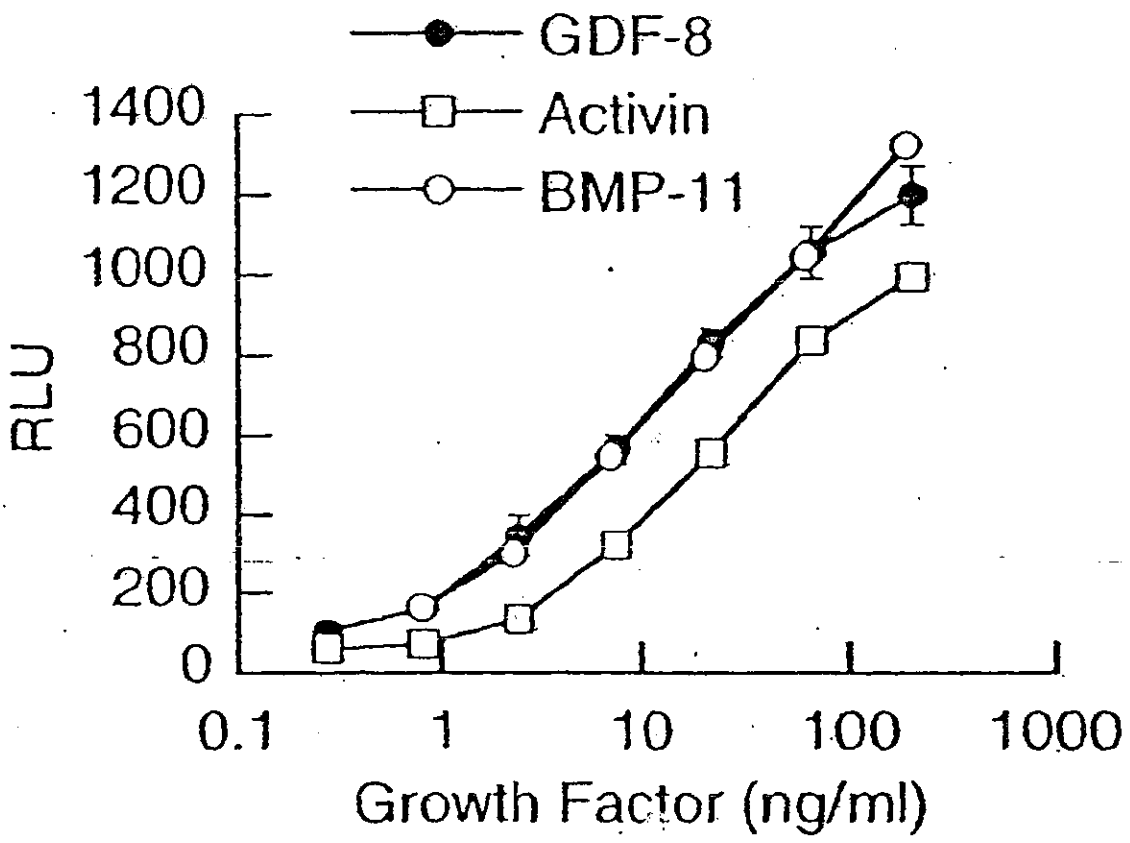

GDF-8
Activin
BMP-11
1400
1200
1000
800
600
400
200
0
RLU
0.1
1
10
100
1000
Growth Factor (ng/ml)

Fig. 1

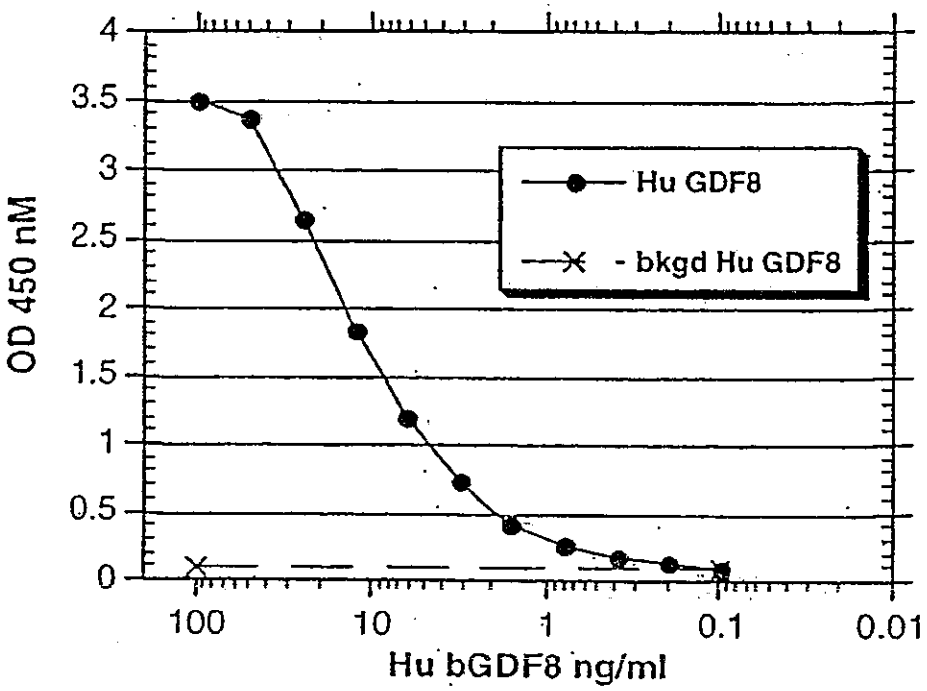

OD 450 nM
4
3.5
3
2.5
2
1.5
1
0.5
0
100
10
1
0.1
0.01
Hu bGDF8 ng/ml
Hu GDF8
- bkgd Hu GDF8

