A.

```
  1 AQVLTQTPAS VSAAVGGTVT INCQSSQSVY DNNWLAWFQQ KPGQPPKLLI
 51 YDASDLASGV PSRFSGSGSG TQFTLTISGV QCADAATYYC QGAYNDVIYA
101 FGGGTEVVVK RTDAAPTVSI FPPSSEQLTS GGASVVCFLN NFYPKDINVK
151 WKIDGSERQN GVLNSWTDQD SKDSTYSMSS TLTLTKDEYE RHNSYTCEAT
201 HKTSTSPIVK SFNRNEC
```

B.

```
  1 QSLEESGGRL VTPGTPLTLT CTASGFSLSS YWMNWVRQAP GEGLEWIGTI
 51 DSGGRTDYAS WAKGRFTISR TSTTMDLKMT SLTTGDTARY FCARNWNLWG
101 QGTLVTVSSA STKGPSVYPL APGSAAQTNS MVTLGCLVKG YFPEPVTVTW
151 NSGSLSSGVH TFPAVLQSDL YTLSSSVTVP SSTWPSETVT CNVAHPASST
201 KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVLTIT LTPKVTCVVV
251 DISKDDPEVQ FSWFVDDVEV HTAQTQPREE QFNSTFRSVS ELPIMHQDWL
301 NGKEFKCRVN SAAFPAPIEK TISKTKGRPK APQVYTIPPP KEQMAKDKVS
351 LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMNTNGSY FVYSKLNVQK
401 SNWEAGNTFT CSVLHEGLHN HHTEKSLSHS PGK
```

Figure 1

A.

```
  1 QIVLTQSPTI VSASPGEKVT LICSASSSVS FVDWFQQKPG TSPKRWIYRT
 51 SNLGFGVPAR FSGGGSGTSH SLTISRMEAE DAATYYCQQR STYPPTFGAG
101 TKLELKRADA APTVSIFPPS SEQLTSGGAS VVCFLNNFYP KDINVKWKID
151 GSERQNGVLN SWTDQDSKDS TYSMSSTLTL TKDEYERHNS YTCEATHKTS
201 TSPIVKSFNR NEC
```

B.

```
  1 QVTLKESGPG ILQPSQTLSL TCSFSGFSLS TSGMGVGWIR HPSGKNLEWL
 51 AHIWWDDVKR YNPVLKSRLT ISKDTSNSQV FLKIANVDTA DTATYYCARI
101 EDFDYDEEYY AMDYWGQGTS VIVSSAKTTP PSVYPLAPGS AAQTNSMVTL
151 GCLVKGYFPE PVTVTWNSGS LSSGVHTFPA VLQSDLYTLS SSVTVPSSTW
201 PSETVTCNVA HPASSTKVDK KIVPRDCGCK PCICTVPEVS SVFIFPPKPK
251 DVLTITLTPK VTCVVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQFNS
301 TFRSVSELPI MHQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV
351 YTIPPPKEQM AKDKVSLTCM ITDFFPEDIT VEWQWNGQPA ENYKNTQPIM
401 DTDGSYFVYS KLNVQKSNWE AGNTFTCSVL HEGLHNHHTE KSLSHSPGK
```

Figure 2

A.

```
  1 DIVLTQSPAS LTVSLGLRAT ISCKASQSVD YDGDSYMNWY QQKPGQPPKL
 51 LIYAASNLES GIPARFSGNG SGTDFTLNIH PVEEEDAVTY YCQQSNEDPW
101 TFGGGTKLEI KRADAAPTVS IFPPSSEQLT SGGASVVCFL NNFYPKDINV
151 KWKIDGSERQ NGVLNSWTDQ DSKDSTYSMS STLTLTKDEY ERHNSYTCEA
201 THKTSTSPIV KSFNRNEC
```

B.

```
  1 EVQLQQSGPE LVKPGTSVKM SCKASGYTFT DCYMNWVKQS HGKSLEWIGD
 51 INPFNGGTTY NQKFKGKATL TVDKSSSTAY MQLNSLTSDD SAVYYCARSH
101 YYFDGRVPWD AMDYWGQGTS VTVSSAKTTP PSVYPLAPGS AAQTNSMVTL
151 GCLVKGYFPE PVTVTWNSGS LSSGVHTFPA VLQSDLYTLS SSVTVPSSTW
201 PSETVTCNVA HPASSTKVDK KIVPRDCGCK PCICTVPEVS SVFIFPPKPK
251 DVLTITLTPK VTCVVVDISK DDPEVQFSWF VDDVEVHTAQ TQPREEQFNS
301 TFRSVSELPI MHQDWLNGKE FKCRVNSAAF PAPIEKTISK TKGRPKAPQV
351 YTIPPPKEQM AKDKVSLTCM ITDFFPEDIT VEWQWNGQPA ENYKNTQPIM
401 DTDGSYFIYS KLNVQKSNWE AGNTFTCSVL HEGLHNHHTE KSLSHSPGK
```

Figure 3

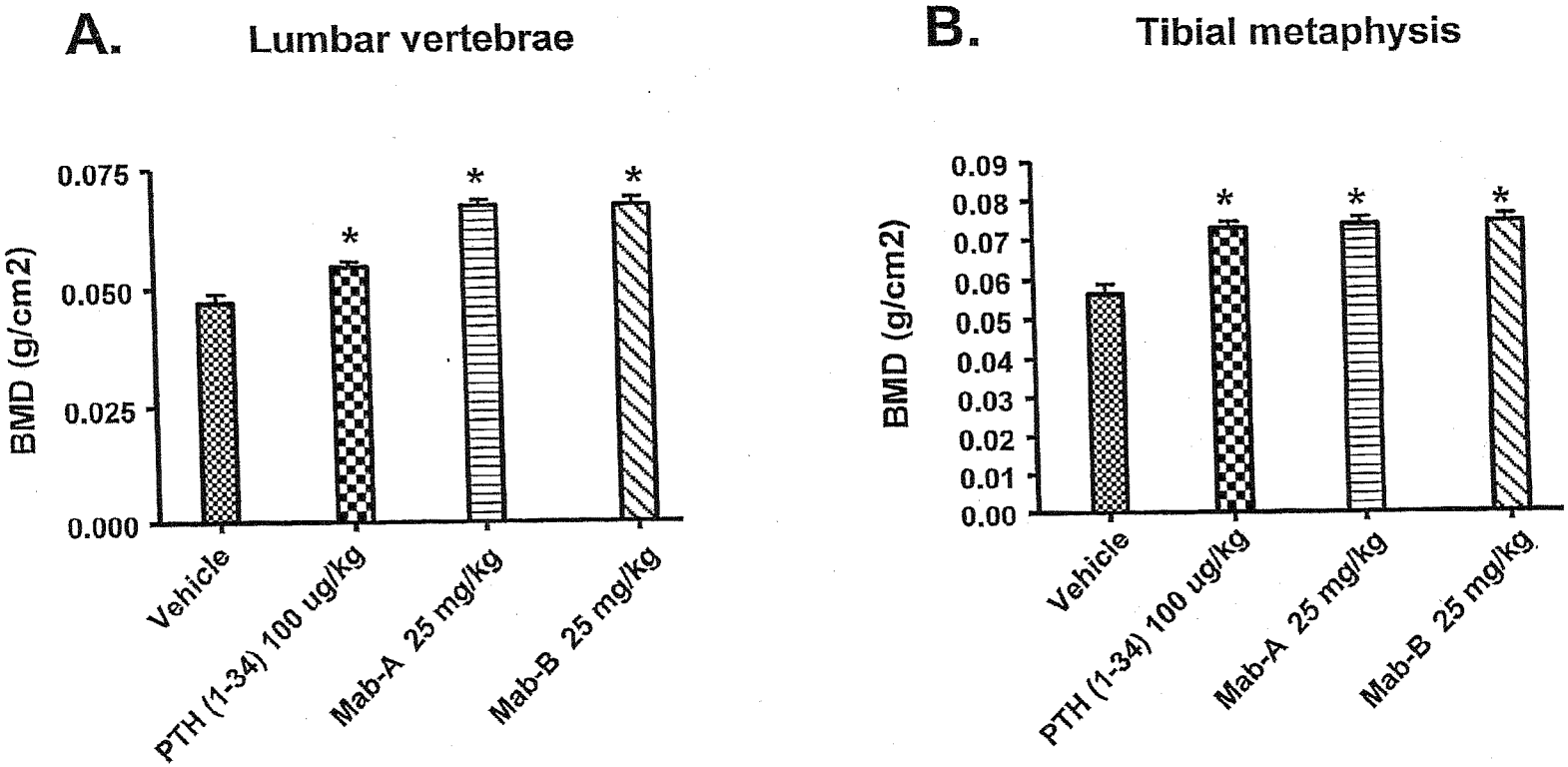
A.

```
  1 DVQMIQSPSS LSASLGDIVT MTCQASQGTS INLNWFQQKP GKAPKLLIYG
 51 SSNLEDGVPS RFSGSRYGTD FTLTISSLED EDLATYFCLQ HSYLPYTFGG
101 GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI
151 DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT
201 STSPIVKSFN RNEC
```

