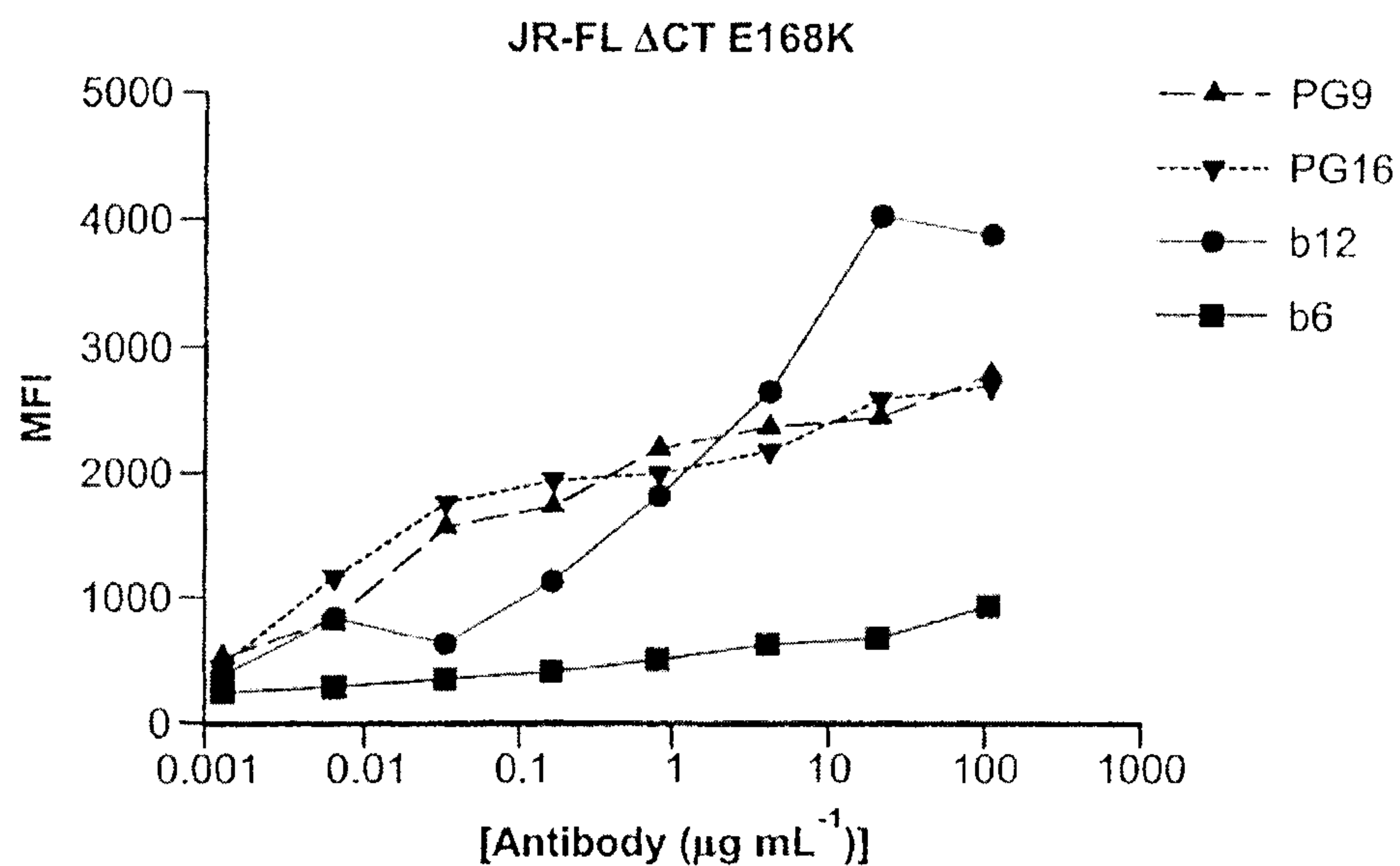


FIG. 16

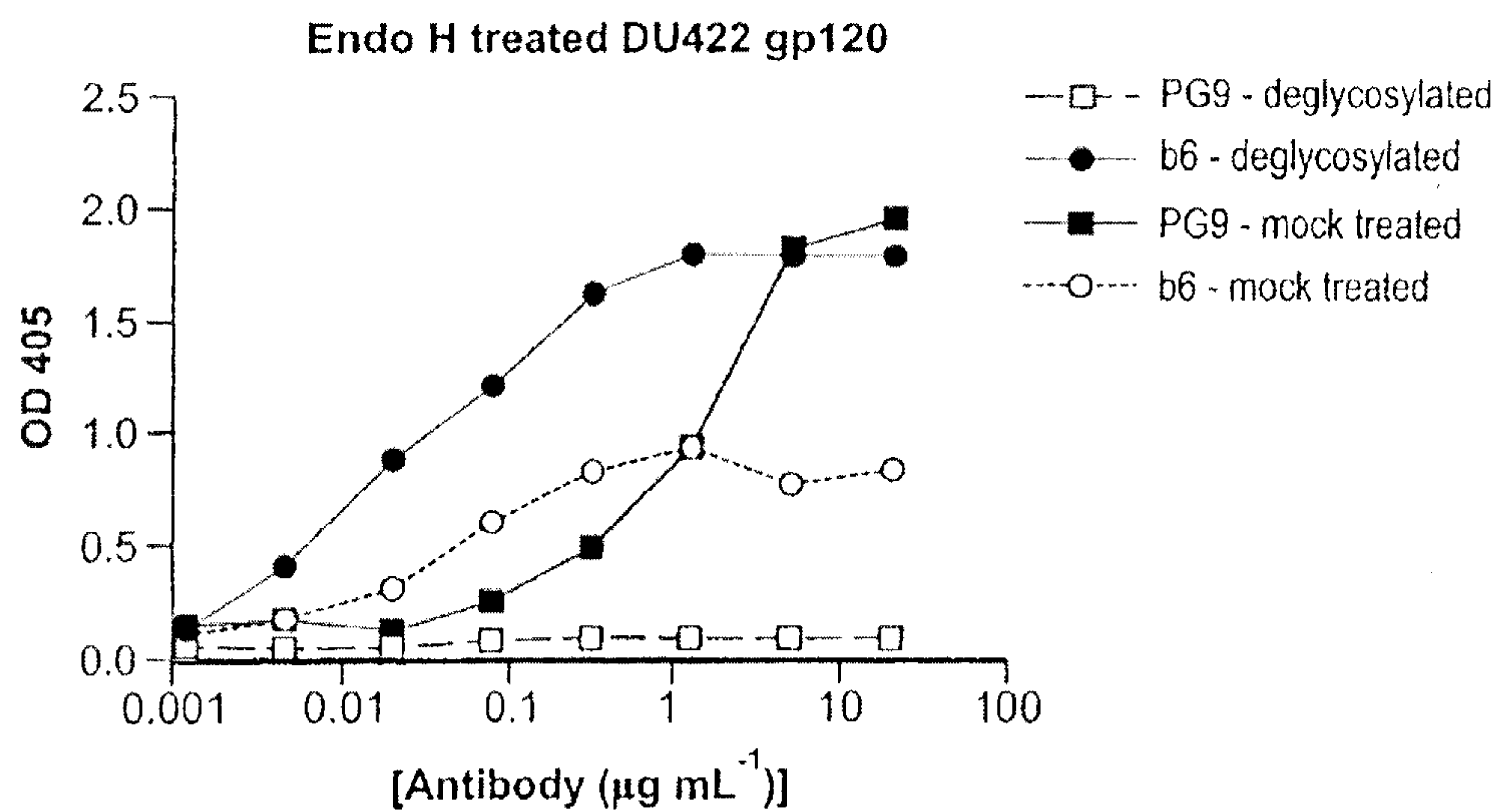
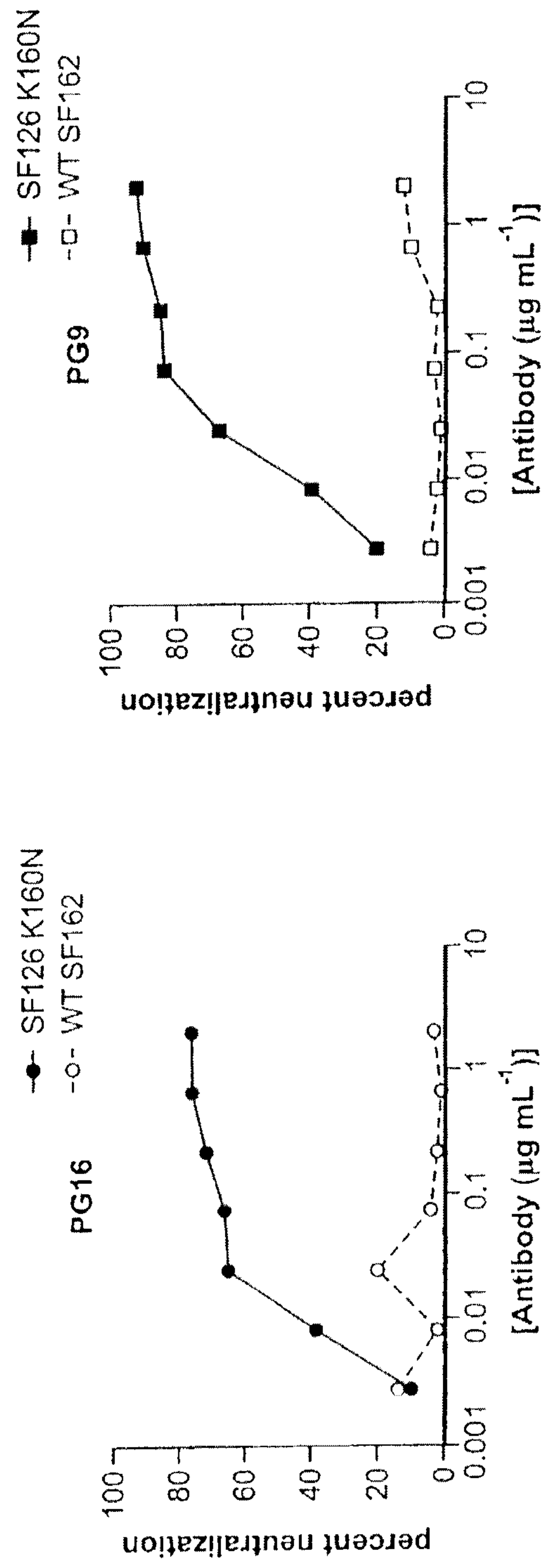