Fig. 2

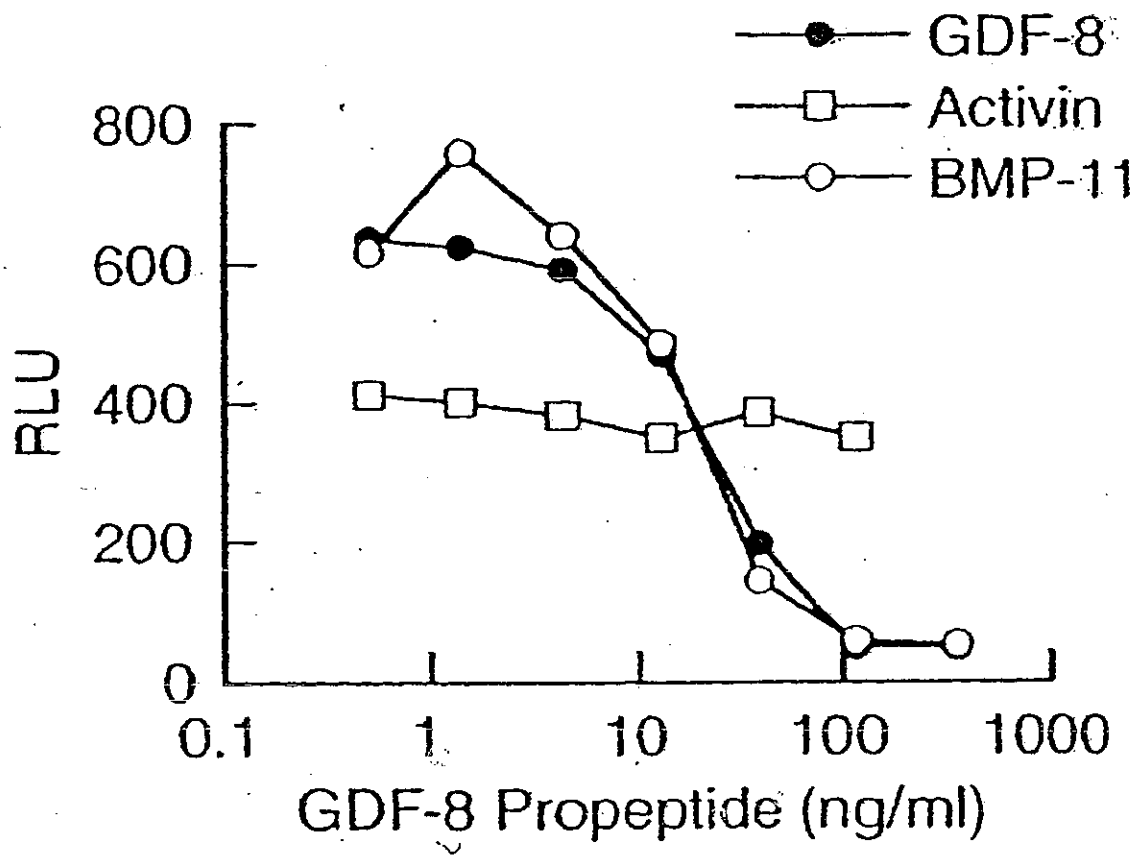

GDF-8
Activin
BMP-11
800
600
400
200
0
RLU
0.1
1
10
100
1000
GDF-8 Propeptide (ng/ml)

Fig. 3

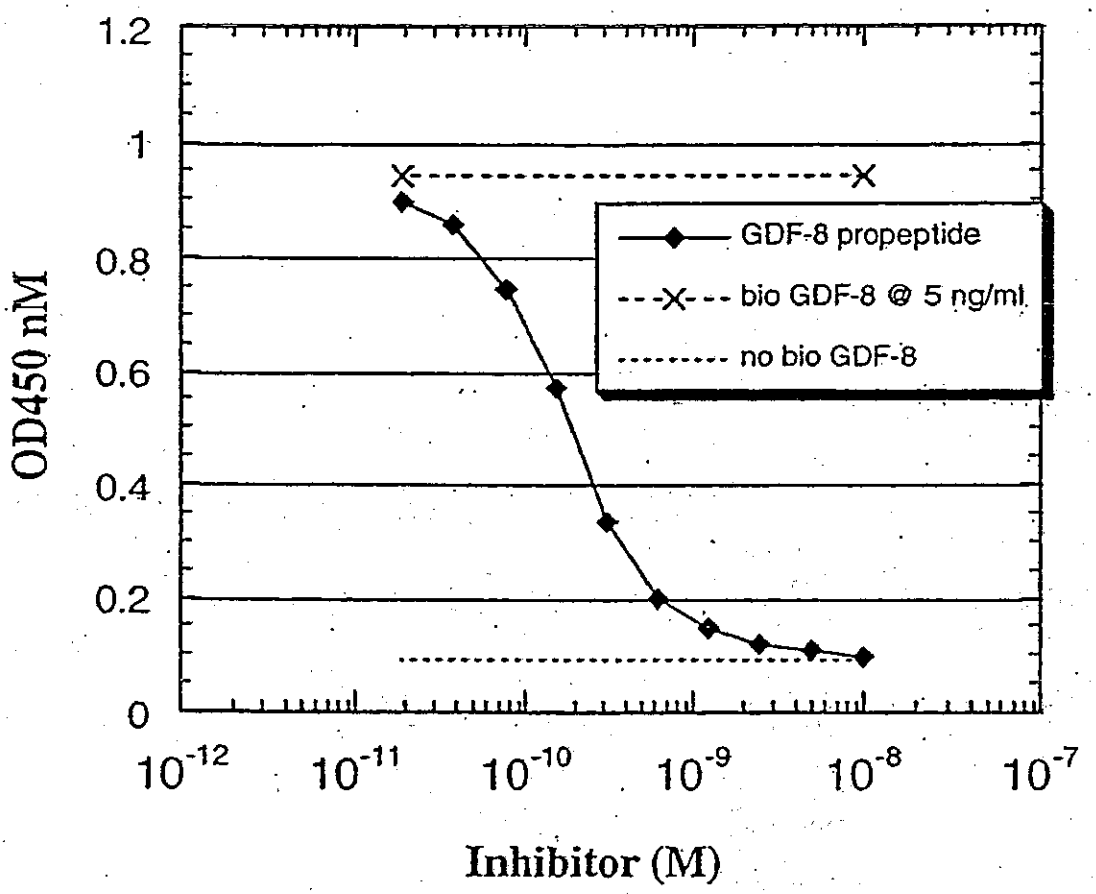

1.2
1
0.8
0.6
0.4
0.2
0
OD450 nM
GDF-8 propeptide
bio GDF-8 @ 5 ng/ml
no bio GDF-8
10-12
10-11
10-10
10-9
10-8
10-7
Inhibitor (M)

