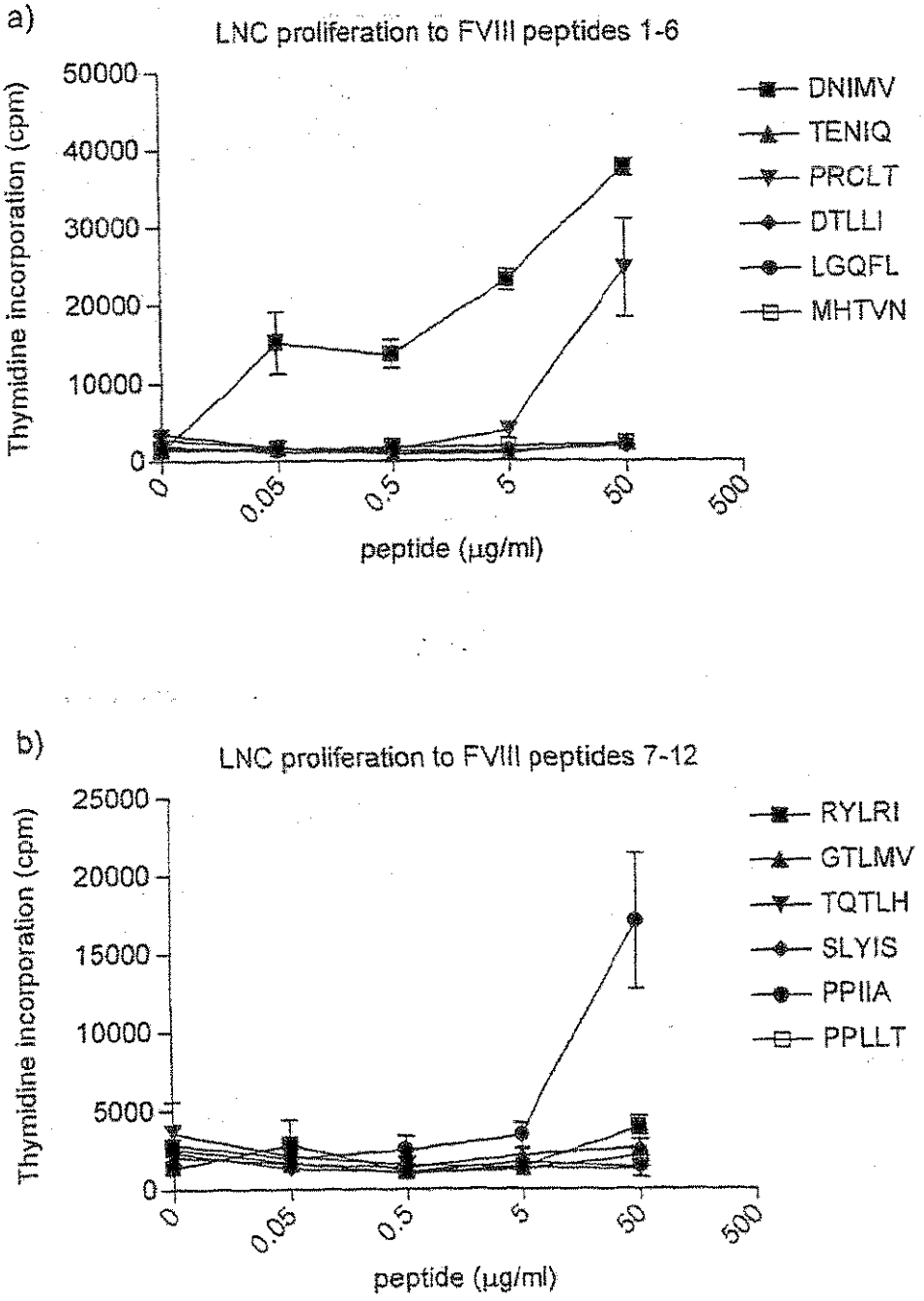

a)
LNC proliferation to FVIII peptides 1-6
Thymidine incorporation (cpm)
50000
40000
30000
20000
10000
0
0
0.05
0.5
5
50
500
peptide (µg/ml)
DNIMV
TENIQ
PRCLT
DTLLI
LGQFL
MHTVN
b)
LNC proliferation to FVIII peptides 7-12
Thymidine incorporation (cpm)
25000
20000
15000
10000
5000
0
0
0.05
0.5
5
50
500
peptide (µg/ml)
RYLRI
GTLMV
TQTLH
SLYIS
PPIIA
PPLLT

FIG. 1

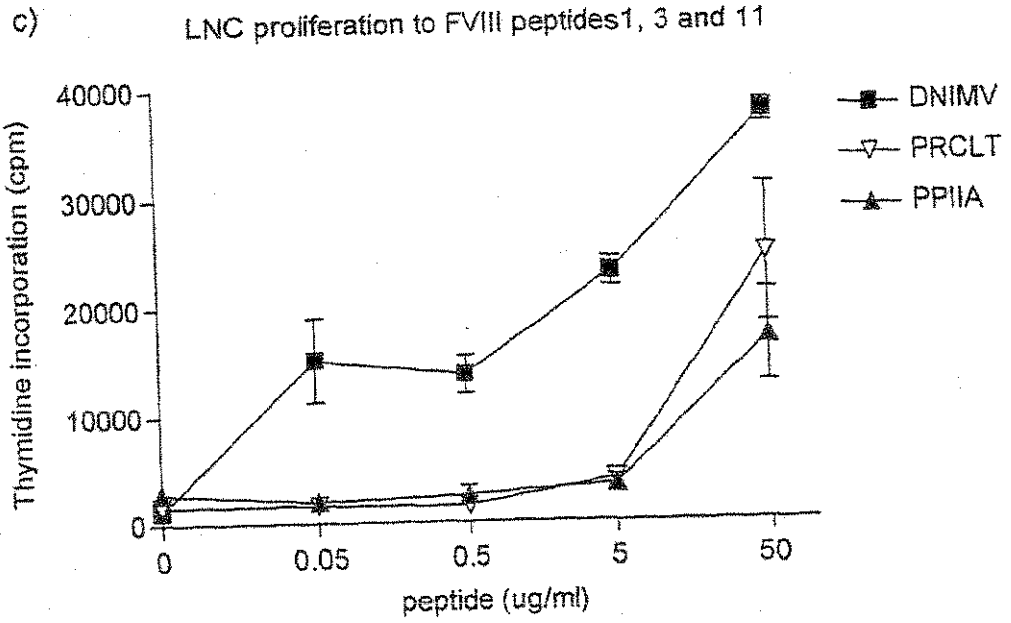

c)
LNC proliferation to FVIII peptides1, 3 and 11
Thymidine incorporation (cpm)
40000
30000
20000
10000
0
0
0.05
0.5
5
50
peptide (ug/ml)
DNIMV
PRCLT
PPIIA

FIG. 1 (cont'd)