B.

```
  1 EVQLQQSGPE LVTPGASVKI SCKASGYTFT DHYMSWVKQS HGKSLEWIGD
 51 INPYSGETTY NQKFKGTATL TVDKSSSIAY MEIRGLTSED SAVYYCARDD
101 YDASPFAYWG QGTLVTVSAA KTTPPSVYPL APGSAAQTNS MVTLGCLVKG
151 YFPEPVTVTW NSGSLSSGVH TFPAVLQSDL YTLSSSVTVP SSTWPSETVT
201 CNVAHPASST KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVLTIT
251 LTPKVTCVVV DISKDDPEVQ FSWFVDDVEV HTAQTQPREE QFNSTFRSVS
301 ELPIMHQDWL NGKEFKCRVN SPAFPAPIEK TISKTKGRPK APQVYTIPPP
351 KEQMAKDKVS LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMDTDGSY
401 FIYSKLNVQK SNWEAGNTFT CSVLHEGLHN HHTEKSLSHS PGK
```

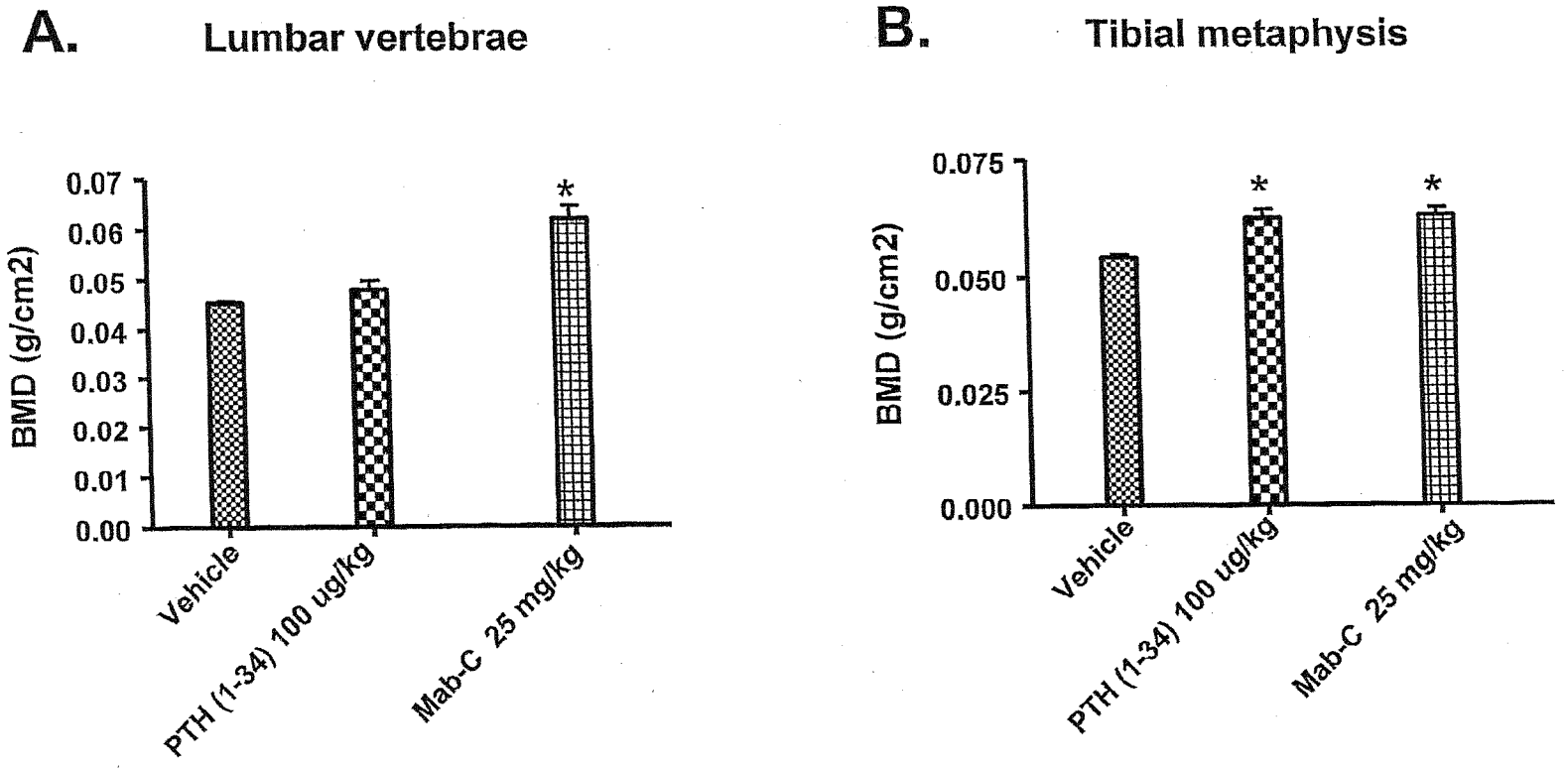
Figure 4



* = statistically significantly different from Vehicle

Error bars = Mean +/- standard deviation

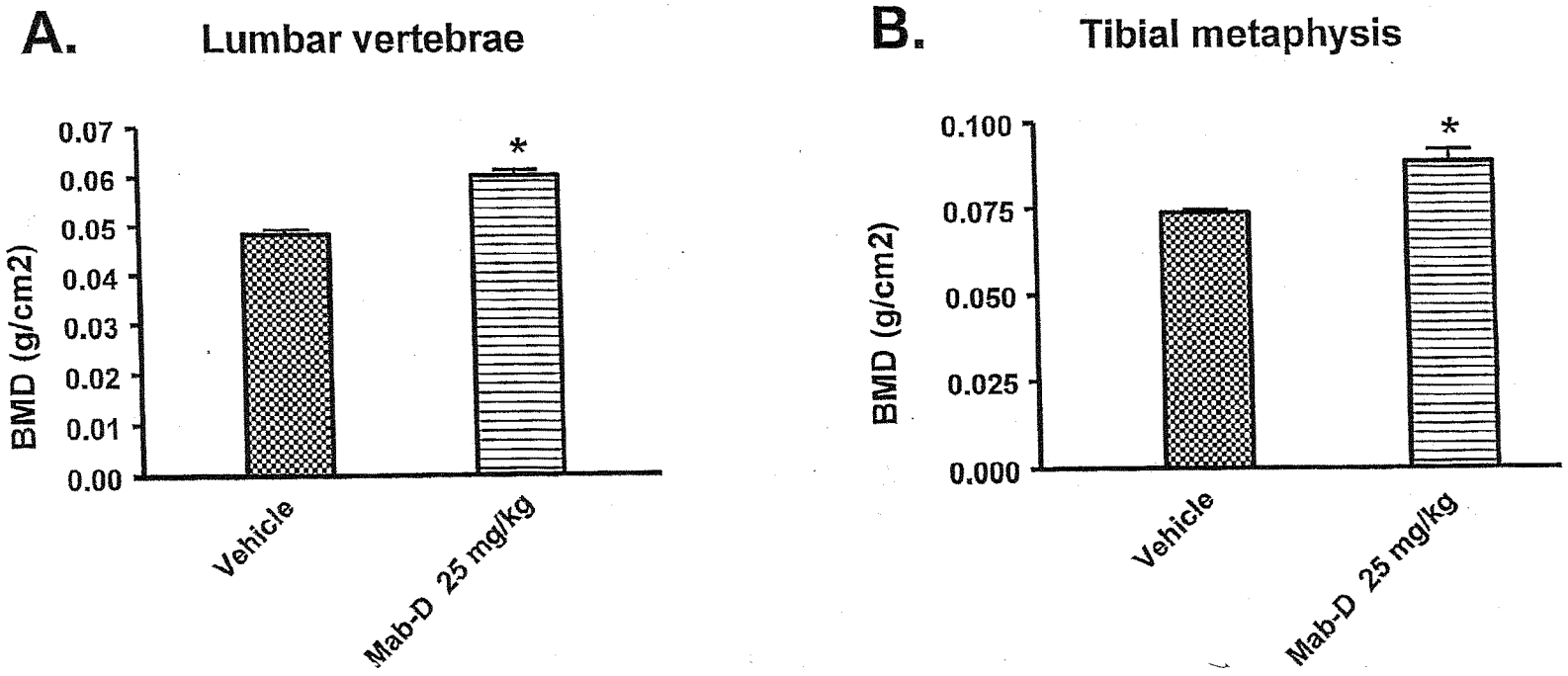
Figure 5



* = statistically significantly different from Vehicle

Error bars = Mean +/- standard deviation

Figure 6



* = statistically significantly different from Vehicle

Error bars = Mean +/- standard deviation

Figure 7

```
1    QGWQAFKNDA TEIIPELGEY PEPPPELENN KTMNRAENGG RPPHHPFETK

51   DVSEYSCREL HFTRYVTDGP CRSAKPVTEL VCSGQCGPAR LLPNAIGRGK
          C1                 C2              C3   C4
101  WWRPSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SCKCKRLTRF
                  C5                 C6                  C7 C8
151  HNQSELKDFG TEAARPQKGR KPRPRARSAK ANQAELENAY
```

```
1    CAGGGGTGGC AGGCGTTCAA GAATGATGCC ACGGAAATCA TCCCCGAGCT
51   CGGAGAGTAC CCCGAGCCTC CACCGGAGCT GGAGAACAAC AAGACCATGA