Fig. 4

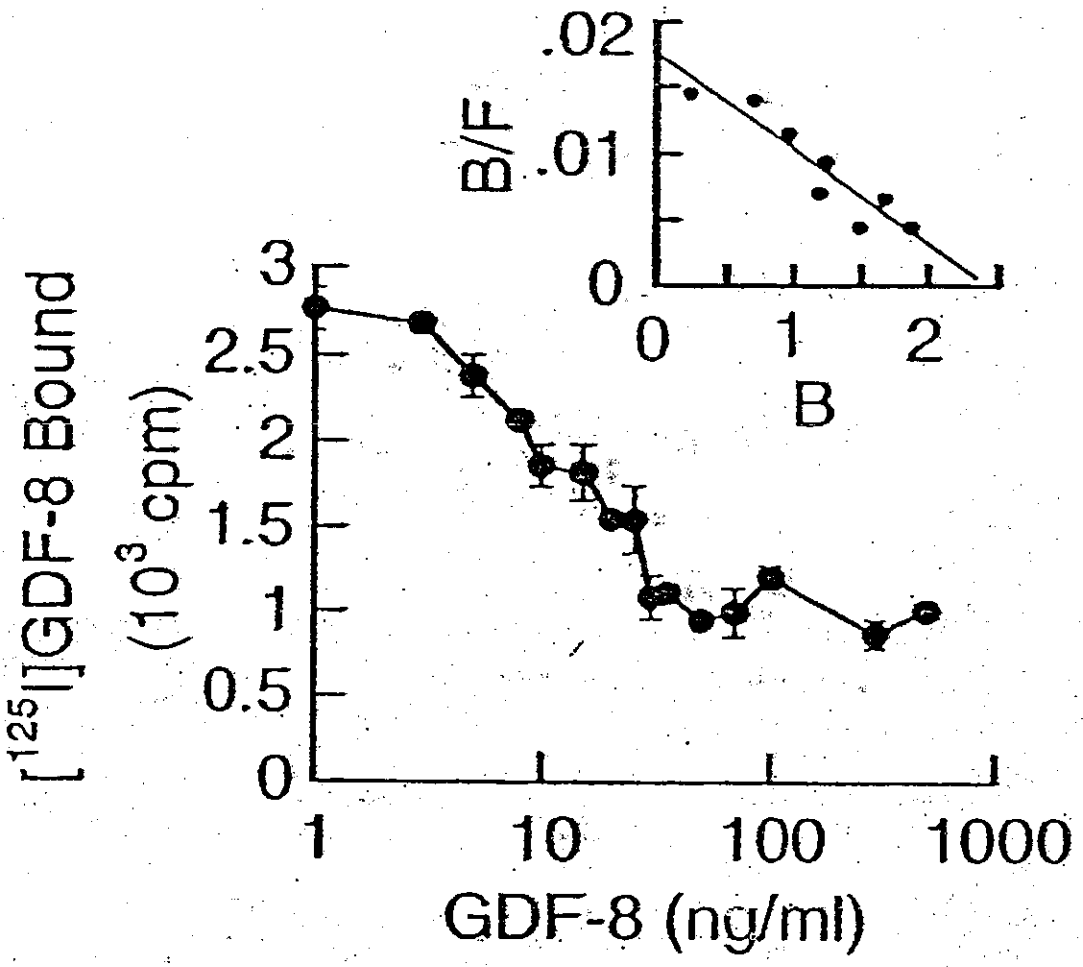

.02
B/F
.01
0
0
1
2
B
3
2.5
2
1.5
1
0.5
0
[125I]GDF-8 Bound
(10³ cpm)
1
10
100
1000
GDF-8 (ng/ml)

Fig. 5

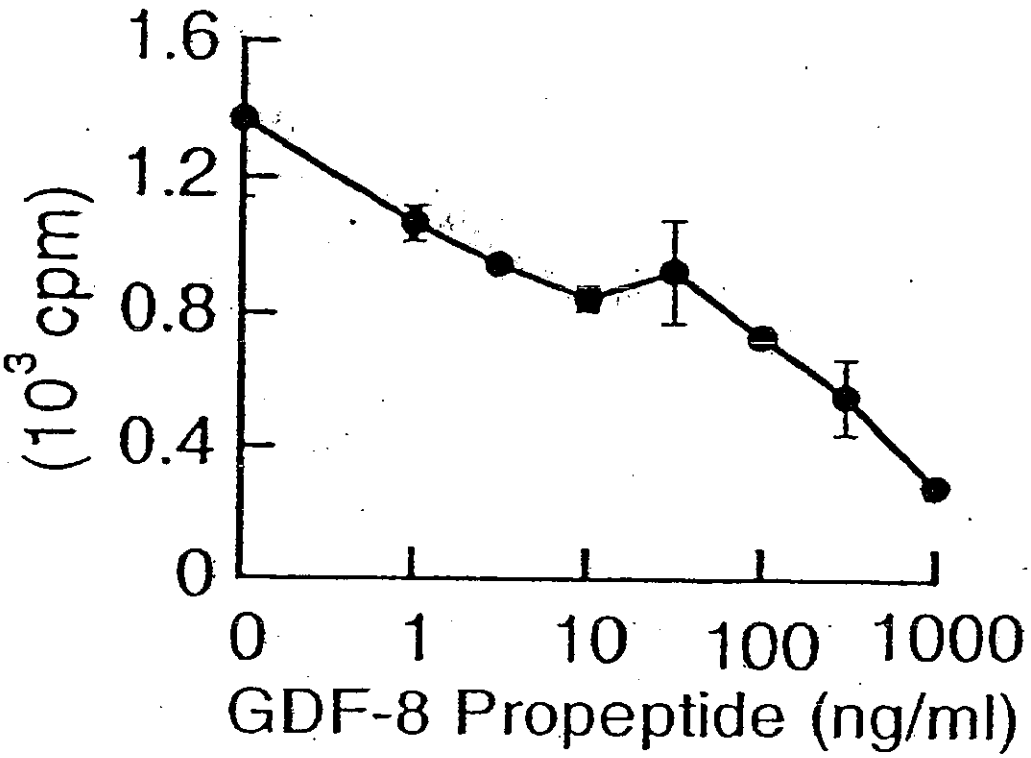
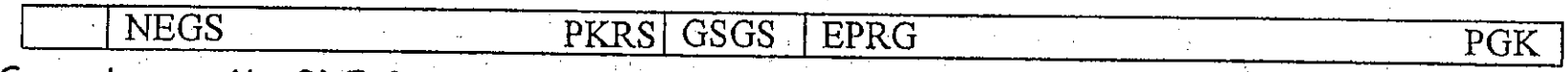


Fig. 6



MMQKLQMYVYIYLFMLIAAGPVDLNEGSEREENVEKEGLCNACAWRQNTRYSRIEAIKIQILSKLRLET
APNISKDAIRQLLPRAPPLRELIDQYDVQRDDSSDGSLEDDDYHATTETIITMPTESDFLMQADGKPKC
CFFKFSSKIQYNKVVKAQLWIYLRPVKTPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMSPGTGIWQSI
DVKTVLQNWLKQPESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKVTDTPKRSEPRGPTIKPCP
PCKCPAPNLEGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHRE
DYNSTLRVVSALPIQHQDWMSGKAFACAVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQV
TLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGL
HNHHTTKSFSRTPGK