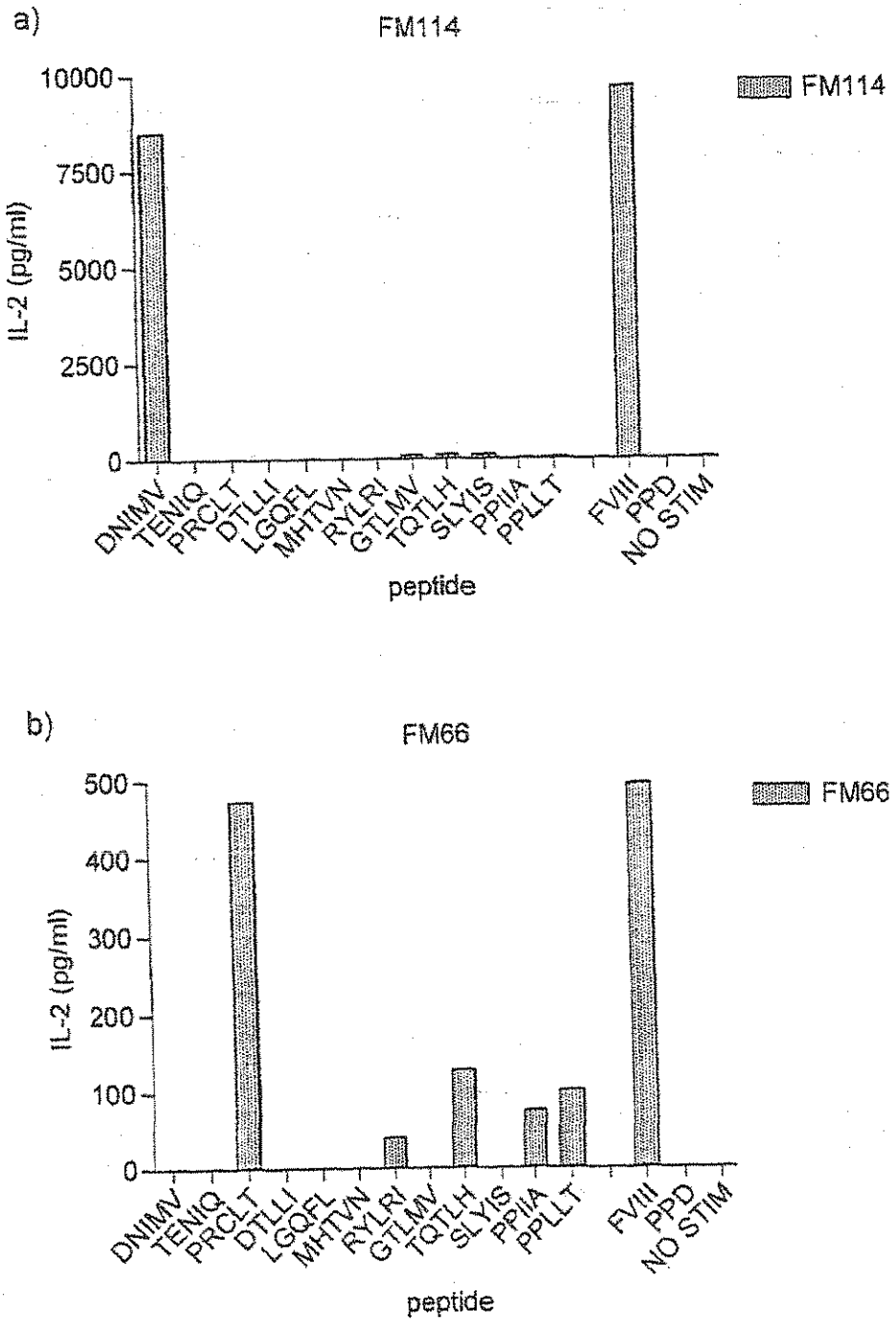

a)
FM114
10000
7500
5000
2500
0
IL-2 (pg/ml)
FM114
DNIMV
TENIQ
PRCLT
DTLLI
LGQFL
MHTVN
RYLRI
GTLMV
TQTLH
SLYIS
PPIIA
PPLLT
FVIII
PPD
NO STIM
peptide
b)
FM66
500
400
300
200
100
0
IL-2 (pg/ml)
FM66
DNIMV
TENIQ
PRCLT
DTLLI
LGQFL
MHTVN
RYLRI
GTLMV
TQTLH
SLYIS
PPIIA
PPLLT
FVIII
PPD
NO STIM
peptide