FIG. 17



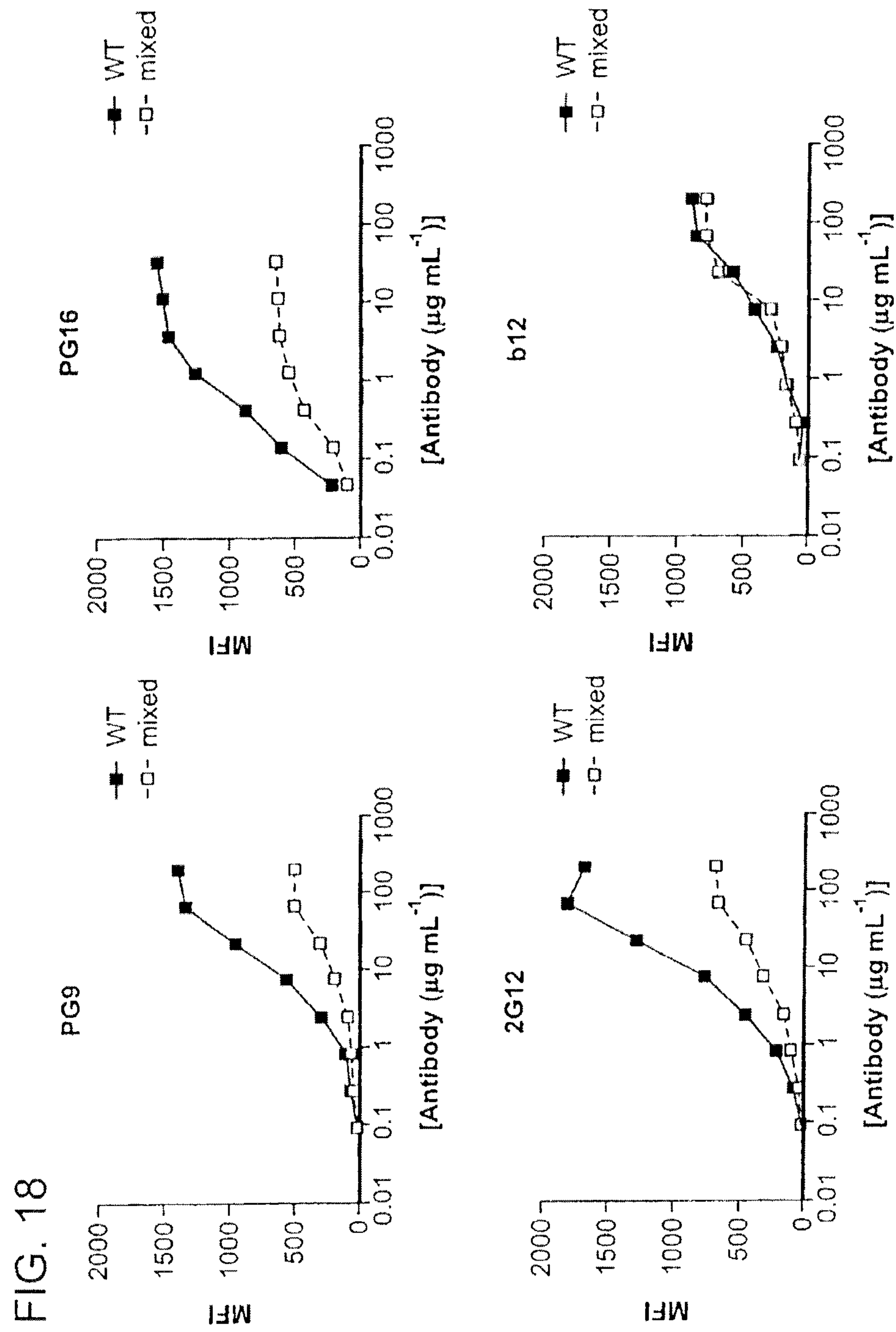


FIG. 19

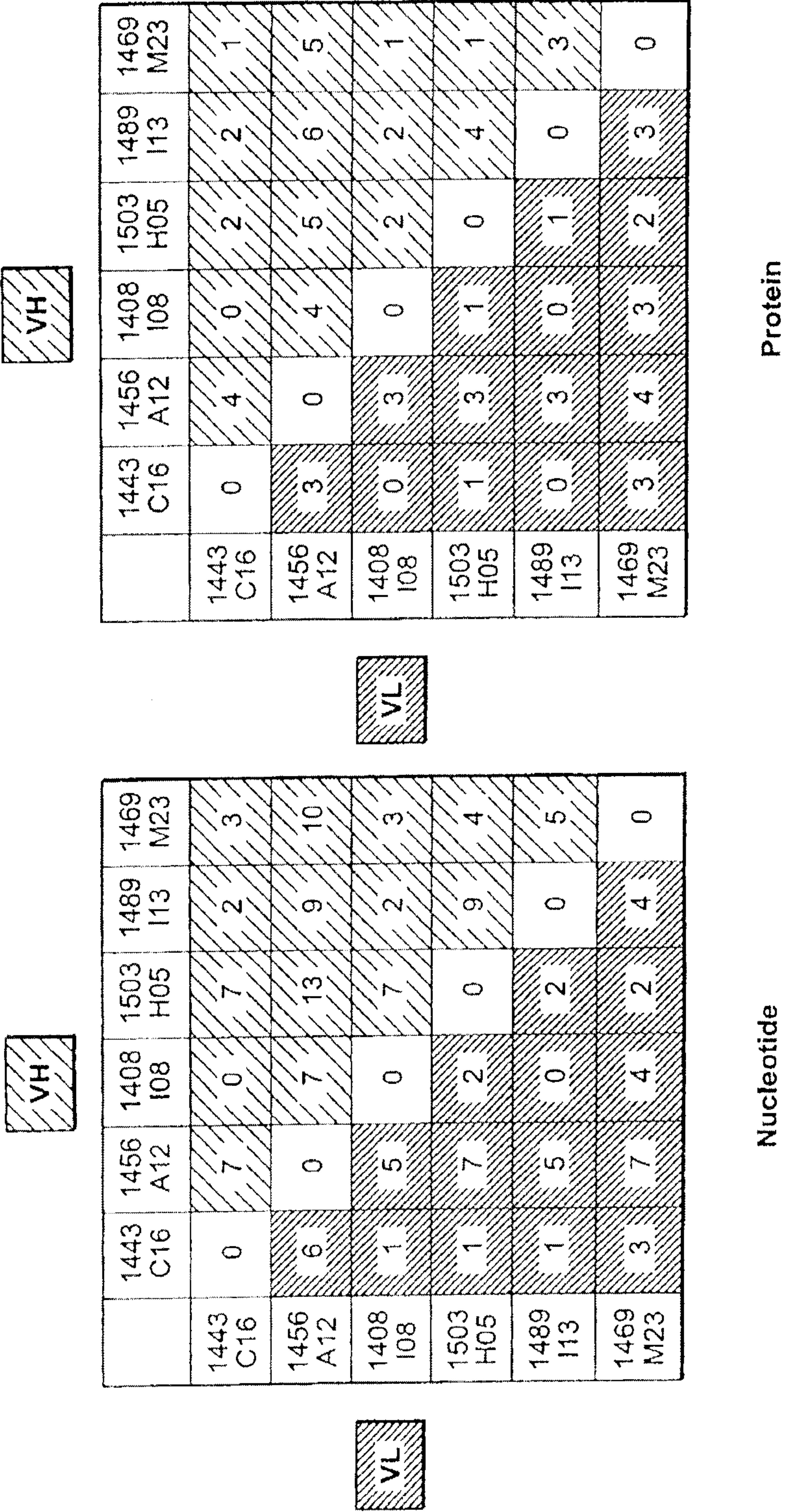


FIG. 20A

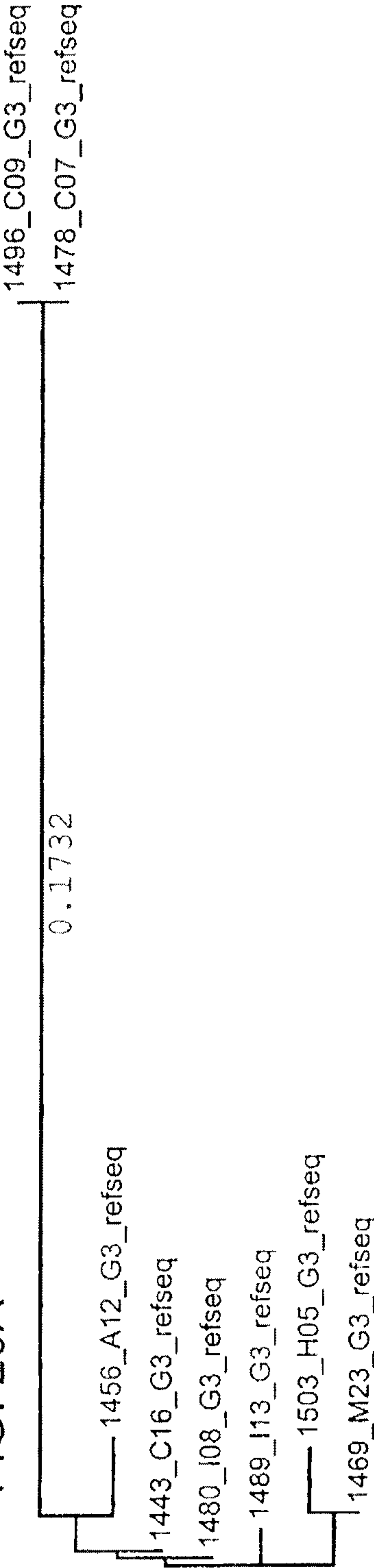


FIG. 20B

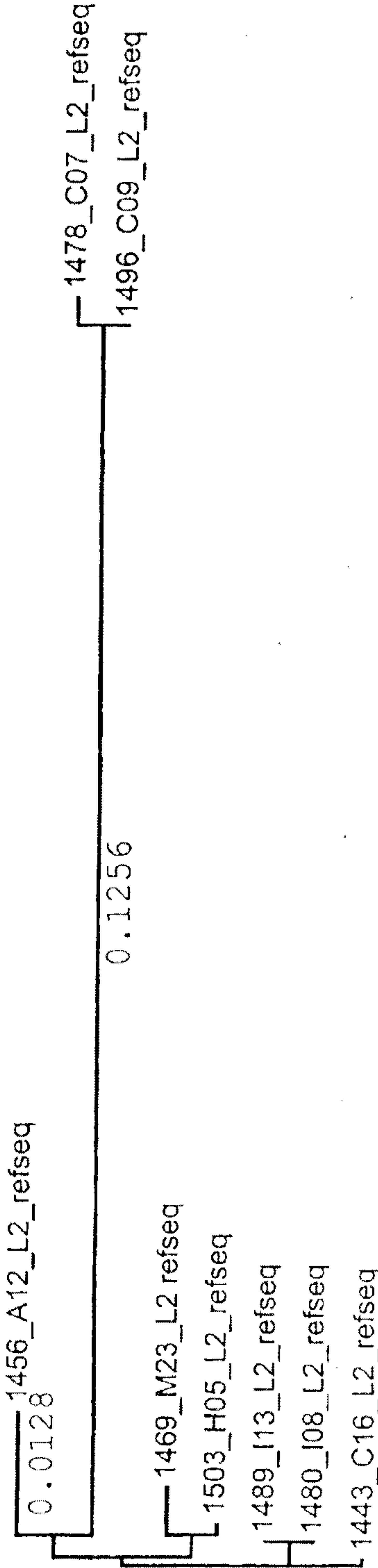


FIG. 21A

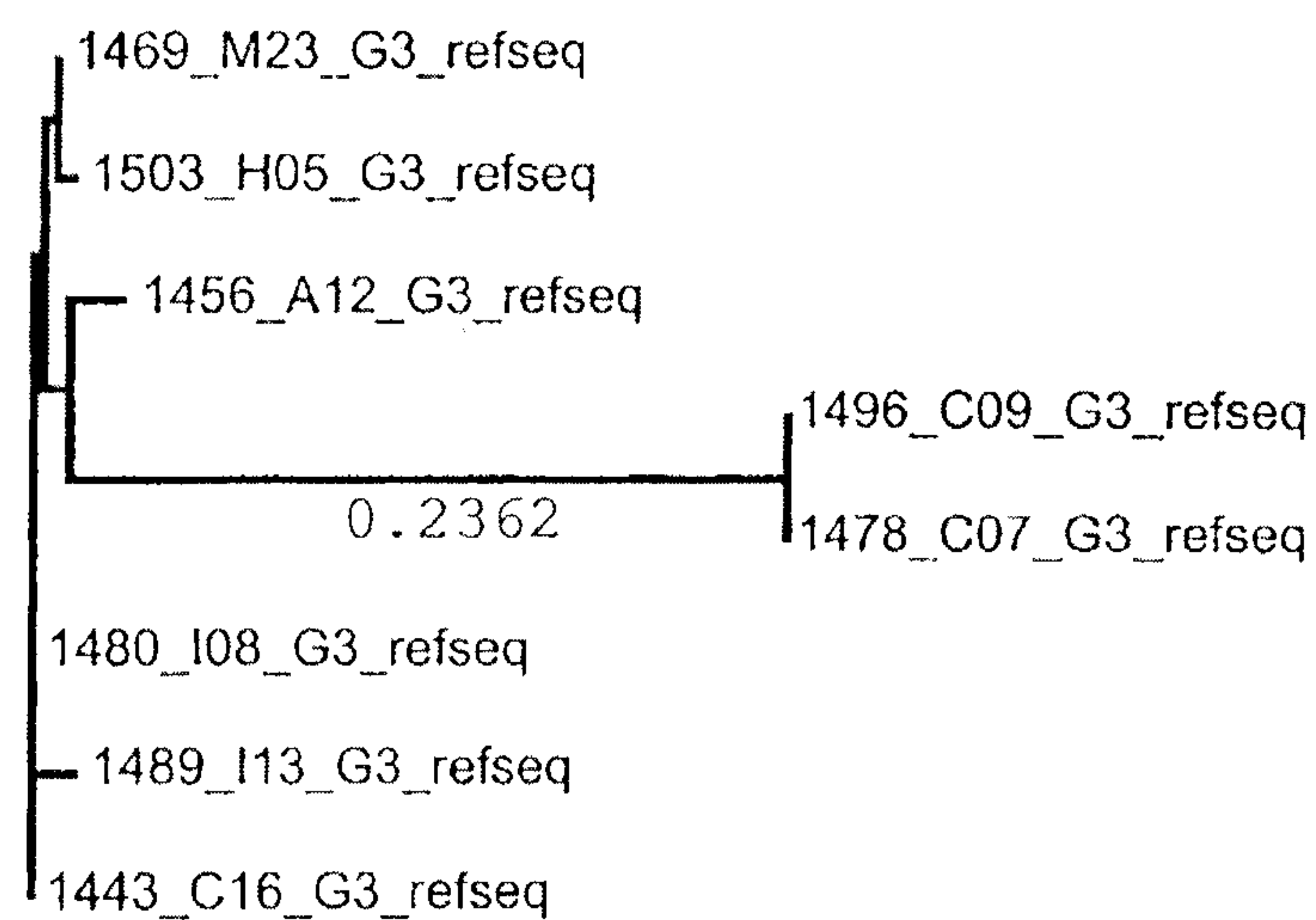


FIG. 21B

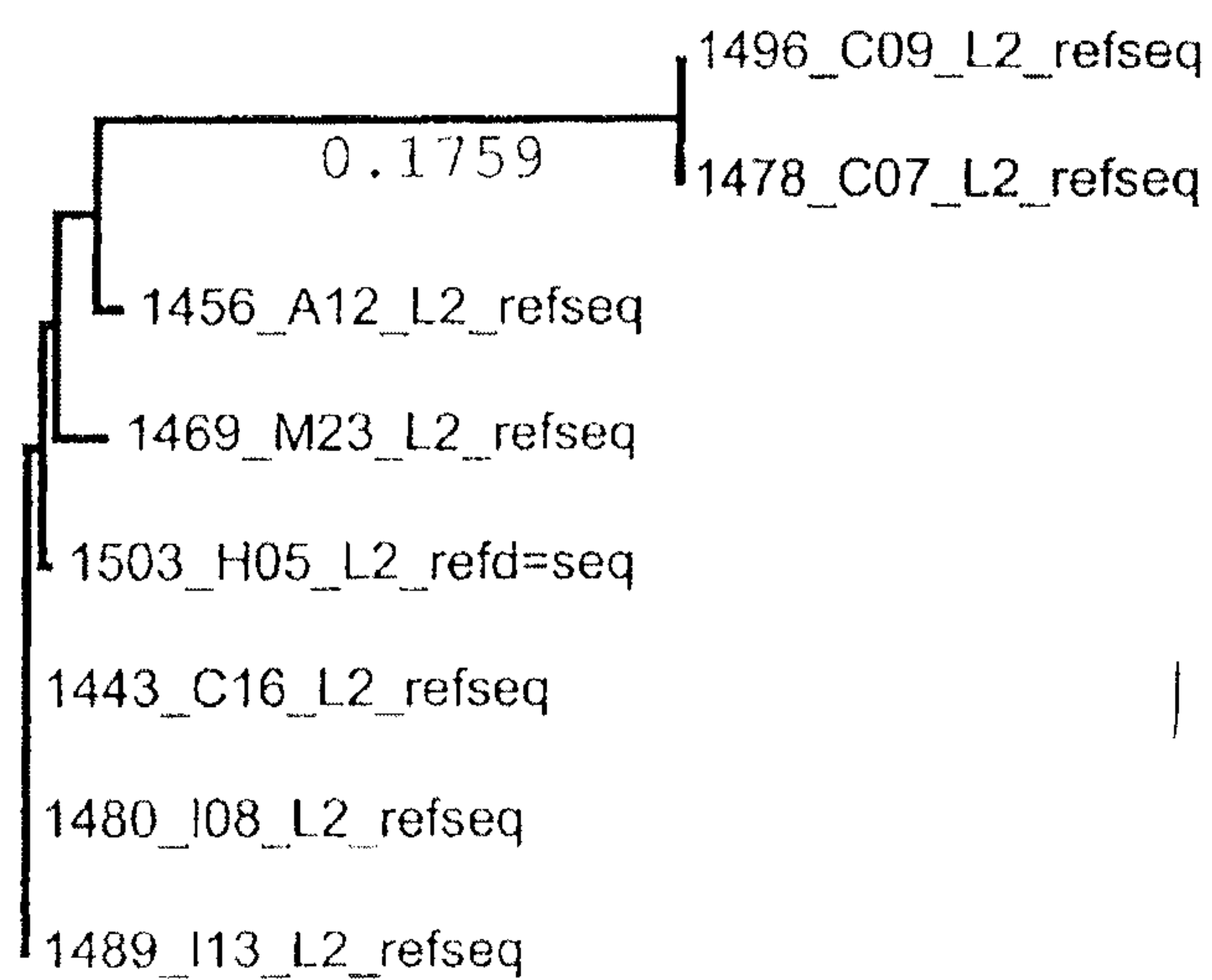


FIGURE 22

Number of HIV-Neutralizing Hits Detected in Primary Screening