Fig. 7A



MMQKLQMYVYIYLFMLIAAGPVDLNEGSEREENVEKEGLCNACAWRQNTRYSRIEAIKIQILSKLRLET
APNISKDAIRQLLPRAPPLRELIDQYDVQRDDSSDGSLEDDDYHATTETIITMPTESDFLMQADGKPKC
CFFKFSSKIQYNKVVKAQLWIYLRPVKTPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMSPGTGIWQSI
DVKTVLQNWLKQPESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKVTDTPKRSGSGSEPRGPTI
KPCPPCKCPAPNLEGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQ
THREDYNSTLRVVSALPIQHQDWMSGKAFACAVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMT
KKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYSCSVV
HEGLHNHHTTKSFSRTPGK

Fig. 7B

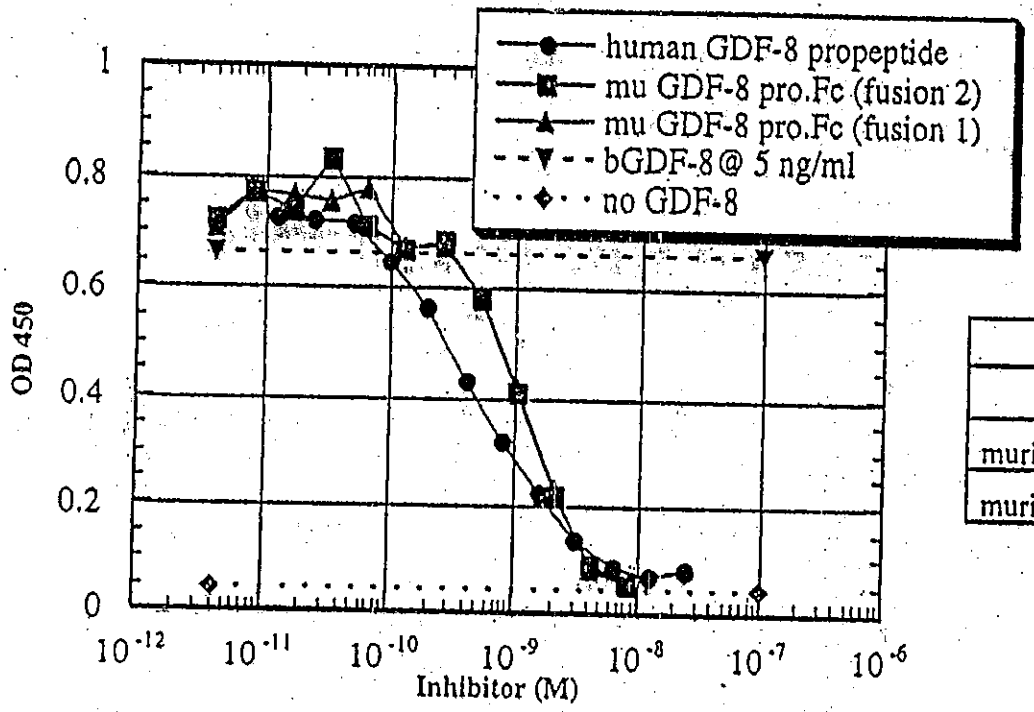


Fig. 8 A

Inhibitor	IC50 (M)
hu GDF-8 propeptide	6 x 10- 10
murine GDF-8 pro.Fc (Fusion 1)	1.3 x 10- 9
murine GDF-8 pro.Fc (Fusion 2)	1.3 x 10- 9

Fig. 8 B

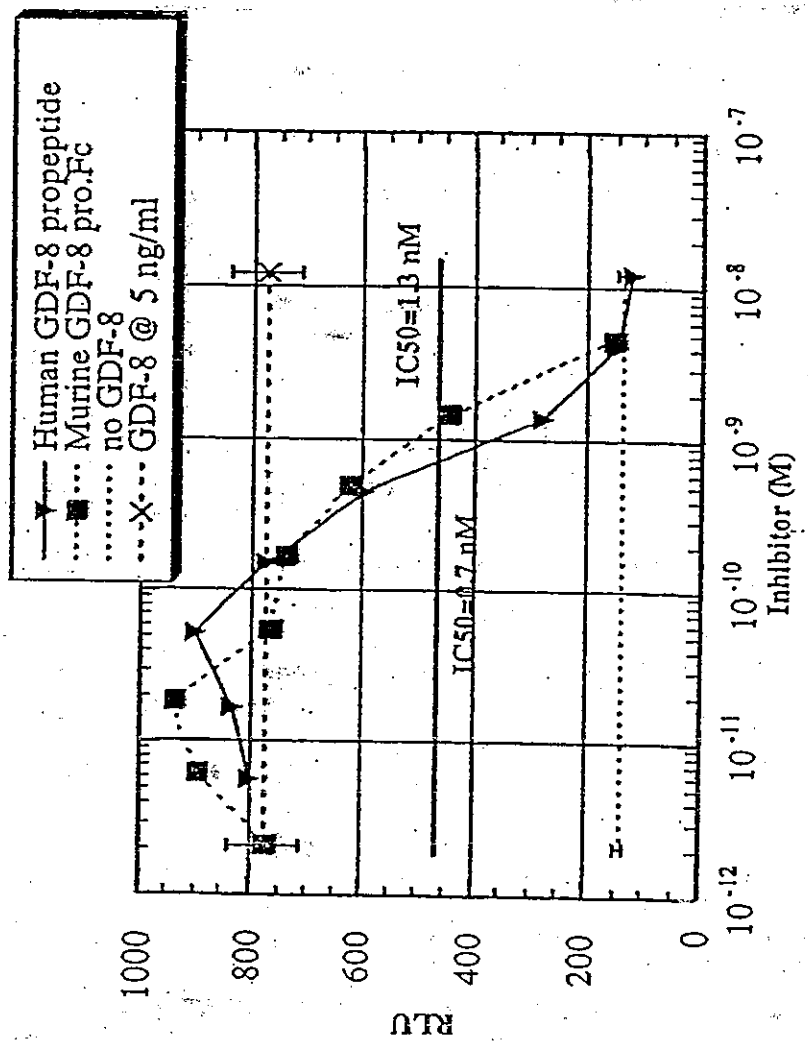

Human GDF-8 propeptide
Murine GDF-8 pro.Fc
no GDF-8
GDF-8 @ 5 ng/ml
IC50=1.3 nM
IC50=0.7 nM
RLU
Inhibitor (M)
0
200
400
600
800
1000
10-12
10-11
10-10
10-9
10-8
10-7