FIG. 2

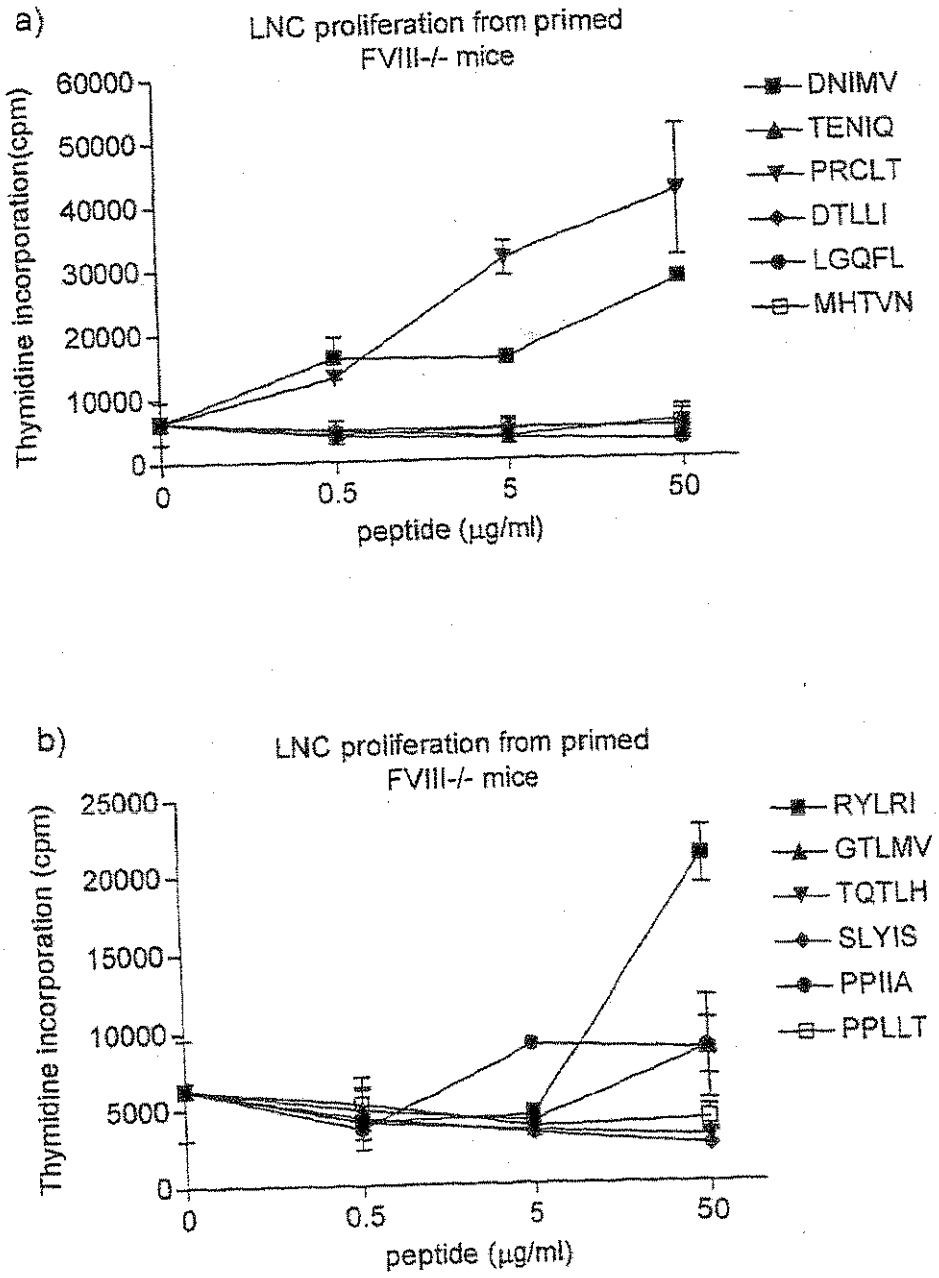

a)
LNC proliferation from primed FVIII-/- mice
Thymidine incorporation(cpm)
60000
50000
40000
30000
20000
10000
0
0
0.5
5
50
peptide (µg/ml)
DNIMV
TENIQ
PRCLT
DTLLI
LGQFL
MHTVN
b)
LNC proliferation from primed FVIII-/- mice
Thymidine incorporation (cpm)
25000
20000
15000
10000
5000
0
0
0.5
5
50
peptide (µg/ml)
RYLRI
GTLMV
TQTLH
SLYIS
PPIIA
PPLLT

FIG. 3

c)

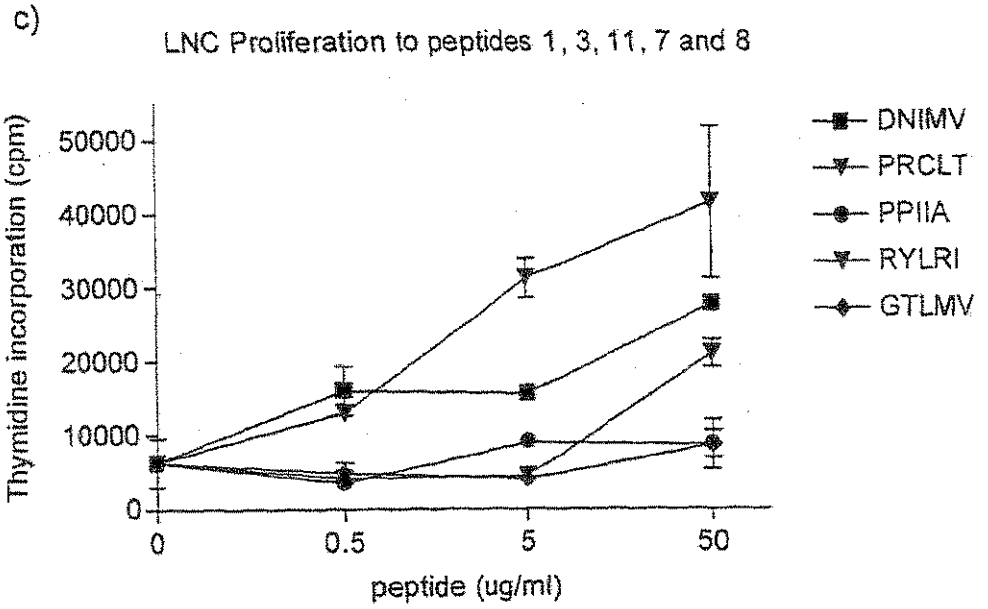

LNC Proliferation to peptides 1, 3, 11, 7 and 8
Thymidine incorporation (cpm)
50000
40000
30000
20000
10000
0
0
0.5
5
50
peptide (ug/ml)
DNIMV
PRCLT
PPIIA
RYLRI
GTLMV

FIG. 3(cont'd)