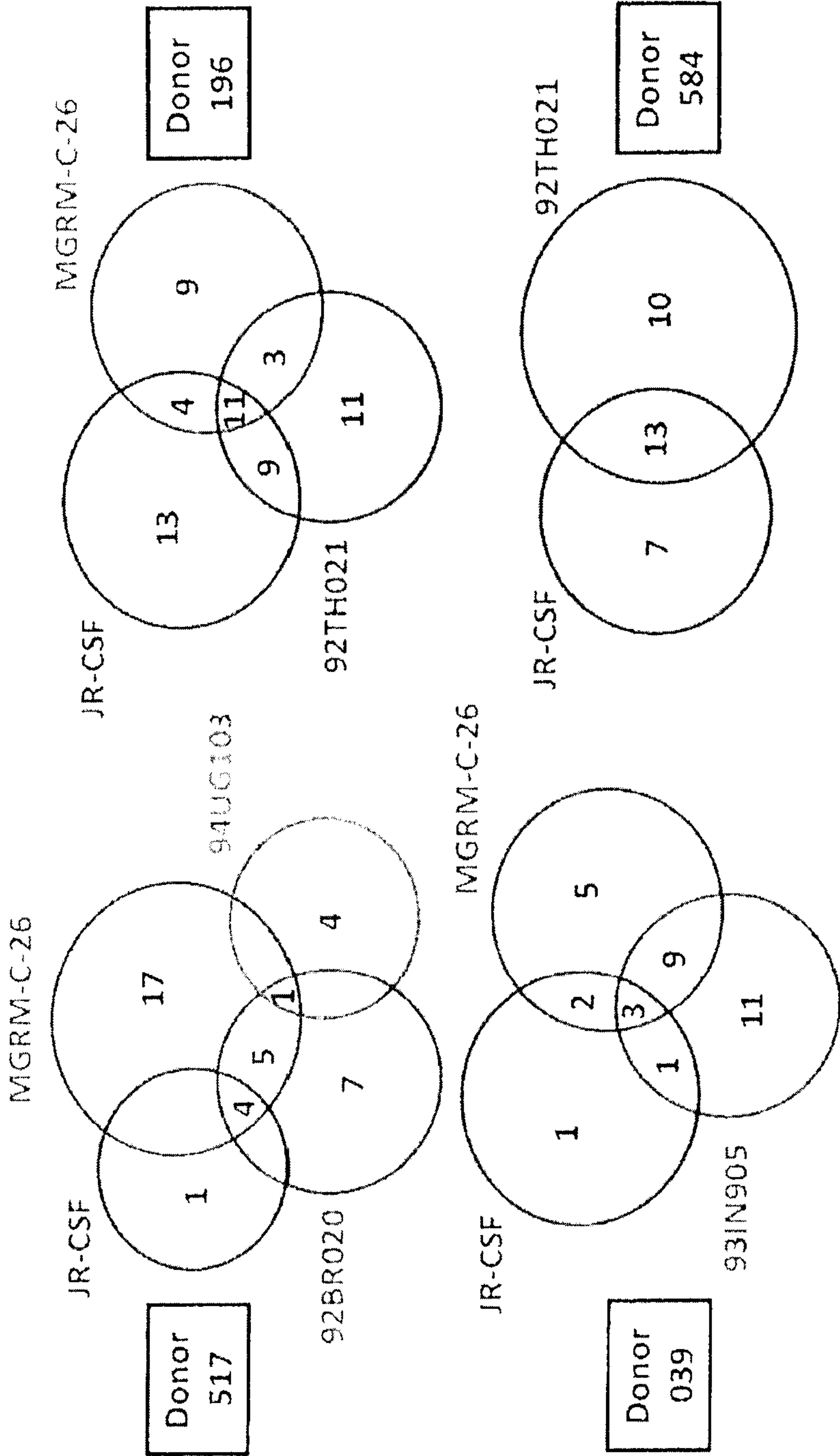
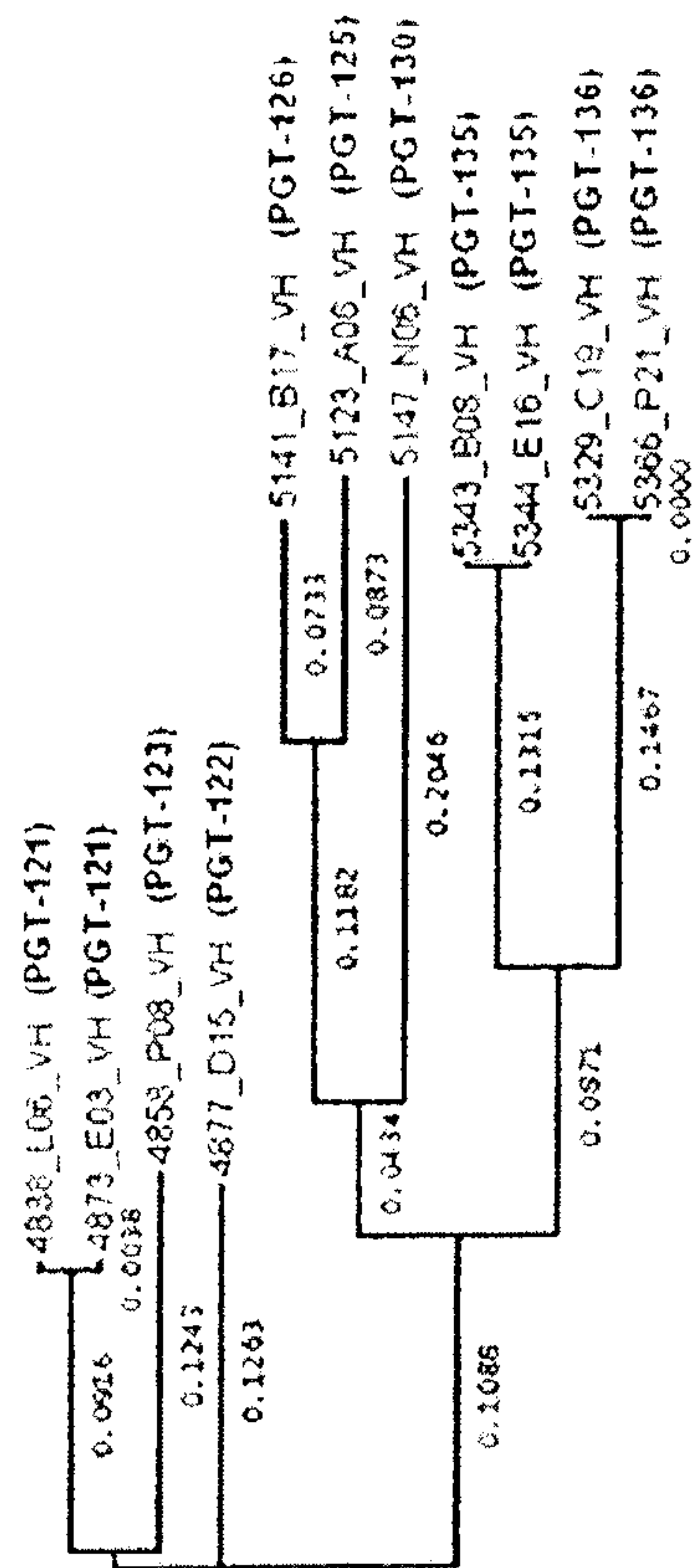


FIGURE 23

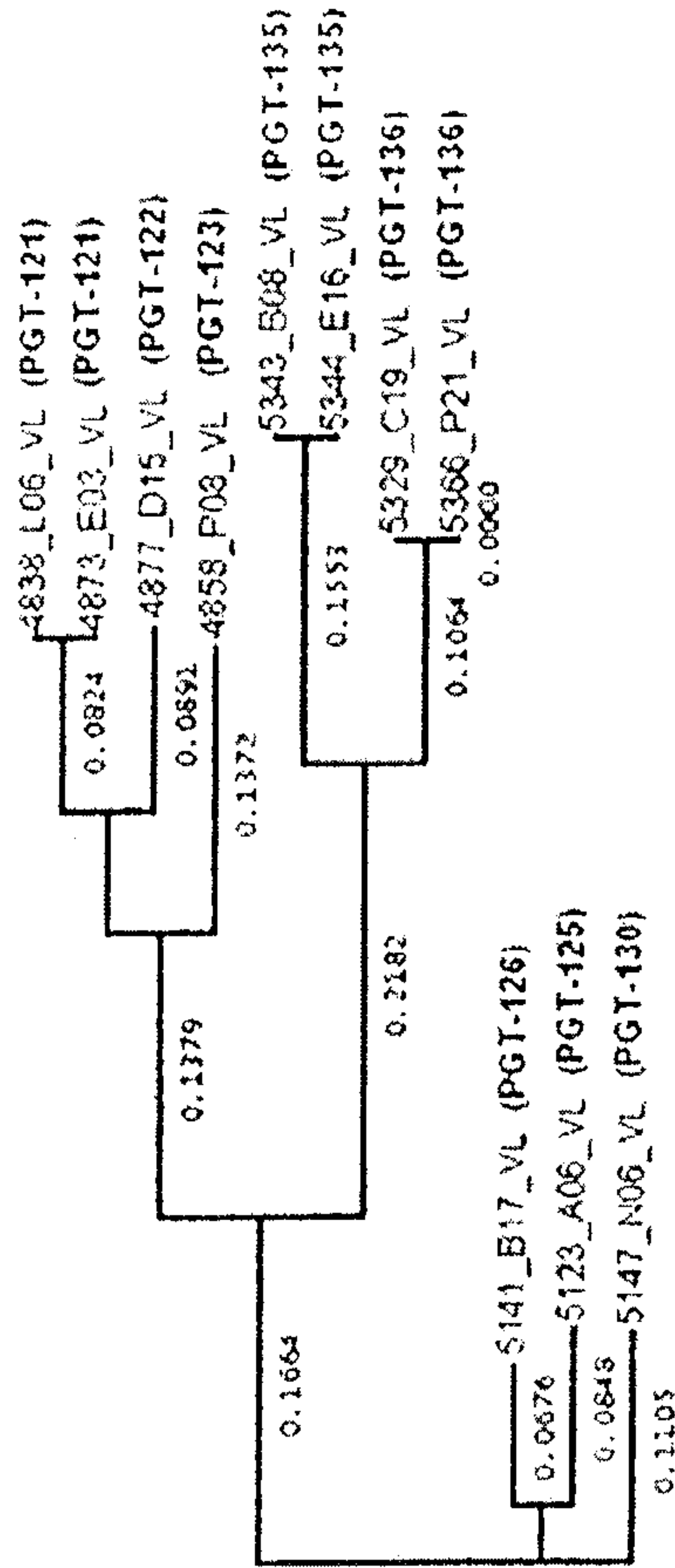
Heavy Chain Variable Gene Relationship Tree



I
0.03

FIGURE 24

Light Chain Variable Gene Relationship Tree



0.04

FIGURE 25

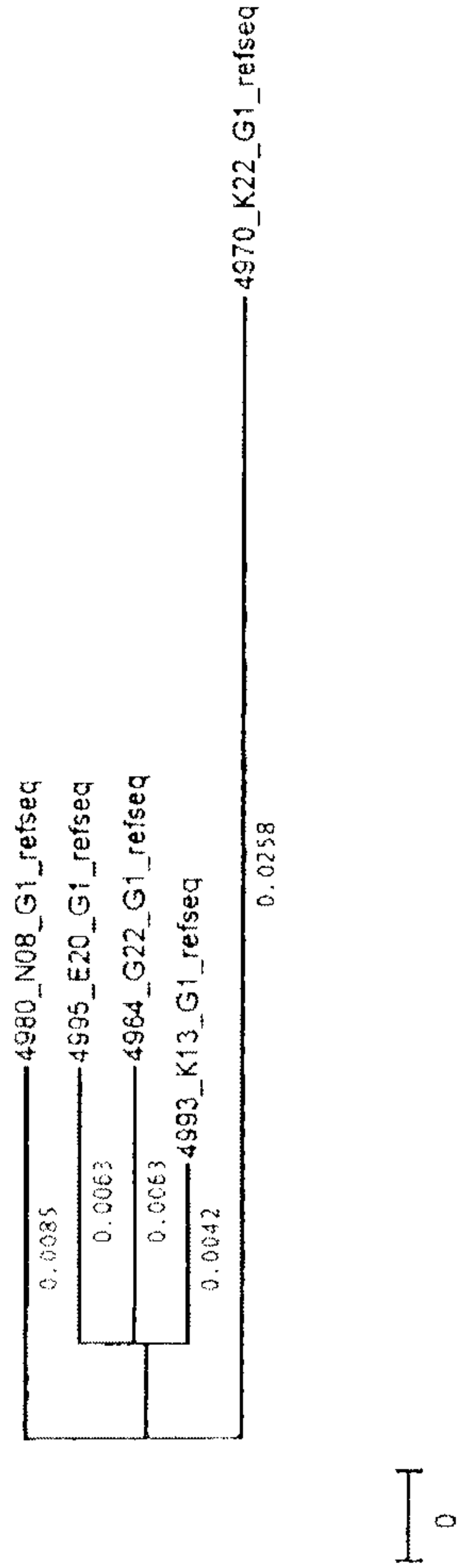
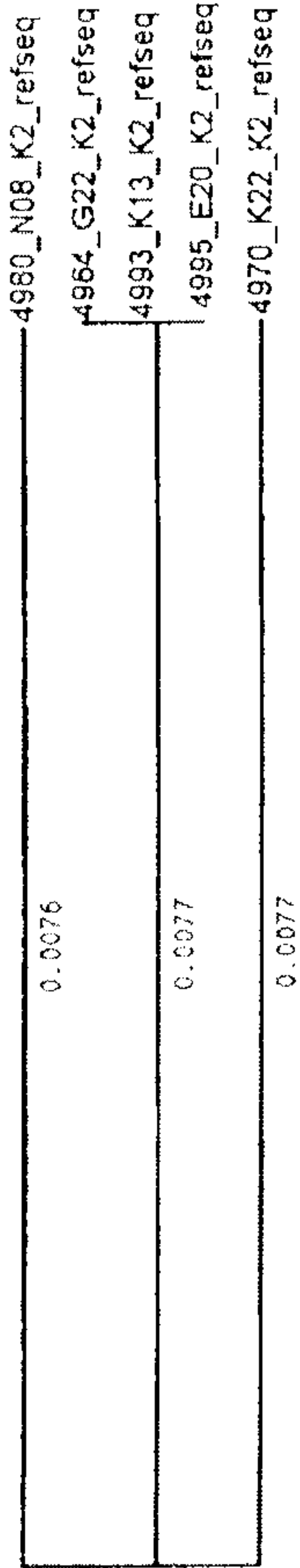