Fig. 9

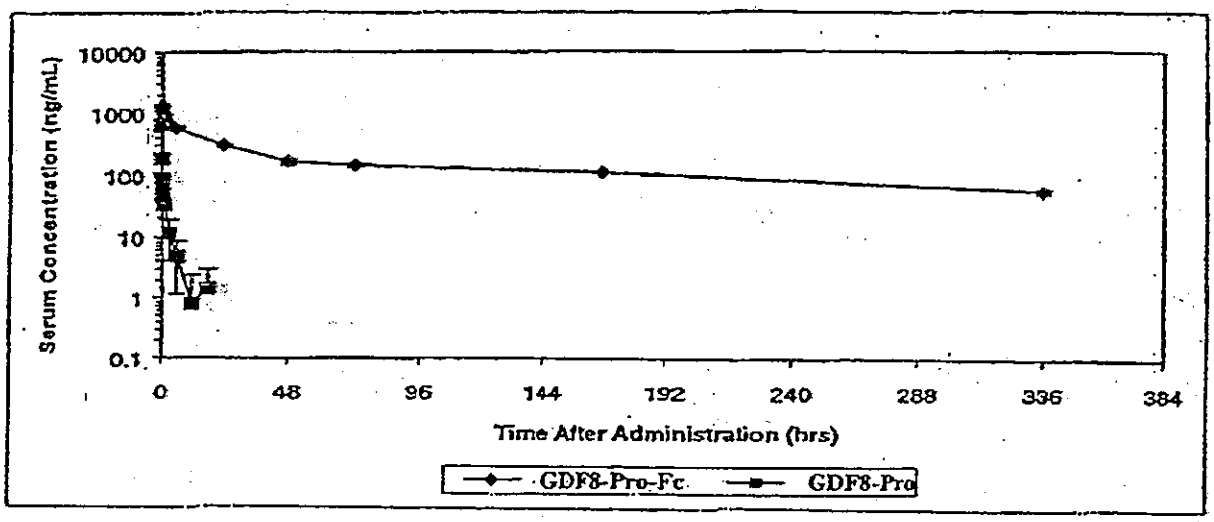

Serum Concentration (ng/mL)
10000
1000
100
10
1
0.1
0
48
96
144
192
240
288
336
384
Time After Administration (hrs)
GDF8-Pro-Fc
GDF8-Pro

Fig. 10



MQKLQLCVYIYLFMLIVAGPVDLNENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSKLRLETAPN
ISKDVIRQLLPKAPPLRELIDQYDVQRDDSSDGSLEDDDYHATTETIITMPTESDFLMQVDGKPKCCFFKF
SSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMNPGTGIWQSIDVKTVLQ
NWLKQPESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKVTDTPKRS**EPKSCDKTHTCPPCPAPELL**
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Fig. 11A



Secretory leader

Hu GDF-8 propeptide

Hu IgG1 Fc mutated

MQKLQLCVYIYLFMLIVAGPVDLNENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSKLRLETAPN
ISKDVIRQLLPKAPPLRELIDQYDVQRDDSSDGSLEDDDYHATTETIITMPTESDFLMQVDGKPKCCFFKF
SSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMNPGTGIWQSIDVKTVLQ
NWLKQPESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEVKVTDTPKRSDKTHTCPPCPAPEALGAPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Fig. 11B

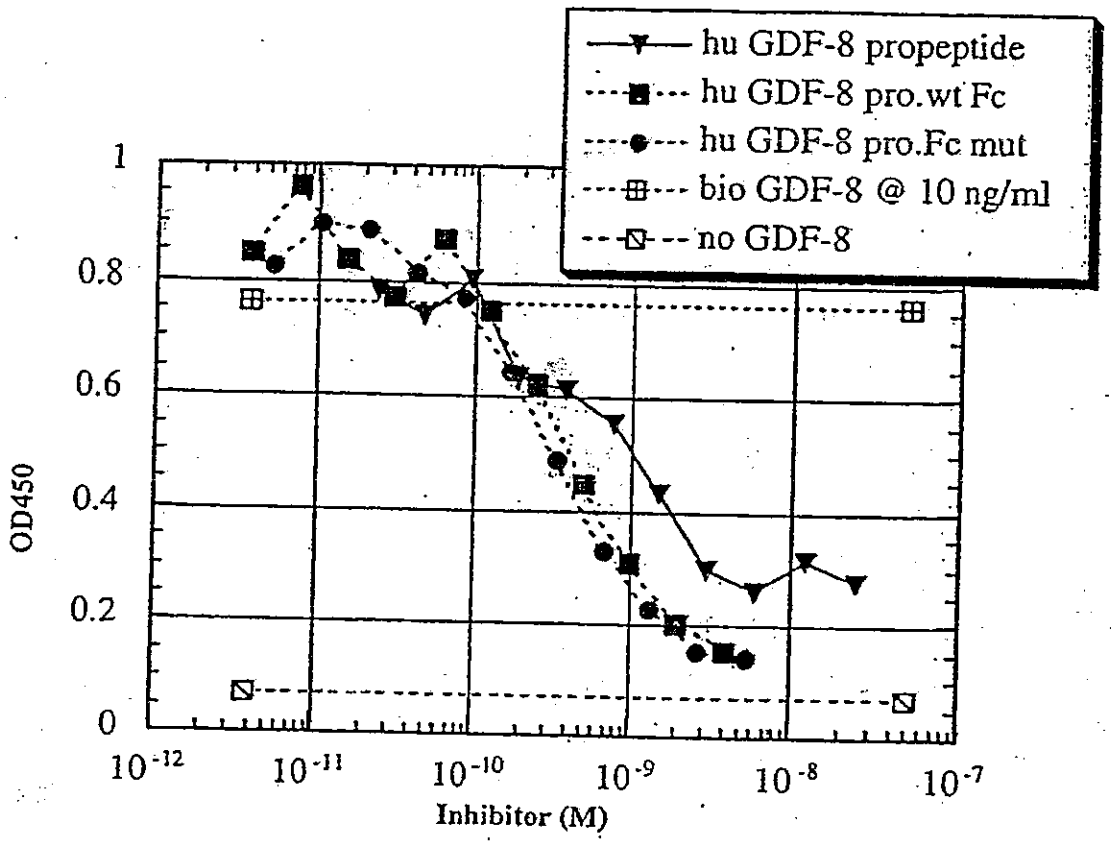

hu GDF-8 propeptide
hu GDF-8 pro.wt Fc
hu GDF-8 pro.Fc mut
bio GDF-8 @ 10 ng/ml
no GDF-8
OD450
1
0.8
0.6
0.4
0.2
0
10-12
10-11
10-10
10-9
10-8
10-7
Inhibitor (M)