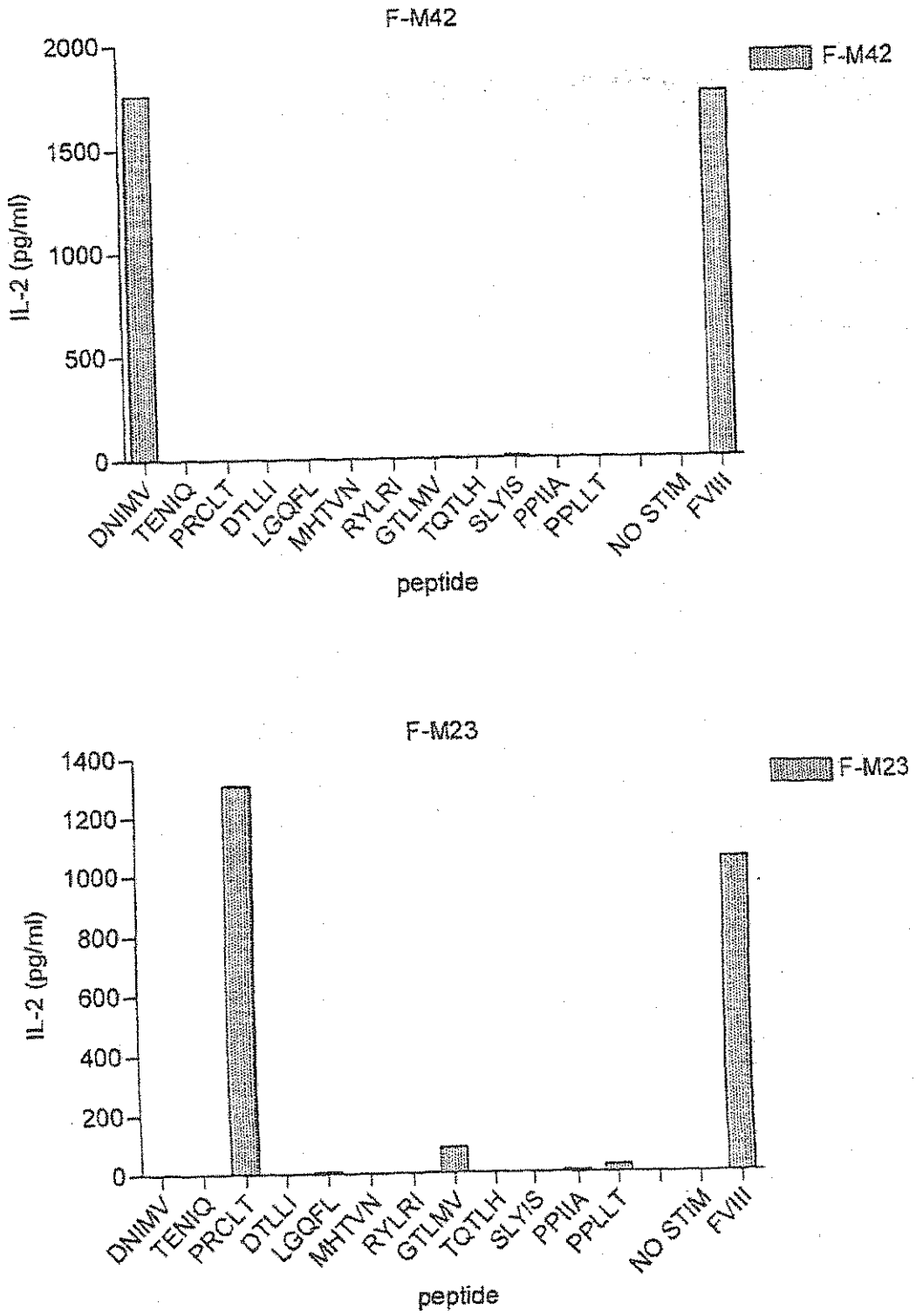

F-M42
F-M42
2000
1500
1000
500
0
IL-2 (pg/ml)
DNIMV
TENIQ
PRCLT
DTLLI
LGQFL
MHTVN
RYLRI
GTLMV
TQTLH
SLYIS
PPIIA
PPLLT
NO STIM
FVIII
peptide
F-M23
F-M23
1400
1200
1000
800
600
400
200
0
IL-2 (pg/ml)
DNIMV
TENIQ
PRCLT
DTLLI
LGQFL
MHTVN
RYLRI
GTLMV
TQTLH
SLYIS
PPIIA
PPLLT
NO STIM
FVIII
peptide

FIG. 4

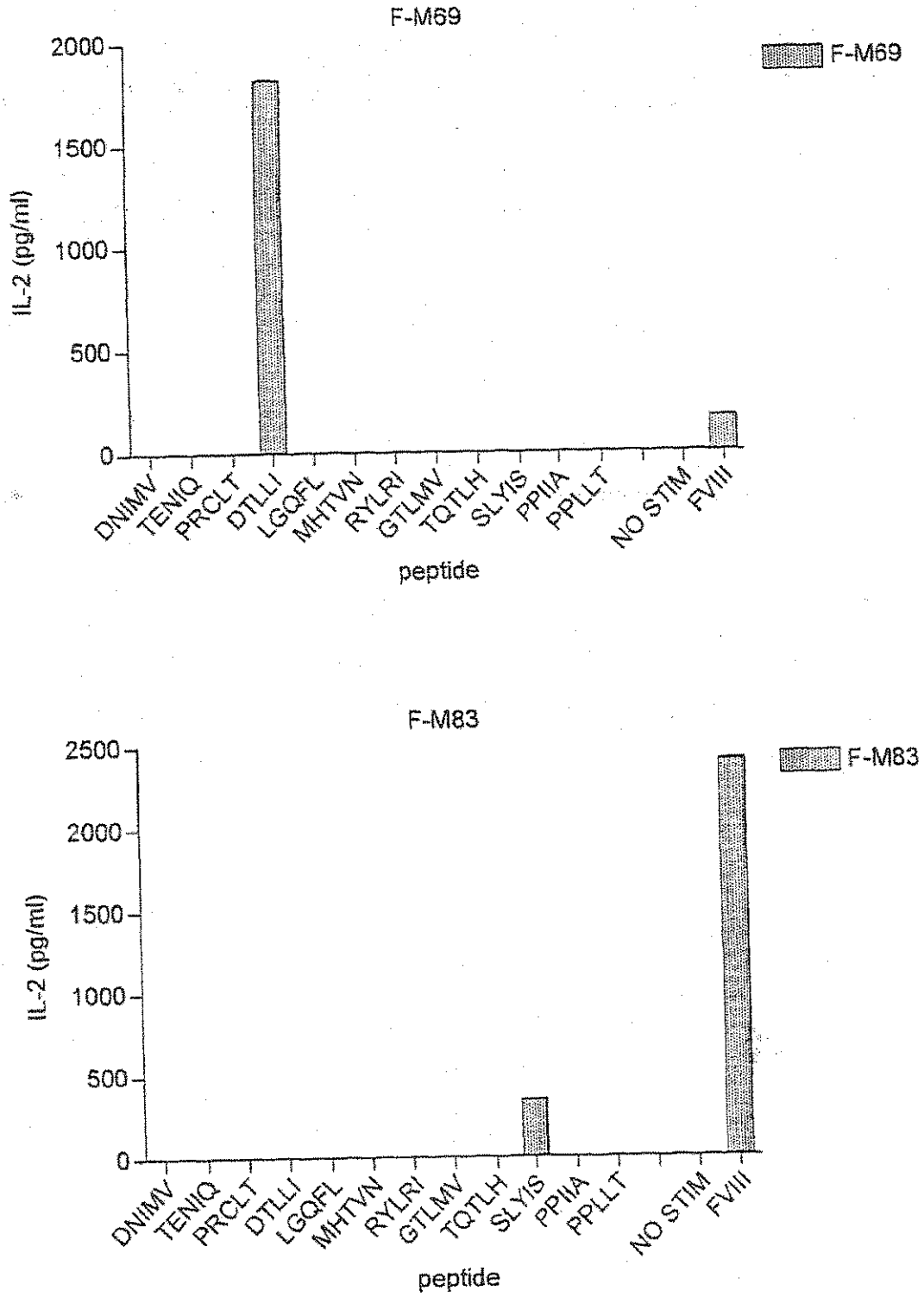

F-M69
F-M69
2000
1500
1000
500
0
IL-2 (pg/ml)
DNIMV
TENIQ
PRCLT
DTLLI
LGQFL
MHTVN
RYLRI
GTLMV
TQTLH
SLYIS
PPIIA
PPLLT
NO STIM
FVIII
peptide
F-M83
F-M83
2500
2000
1500
1000
500
0
IL-2 (pg/ml)
DNIMV
TENIQ
PRCLT
DTLLI
LGQFL
MHTVN
RYLRI
GTLMV
TQTLH
SLYIS
PPIIA
PPLLT
NO STIM
FVIII
peptide

FIG. 4(cont'd)

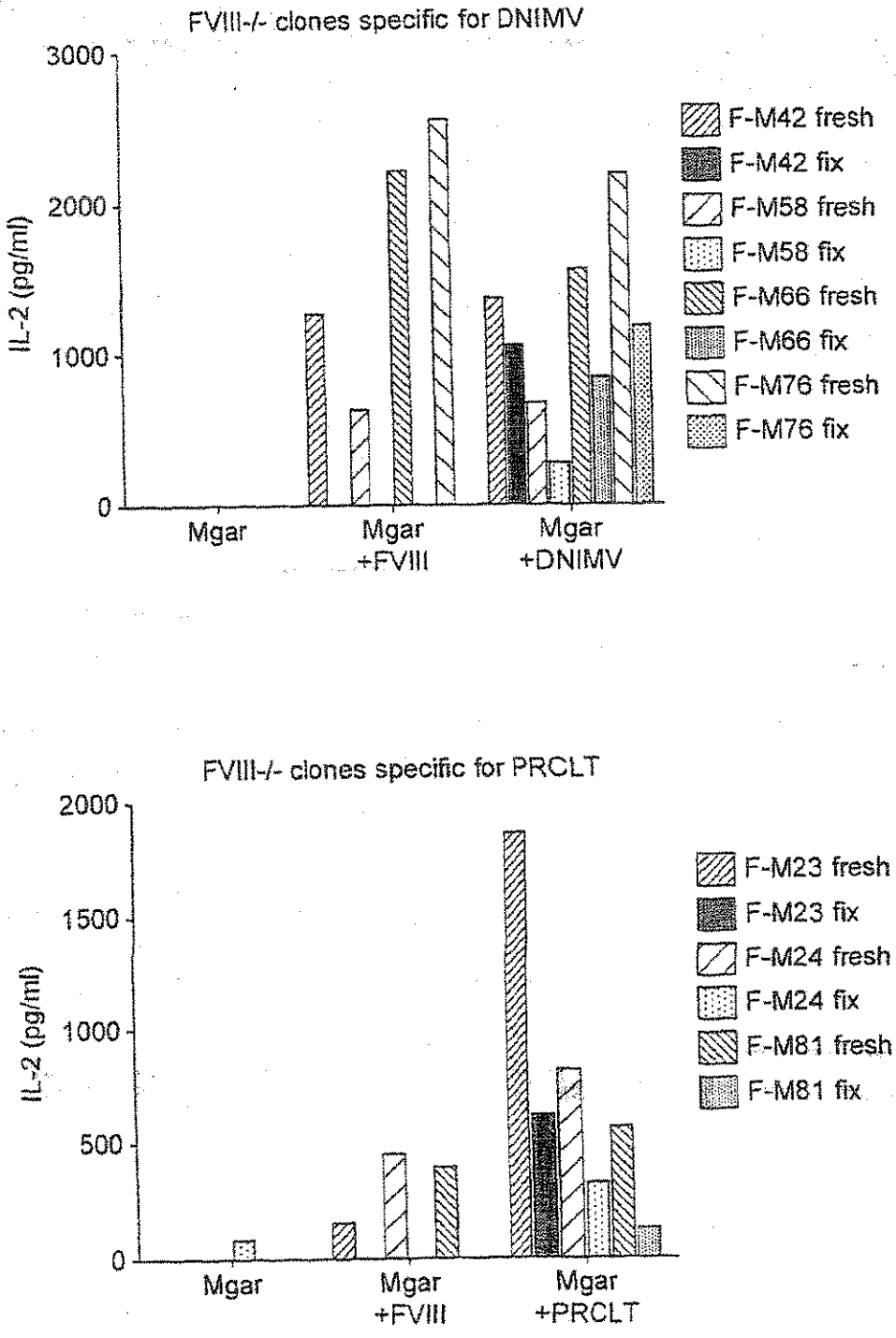

FVIII-/- clones specific for DNIMV
IL-2 (pg/ml)
3000
2000
1000
0
Mgar
Mgar +FVIII
Mgar +DNIMV
F-M42 fresh
F-M42 fix
F-M58 fresh
F-M58 fix
F-M66 fresh
F-M66 fix
F-M76 fresh
F-M76 fix
FVIII-/- clones specific for PRCLT
IL-2 (pg/ml)
2000
1500
1000
500
0
Mgar
Mgar +FVIII
Mgar +PRCLT
F-M23 fresh
F-M23 fix
F-M24 fresh
F-M24 fix
F-M81 fresh
F-M81 fix

FIG. 5

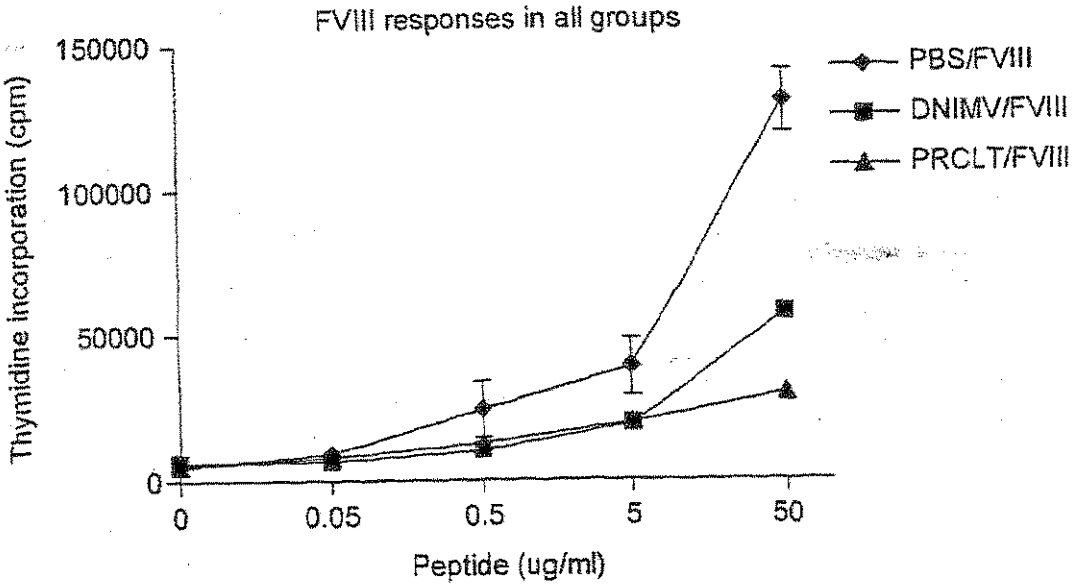

FVIII responses in all groups
Thymidine incorporation (cpm)
150000
100000
50000
0
0
0.05
0.5
5
50
Peptide (ug/ml)
PBS/FVIII
DNIMV/FVIII
PRCLT/FVIII

FIG. 6

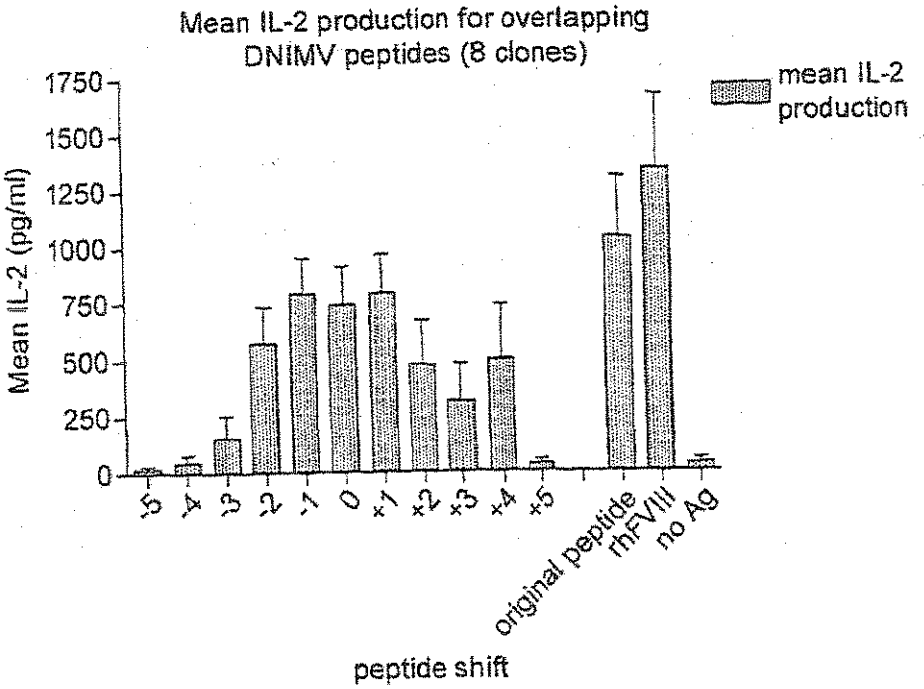

Mean IL-2 production for overlapping
DNIMV peptides (8 clones)
mean IL-2
production
Mean IL-2 (pg/ml)
1750
1500
1250
1000
750
500
250
0
-5
-4
-3
-2
-1
0
+1
+2
+3
+4
+5
original peptide
rhFVIII
no Ag
peptide shift

FIG. 7a

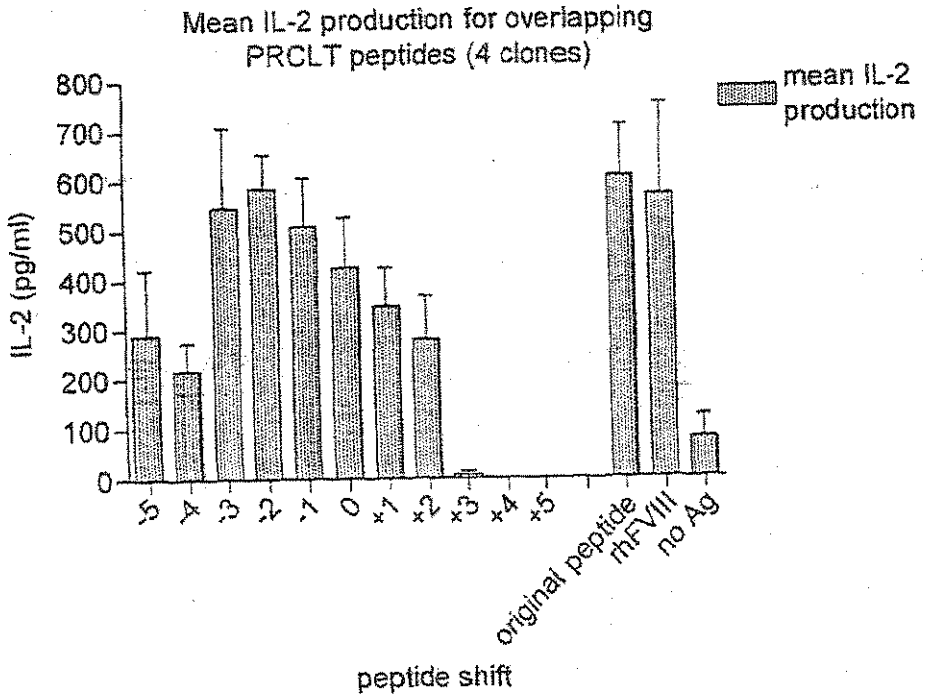
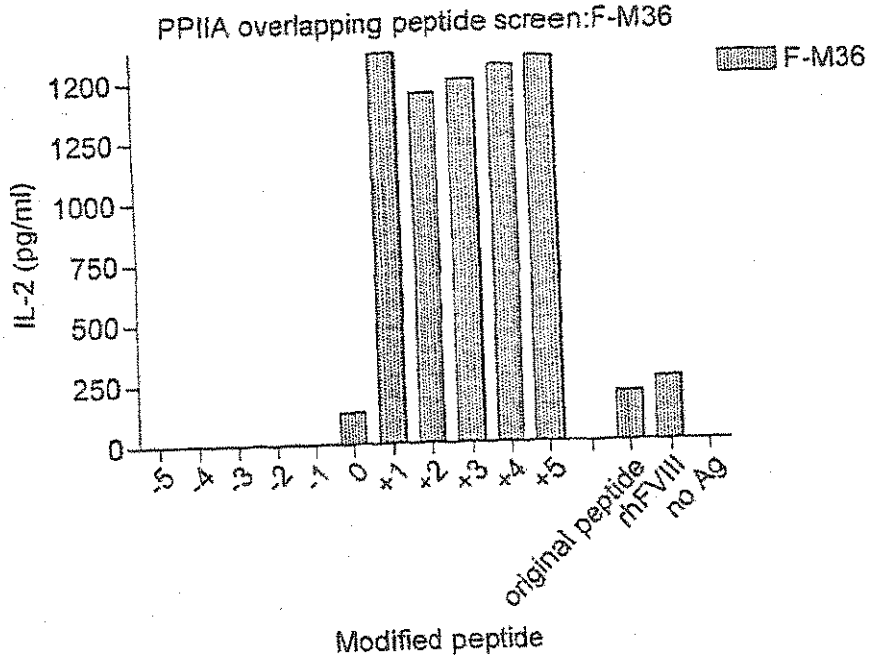

Mean IL-2 production for overlapping
PRCLT peptides (4 clones)
mean IL-2
production
IL-2 (pg/ml)
800
700
600
500
400
300
200
100
0
-5
-4
-3
-2
-1
0
+1
+2
+3
+4
+5
original peptide
rhFVIII
no Ag
peptide shift

FIG. 7b

Mean IL-2 production for overlapping peptides
PPIIA, DTLLI, SLYIS and RYLRI



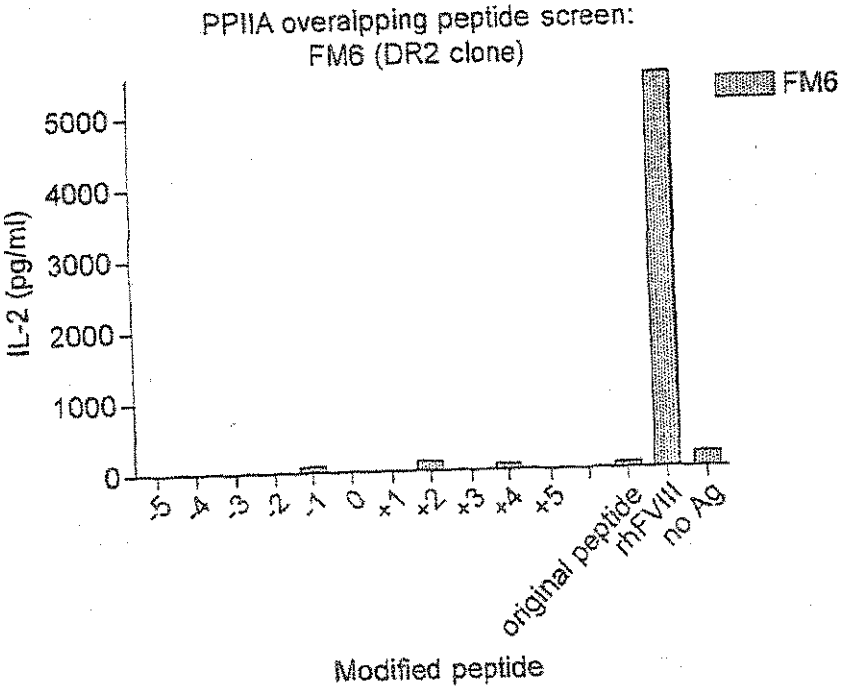
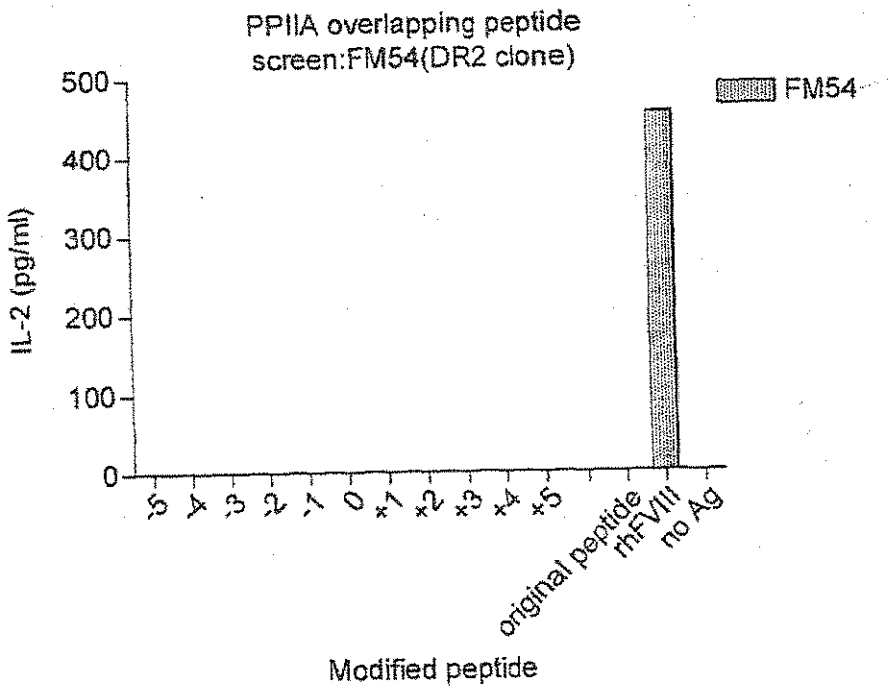


FIG. 7c


PPIIA overlapping peptide screen:FM54(DR2 clone)
FM54
IL-2 (pg/ml)
500
400
300
200
100
0
-5
-4
-3
-2
-1
0
+1
+2
+3
+4
+5
original peptide
rhFVIII
no Ag
Modified peptide

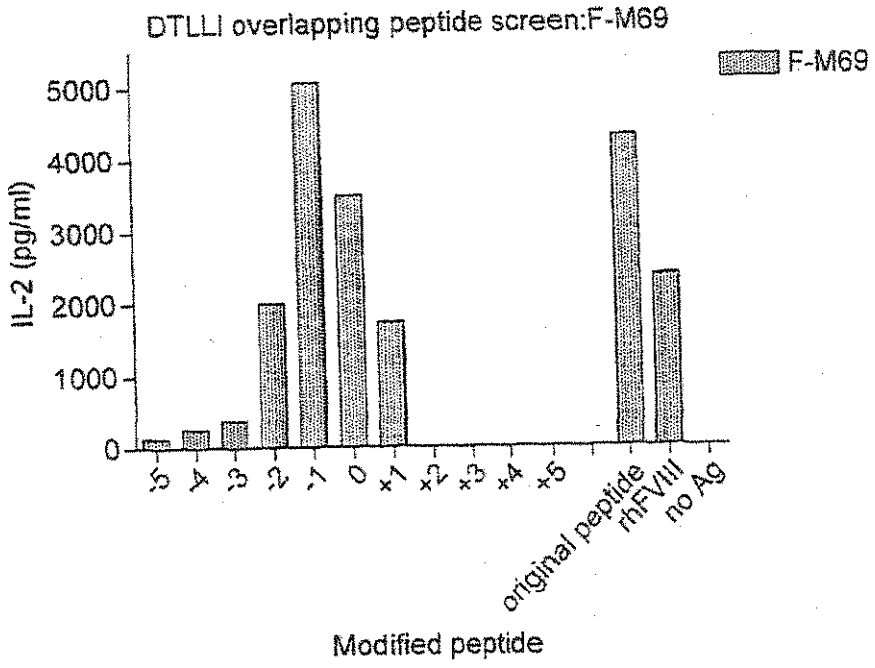
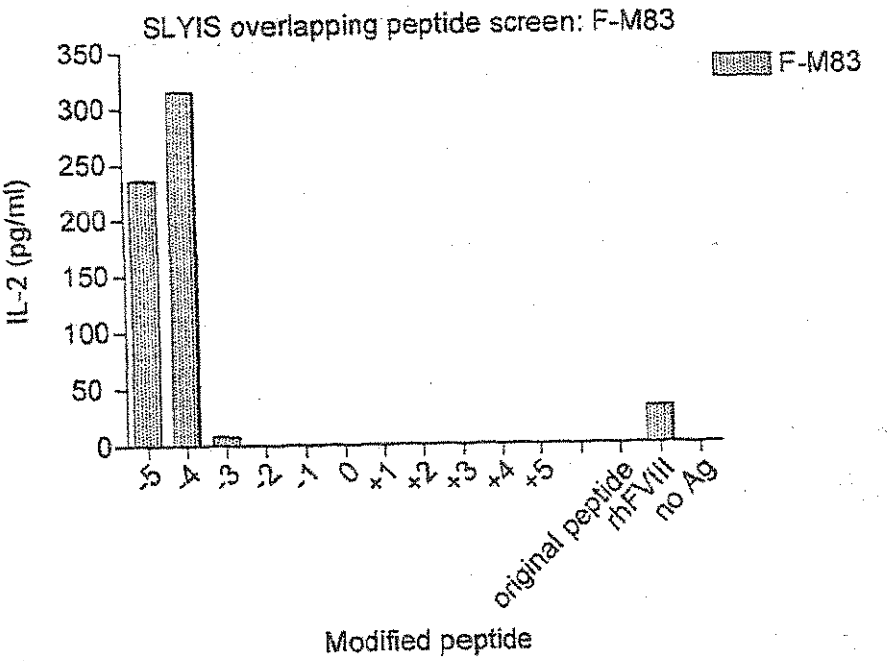

DTLLI overlapping peptide screen:F-M69
F-M69
IL-2 (pg/ml)
5000
4000
3000
2000
1000
0
-5
-4
-3
-2
-1
0
+1
+2
+3
+4
+5
original peptide
rhFVIII
no Ag
Modified peptide

FIG. 7 (cont'd)


SLYIS overlapping peptide screen: F-M83
F-M83
IL-2 (pg/ml)
350
300
250
200
150
100
50
0
-5
-4
-3
-2
-1
0
+1
+2
+3
+4
+5
original peptide
rhFVIII
no Ag
Modified peptide

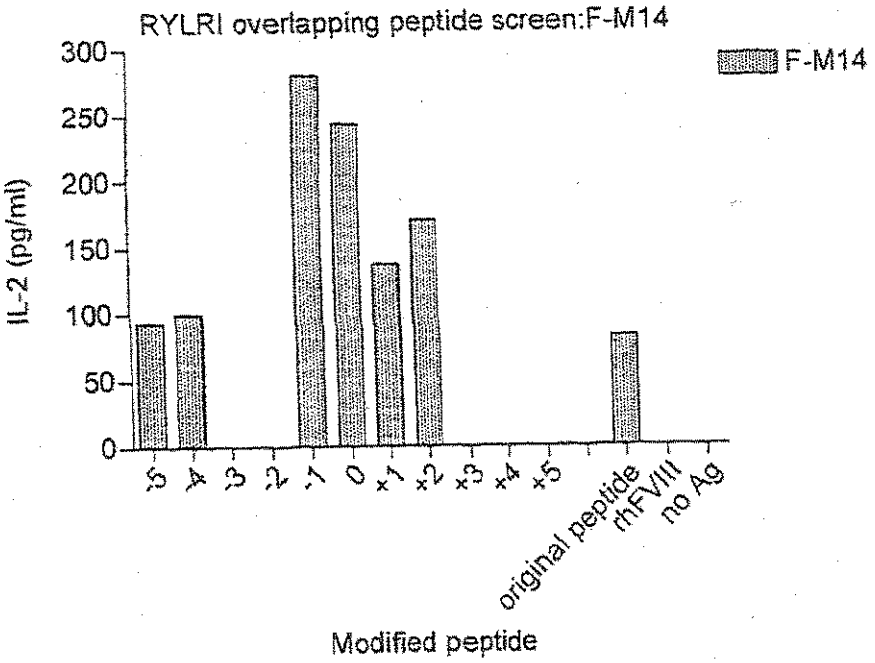

RYLRI overlapping peptide screen:F-M14
F-M14
IL-2 (pg/ml)
300
250
200
150
100
50
0
-5
-4
-3
-2
-1
0
+1
+2
+3
+4
+5
original peptide
rhFVIII
no Ag
Modified peptide

FIG. 7 (cont'd)

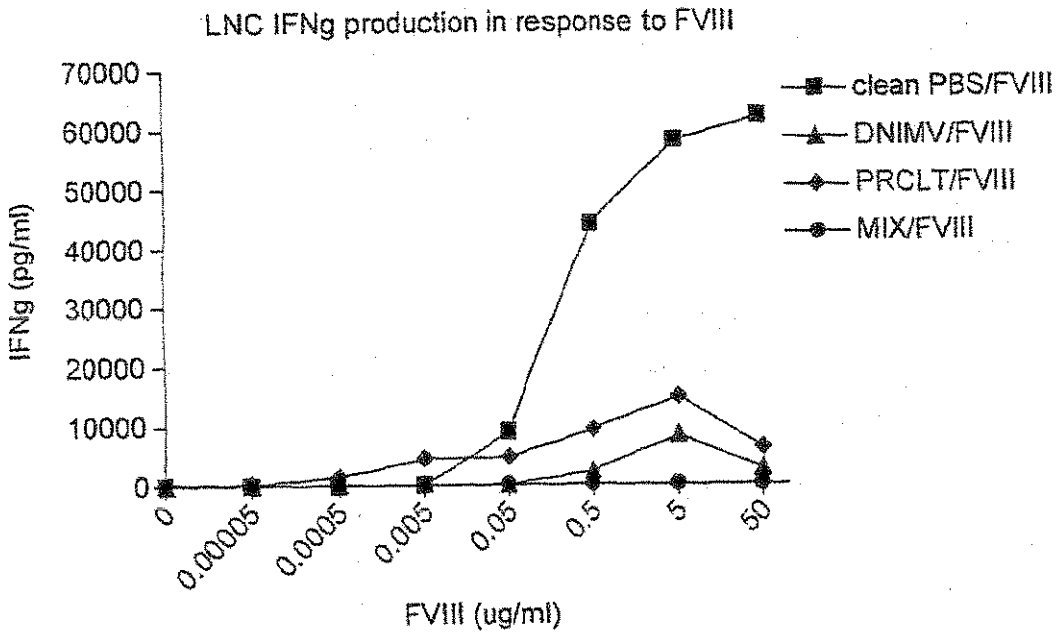

LNC IFNg production in response to FVIII
IFNg (pg/ml)
70000
60000
50000
40000
30000
20000
10000
0
0
0.00005
0.0005
0.005
0.05
0.5
5
50
FVIII (ug/ml)
clean PBS/FVIII
DNIMV/FVIII
PRCLT/FVIII
MIX/FVIII

FIG. 8

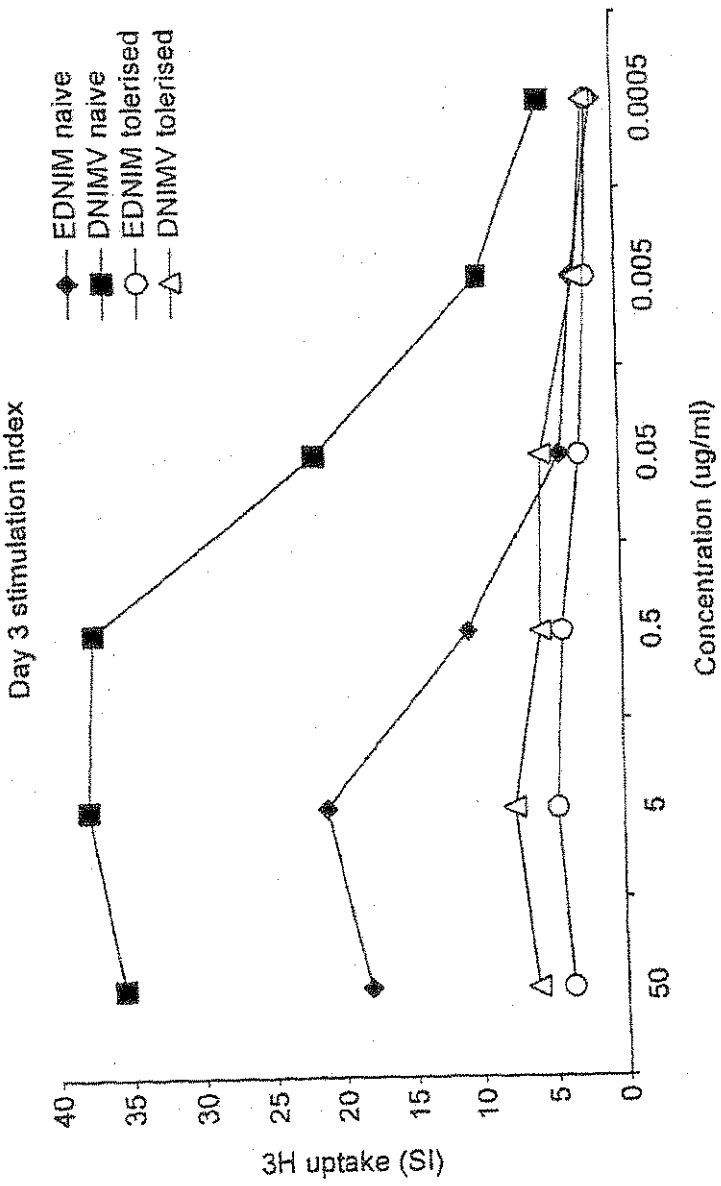

EDNIM naive
DNIMV naive
EDNIM tolerised
DNIMV tolerised
Day 3 stimulation index
3H uptake (SI)
0
5
10
15
20
25
30
35
40
50
5
0.5
0.05
0.005
0.0005
Concentration (ug/ml)

FIG. 9