FIGURE 26



0

FIGURE 27

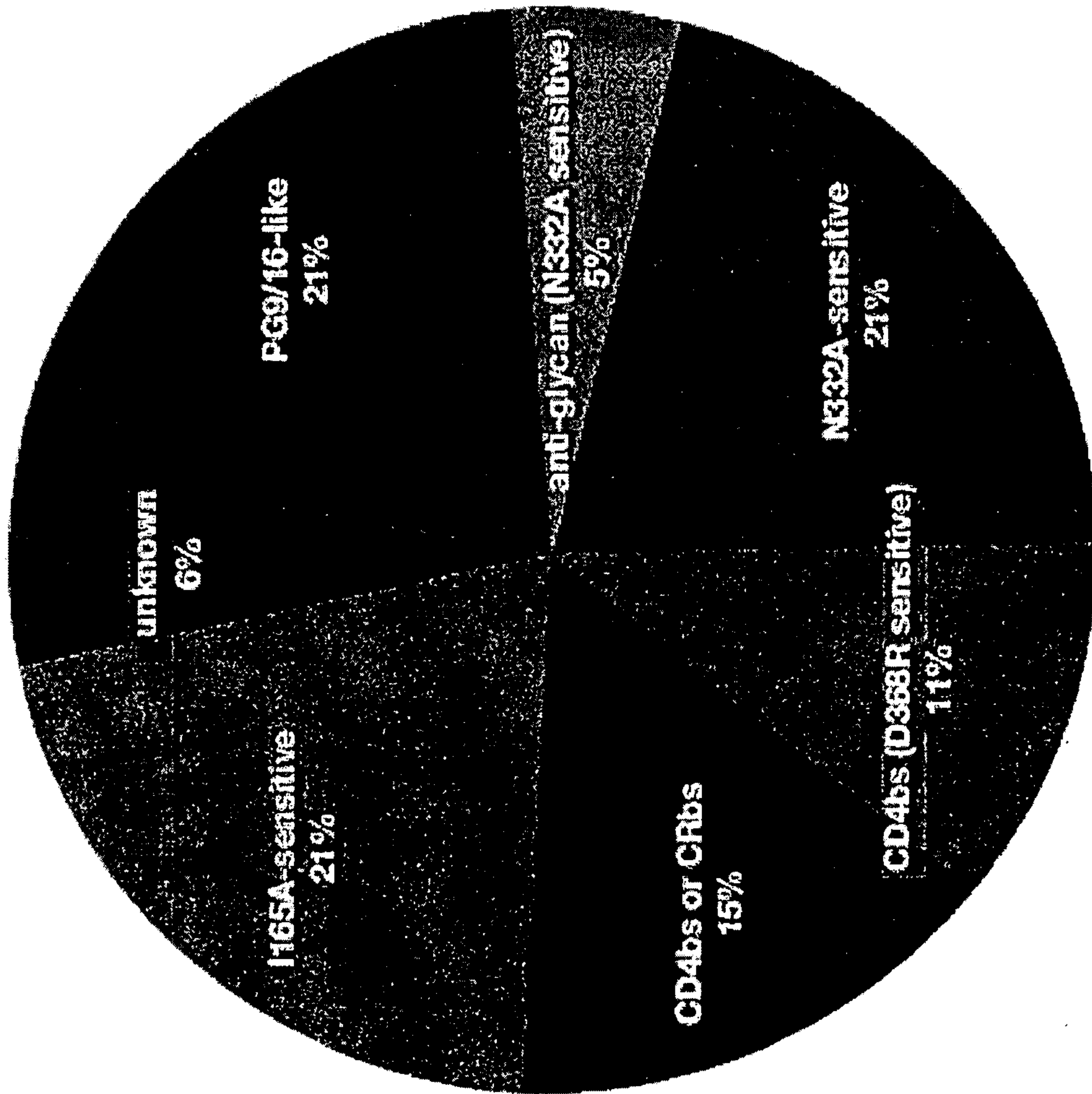


FIGURE 28

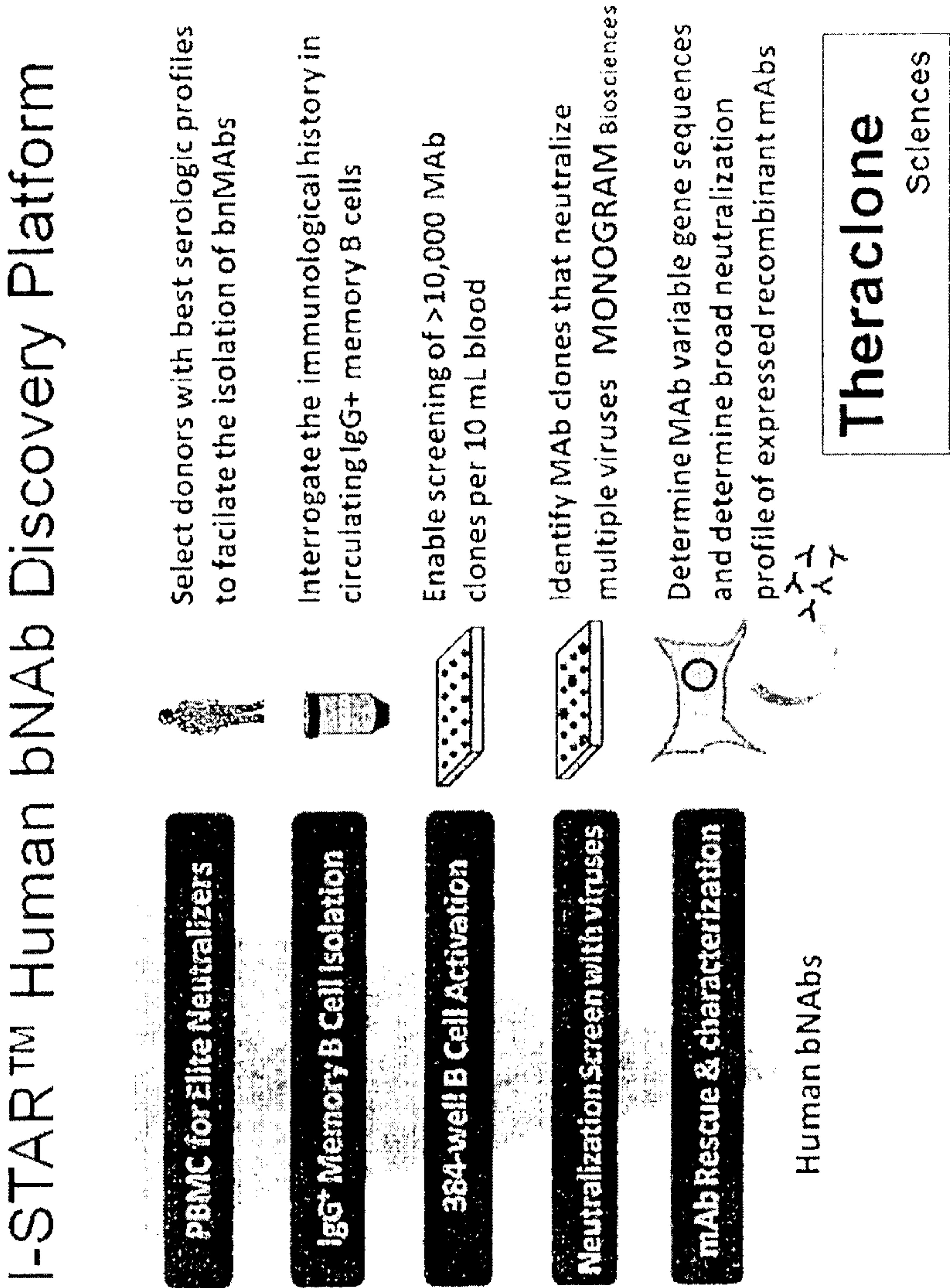


FIGURE 29

bnMAb Isolation from IgG⁺ Memory B Cells

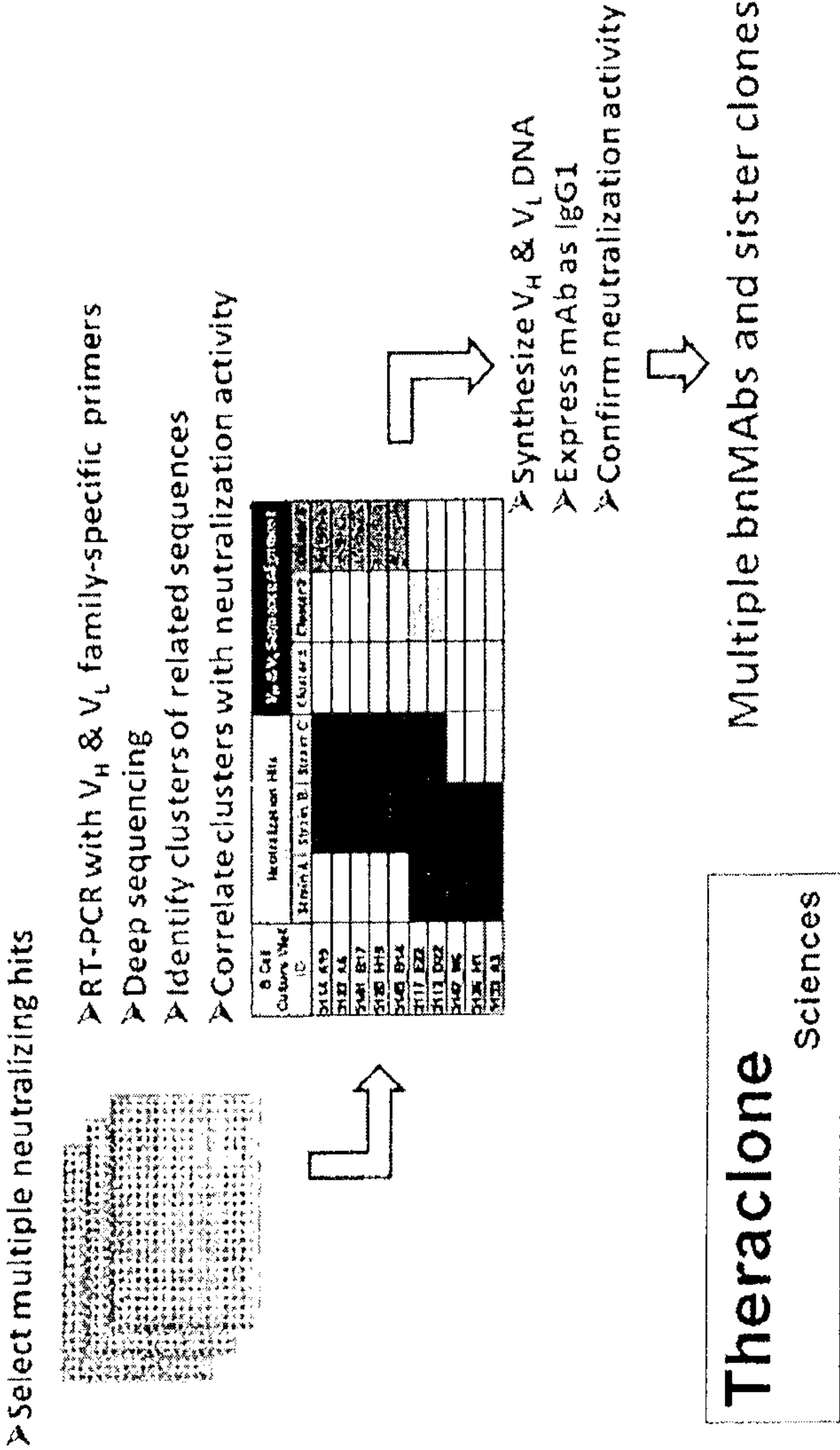
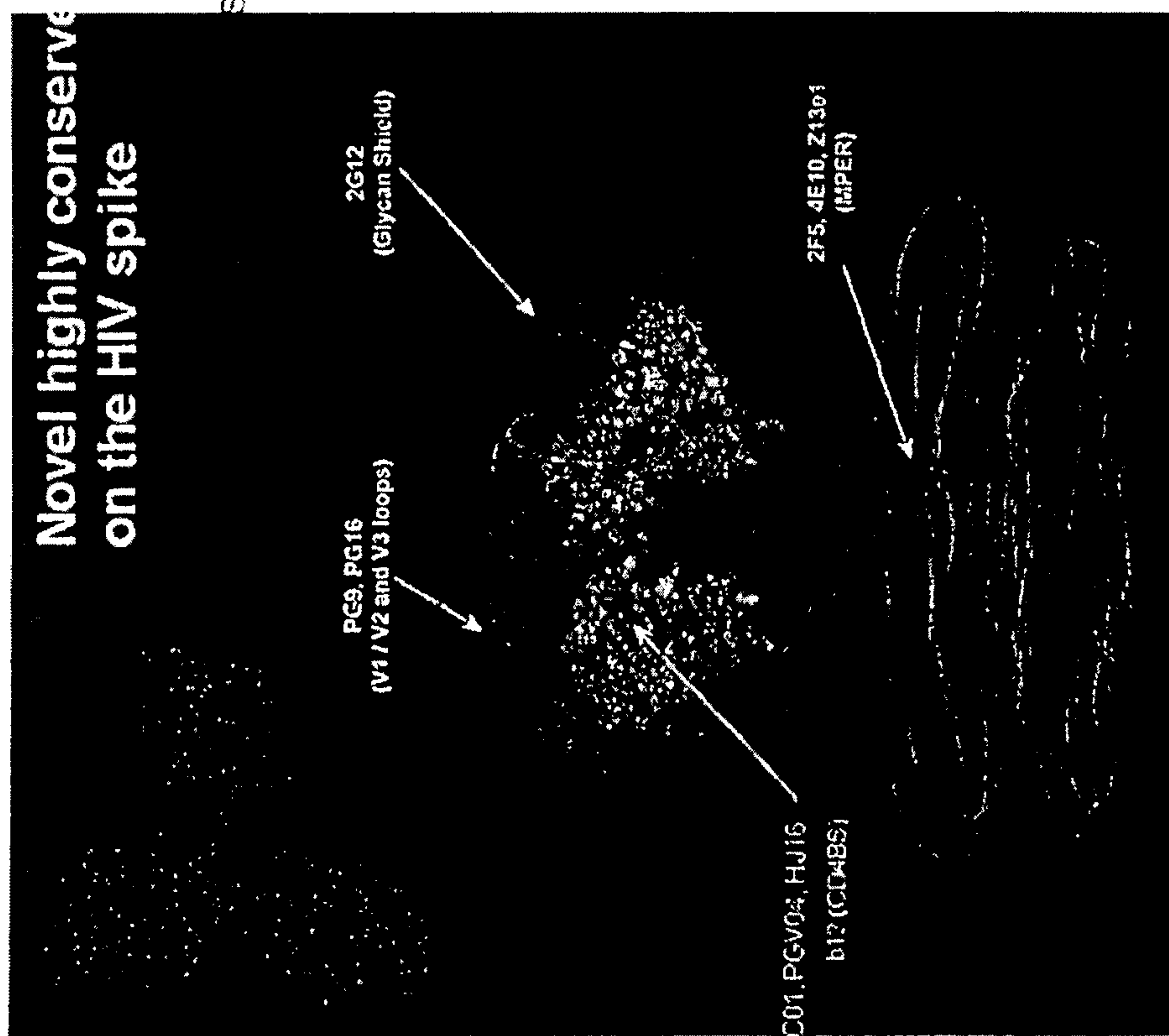