Fig. 12

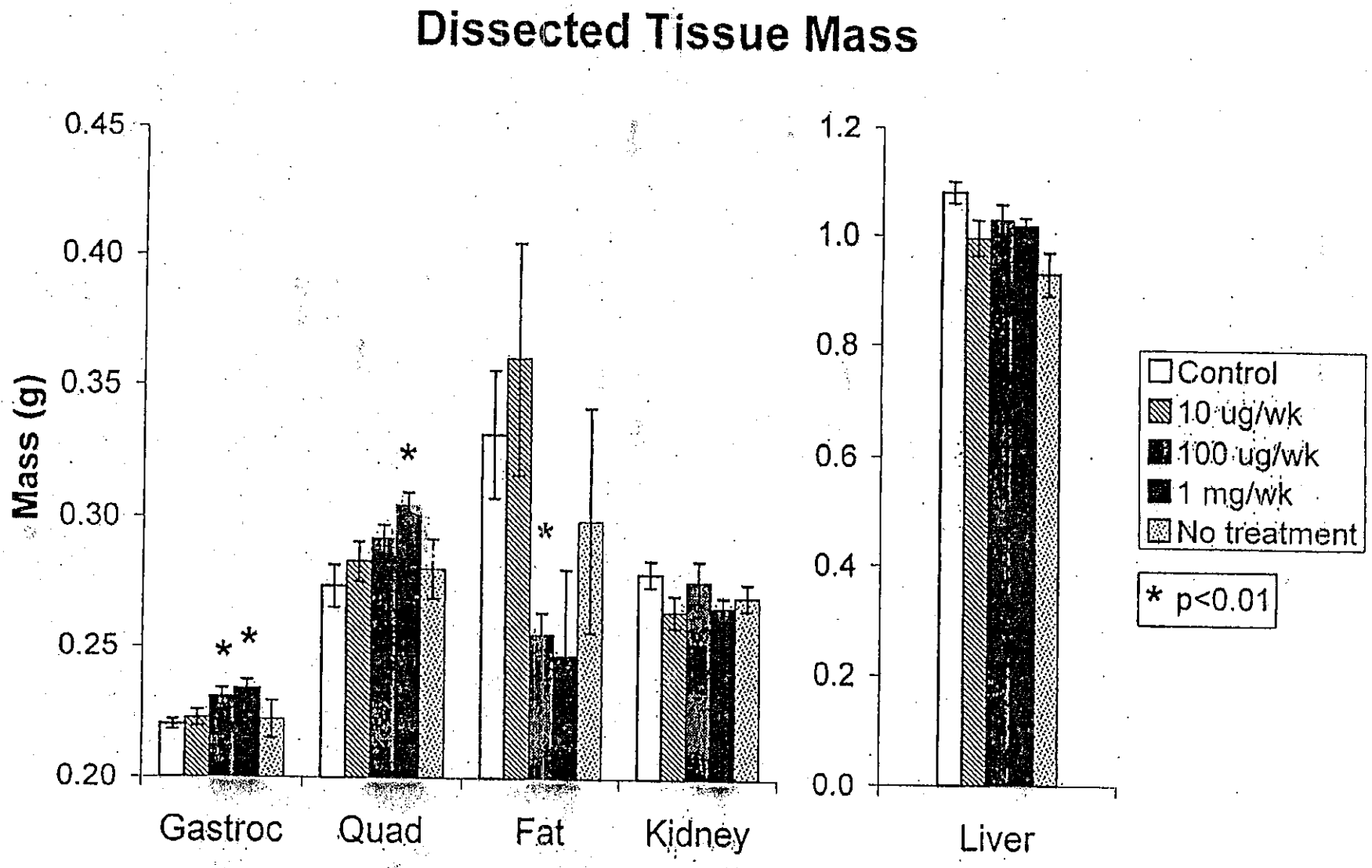

Dissected Tissue Mass
Mass (g)
0.45
0.40
0.35
0.30
0.25
0.20
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Gastroc
Quad
Fat
Kidney
Liver
Control
10 ug/wk
100 ug/wk
1 mg/wk
No treatment
* p<0.01

Figure 13

Fig. 14A

SEQ ID NO:1 Human GDF-8 precursor protein - protein sequence

MQKLQLCVYIYLFMLIVAGPVDLNENSEQKENVEKEGLCNACTWRQNTKSS
RIEAIKIQILSKLRLETAPNISKDVIRQLLPKAPPLRELIDQYDVQRDDSS
DGSLEDDDYHATTETIITMPTESDFLMQVDGKPKCCFFKFSSKIQYNKVVK
AQLWIYLRPVETPTTVFVQILRLIKPMKDGTRYTGIRSLKLDMNPGTGIWQ
SIDVKTVLQNWLKQPESNLGIEIKALDENGHDLAVTFPGPGEDGLNPFLEV
KVTDTPKRSRRDFGLDCDEHSTESRCCRYPLTVDFEAFGWDWIIAPKRYKA
NYCSGECEFVFLQKYPHTHLVHQANPRGSAGPCCTPTKMSPINMLYFNGKE
QIIYGKIPAMVVDRCGCS