101  ACCGGGCGGA GAACGGAGGG CGGCCTCCCC ACCACCCCTT TGAGACCAAA
151  GACGTGTCCG AGTACAGCTG CCGCGAGCTG CACTTCACCC GCTACGTGAC
201  CGATGGGCCG TGCCGCAGCG CCAAGCCGGT CACCGAGCTG GTGTGCTCCG
251  GCCAGTGCGG CCCGGCGCGC CTGCTGCCCA ACGCCATCGG CCGCGGCAAG
301  TGGTGGCGAC CTAGTGGGCC CGACTTCCGC TGCATCCCCG ACCGCTACCG
351  CGCGCAGCGC GTGCAGCTGC TGTGTCCCGG TGGTGAGGCG CCGCGCGCGC
401  GCAAGGTGCG CCTGGTGGCC TCGTGCAAGT GCAAGCGCCT CACCCGCTTC
451  CACAACCAGT CGGAGCTCAA GGACTTCGGG ACCGAGGCCG CTCGGCCGCA
501  GAAGGGCCGG AAGCCGCGGC CCCGCGCCCG GAGCGCCAAA GCCAACCAGG
551  CCGAGCTGGA GAACGCCTAC
```

Figure 8

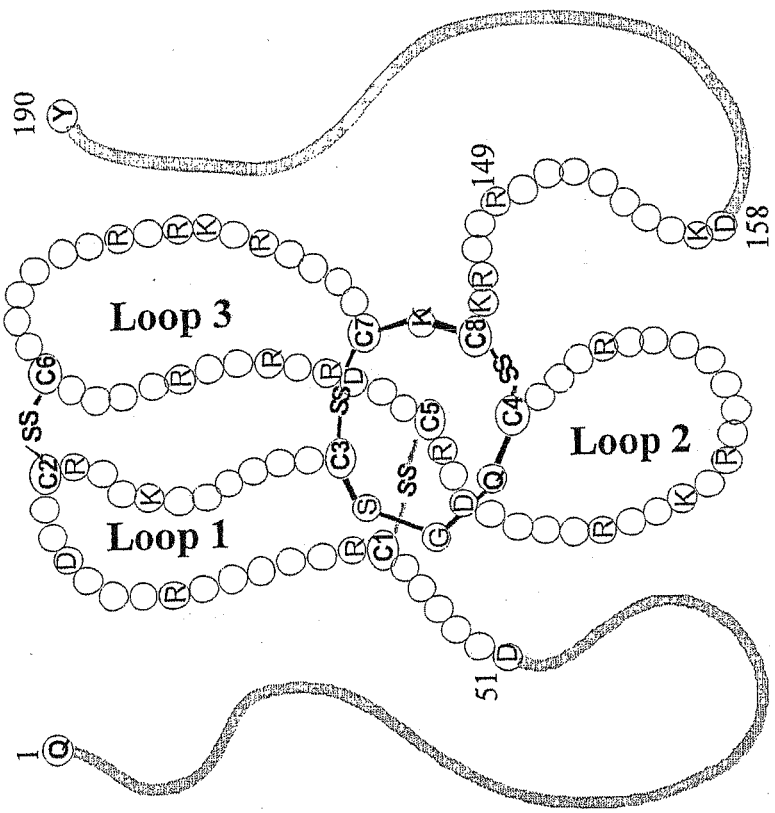


Figure 9

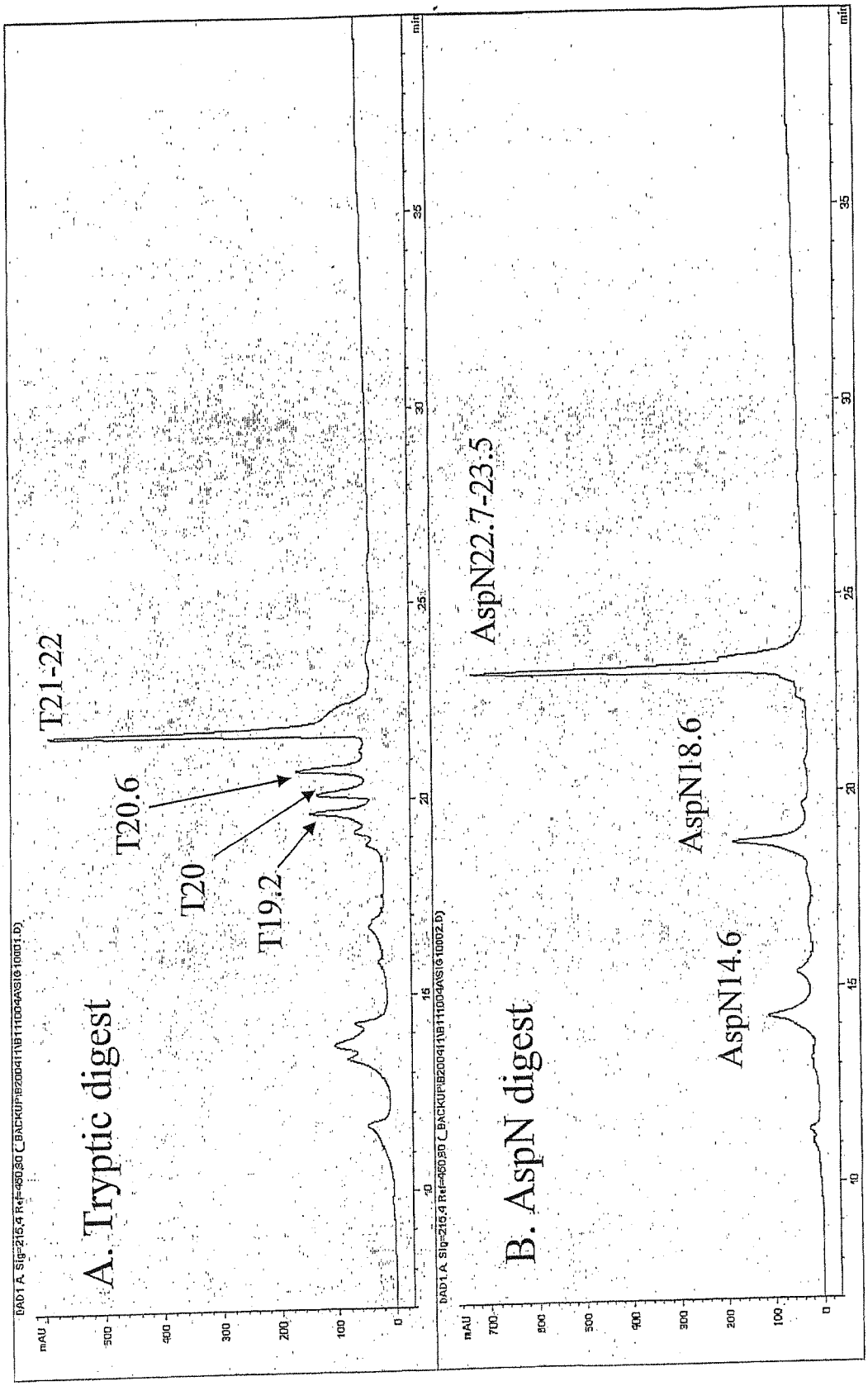

A. Tryptic digest
T21-22
T20.6
T20
T19.2
B. AspN digest
AspN22.7-23.5
AspN18.6
AspN14.6
mAU
min

Figure 10

Peptides	Seq.pos.	Obs. Mass	Sequence
T19.2	65-72	2146.34	1. YVTDGP CR (910) C2
	121-132	(2145.8)	2. VQLLCPGGEA PR (1239) C6
T20		9620.8 (MALDI); 9638.41 (ESI-MS)	
	51-90	(4419.1)	1. DVSEYSCREL HFTRYVTDGP CRSAKPVTEL VCSGQCGPAR
	104-149	(5226.2)	2. PSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SCKCKRLT R
T20.6		7105.7 (MALDI); 7122.0 (ESI-MS)	
	51-64	3944.5	1. DVSEYSCREL HFTR (1740.9) C1
	101-117		2. WWRPSGPPFR CIPDRYR (2206.6) C5
	73-90	3177.0	3. SAKPVTELVC SGQCGPAR (1802.2) C3,C4
	138-149		4. LVASCKCKRL TR (1378.5) C7,C8
T21-22		10,147 (MALDI); 10170.3 (ESI-MS)	
	51-90	(4419.1)	1. DVSEYSCREL HFTRYVTDGP CRSAKPVTEL VCSGQCGPAR
	101-149	(5754.8)	2. WWRPSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SCKCKRLTR

Figure 11

Peptides	Seq.pos.	Obs.Mass	Sequence
AspN14.6	34-47	1245.5	ENGGRPPHHPF
	12-25	1585.4	EIIPELGFYP EPPP
	158-184	2964.5	DFGTEAARPQ KGRKPRPRAR SAKANQA
AspN18.6	9-50		DATEIIPELG EYPEPPPELE NNKTMNRAEN GGRPPHHPFE TK (Glycopeptide)
AspN22.7-23.5	51-154	11,740	DVSEYSCREL HFTRYVTDGP CRSAKPVTEL VCSGQCGPAR LLPNAIGRGK WWRPSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SCKCKRLTRF HNQS

Figure 12

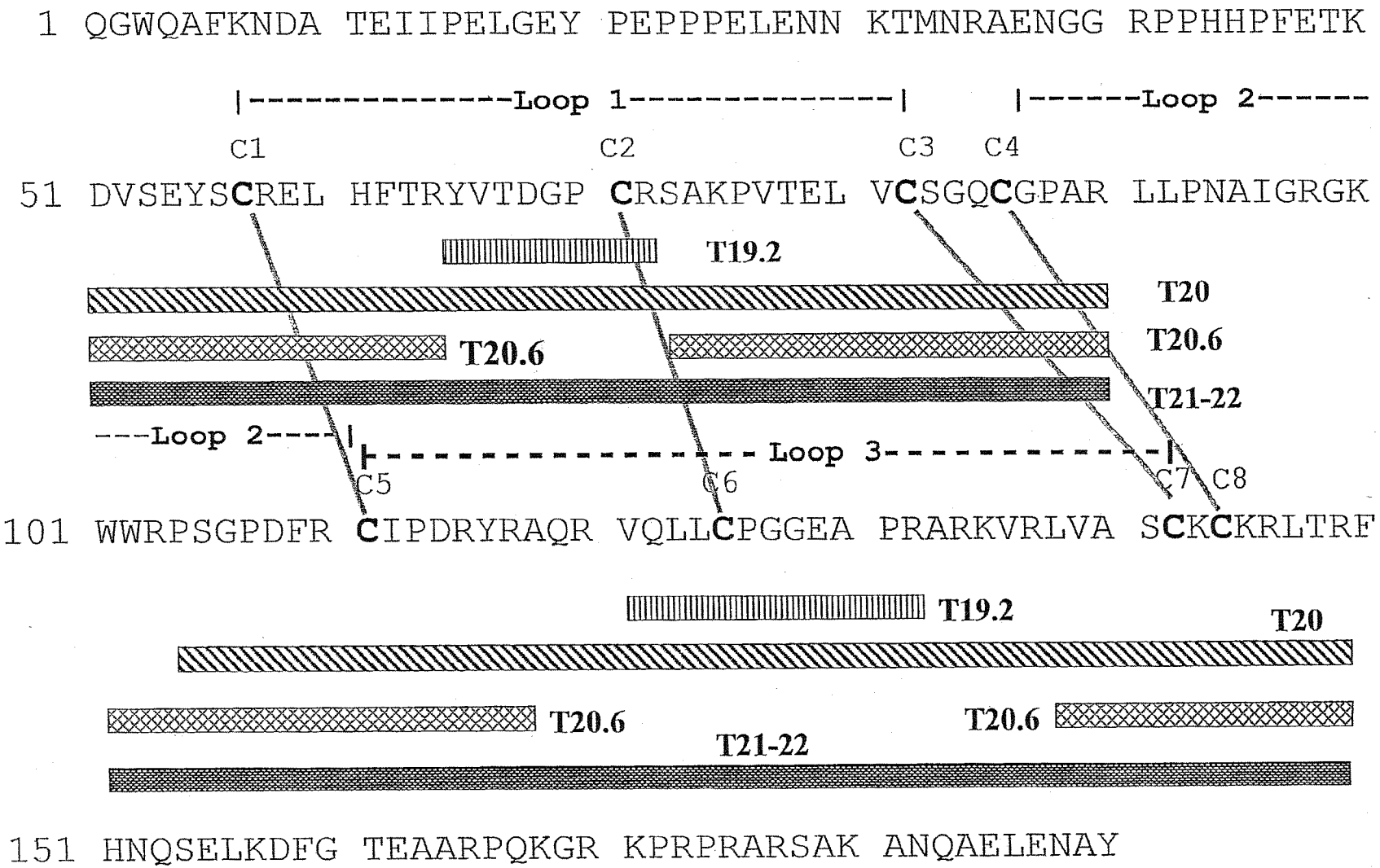

1 QGWQAFKNDA TEIIPELGEY PEPPPELENN KTMNRAENGG RPPHHPFETK
Loop 1
Loop 2
C1
C2
C3
C4
51 DVSEYSCREL HFTRYVTDGP CRSAKPVTEL VCSGQCGPAR LLPNAIGRGK
T19.2
T20
T20.6
T20.6
T21-22
Loop 2
Loop 3
C5
C6
C7
C8
101 WWRPSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SCKCKRLTRF
T19.2
T20
T20.6
T20.6
T21-22
151 HNQSELKDFG TEAARPQKGR KPRPRARSAK ANQAELENAY

Figure 13

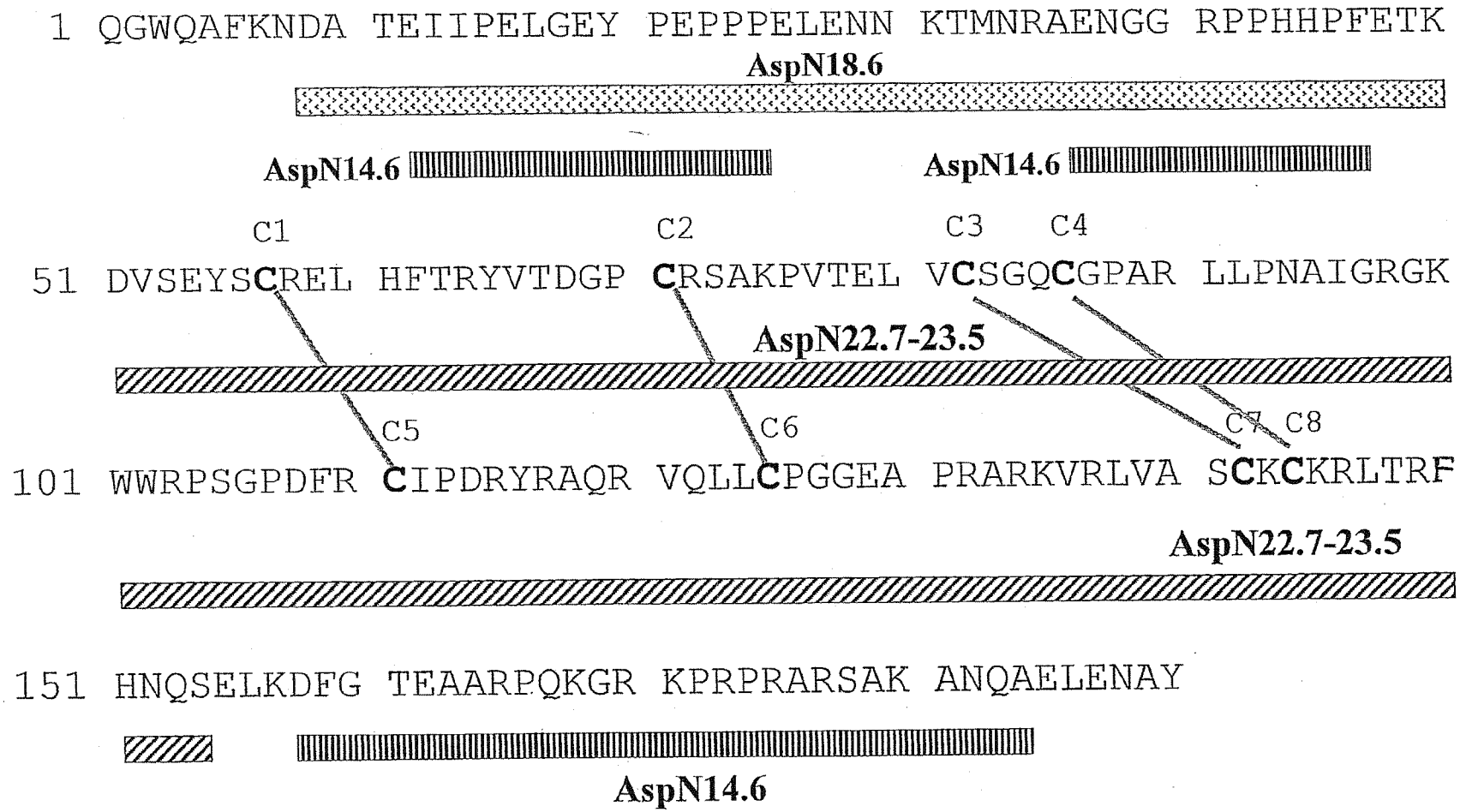

1 QGWQAFKNDA TEIIPELGEY PEPPPELENN KTMNRAENGG RPPHHPFETK
AspN18.6
AspN14.6
AspN14.6
C1
C2
C3
C4
51 DVSEYSCREL HFTRYVTDGP CRSAKPVTEL VCSGQCGPAR LLPNAIGRGK
AspN22.7-23.5
C5
C6
C7
C8
101 WWRPSGPDFR CIPDRYRAQR VQLLCPGGEA PRARKVRLVA SCKCKRLTRF
AspN22.7-23.5
151 HNQSELKDFG TEAARPQKGR KPRPRARSAK ANQAELENAY
AspN14.6

Figure 14

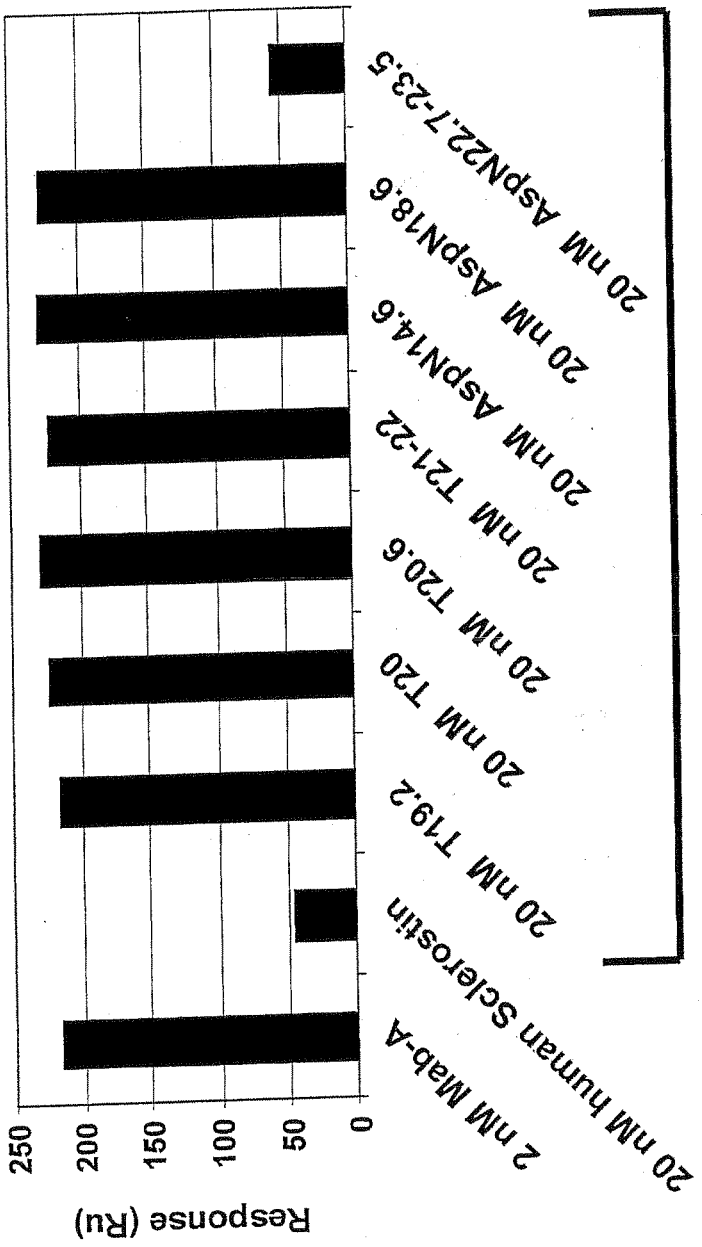

Response (Ru)
250
200
150
100
50
0
2 nM Mab-A
20 nM human Sclerostin
20 nM T19.2
20 nM T20
20 nM T20.6
20 nM T21-22
20 nM AspN14.6
20 nM AspN18.6
20 nM AspN22.7-23.5
2 nM Mab-A +

Figure 15

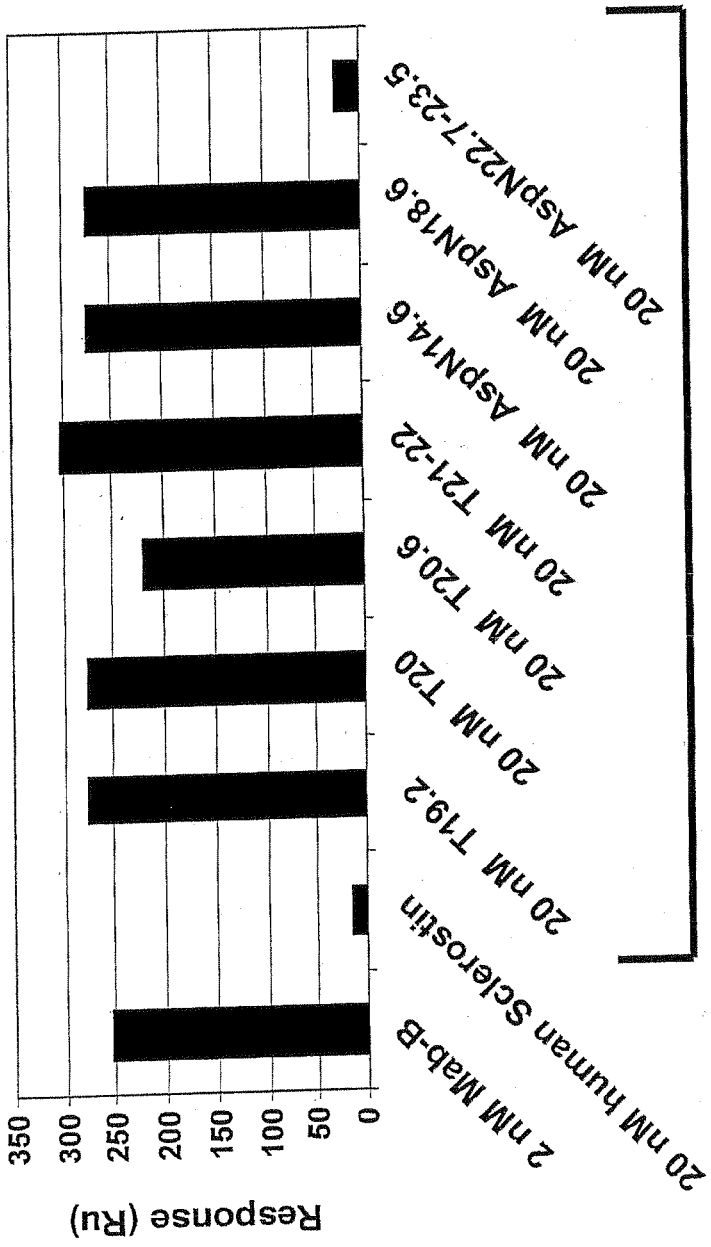

Response (Ru)
350
300
250
200
150
100
50
0
2 nM Mab-B
20 nM human Sclerostin
20 nM T19.2
20 nM T20
20 nM T20.6
20 nM T21-22
20 nM AspN14.6
20 nM AspN18.6
20 nM AspN22.7-23.5
2 nM Mab-B +

Figure 16

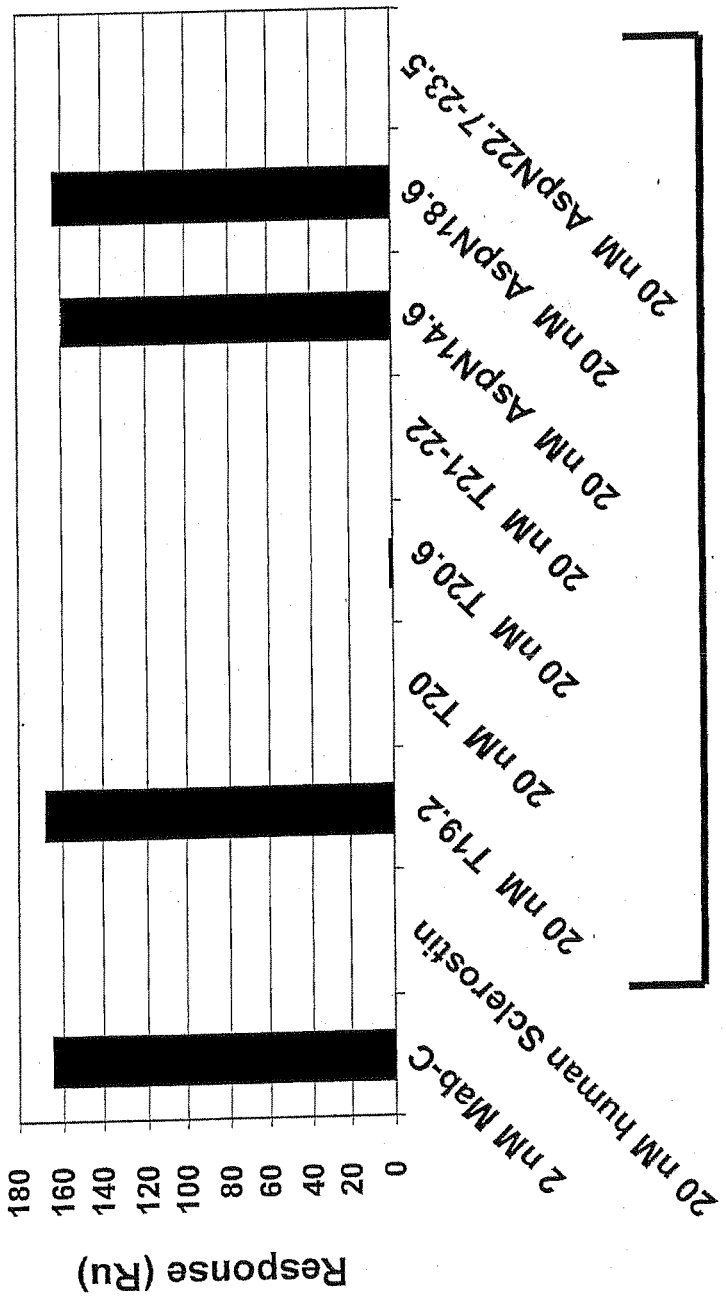

Response (Ru)
0
20
40
60
80
100
120
140
160
180
2 nM Mab-C
20 nM human Sclerostin
20 nM T19.2
20 nM T20
20 nM T20.6
20 nM T21-22
20 nM AspN14.6
20 nM AspN18.6
20 nM AspN22.7-23.5
2 nM Mab-C +

Figure 17

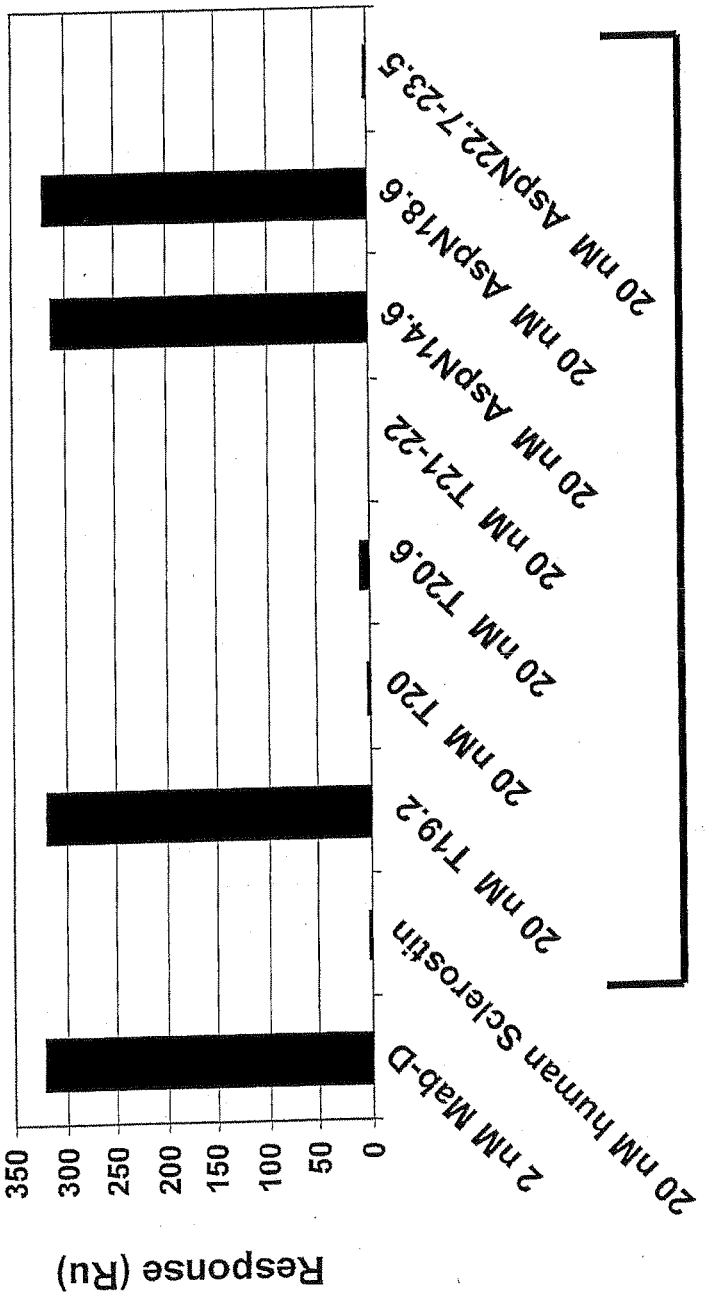

Response (Ru)
350
300
250
200
150
100
50
0
2 nM Mab-D
20 nM human Sclerostin
20 nM T19.2
20 nM T20
20 nM T20.6
20 nM T21-22
20 nM AspN14.6
20 nM AspN18.6
20 nM AspN22.7-23.5
2 nM Mab-D +

Figure 18

A. Loop 2 epitope for Mab-A and Mab-B

C4GPARLLPNAIGRGKWWRPSGPDFR**C5**

B. T20.6 epitope for Mab-C and Mab-D

DVSEYS**C1**RELHFTR SAKPVTELV**C3**SGQ**C4**GPAR

WWRPSGPDFR**C5**IPDRYR LVAS**C7**K**C8**KRLTR

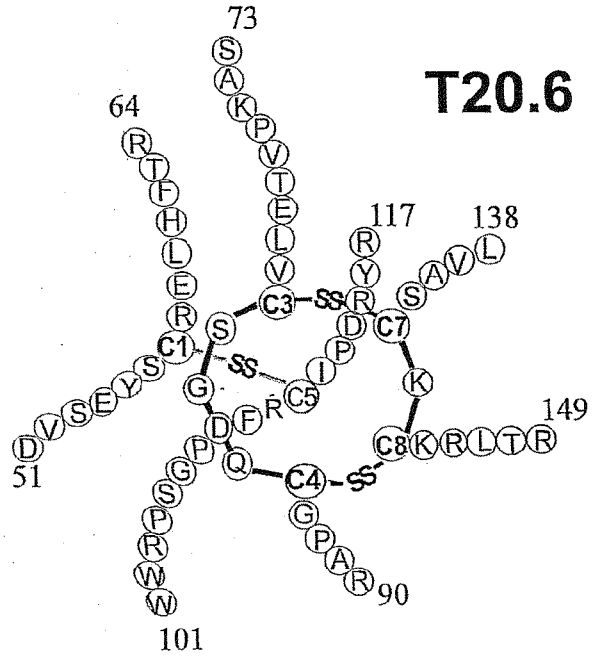


Figure 19

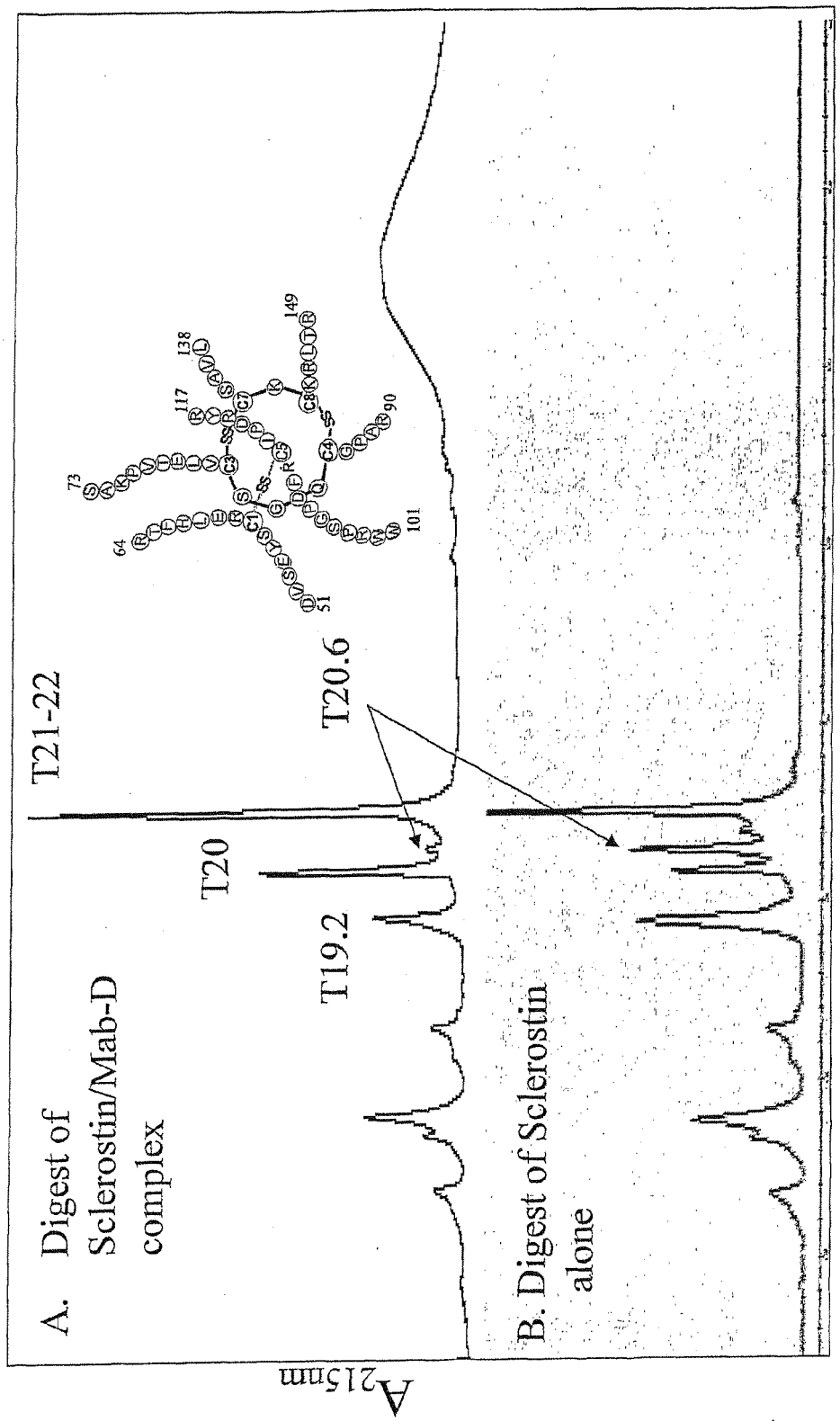
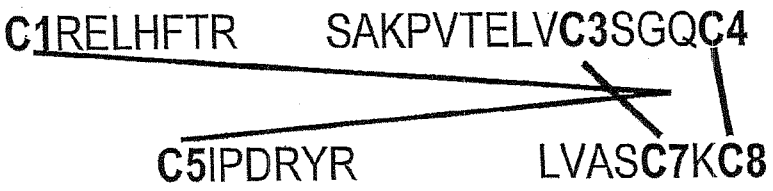

A. Digest of Sclerostin/Mab-D complex
B. Digest of Sclerostin alone
T21-22
T20.6
T20
T19.2
A215nm

Figure 20

"T20.6 derivative 1 (cystine-knot + 4 arms)" epitope for Mab-D



"T20.6 derivative 1 (cystine-knot + 4 arms)"

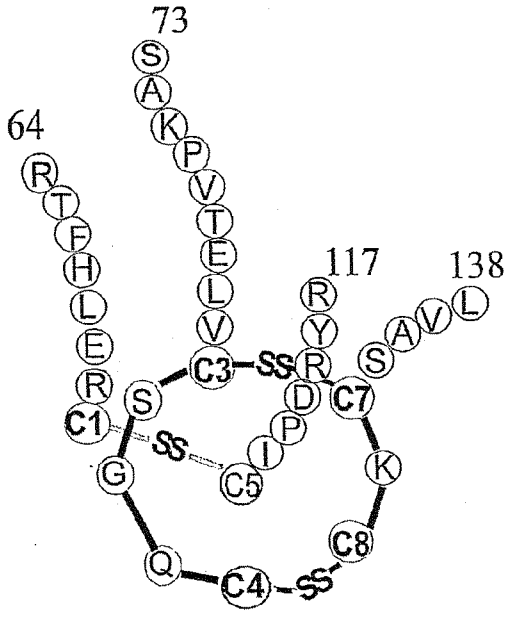


Figure 21

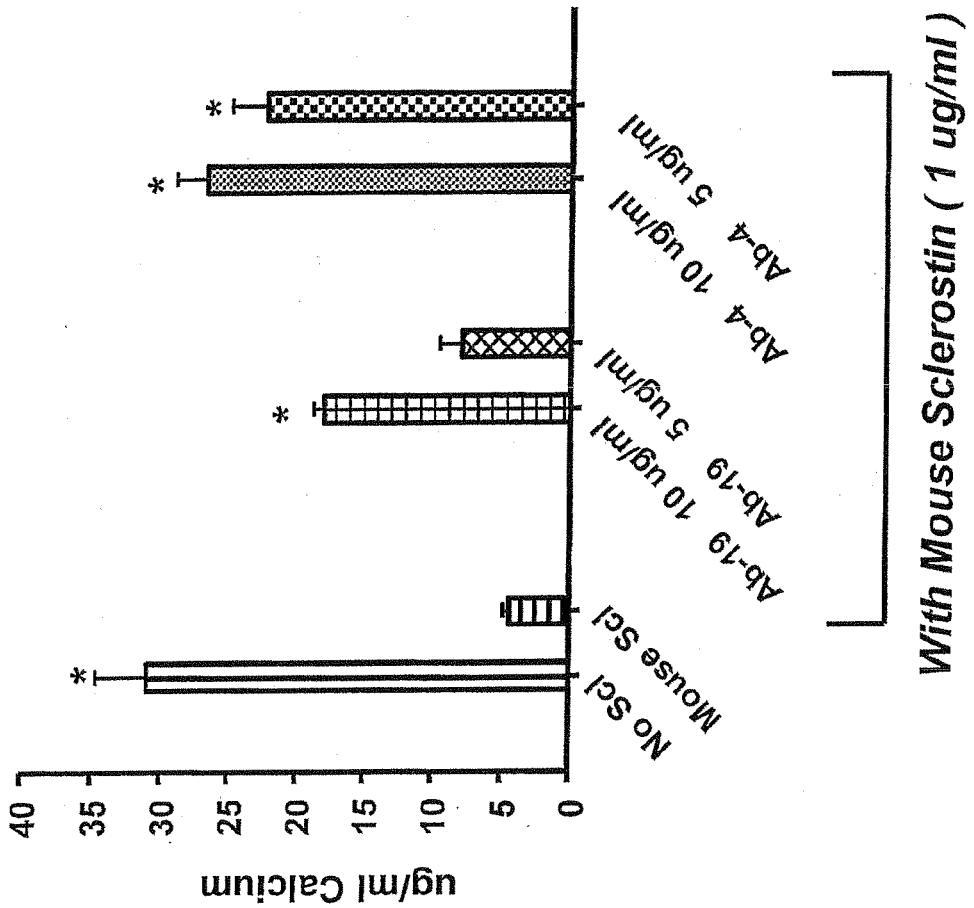
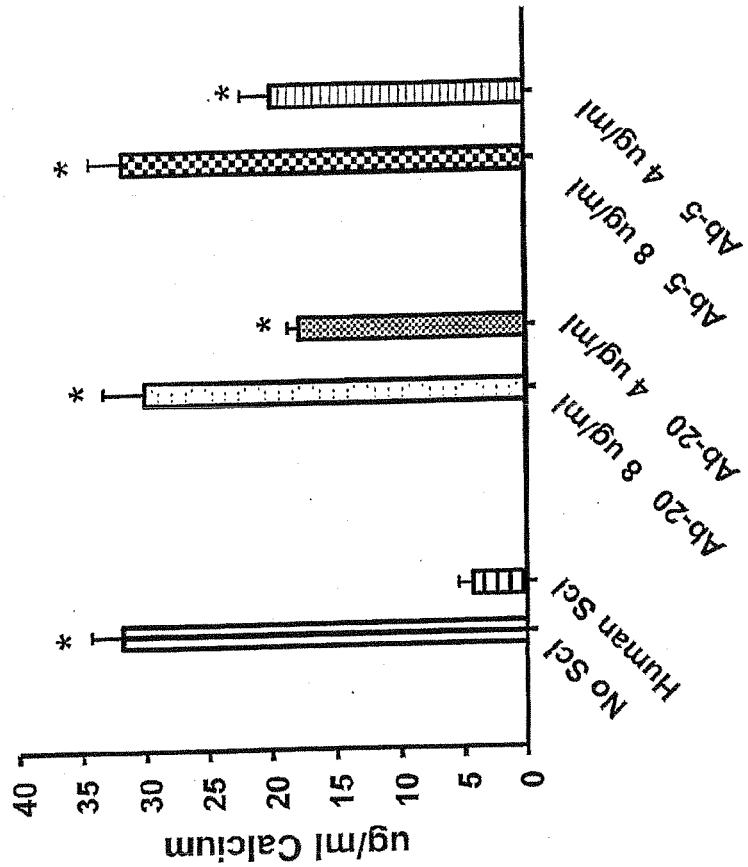

ug/ml Calcium
0
5
10
15
20
25
30
35
40
No Scl
Mouse Scl
Ab-19 10 ug/ml
Ab-19 5 ug/ml
Ab-4 10 ug/ml
Ab-4 5 ug/ml
With Mouse Sclerostin (1 ug/ml)
* = statistically significantly different from Mouse Scl group.
Error bars = Mean +/- SEM

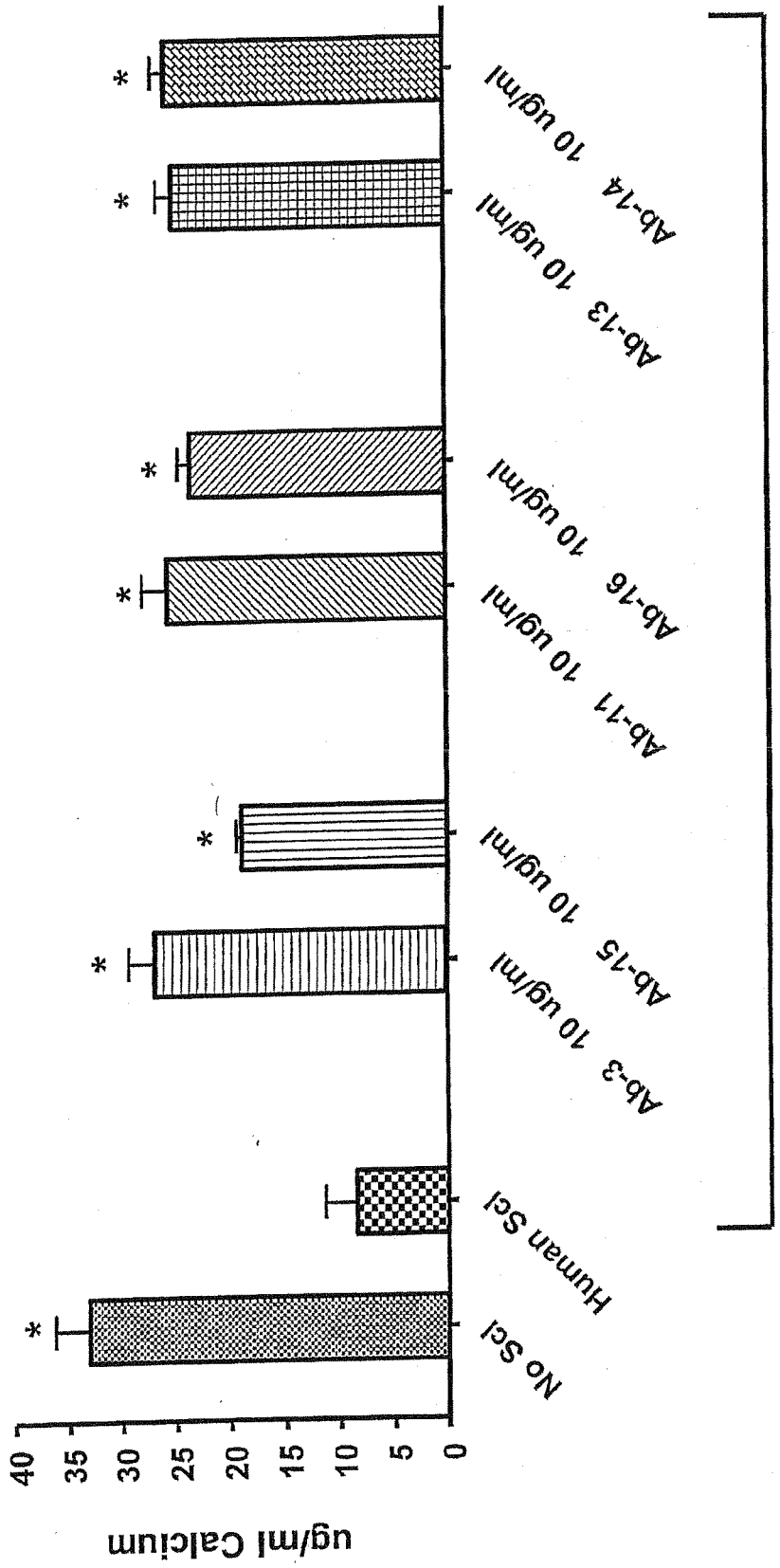
Figure 22



* = statistically significantly different from Human Scl group.

Error bars = Mean +/- SEM

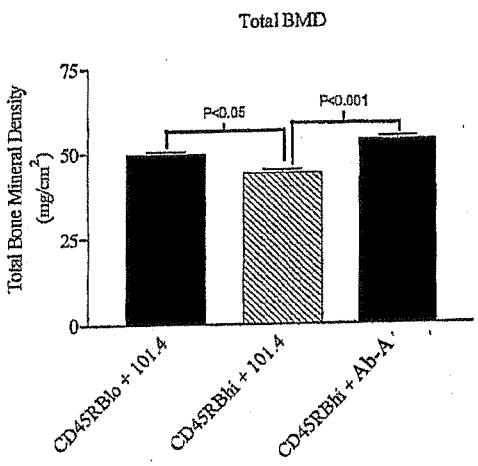
Figure 23



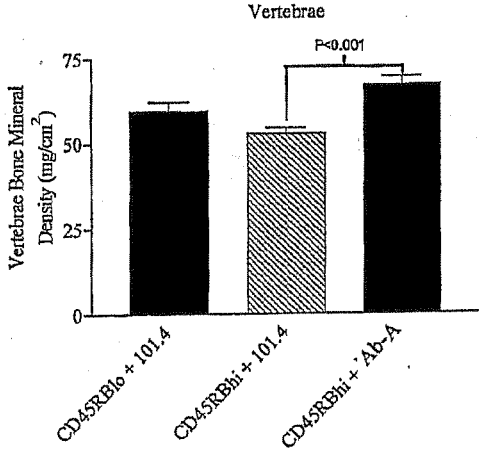
* = statistically significantly different from Human Scl group.

Error bars = Mean +/- SEM

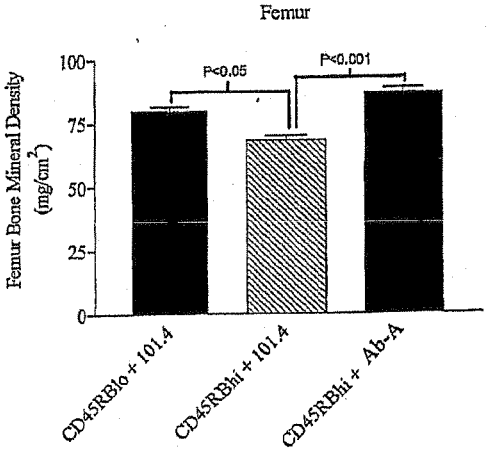
Figure 24



A



B



C

FIGURE 25