FIGURE 30



FIGURE 31



s 17, 36 and 39

FIGURE 32

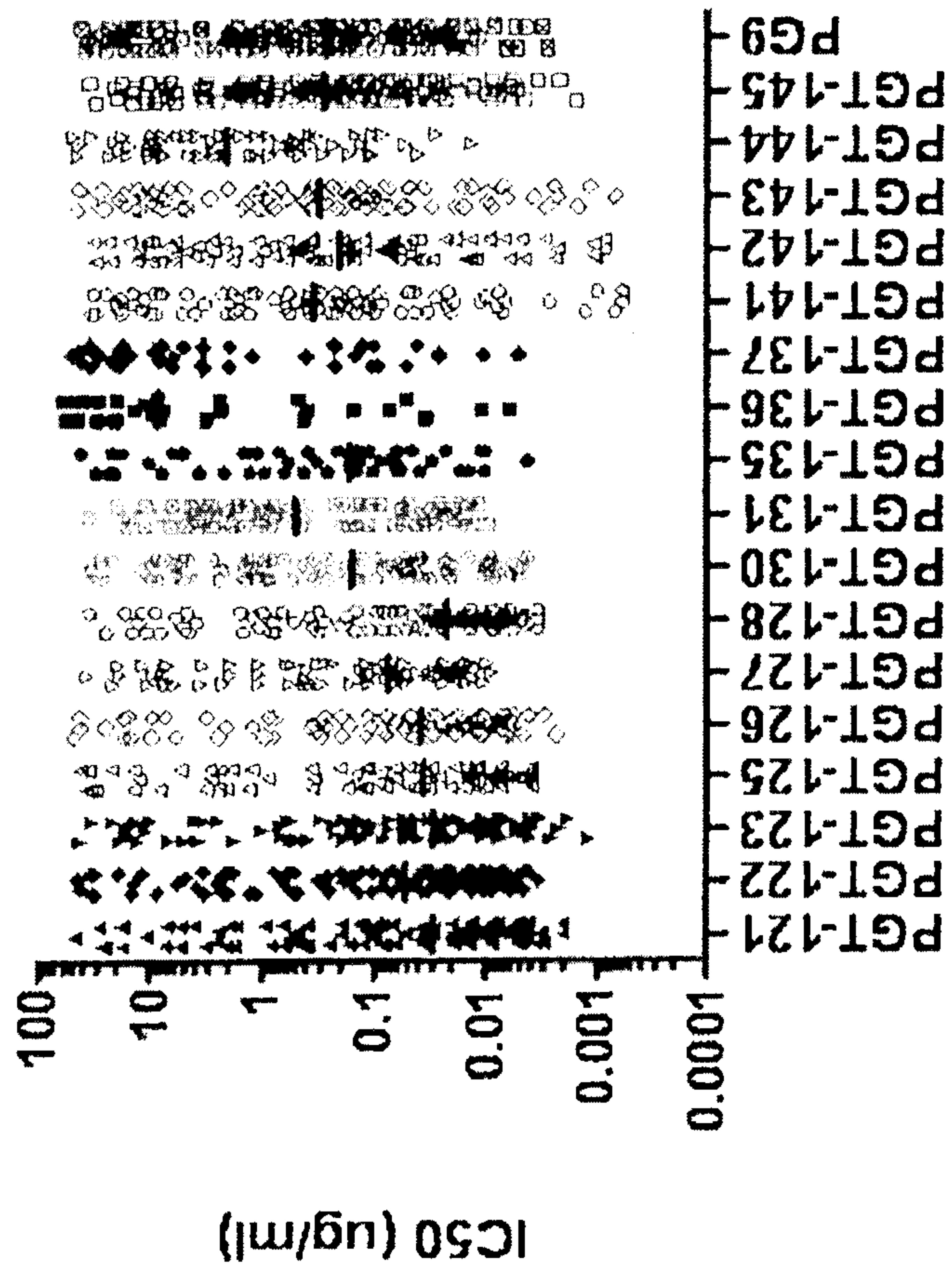
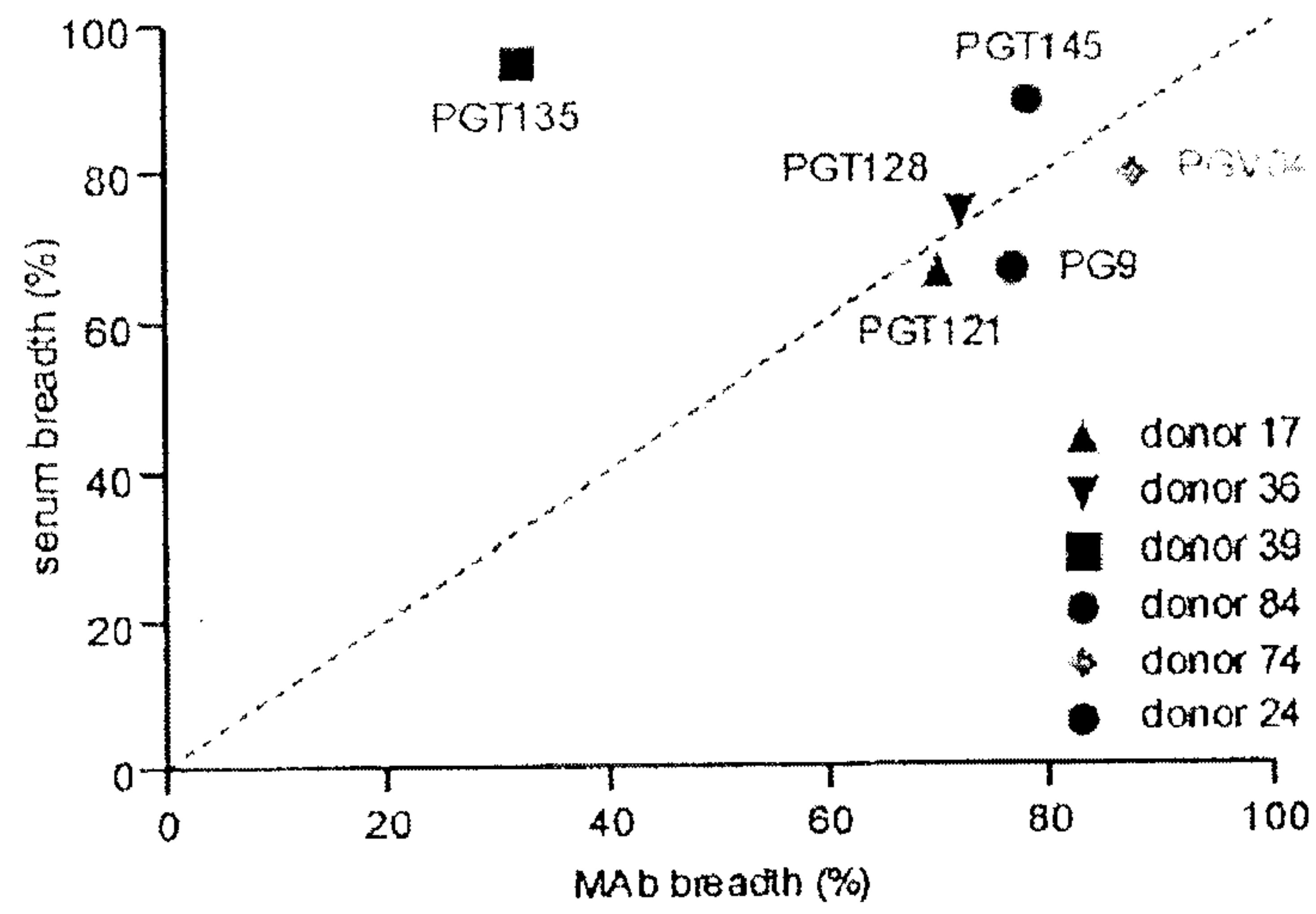


FIGURE 33

A



B

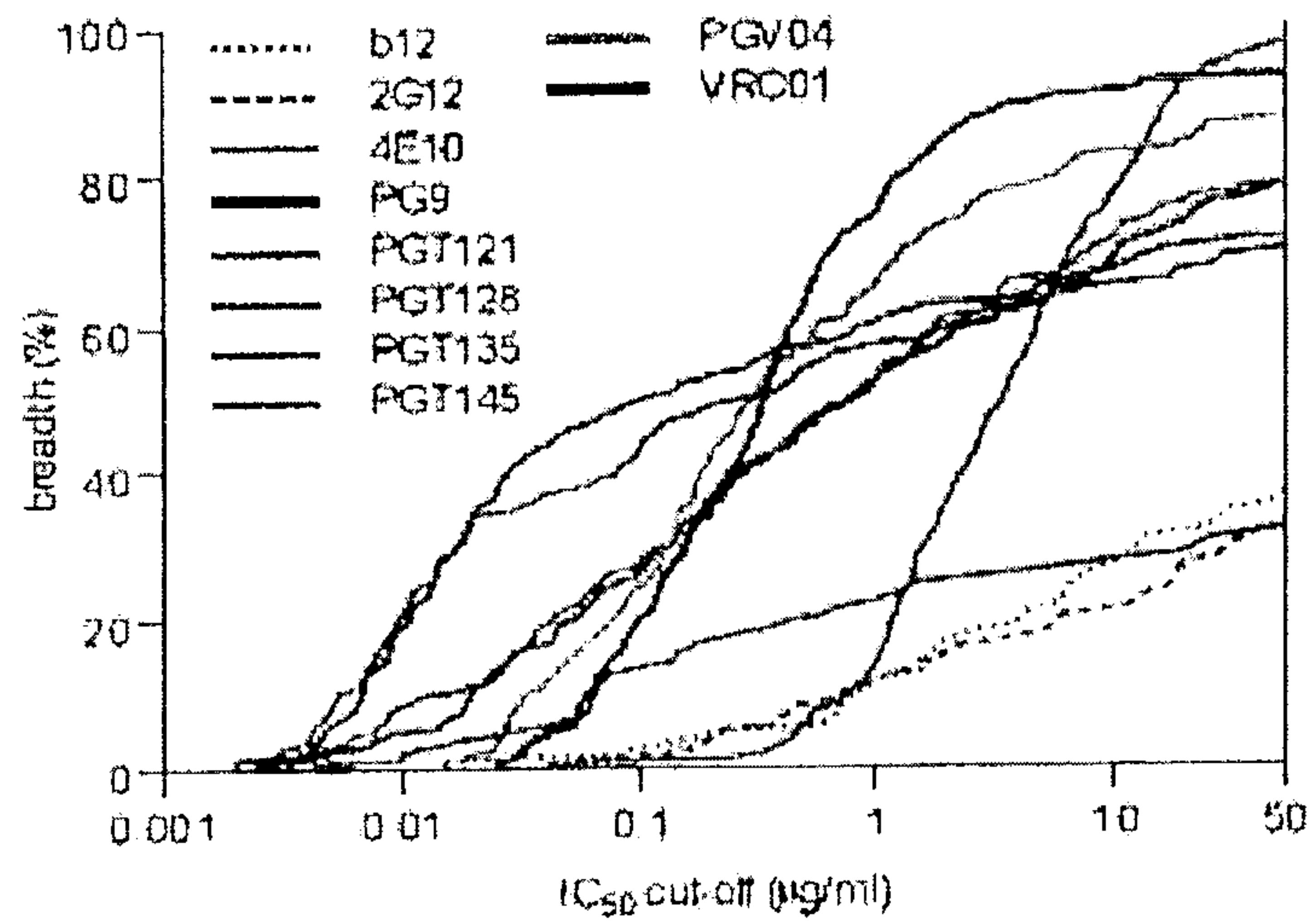
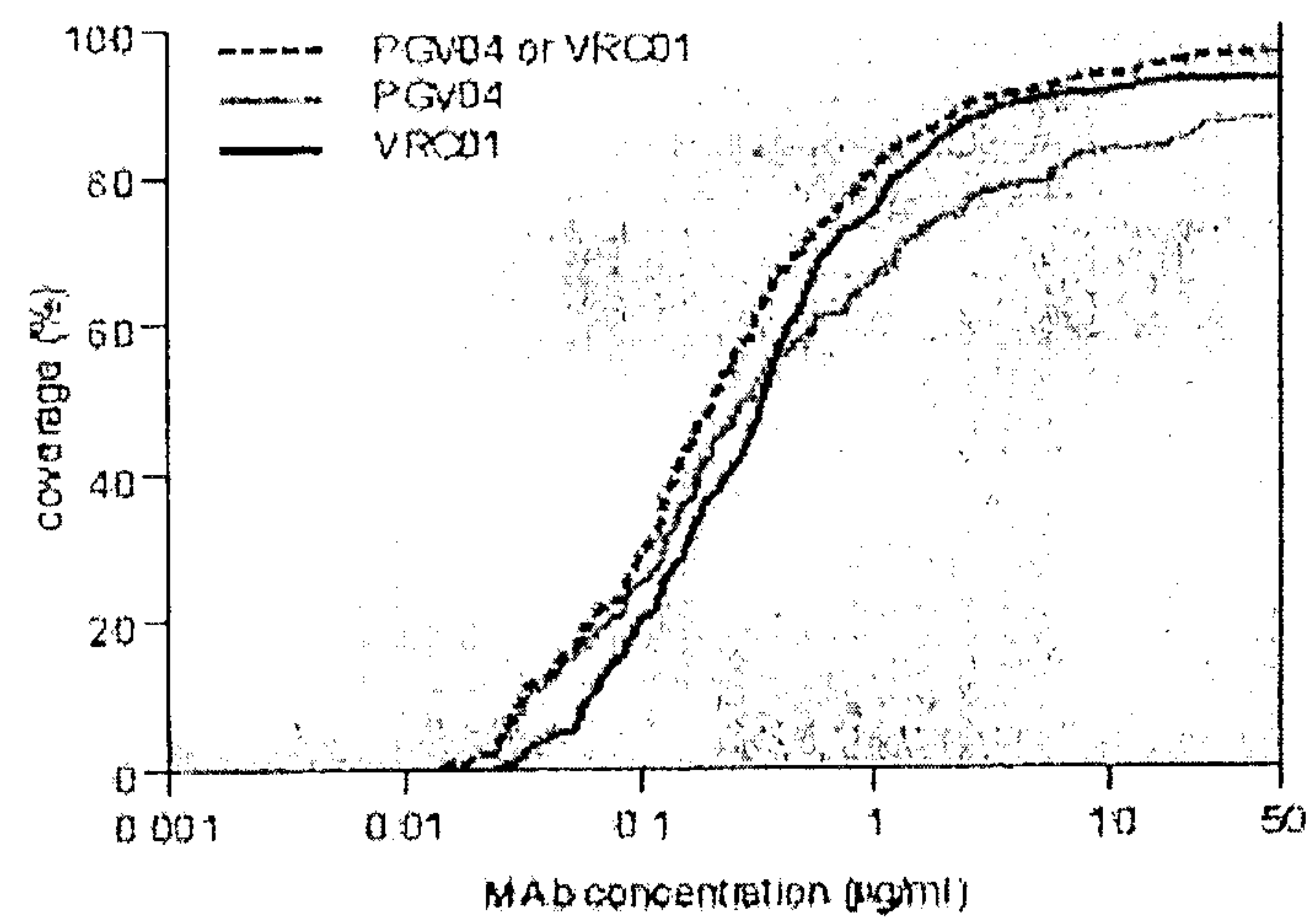


FIGURE 33

C



D

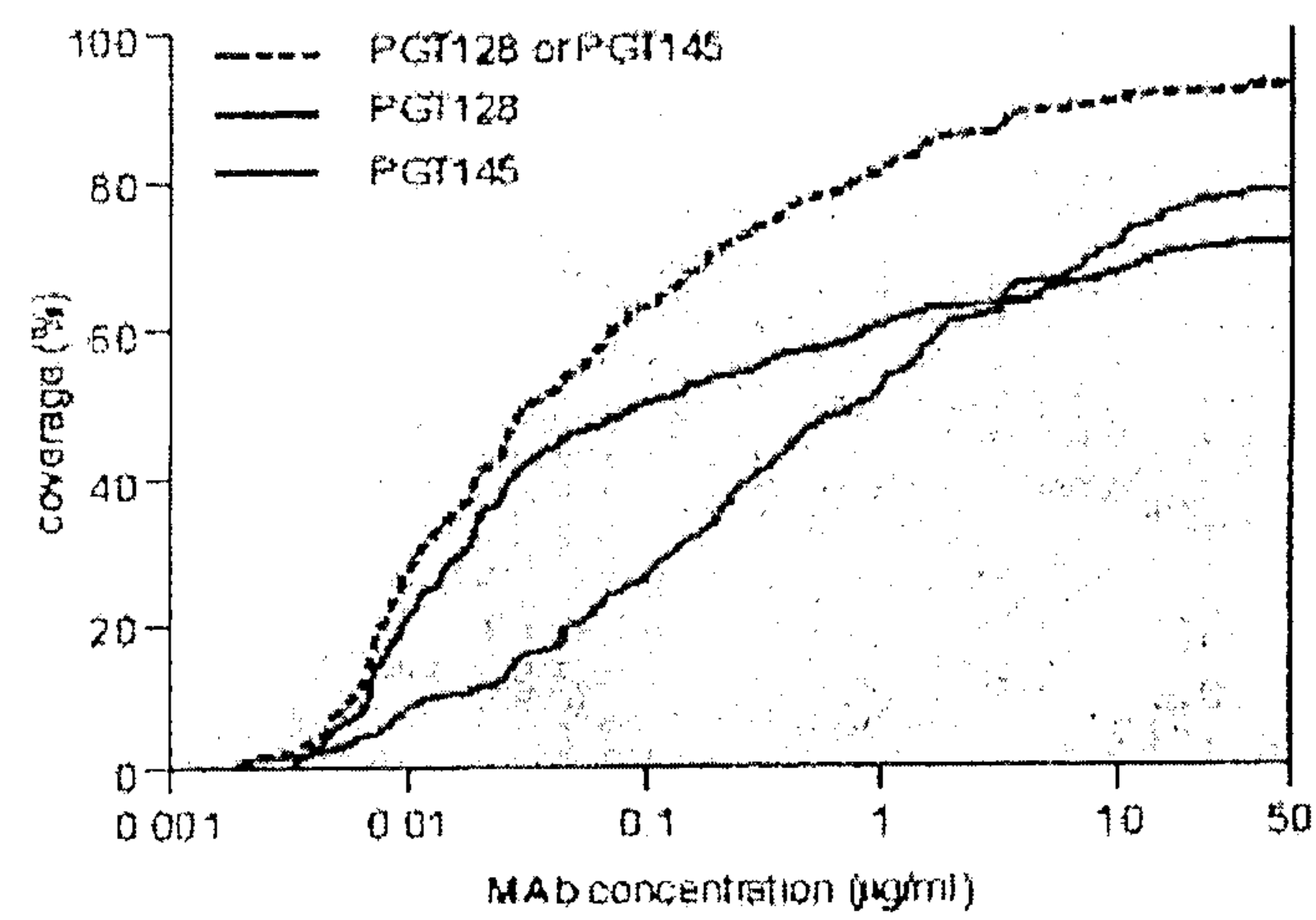


FIGURE 34

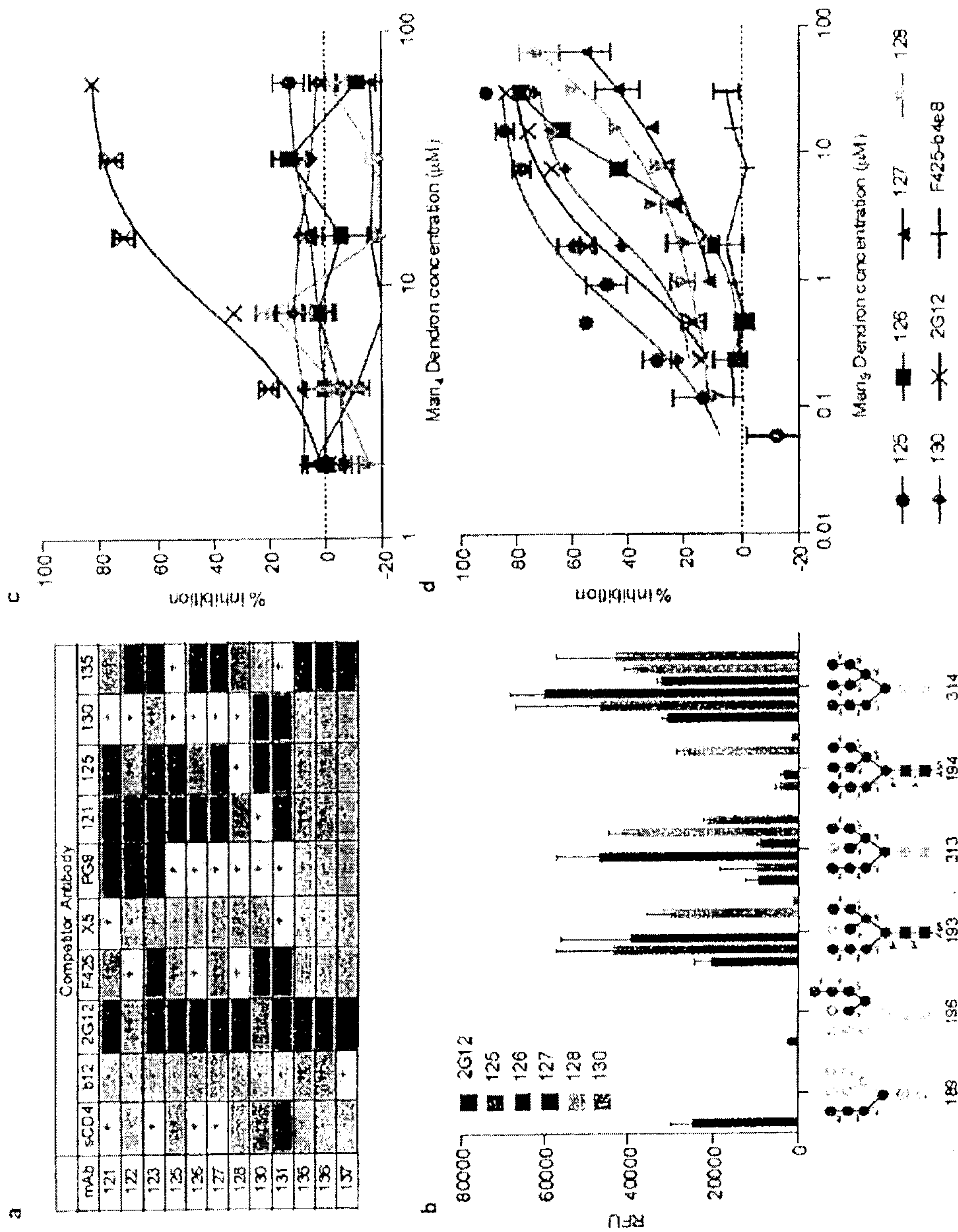


FIGURE 35

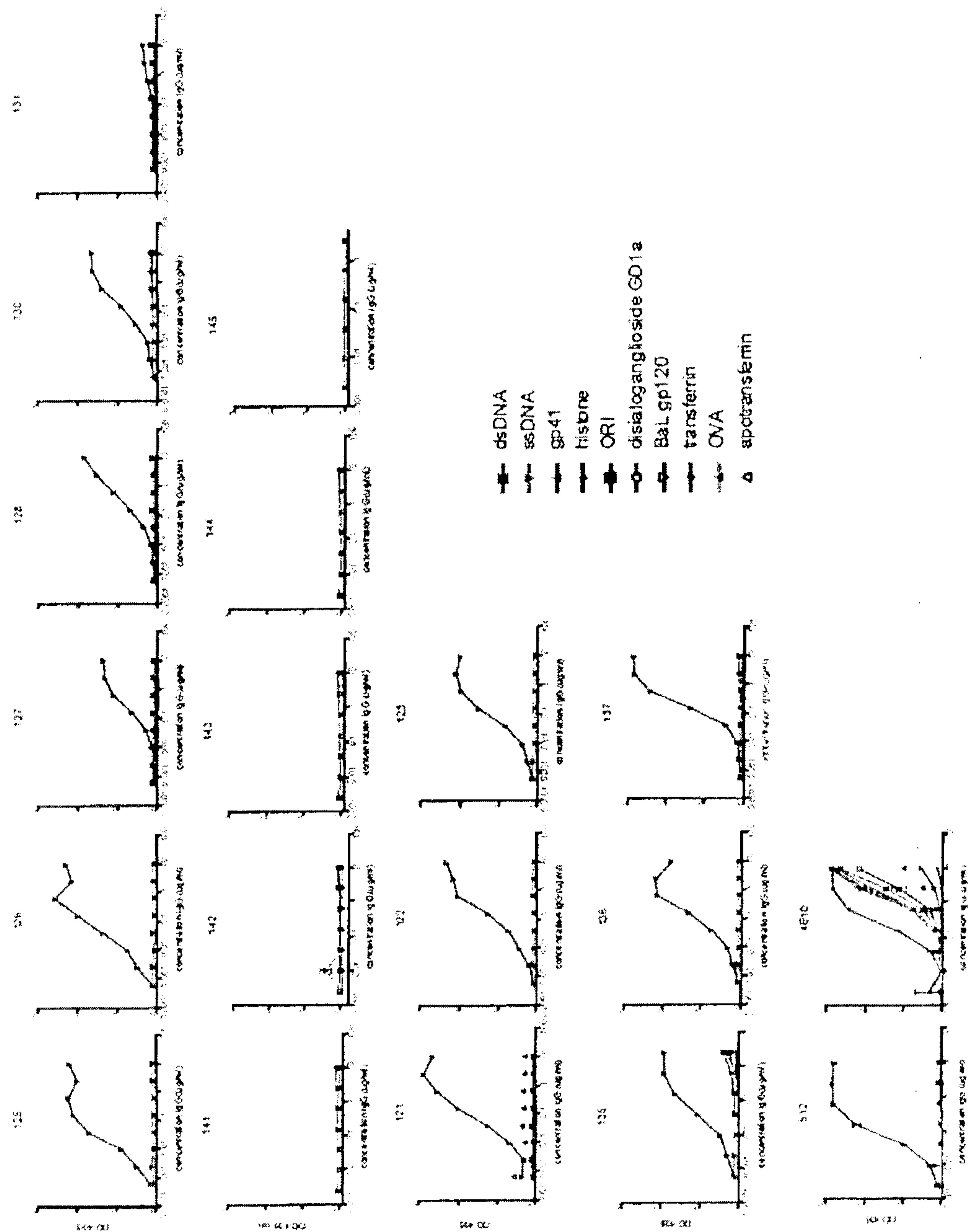


FIGURE 36

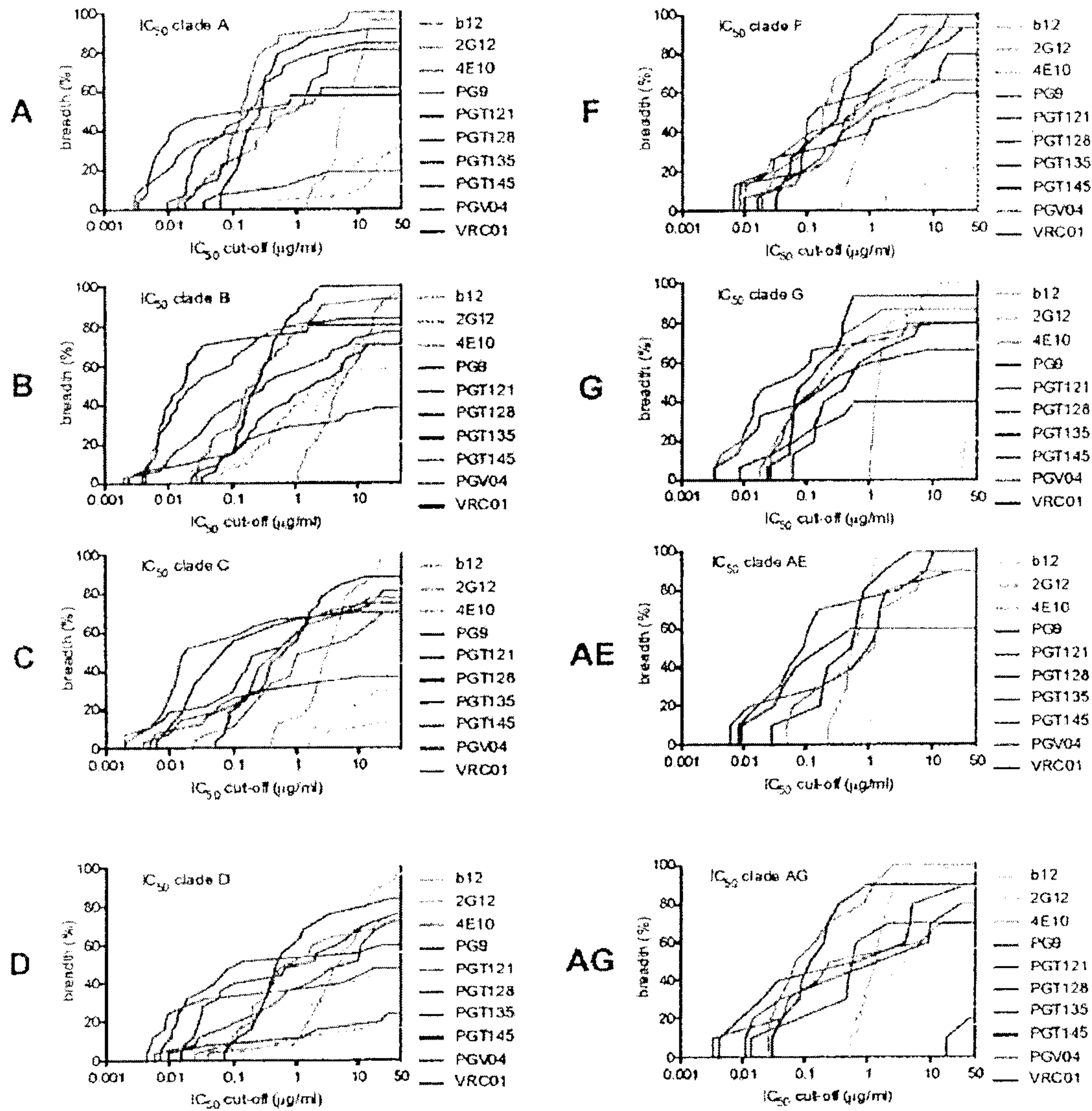


FIGURE 37

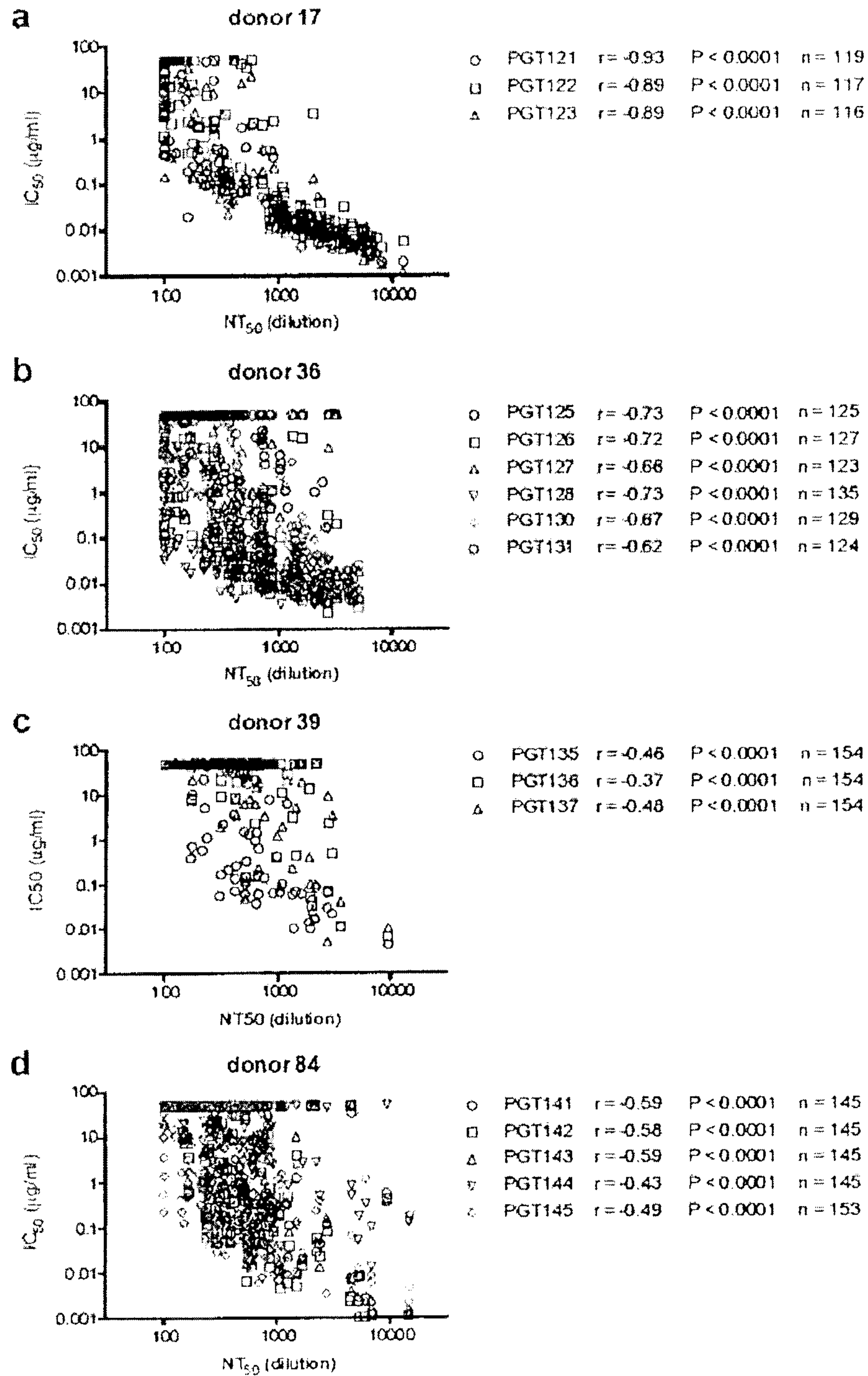


FIGURE 38

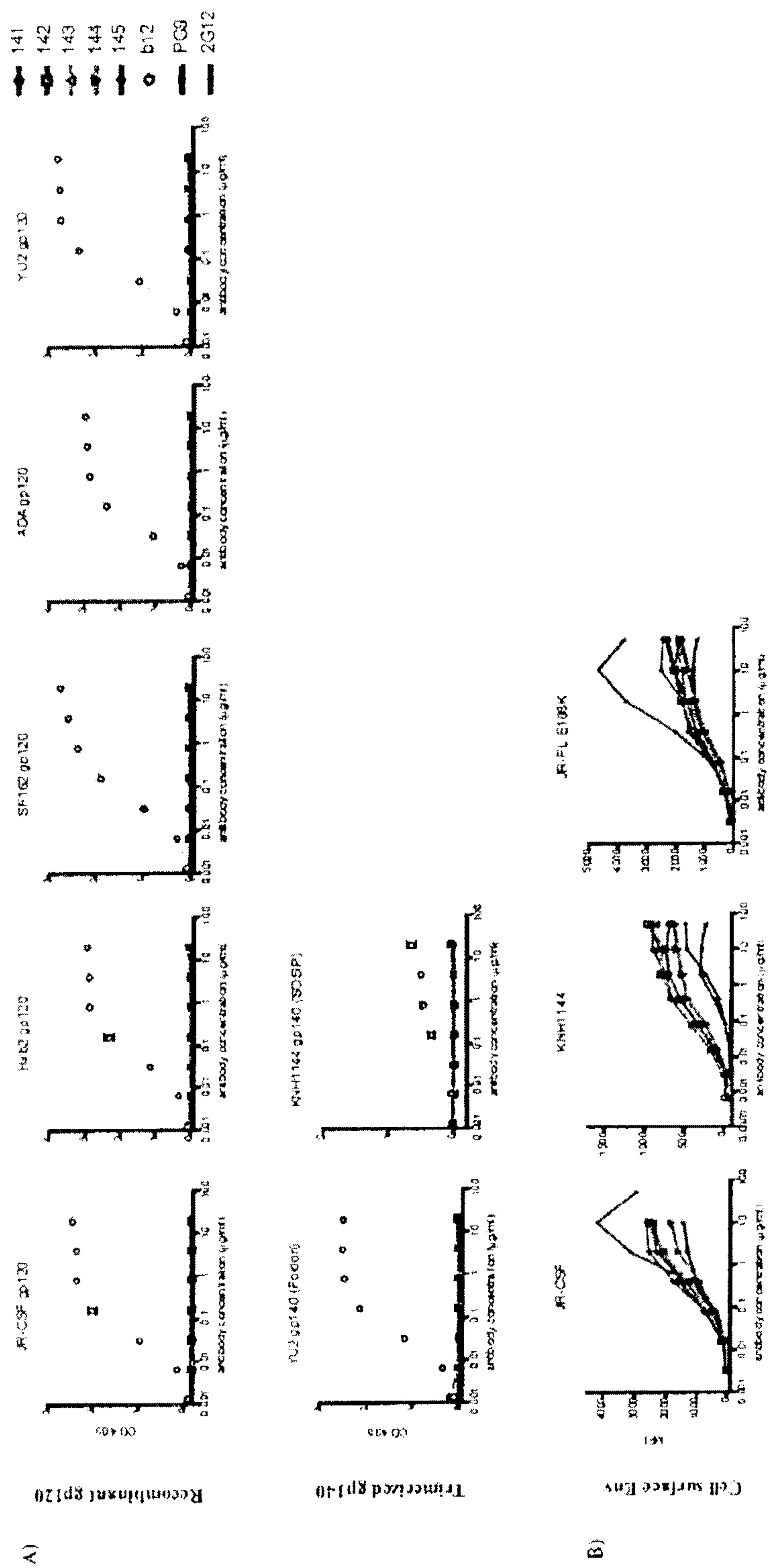


FIGURE 39

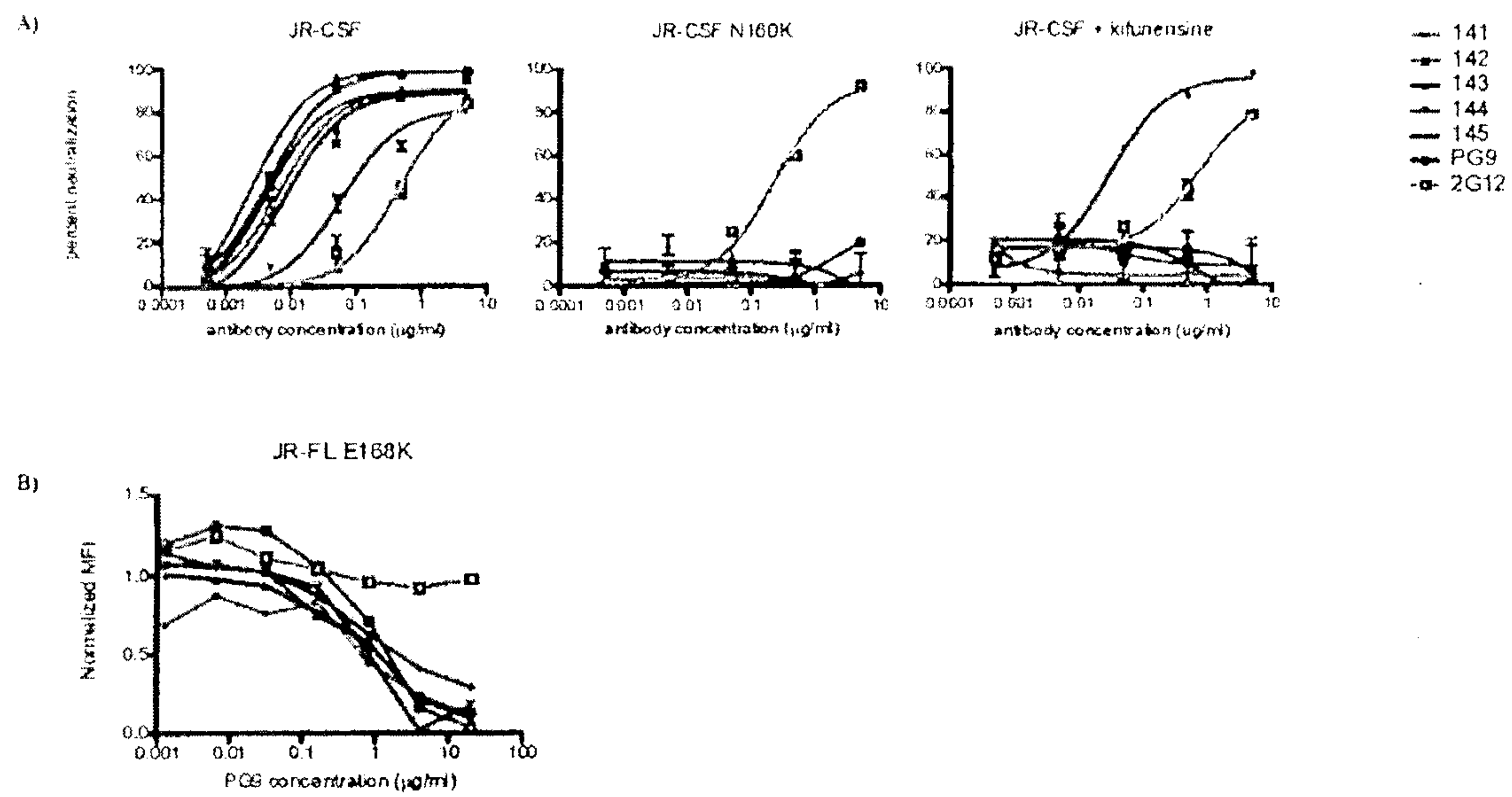


FIGURE 40

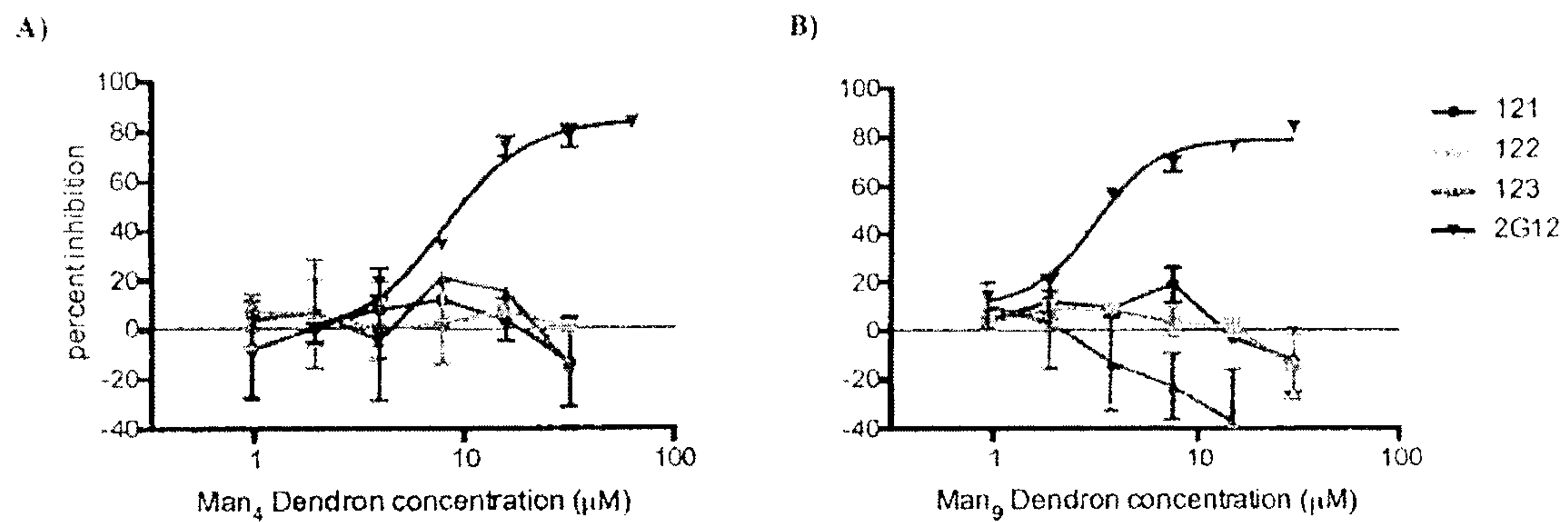


FIGURE 41

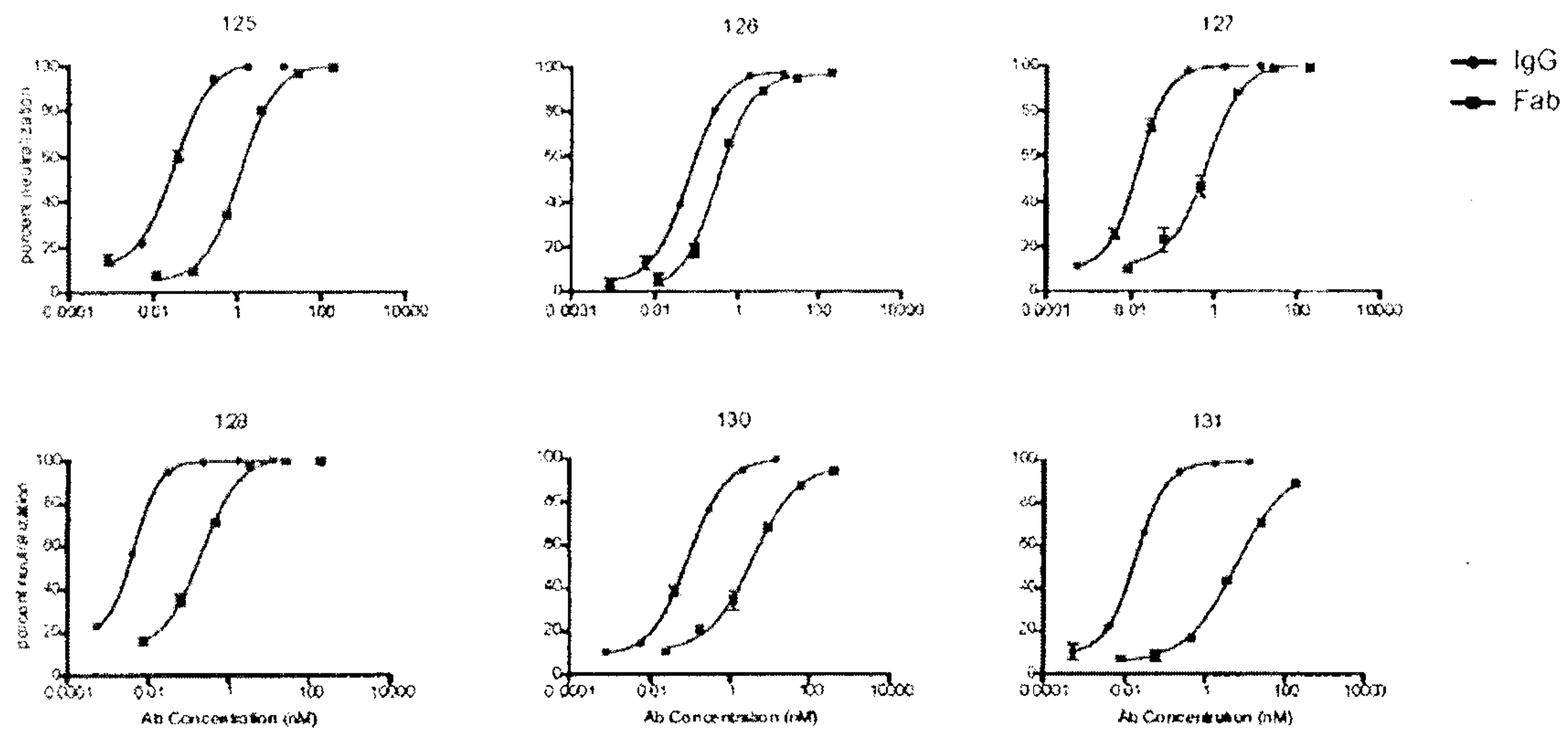


FIGURE 42

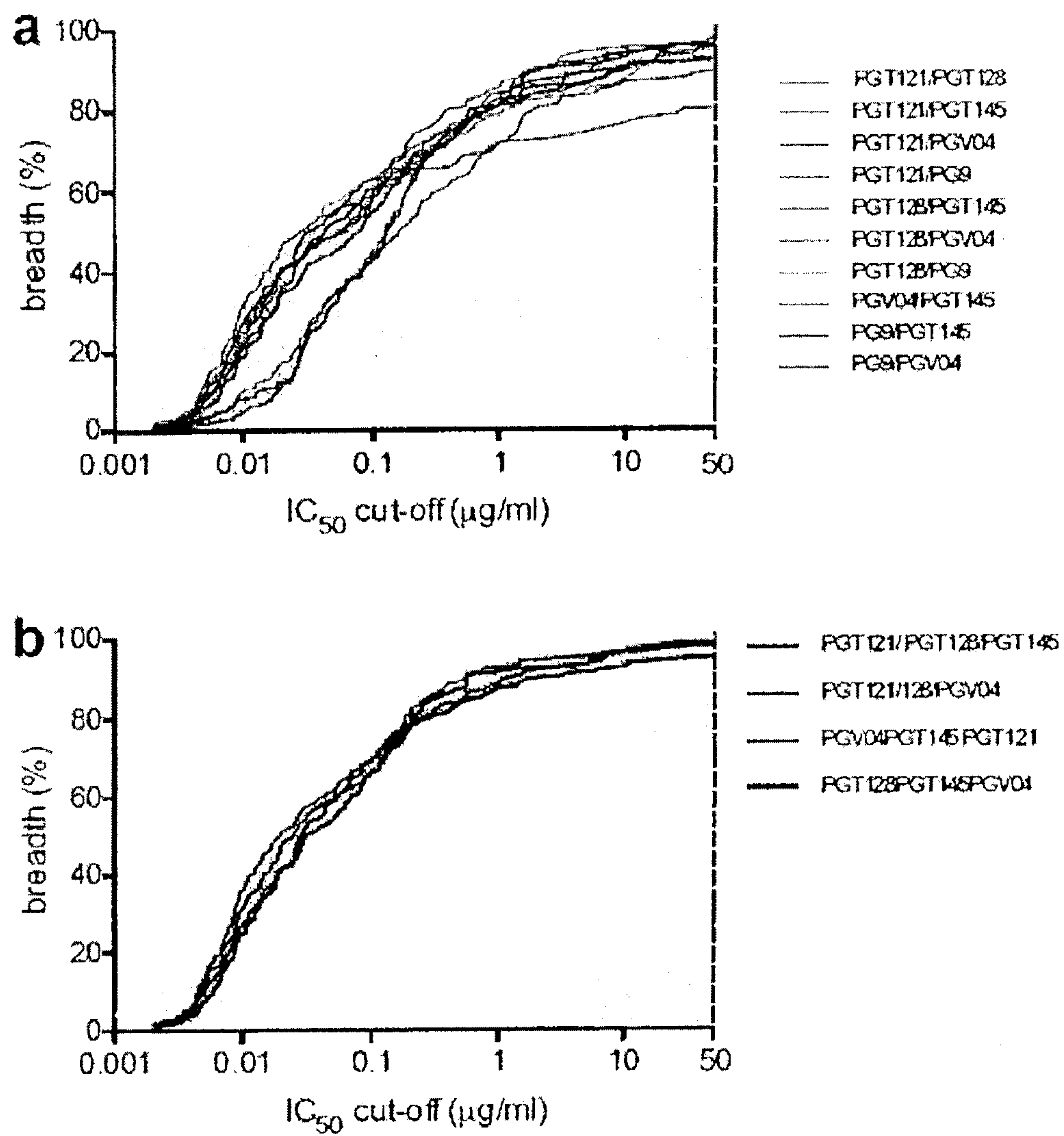


FIGURE 43

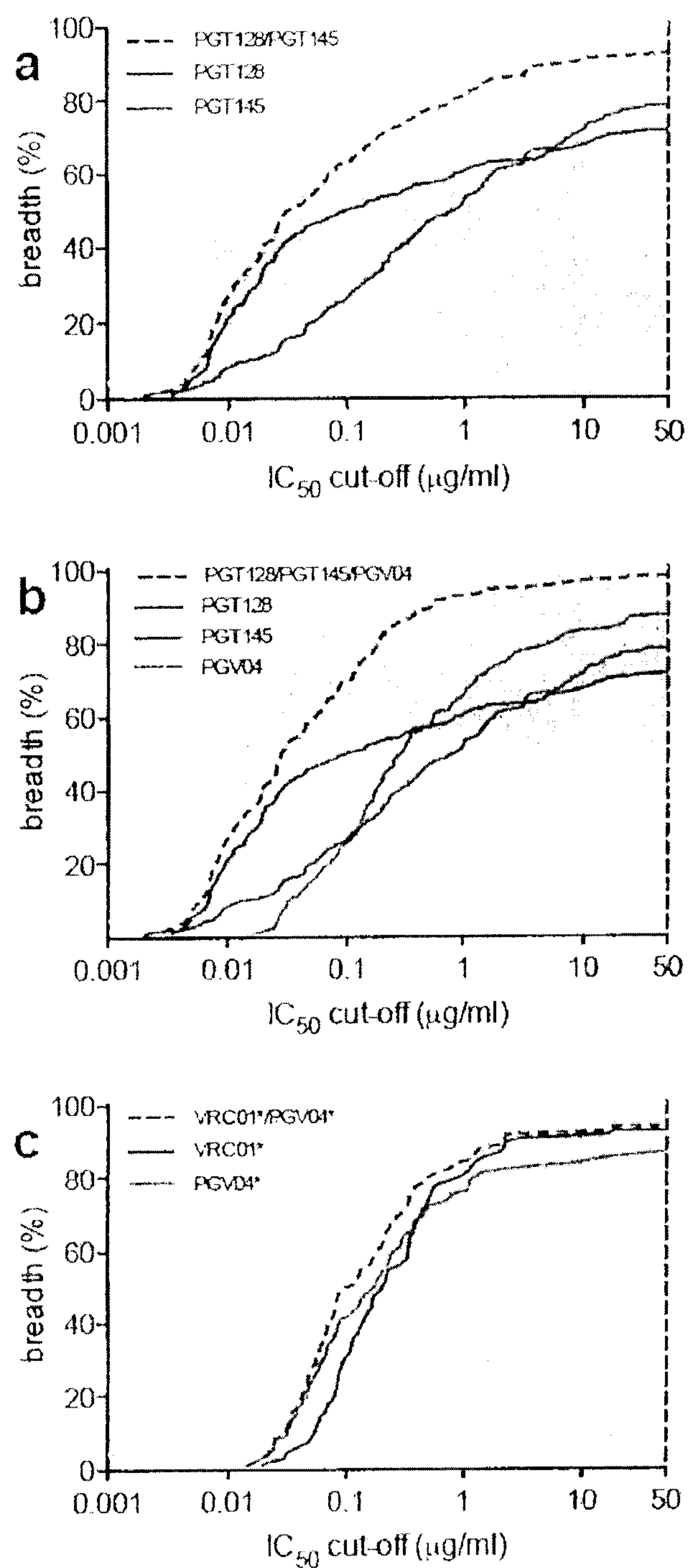


FIGURE 44