Fig. 14B

SEQ ID NO:2 Human GDF-8 precursor protein - DNA sequence

ATGCAAAAACTGCAACTCTGTGTTTATATTTACCTGTTTATGCTGATTGT
TGCTGGTCCAGTGGATCTAAATGAGAACAGTGAGCAAAAAGAAAATGTGG
AAAAAGAGGGGCTGTGTAATGCATGTACTTGGAGACAAAACACTAAATCT
TCAAGAATAGAAGCCATTAAGATACAAATCCTCAGTAAACTTCGTCTGGA
AACAGCTCCTAACATCAGCAAAGATGTTATAAGACAACTTTTACCCAAAG
CTCCTCCACTCCGGGAACTGATTGATCAGTATGATGTCCAGAGGGATGAC
AGCAGCGATGGCTCTTTGGAAGATGACGATTATCACGCTACAACGGAAAC
AATCATTACCATGCCTACAGAGTCTGATTTTCTAATGCAAGTGGATGGAA
AACCCAAATGTTGCTTCTTTAAATTTAGCTCTAAAATACAATACAATAAA
GTAGTAAAGGCCCAACTATGGATATATTTGAGACCCGTCGAGACTCCTAC
AACAGTGTTTGTGCAAATCCTGAGACTCATCAAACCTATGAAAGACGGTA
CAAGGTATACTGGAATCCGATCTCTGAAACTTGACATGAACCCAGGCACT
GGTATTTGGCAGAGCATTGATGTGAAGACAGTGTTGCAAAATTGGCTCAA
ACAACCTGAATCCAACTTAGGCATTGAAATAAAAGCTTTAGATGAGAATG
GTCATGATCTTGCTGTAACCTTCCCAGGACCAGGAGAAGATGGGCTGAAT
CCGTTTTTAGAGGTCAAGGTAACAGACACACCAAAAAGATCCAGAAGGGA
TTTTGGTCTTGACTGTGATGAGCACTCAACAGAATCACGATGCTGTCGTT
ACCCTCTAACTGTGGATTTTGAAGCTTTTGGATGGGATTGGATTATCGCT
CCTAAAAGATATAAGGCCAATTACTGCTCTGGAGAGTGTGAATTTGTATT
TTTACAAAAATATCCTCATACTCATCTGGTACACCAAGCAAACCCCAGAG
GTTCAGCAGGCCCTTGCTGTACTCCCACAAAGATGTCTCCAATTAATATG
CTATATTTTAATGGCAAAGAACAAATAATATATGGGAAAATTCCAGCGAT
GGTAGTAGACCGCTGTGGGTGCTCA

Fig. 14C

SEQ ID NO:3 Human mature GDF-8 - protein sequence

DFGLDCDEHSTESRCCRYPLTVDFEAFGWDWIIAPKRYKANYCSGECEFVF
LQKYPHTHLVHQANPRGSAGPCCTPTKMSPINMLYFNGKEQIIYGKIPAMV
VDRCGCS

Fig. 14D

SEQ ID NO:4 Human mature GDF-8 - DNA sequence

GATTTTGGTCTTGACTGTGATGAGCACTCAACAGAATCACGATGCTGTCG
TTACCCTCTAACTGTGGATTTTGAAGCTTTTGGATGGGATTGGATTATCG
CTCCTAAAAGATATAAGGCCAATTACTGCTCTGGAGAGTGTGAATTTGTA
TTTTTACAAAAATATCCTCATACTCATCTGGTACACCAAGCAAACCCCAG
AGGTTCAGCAGGCCCTTGCTGTACTCCCACAAAGATGTCTCCAATTAATA
TGCTATATTTTAATGGCAAAGAACAAATAATATATGGGAAAATTCCAGCG
ATGGTAGTAGACCGCTGTGGGTGCTCA

Fig.14E

SEQ ID NO:5 Human GDF-8 propeptide - protein sequence

NENSEQKENVEKEGLCNACTWRQNTKSSRIEAIKIQILSKLRLETAPNISK
DVIRQLLPKAPPLRELIDQYDVQRDDSSDGSLEDDDYHATTETIITMPTES
DFLMQVDGKPKCCFFKFSSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRL
IKPMKDGTRYTGIRSLKLDMNPGTGIWQSIDVKTVLQNWLKQPESNLGIEI
KALDENGHDLAVTFPGPGEDGLNPFLEVKVTDTPKRSRR

Fig. 14F

SEQ ID NO:6 Human GDF-8 propeptide - DNA sequence

AATGAGAACAGTGAGCAAAAAGAAAATGTGGAAAAAGAGGGGCTGTGTAAT
GCATGTACTTGGAGACAAAACACTAAATCTTCAAGAATAGAAGCCATTAAG
ATACAAATCCTCAGTAAACTTCGTCTGGAAACAGCTCCTAACATCAGCAAA
GATGTTATAAGACAACTTTTACCCAAAGCTCCTCCACTCCGGGAACTGATT
GATCAGTATGATGTCCAGAGGGATGACAGCAGCGATGGCTCTTTGGAAGAT
GACGATTATCACGCTACAACGGAAACAATCATTACCATGCCTACAGAGTCT
GATTTTCTAATGCAAGTGGATGGAAAACCCAAATGTTGCTTCTTTAAATTT
AGCTCTAAAATACAATACAATAAAGTAGTAAAGGCCCAACTATGGATATAT
TTGAGACCCGTCGAGACTCCTACAACAGTGTTTGTGCAAATCCTGAGACTC
ATCAAACCTATGAAAGACGGTACAAGGTATACTGGAATCCGATCTCTGAAA
CTTGACATGAACCCAGGCACTGGTATTTGGCAGAGCATTGATGTGAAGACA
GTGTTGCAAAATTGGCTCAAACAACCTGAATCCAACTTAGGCATTGAAATA
AAAGCTTTAGATGAGAATGGTCATGATCTTGCTGTAACCTTCCCAGGACCA
GGAGAAGATGGGCTGAATCCGTTTTTAGAGGTCAAGGTAACAGACACACCA
AAAAGATCCAGAAGG

Fig. 14G

SEQ ID NO:7 Human BMP-11 precursor protein - protein sequence

MVLAAPLLLGFLLLALELRPRGEAAEGPAAAAAAAAAAAAAGVGGERSSRP
APSVAPEPDGCPVCVWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQ
LLPKAPPLQQILDLHDFQGDALQPEDFLEEDEYHATTETVISMAQETDPAV
QTDGSPLCCHFHFSPKVMFTKVLKAQLWVYLRPVPRPATVYLQILRLKPLT
GEGTAGGGGGRRHIRIRSLKIELHSRSGHWQSIDFKQVLHSWFRQPQSNW
GIEINAFDPSGTDLAVTSLGPGAEGLHPFMELRVLENTKRSRRNLGLDCDE
HSSESRCCRYPLTVDFEAFGWDWIIAPKRYKANYCSGQCEYMFMQKYPHTH
LVQQANPRGSAGPCCTPTKMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS

Fig. 14H

SEQ ID NO:8 Human BMP-11 precursor protein - DNA sequence

ATGGTGCTCGCGGCCCCGCTGCTGCTGGGCTTCCTGCTCCTCGCCCTGGA
GCTGCGGCCCCGGGGGGAGGCGGCCGAGGGCCCCGCGGCGGCGGCGGCGG
CGGCGGCGGCGGCGGCAGCGGCGGGGGTCGGGGGGGAGCGCTCCAGCCGG
CCAGCCCCGTCCGTGGCGCCCGAGCCGGACGGCTGCCCCGTGTGCGTTTG
GCGGCAGCACAGCCGCGAGCTGCGCCTAGAGAGCATCAAGTCGCAGATCT
TGAGCAAACTGCGGCTCAAGGAGGCGCCCAACATCAGCCGCGAGGTGGTG
AAGCAGCTGCTGCCCAAGGCGCCGCCGCTGCAGCAGATCCTGGACCTACA
CGACTTCCAGGGCGACGCGCTGCAGCCCGAGGACTTCCTGGAGGAGGACG
AGTACCACGCCACCACCGAGACCGTCATTAGCATGGCCCAGGAGACGGAC
CCAGCAGTACAGACAGATGGCAGCCCTCTCTGCTGCCATTTTCACTTCAG
CCCCAAGGTGATGTTCACAAAGGTACTGAAGGCCCAGCTGTGGGTGTACC
TACGGCCTGTACCCCGCCCAGCCACAGTCTACCTGCAGATCTTGCGACTA
AAACCCCTAACTGGGGAAGGGACCGCAGGGGGAGGGGGCGGAGGCCGGCG
TCACATCCGTATCCGCTCACTGAAGATTGAGCTGCACTCACGCTCAGGCC
ATTGGCAGAGCATCGACTTCAAGCAAGTGCTACACAGCTGGTTCCGCCAG
CCACAGAGCAACTGGGGCATCGAGATCAACGCCTTTGATCCCAGTGGCAC
AGACCTGGCTGTCACCTCCCTGGGGCCGGGAGCCGAGGGGCTGCATCCAT
TCATGGAGCTTCGAGTCCTAGAGAACACAAAACGTTCCCGGCGGAACCTG
GGTCTGGACTGCGACGAGCACTCAAGCGAGTCCCGCTGCTGCCGATATCC
CCTCACAGTGGACTTTGAGGCTTTCGGCTGGGACTGGATCATCGCACCTA
AGCGCTACAAGGCCAACTACTGCTCCGGCCAGTGCGAGTACATGTTCATG
CAAAAATATCCGCATACCCATTTGGTGCAGCAGGCCAATCCAAGAGGCTC
TGCTGGGCCCTGTTGTACCCCCACCAAGATGTCCCCAATCAACATGCTCT
ACTTCAATGACAAGCAGCAGATTATCTACGGCAAGATCCCTGGCATGGTG
GTGGATCGCTGTGGCTGCTCT

Fig. 14I

SEQ ID NO:9 Human BMP-11 mature - protein sequence

NLGLDCDEHSSESRCCRYPLTVDFEAFGWDWIIAPKRYKANYCSGQCEYMF
MQKYPHTHLVQQANPRGSAGPCCTPTKMSPINMLYFNDKQQIIYGKIPGMV
VDRCGCS

Fig. 14J

SEQ ID NO:10 Human BMP-11 mature - DNA sequence

AACCTGGGTCTGGACTGCGACGAGCACTCAAGCGAGTCCCGCTGCTGCCG
ATATCCCCTCACAGTGGACTTTGAGGCTTTCGGCTGGGACTGGATCATCG
CACCTAAGCGCTACAAGGCCAACTACTGCTCCGGCCAGTGCGAGTACATG
TTCATGCAAAAATATCCGCATACCCATTTGGTGCAGCAGGCCAATCCAAG
AGGCTCTGCTGGGCCCTGTTGTACCCCCACCAAGATGTCCCCAATCAACA
TGCTCTACTTCAATGACAAGCAGCAGATTATCTACGGCAAGATCCCTGGC
ATGGTGGTGGATCGCTGTGGCTGCTCT

Fig. 14K

SEQ ID NO:11 Human BMP-11 propeptide - protein sequence

AEGPAAAAAAAAAAAAAGVGGERSSRPAPSVAPEPDGCPVCVWRQHSRELR
LESIKSQILSKLRLKEAPNISREVVKQLLPKAPPLQQILDLHDFQGDALQP
EDFLEEDEYHATTETVISMAQETDPAVQTDGSPLCCHFHFSPKVMFTKVLK
AQLWVYLRPVPRPATVYLQILRLKPLTGEGTAGGGGGRRHIRIRSLKIEL
HSRSGHWQSIDFKQVLHSWFRQPQSNWGIEINAFDPSGTDLAVTSLGPGAE
GLHPFMELRVLENTKRSRR

Fig. 14L

SEQ ID NO:12 Human BMP-11 propeptide - DNA sequence

GCCGAGGGCCCCGCGGCGGCGGCGGCGGCGGCGGCGGCGGCGGCAGCGGC
GGGGGTCGGGGGGGGAGCGCTCCAGCCGGCCAGCCCCGTCCGTGGCGCCCG
AGCCGGACGGCTGCCCCGTGTGCGTTTGGCGGCAGCACAGCCGCGAGCTG
CGCCTAGAGAGCATCAAGTCGCAGATCTTGAGCAAACTGCGGCTCAAGGA
GGCGCCCAACATCAGCCGCGAGGTGGTGAAGCAGCTGCTGCCCAAGGCGC
CGCCGCTGCAGCAGATCCTGGACCTACACGACTTCCAGGGCGACGCGCTG
CAGCCCGAGGACTTCCTGGAGGAGGACGAGTACCACGCCACCACCGAGAC
CGTCATTAGCATGGCCCAGGAGACGGACCCAGCAGTACAGACAGATGGCA
GCCCTCTCTGCTGCCATTTTCACTTCAGCCCCAAGGTGATGTTCACAAAG
GTACTGAAGGCCCAGCTGTGGGTGTACCTACGGCCTGTACCCCGCCCAGC
CACAGTCTACCTGCAGATCTTGCGACTAAAACCCCTAACTGGGGAAGGGA
CCGCAGGGGGAGGGGGCGGAGGCCGGCGTCACATCCGTATCCGCTCACTG
AAGATTGAGCTGCACTCACGCTCAGGCCATTGGCAGAGCATCGACTTCAA
GCAAGTGCTACACAGCTGGTTCCGCCAGCCACAGAGCAACTGGGGCATCG
AGATCAACGCCTTTGATCCCAGTGGCACAGACCTGGCTGTCACCTCCCTG
GGGCCGGGAGCCGAGGGGCTGCATCCATTCATGGAGCTTCGAGTCCTAGA
GAACACAAAACGTTCCCGGCGG

Fig. 14M

SEQ ID NO:13 GDF-8 signal sequence - protein sequence

MQKLQLCVYIYLFMLIVAGPVDL

Fig. 14N

SEQ ID NO:14 BMP-11 signal sequence - protein sequence

MVLAAPLLLGFLLLALELRPRGEA

Fig. 14O

SEQ ID NO:15 Human IgG1-Fc - protein sequence

EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL
VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK

Fig. 14P

SEQ ID NO:16 Human IgG1-Fc modified - protein sequence

DKTHTCPPCPAPEALGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPGK