FIG. 1A

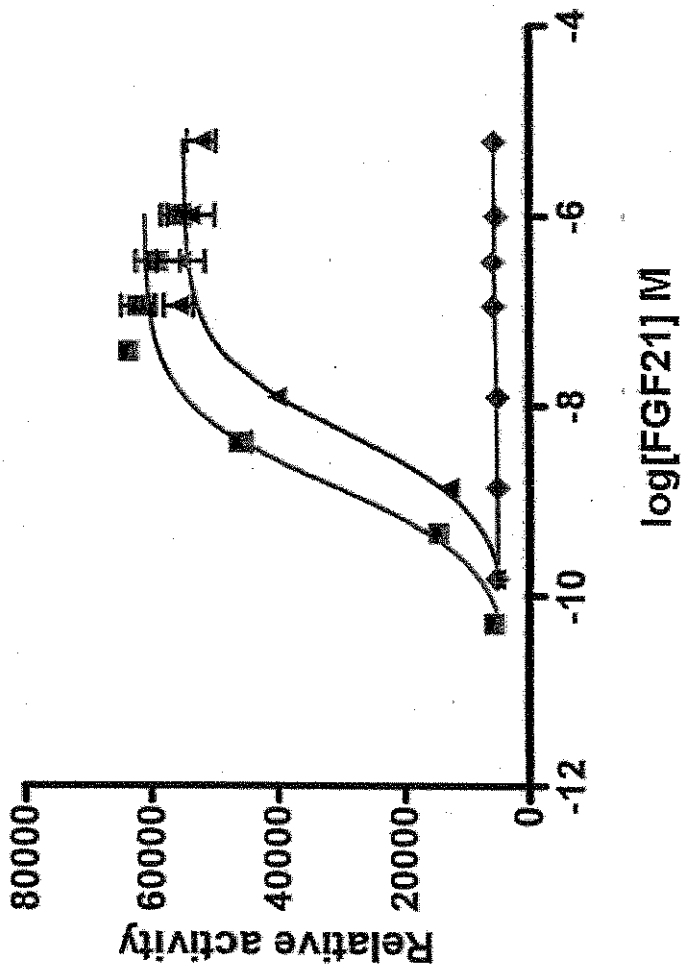

FGF21
7-181
8-181
Relative activity
80000
60000
40000
20000
0
-12
-10
-8
-6
-4
log[FGF21] M

FIG. 1B

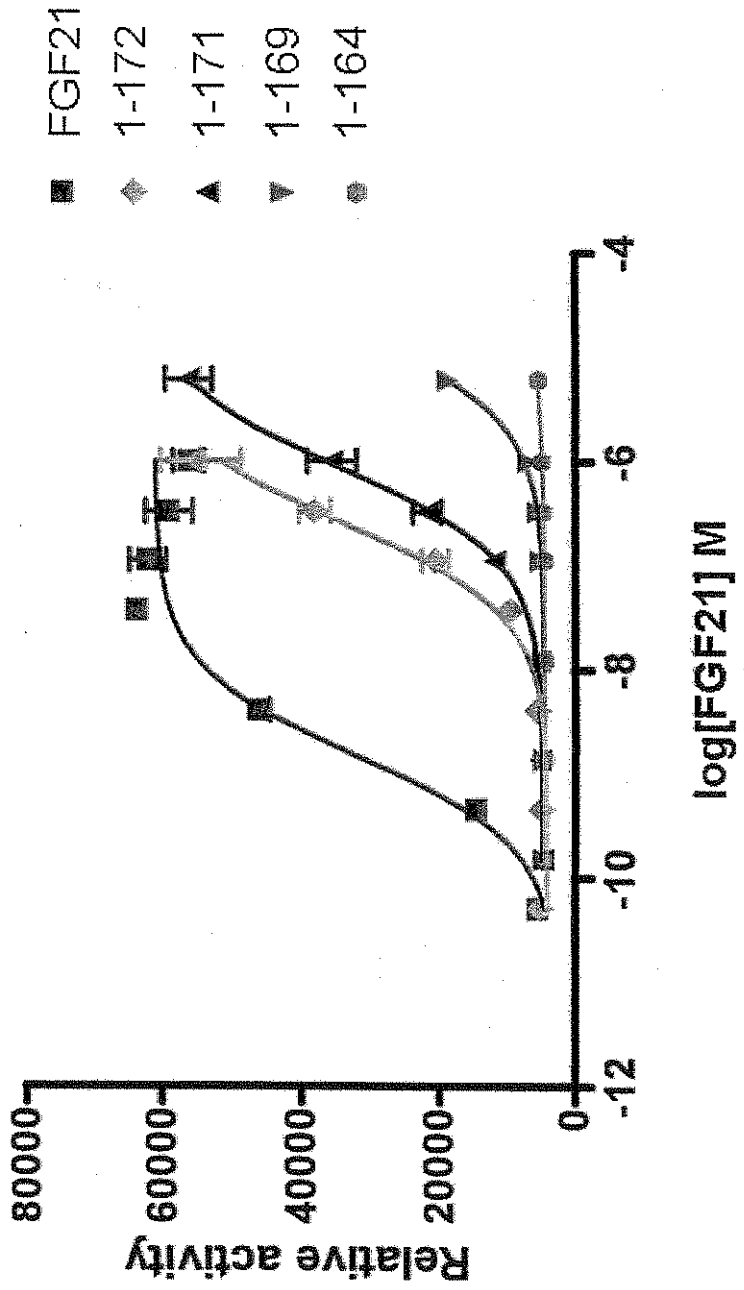

FGF21
1-172
1-171
1-169
1-164
Relative activity
80000
60000
40000
20000
0
-12
-10
-8
-6
-4
log[FGF21] M

FIG. 2

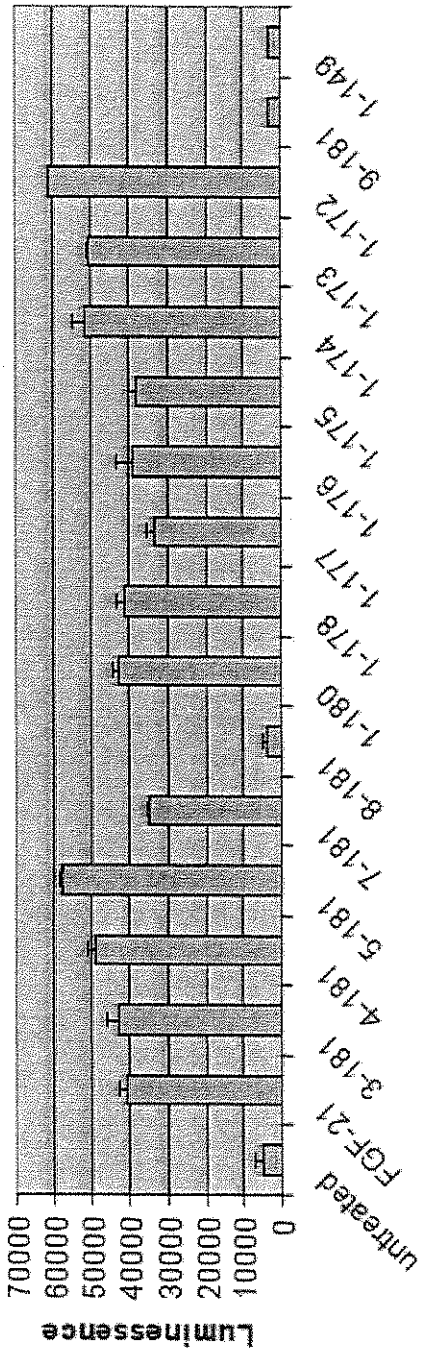

Luminessence
70000
60000
50000
40000
30000
20000
10000
0
untreated
FGF-21
3-181
4-181
5-181
7-181
8-181
1-180
1-178
1-177
1-176
1-175
1-174
1-173
1-172
9-181
1-149

FIG. 3

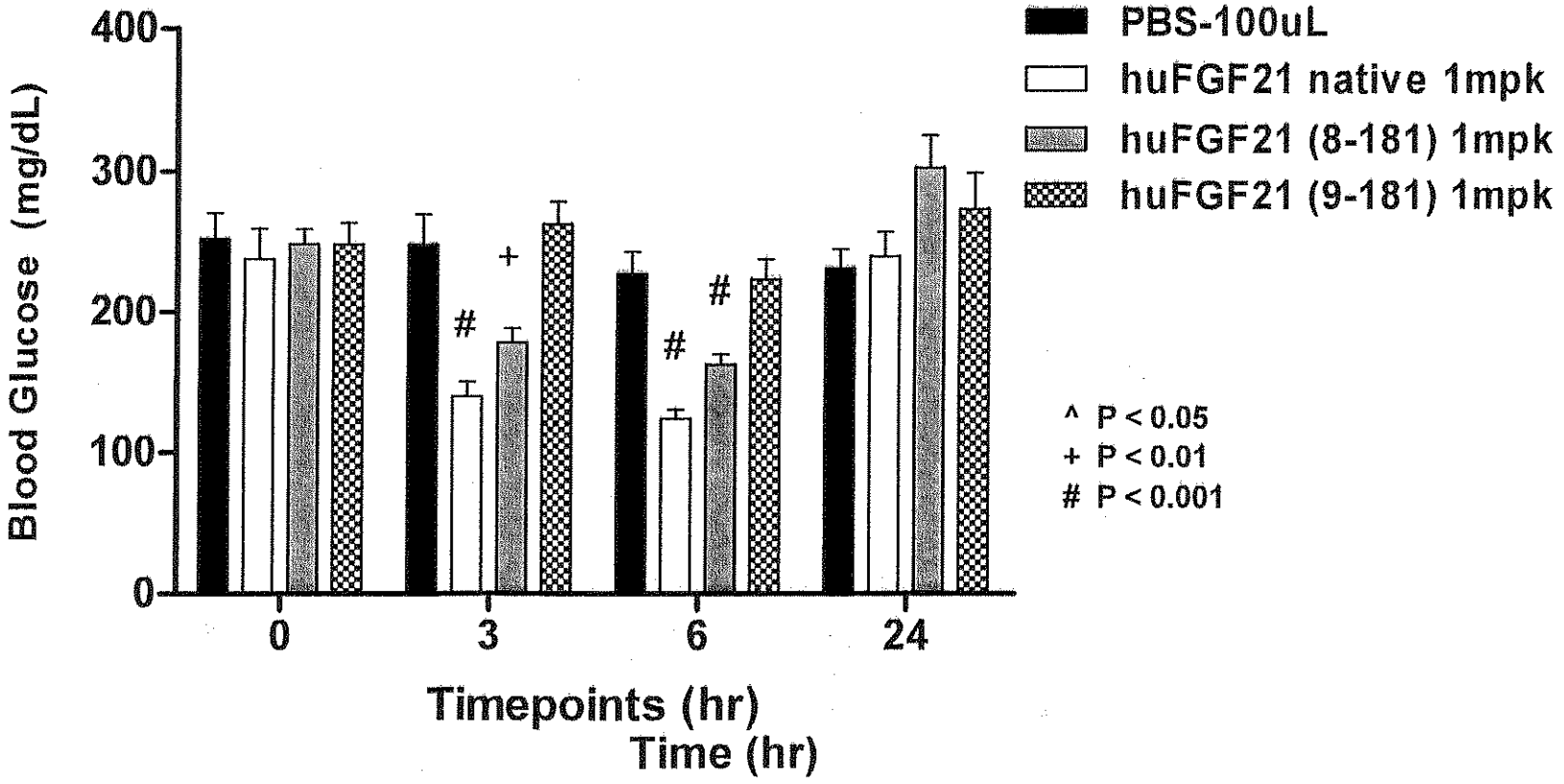

Blood Glucose (mg/dL)
400
300
200
100
0
0
3
6
24
Timepoints (hr)
Time (hr)
PBS-100uL
huFGF21 native 1mpk
huFGF21 (8-181) 1mpk
huFGF21 (9-181) 1mpk
^ P < 0.05
+ P < 0.01
# P < 0.001

FIG. 4

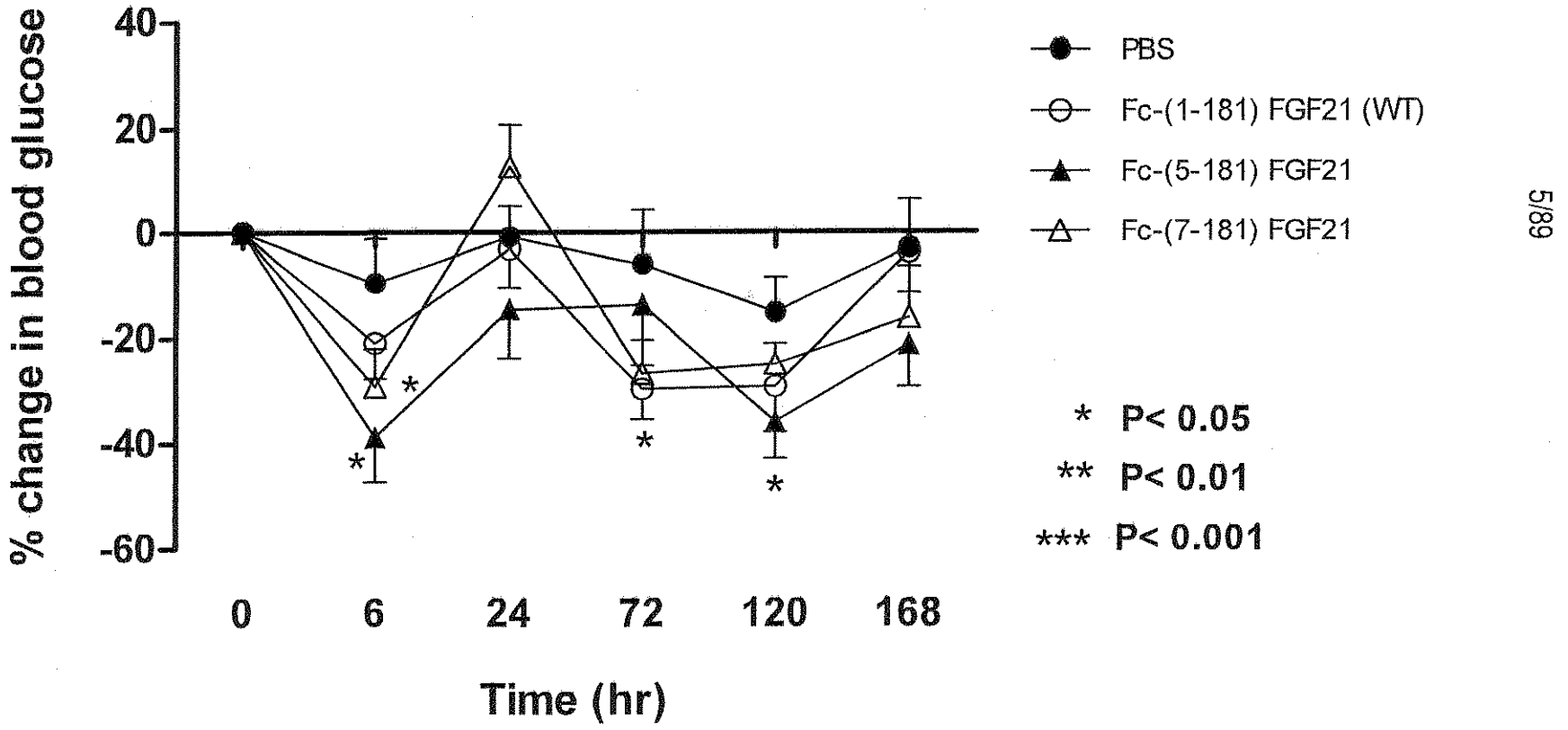

% change in blood glucose
40
20
0
-20
-40
-60
0
6
24
72
120
168
Time (hr)
PBS
Fc-(1-181) FGF21 (WT)
Fc-(5-181) FGF21
Fc-(7-181) FGF21
* P< 0.05
** P< 0.01
*** P< 0.001

FIG. 5

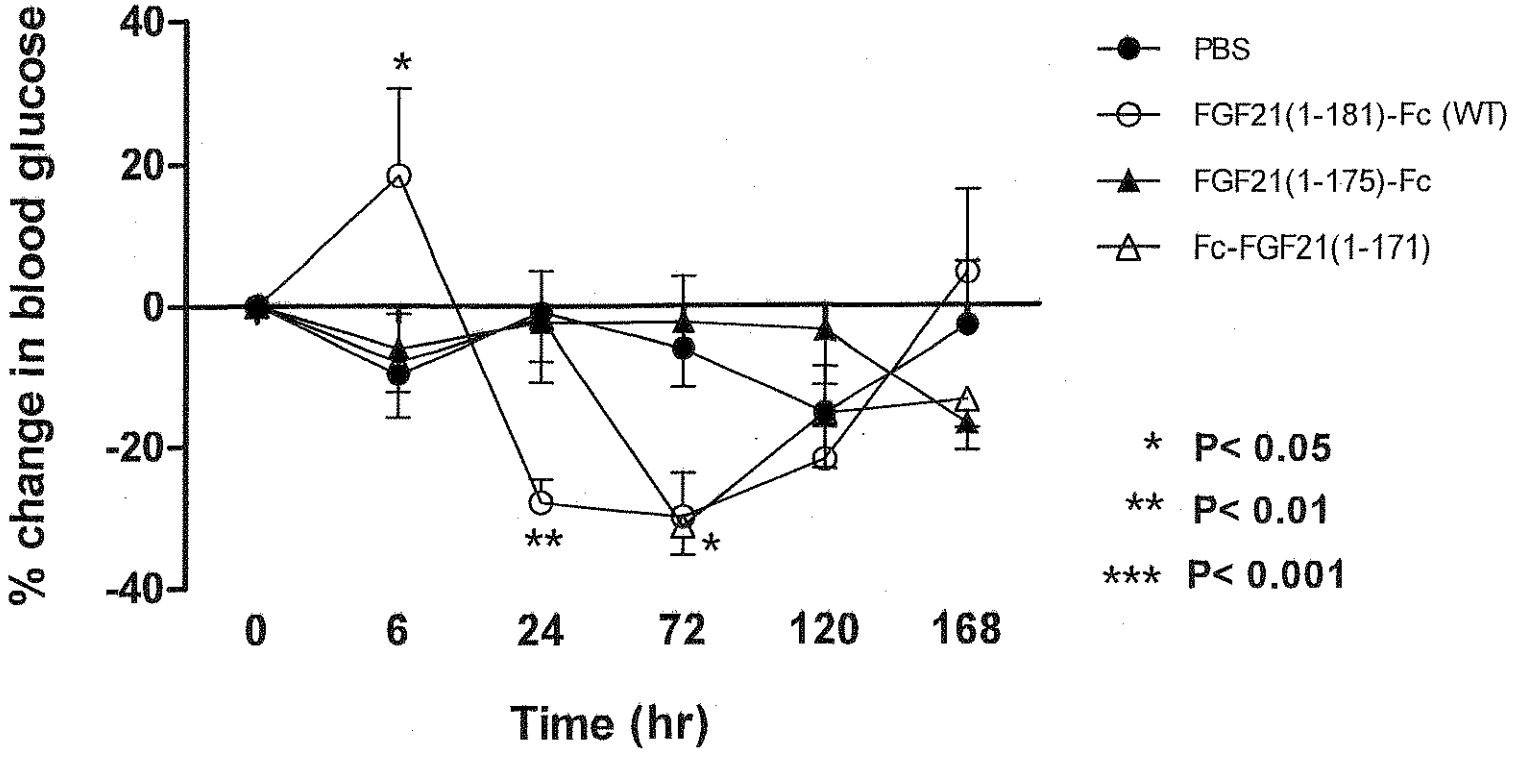

% change in blood glucose
40
20
0
-20
-40
0
6
24
72
120
168
Time (hr)
*
**
*
PBS
FGF21(1-181)-Fc (WT)
FGF21(1-175)-Fc
Fc-FGF21(1-171)
* P< 0.05
** P< 0.01
*** P< 0.001

FIG. 6A

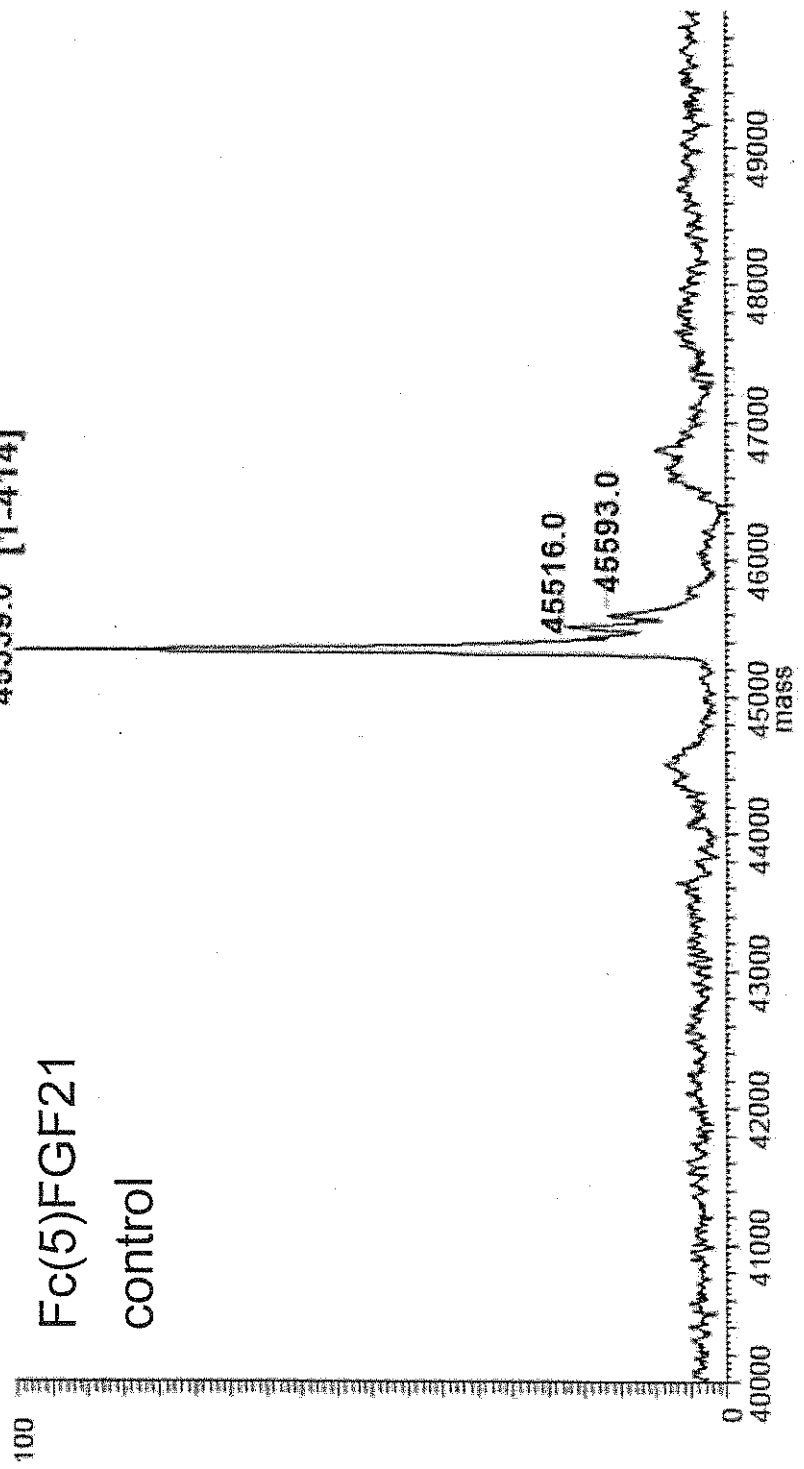

Fc(5)FGF21
control
45339.0 [1-414]
45516.0
45593.0
100
0
40000
41000
42000
43000
44000
45000
46000
47000
48000
49000
mass

FIG. 6B

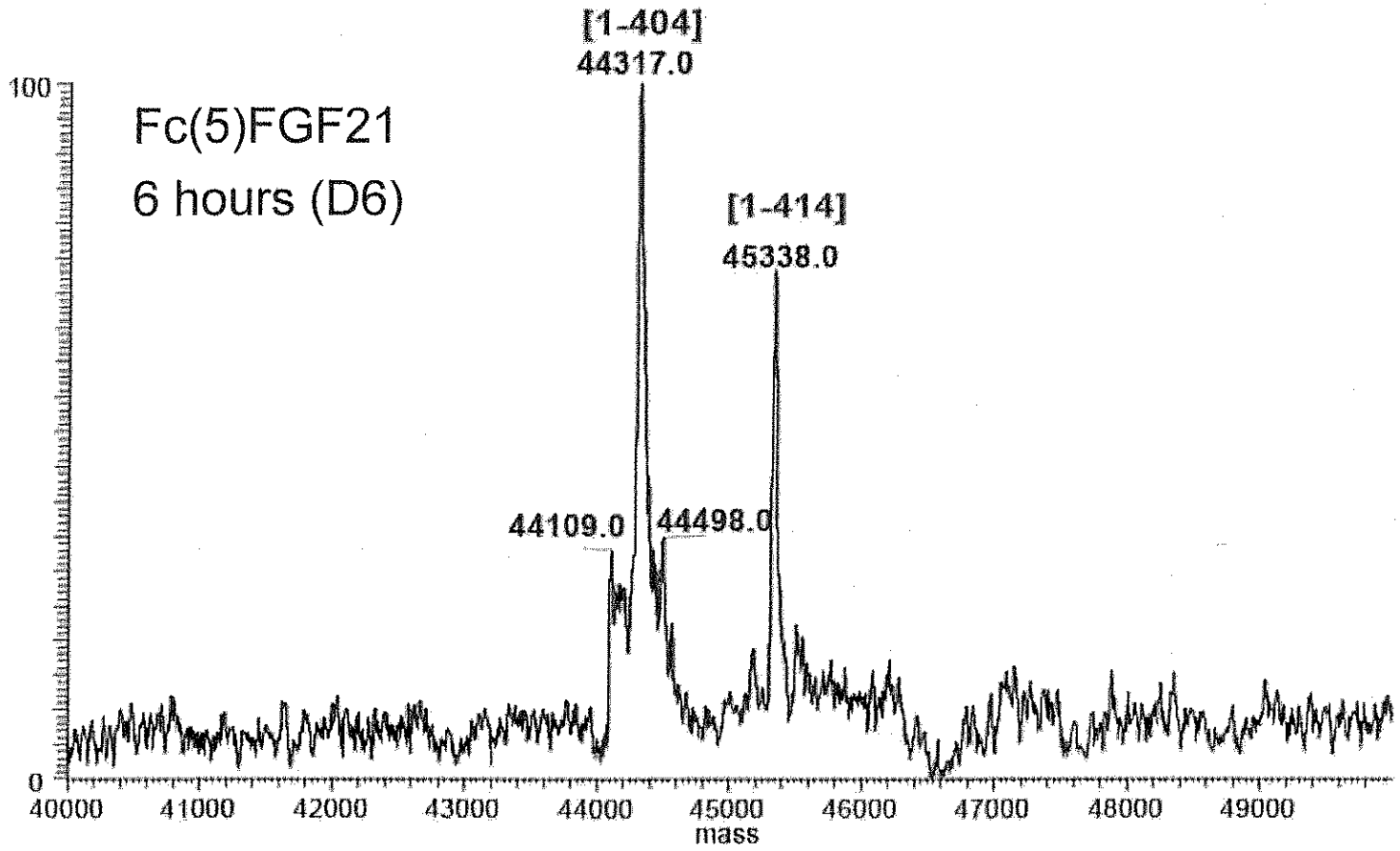

[1-404]
44317.0
Fc(5)FGF21
6 hours (D6)
[1-414]
45338.0
44109.0
44498.0
100
0
40000
41000
42000
43000
44000
45000
46000
47000
48000
49000
mass

FIG. 6C

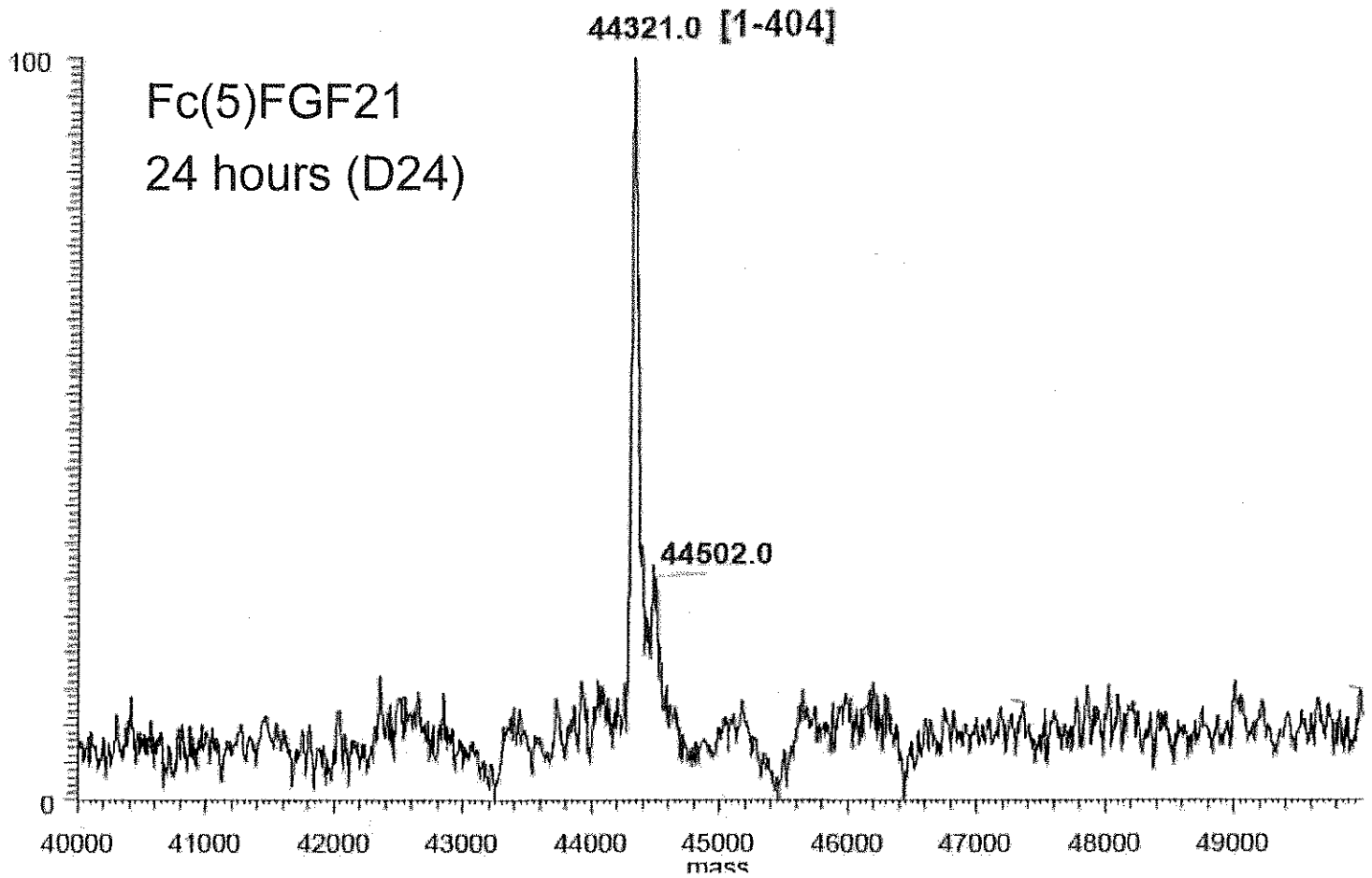

44321.0 [1-404]
Fc(5)FGF21
24 hours (D24)
44502.0
100
0
40000
41000
42000
43000
44000
45000
46000
47000
48000
49000
mass

FIG. 6D

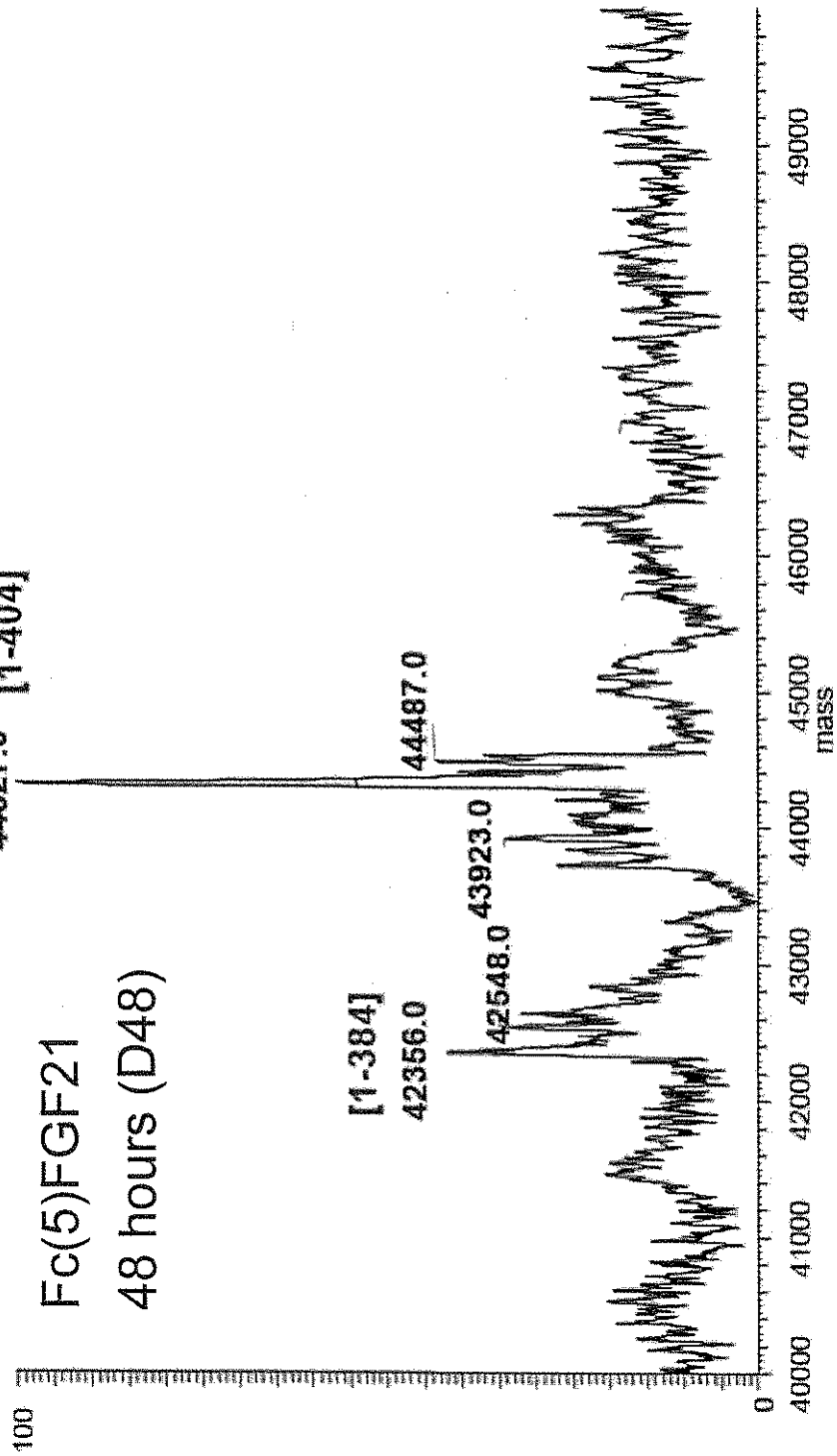

Fc(5)FGF21
48 hours (D48)
44327.0
[1-404]
44487.0
[1-384]
42356.0
42548.0
43923.0
100
0
40000
41000
42000
43000
44000
45000
46000
47000
48000
49000
mass

FIG. 7A

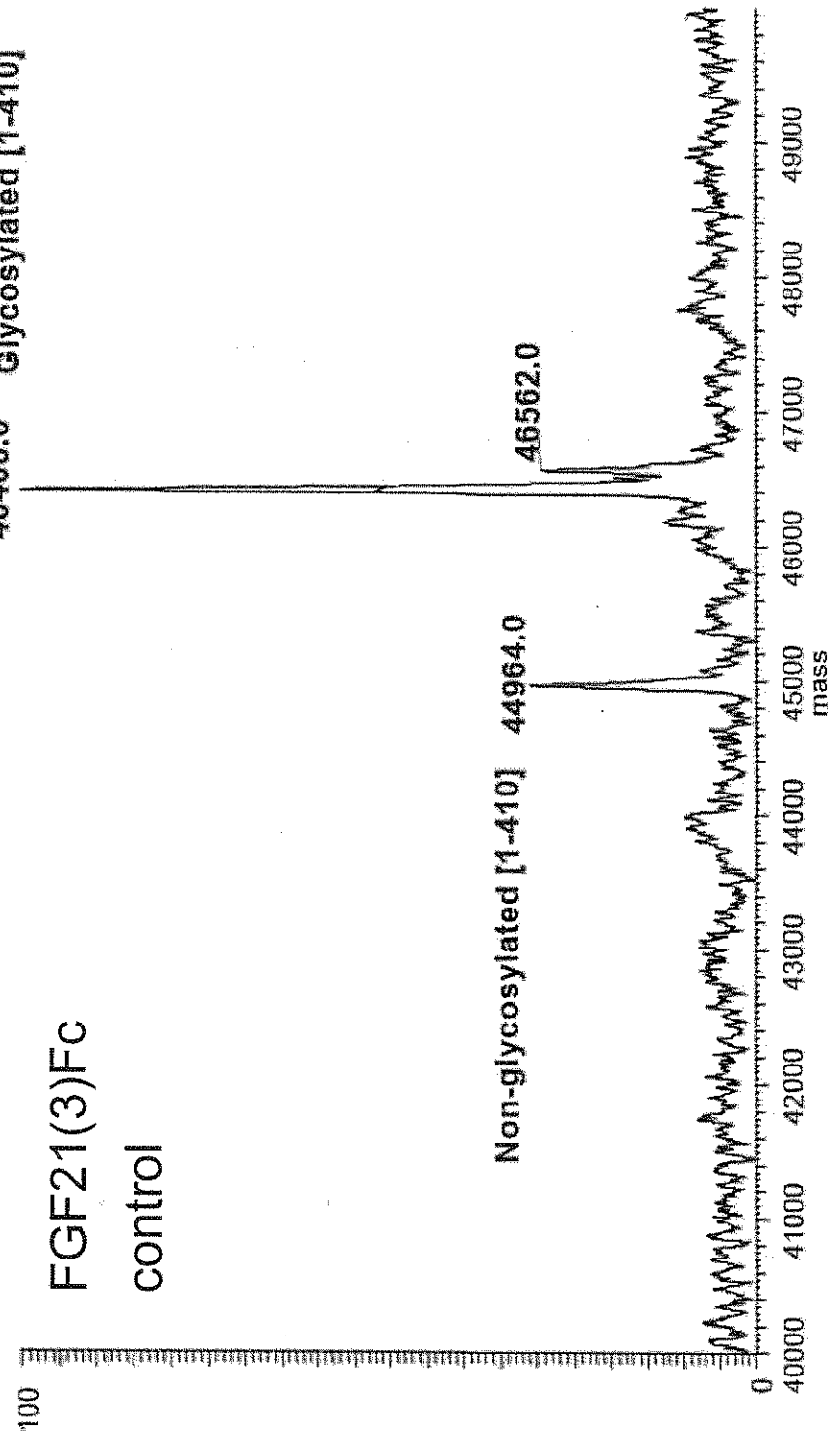

FGF21(3)Fc
control
Glycosylated [1-410]
46408.0
46562.0
Non-glycosylated [1-410]
44964.0
100
0
40000
41000
42000
43000
44000
45000
46000
47000
48000
49000
mass

FIG. 7B

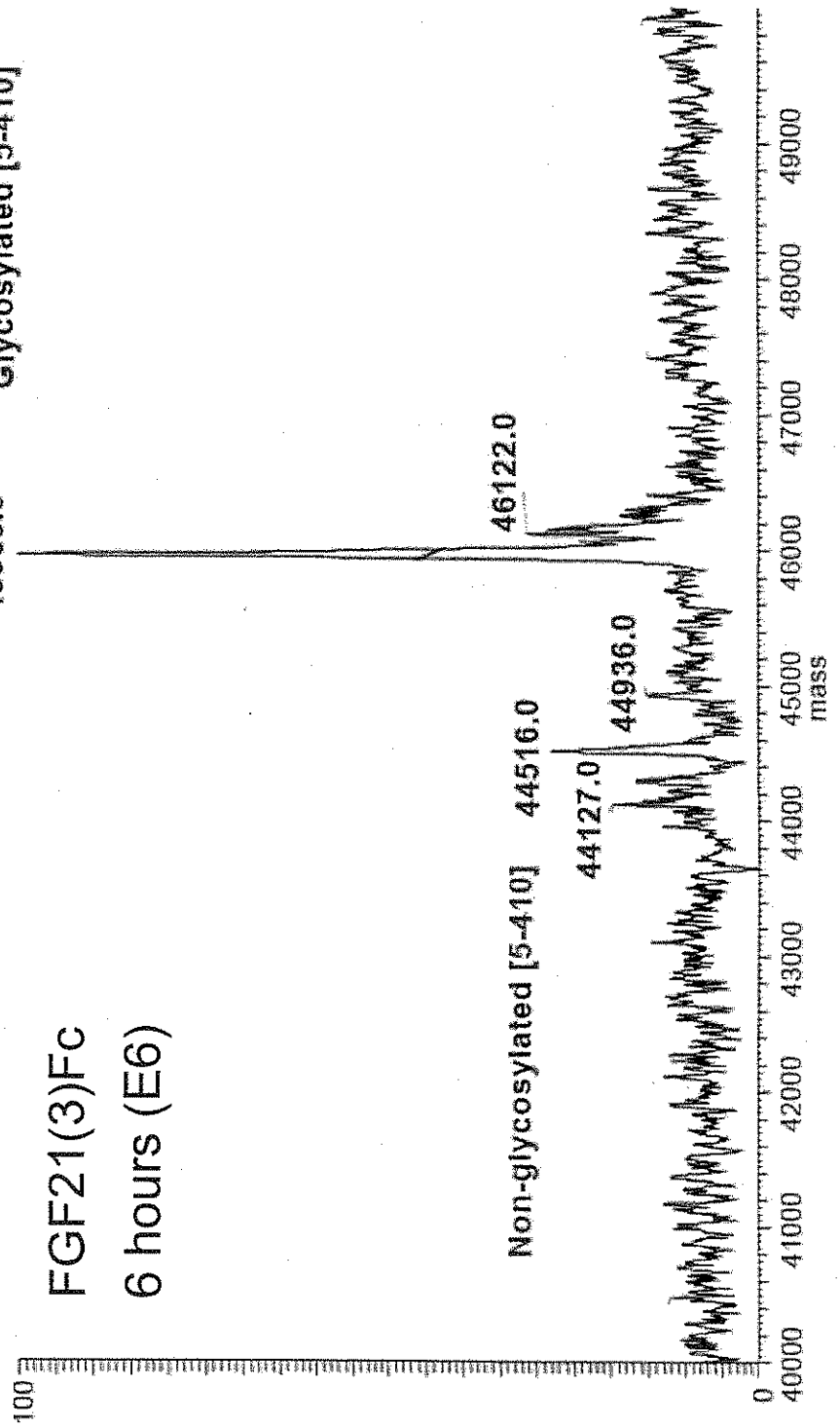

FGF21(3)Fc
6 hours (E6)
Glycosylated [5-410]
45963.0
46122.0
Non-glycosylated [5-410]
44516.0
44127.0
44936.0
100
0
40000
41000
42000
43000
44000
45000
46000
47000
48000
49000
mass

FIG. 7C

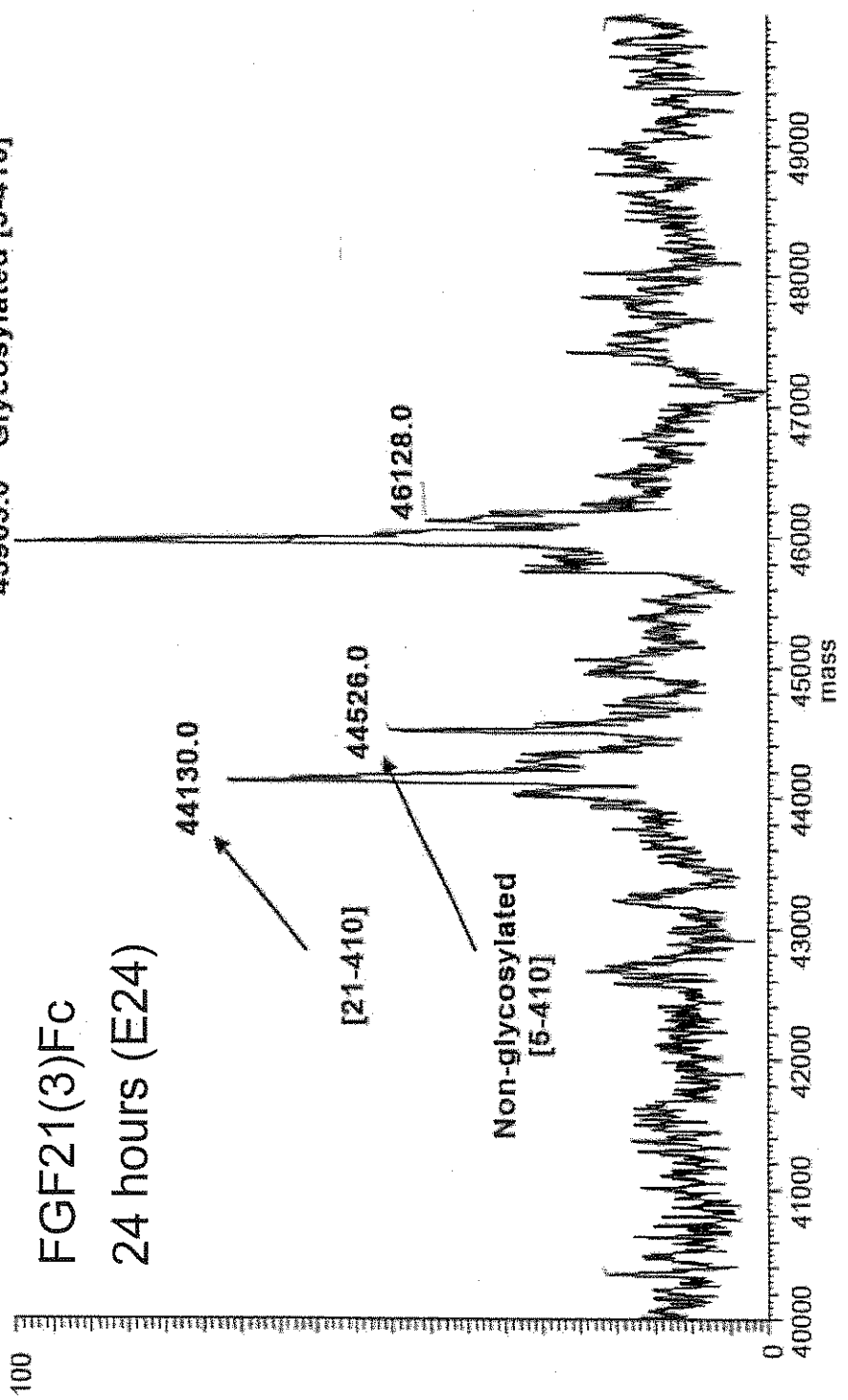

FGF21(3)Fc
24 hours (E24)
45963.0 Glycosylated [5-410]
46128.0
44130.0
[21-410]
44526.0
Non-glycosylated
[5-410]
100
0
40000
41000
42000
43000
44000
45000
46000
47000
48000
49000
mass

FIG. 7D

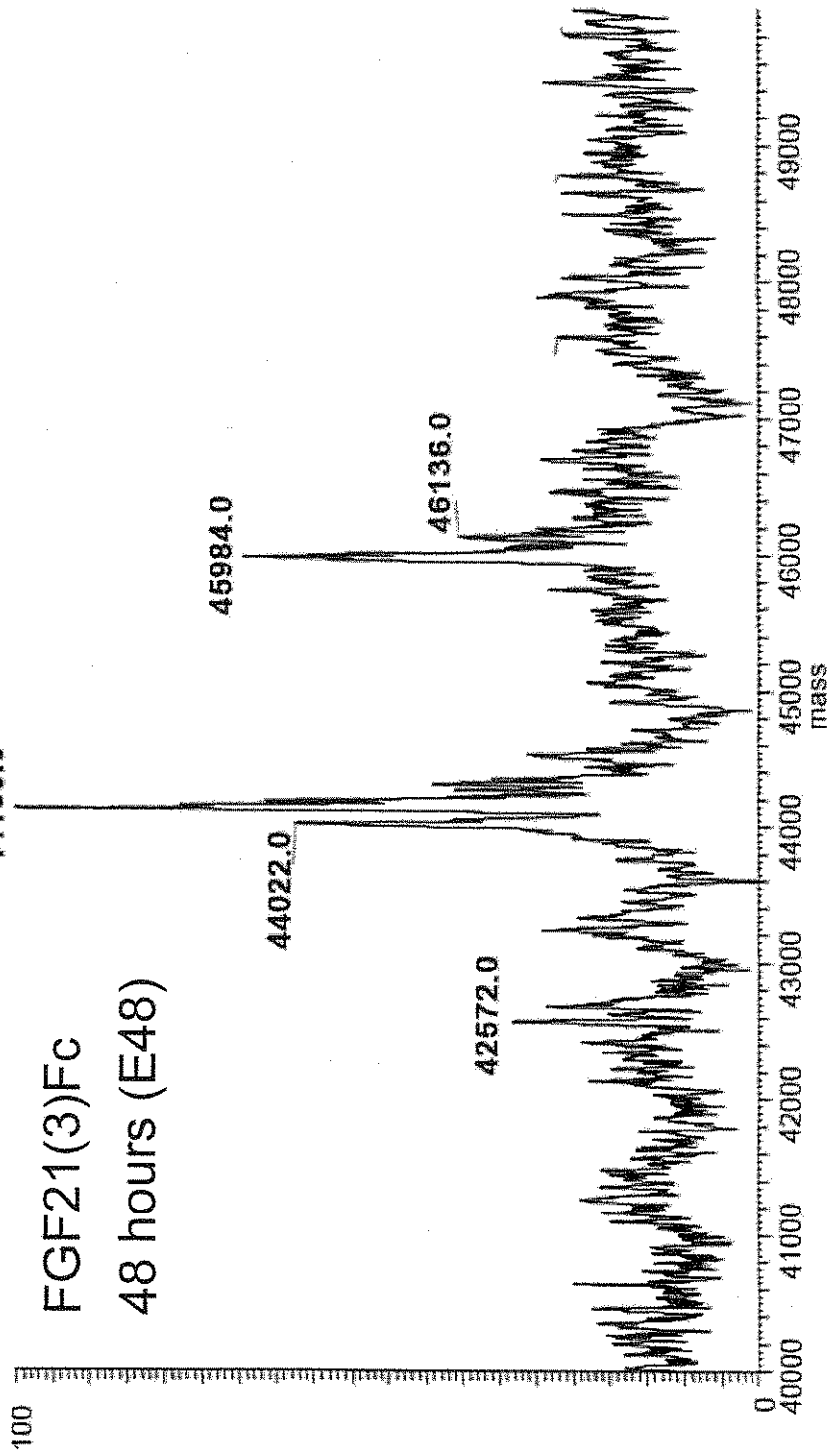

FGF21(3)Fc
48 hours (E48)
[21-410]
44130.0
45984.0
46136.0
44022.0
42572.0
100
0
40000
41000
42000
43000
44000
45000
46000
47000
48000
49000
mass

FIG. 8A

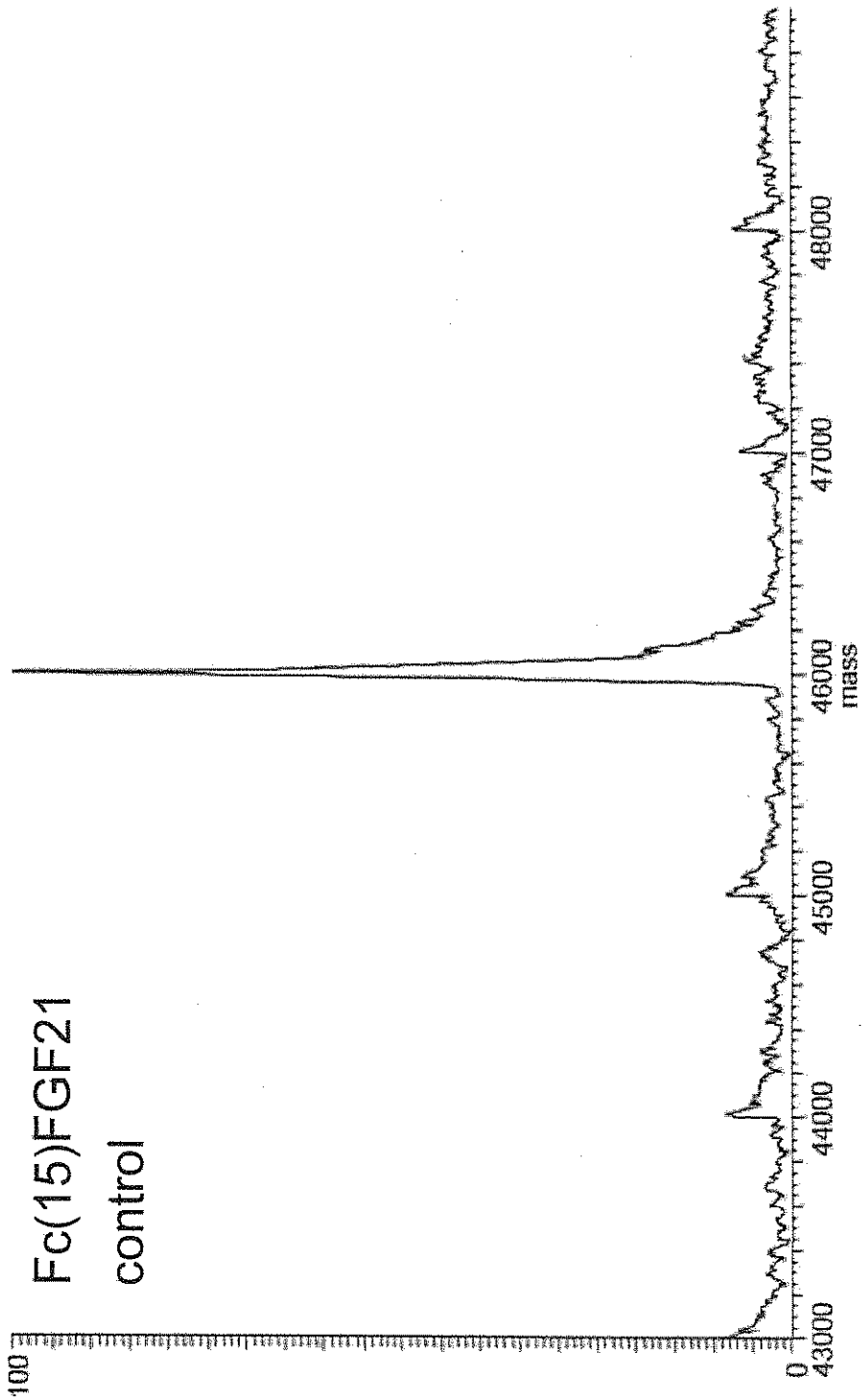

Fc(15)FGF21
control
[1-424]
46002.0
100
0
43000
44000
45000
46000
47000
48000
mass

FIG. 8B

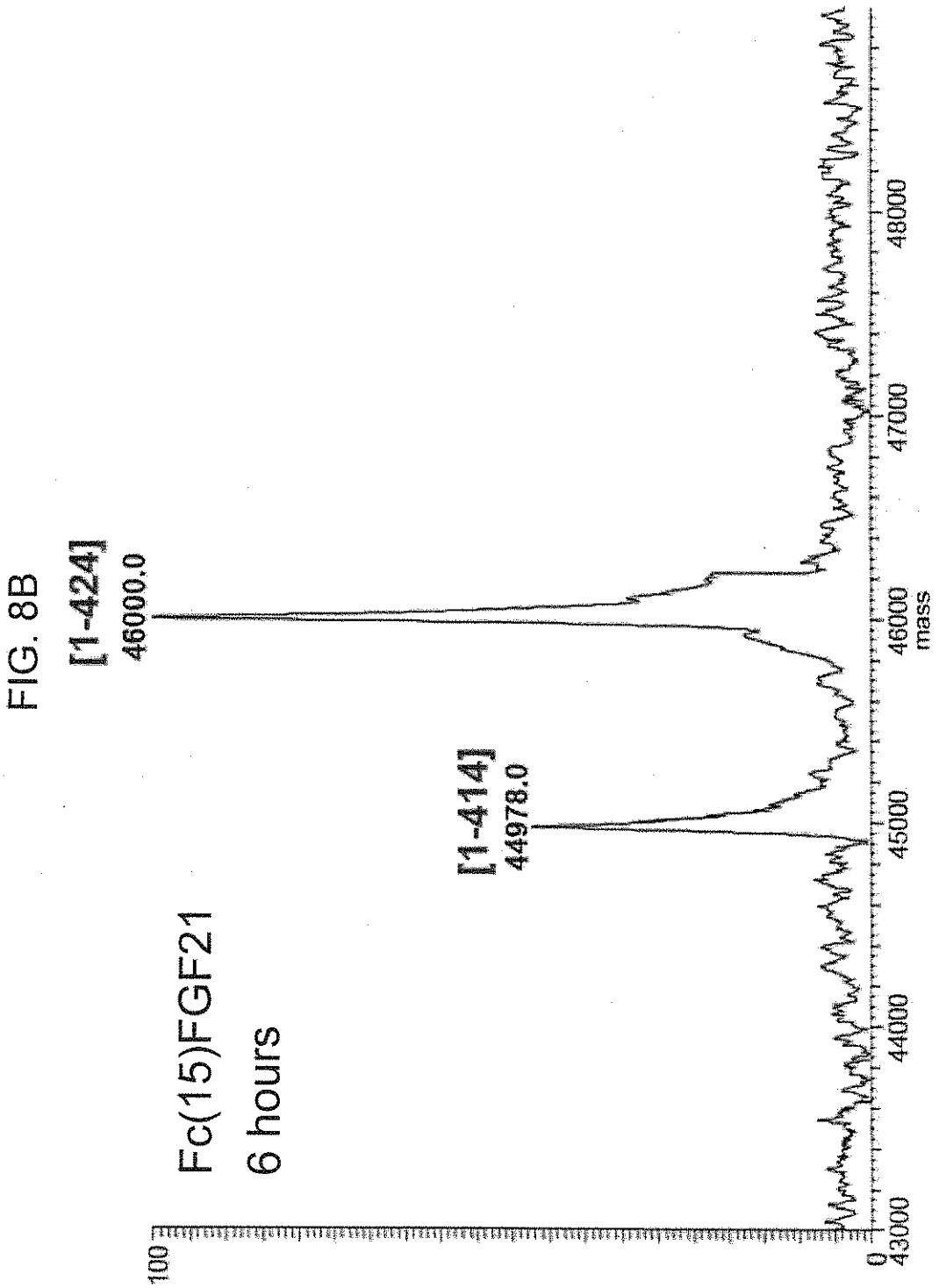

Fc(15)FGF21
6 hours
[1-424]
46000.0
[1-414]
44978.0
100
0
43000
44000
45000
46000
47000
48000
mass

FIG. 8C

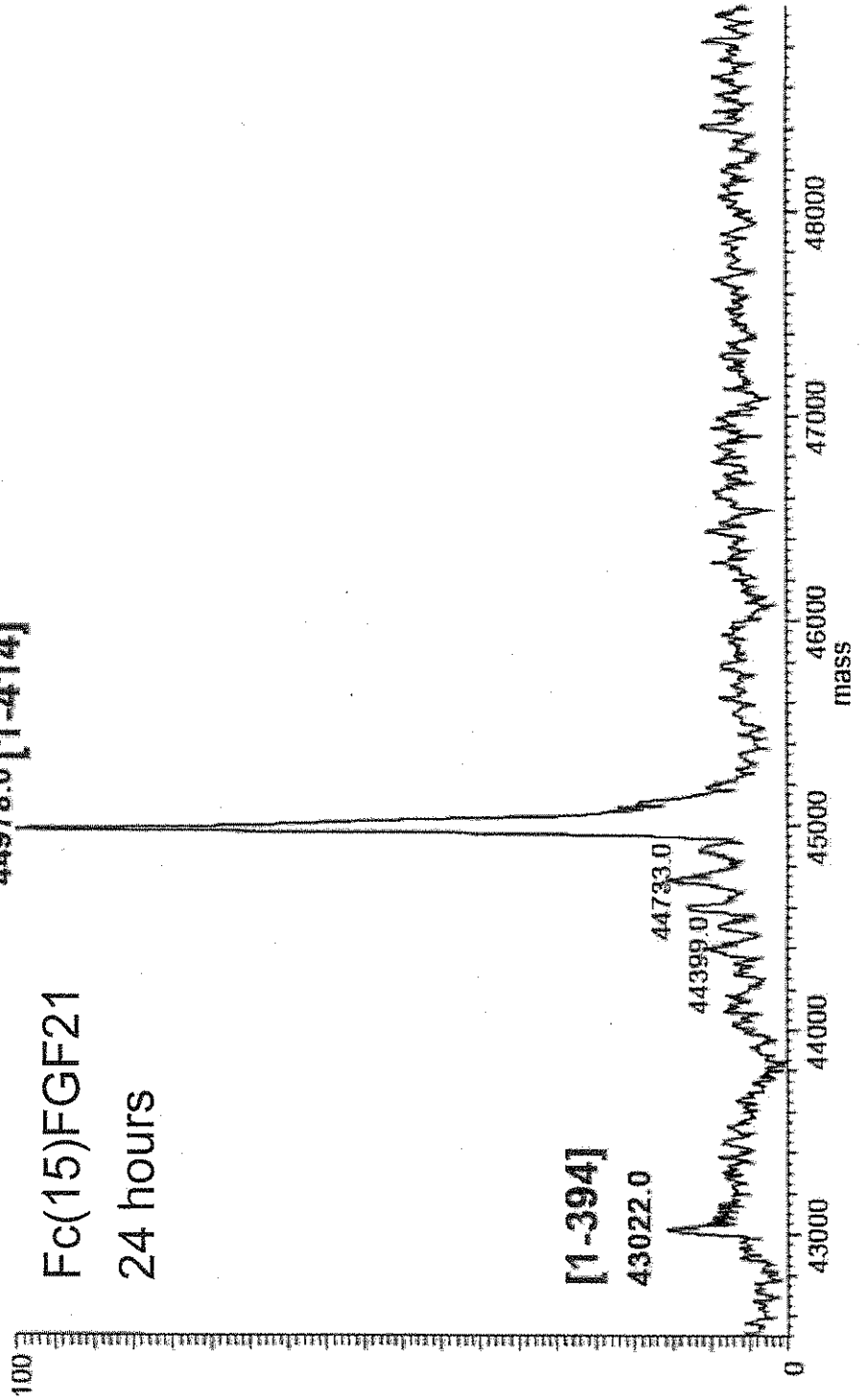

Fc(15)FGF21
24 hours
44978.0 [1-414]
[1-394]
43022.0
44733.0
44389.0
100
0
43000
44000
45000
46000
47000
48000
mass

FIG. 8D

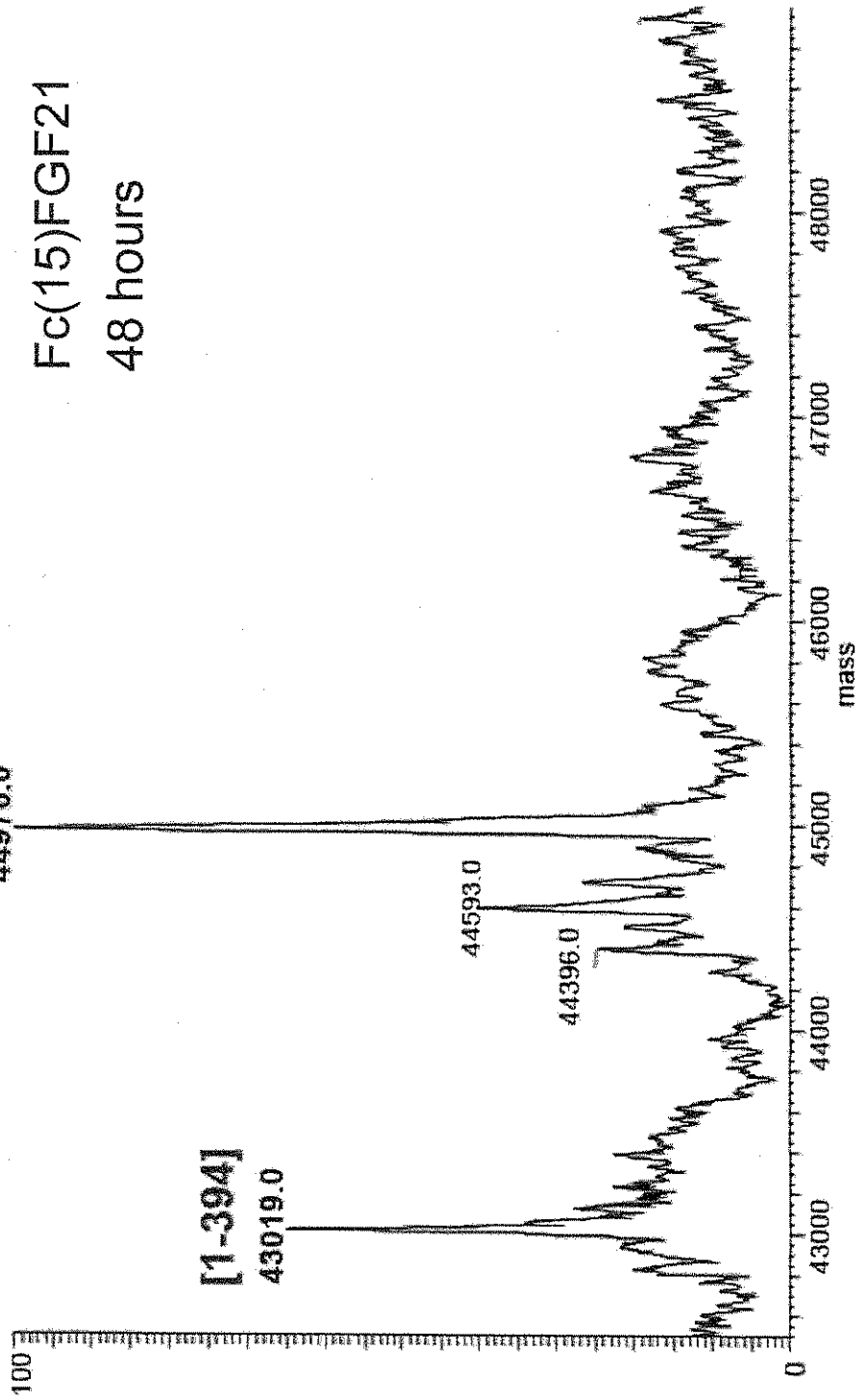

Fc(15)FGF21
48 hours
[1-414]
44976.0
[1-394]
43019.0
44593.0
44396.0
100
0
43000
44000
45000
46000
47000
48000
mass

FIG. 9A

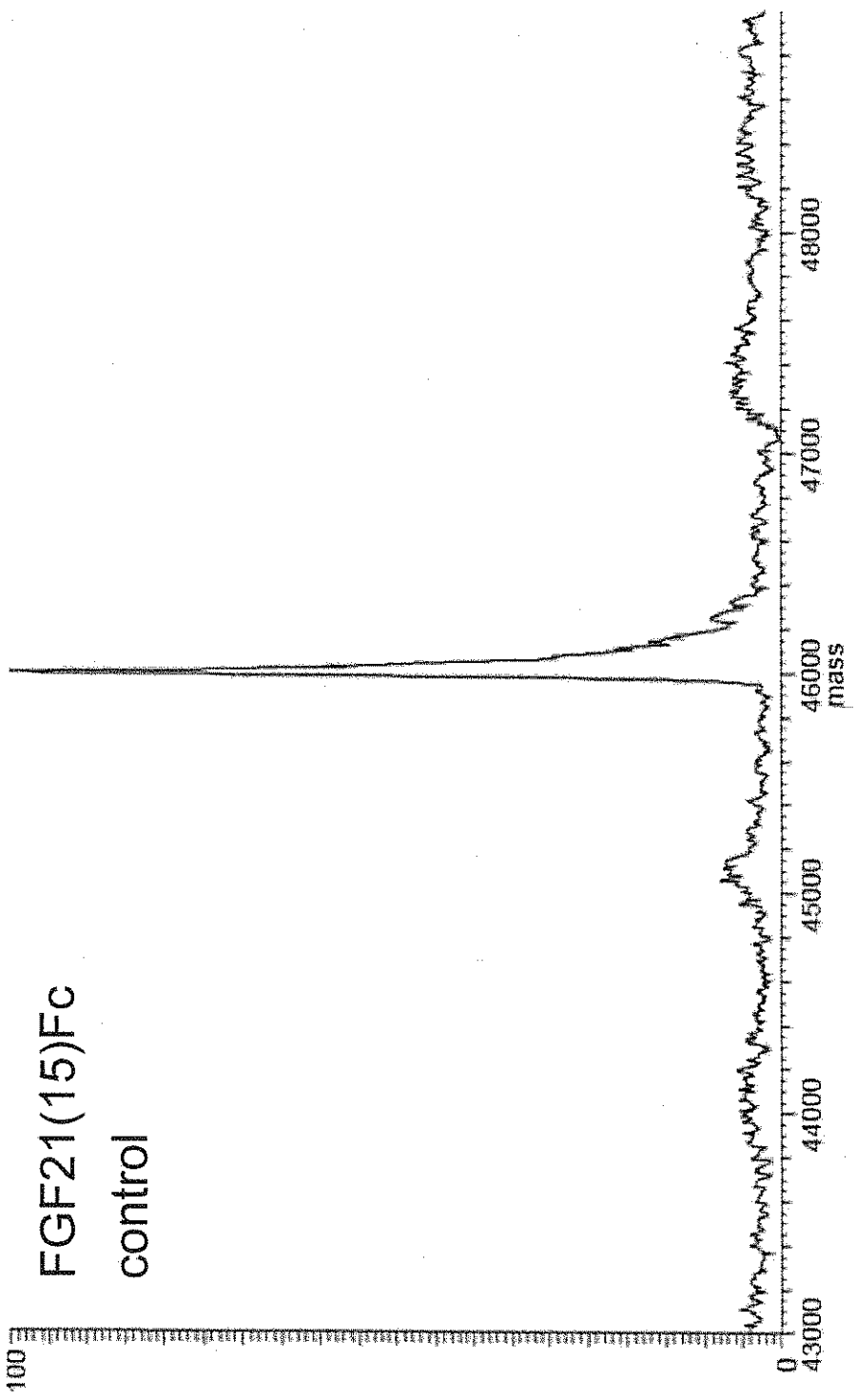

FGF21(15)Fc
control
[1-424]
45999.0
100
0
43000
44000
45000
46000
47000
48000
mass

FIG. 9B

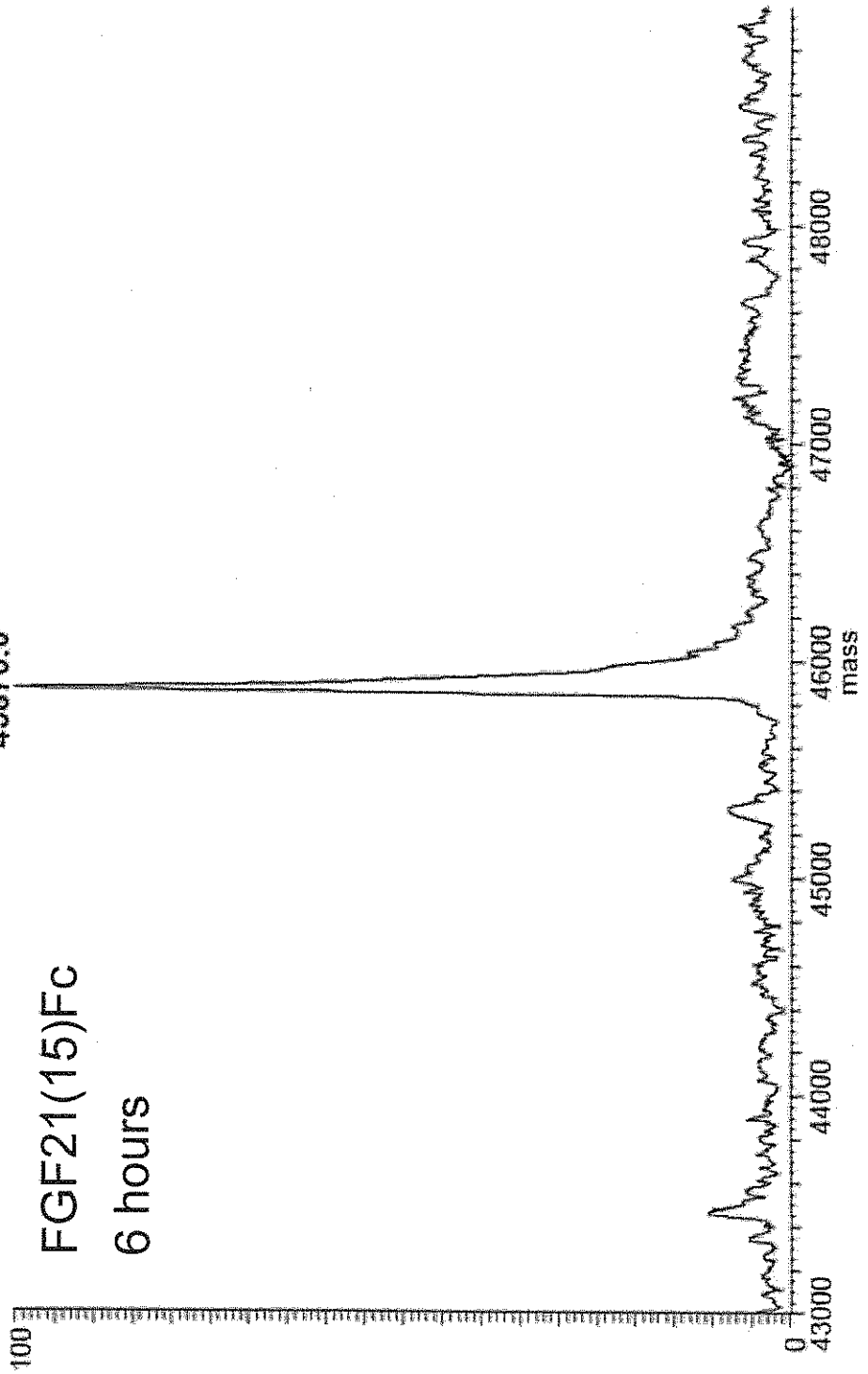

[1-423]
45870.0
FGF21(15)Fc
6 hours
100
0
43000
44000
45000
46000
47000
48000
mass

FIG. 9C

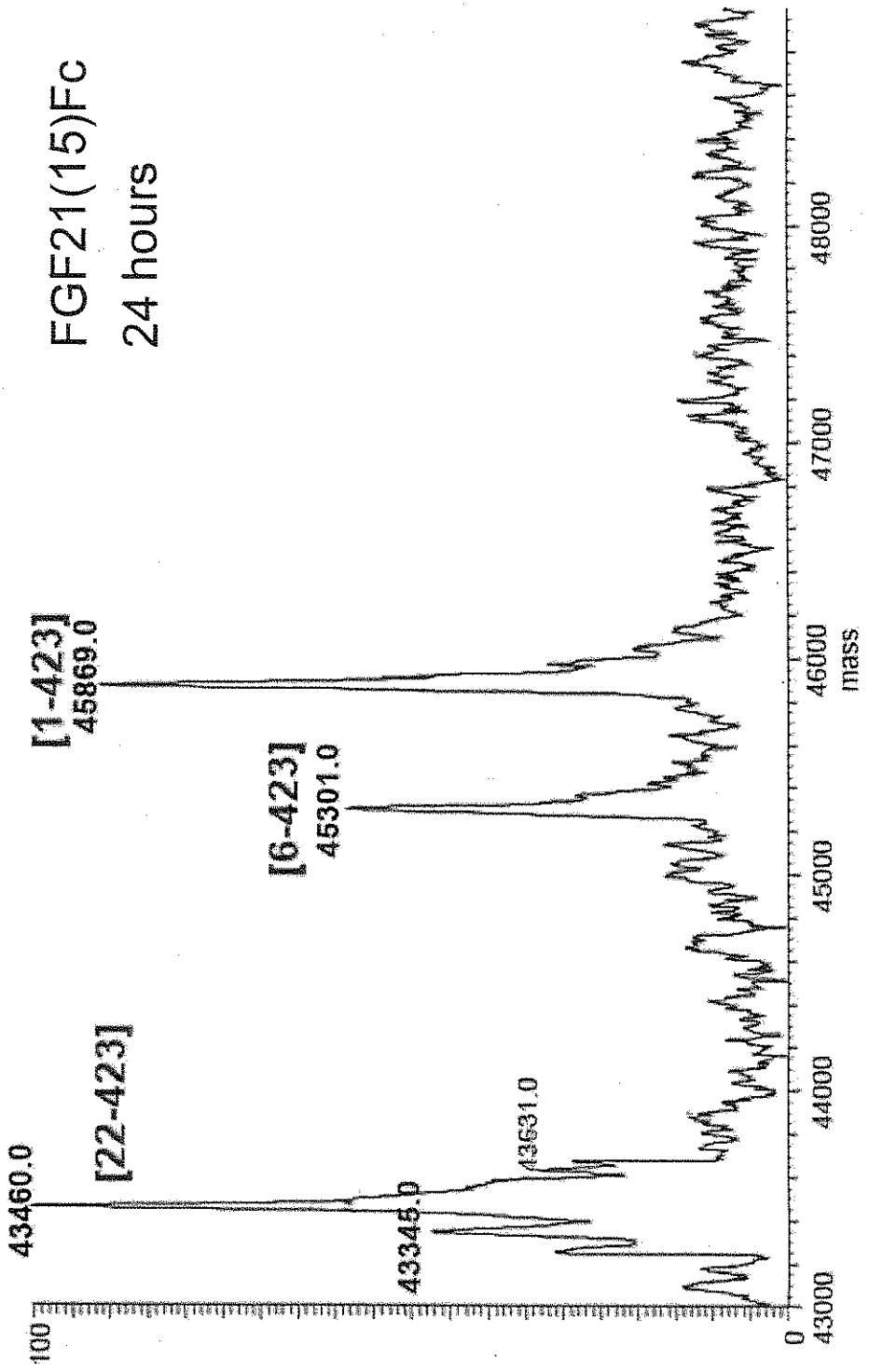

FGF21(15)Fc
24 hours
[1-423]
45869.0
[6-423]
45301.0
[22-423]
43460.0
43345.0
43631.0
100
0
43000
44000
45000
46000
47000
48000
mass

FIG. 9D

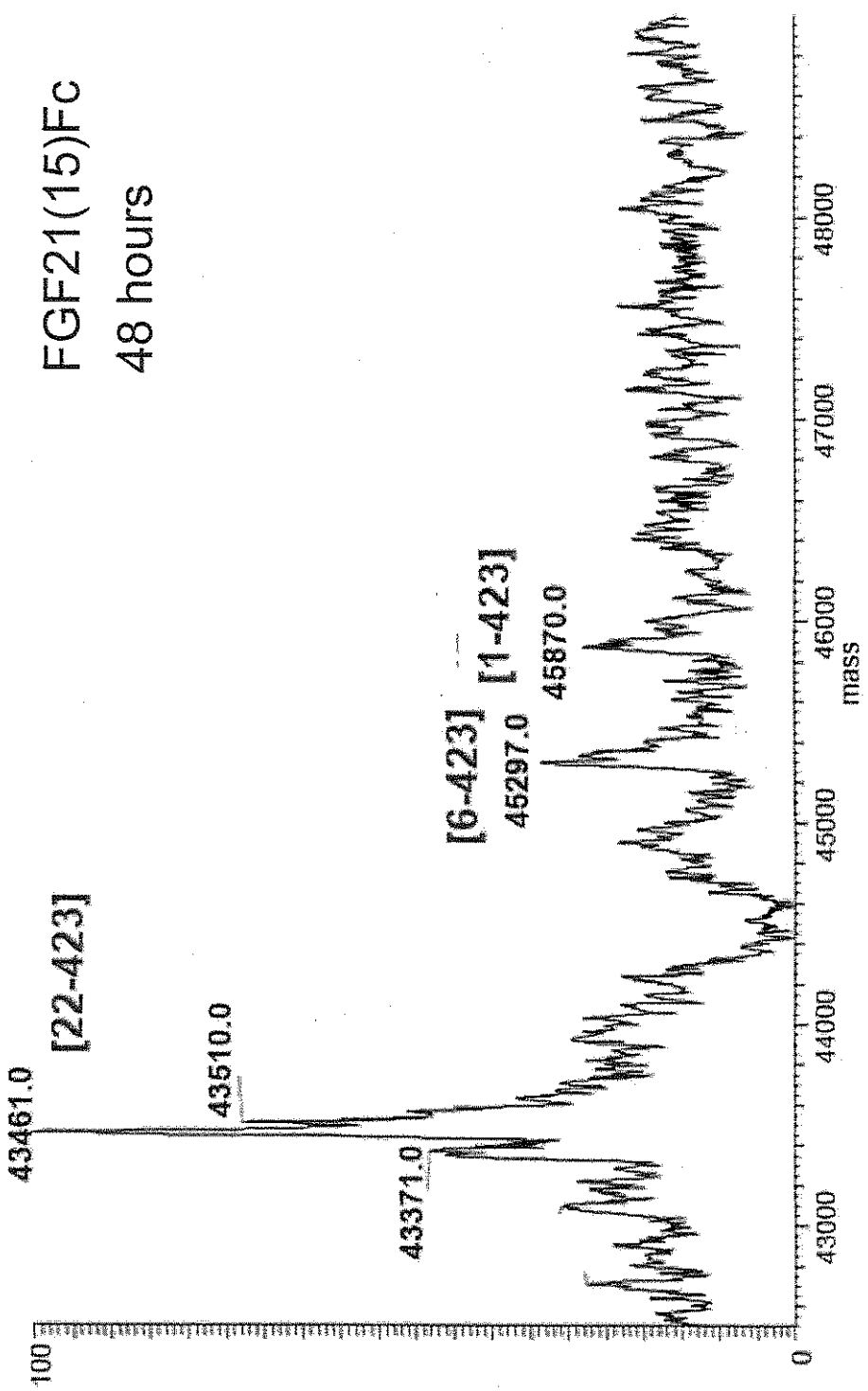

FGF21(15)Fc
48 hours
[22-423]
43461.0
43510.0
43371.0
[6-423]
45297.0
[1-423]
45870.0
100
0
43000
44000
45000
46000
47000
48000
mass

FIG. 10A

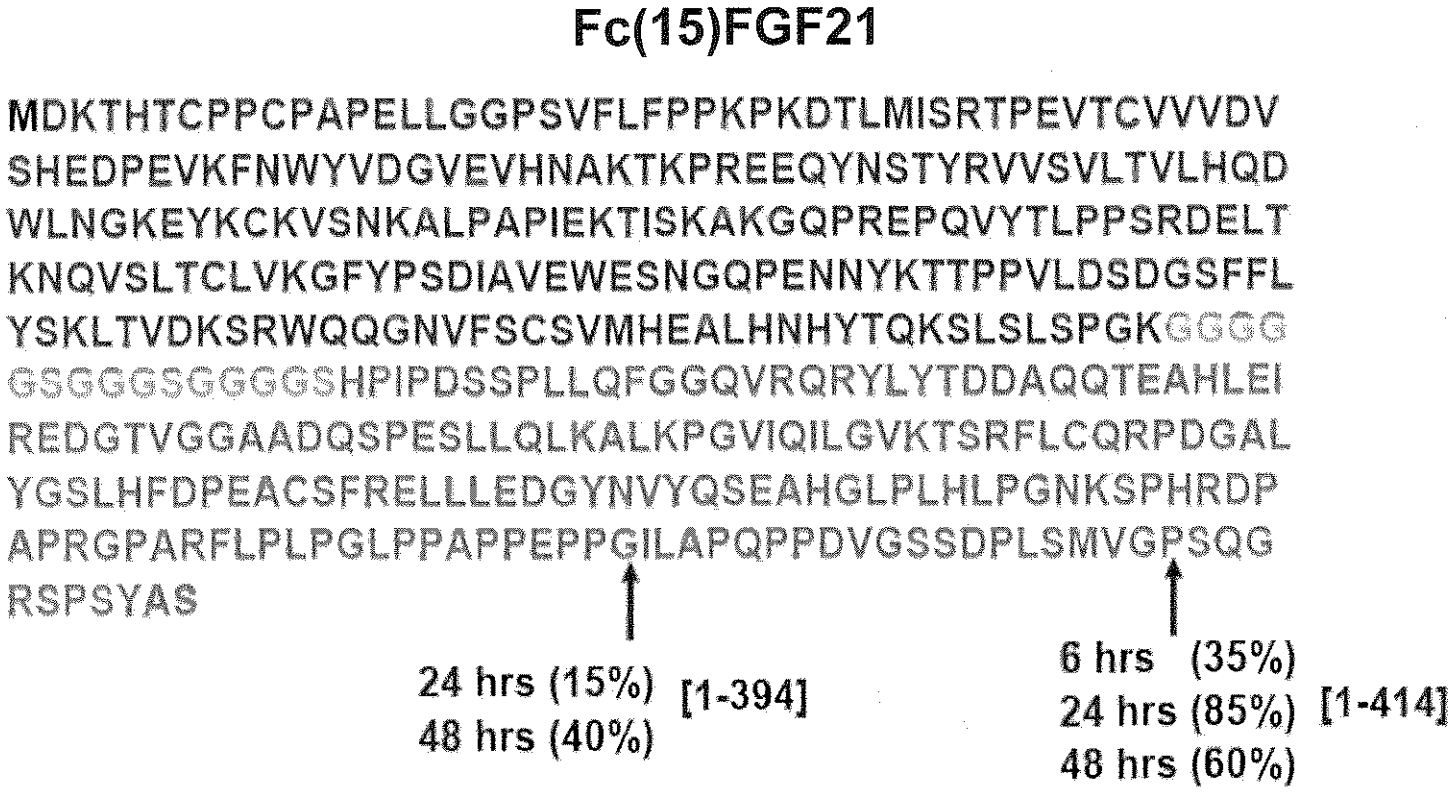

Fc(15)FGF21
MDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGG
GSGGGSGGGGSHPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEI
REDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQRPDGAL
YGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDP
APRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGPSQG
RSPSYAS
24 hrs (15%)
48 hrs (40%)
[1-394]
6 hrs (35%)
24 hrs (85%)
48 hrs (60%)
[1-414]

FIG. 10B

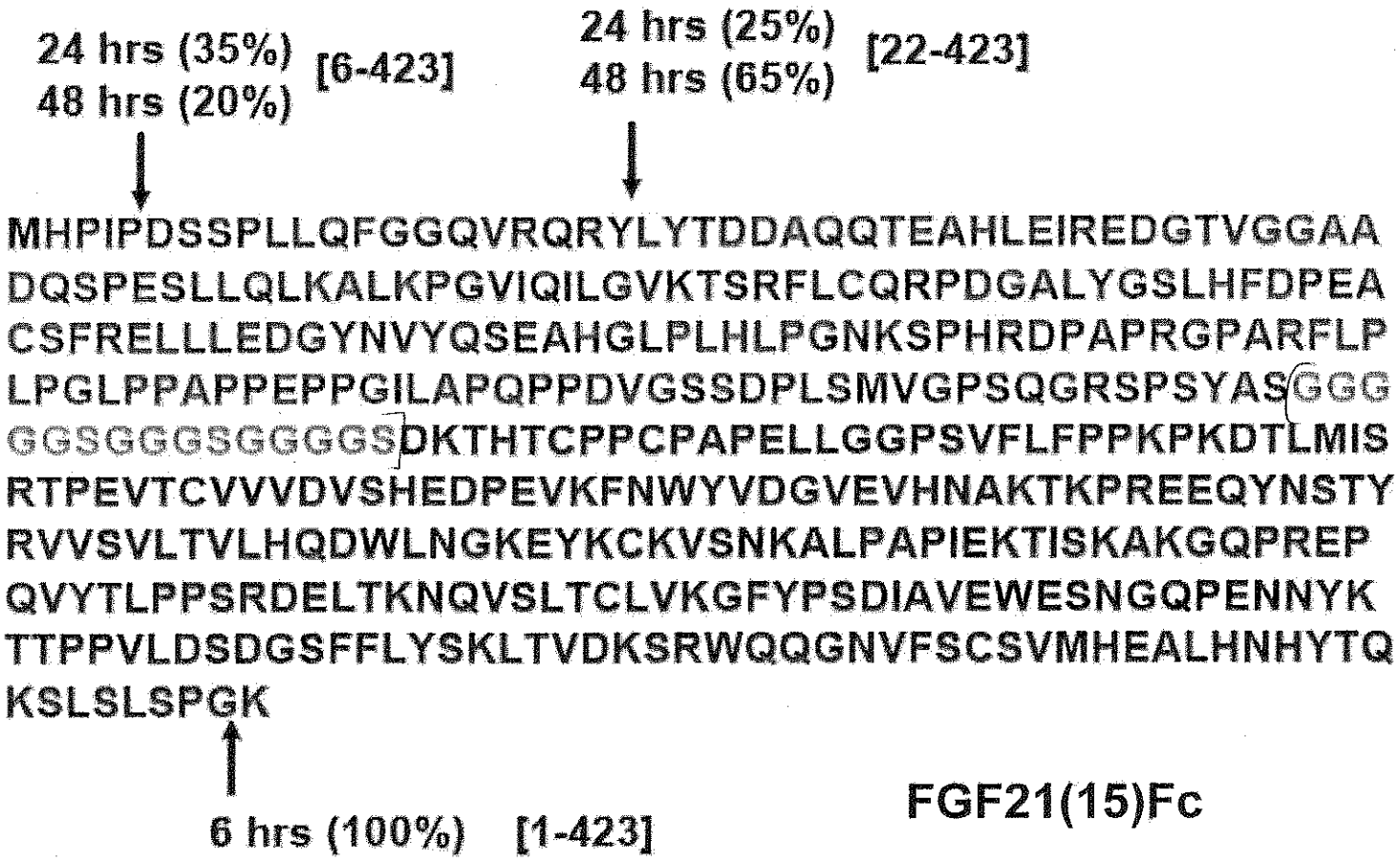

24 hrs (35%)
48 hrs (20%)
[6-423]
24 hrs (25%)
48 hrs (65%)
[22-423]
MHPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAA
DQSPESLLQLKALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEA
CSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPARFLP
LPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYASGGG
GGSGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP
QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK
6 hrs (100%) [1-423]
FGF21(15)Fc

FIG. 11

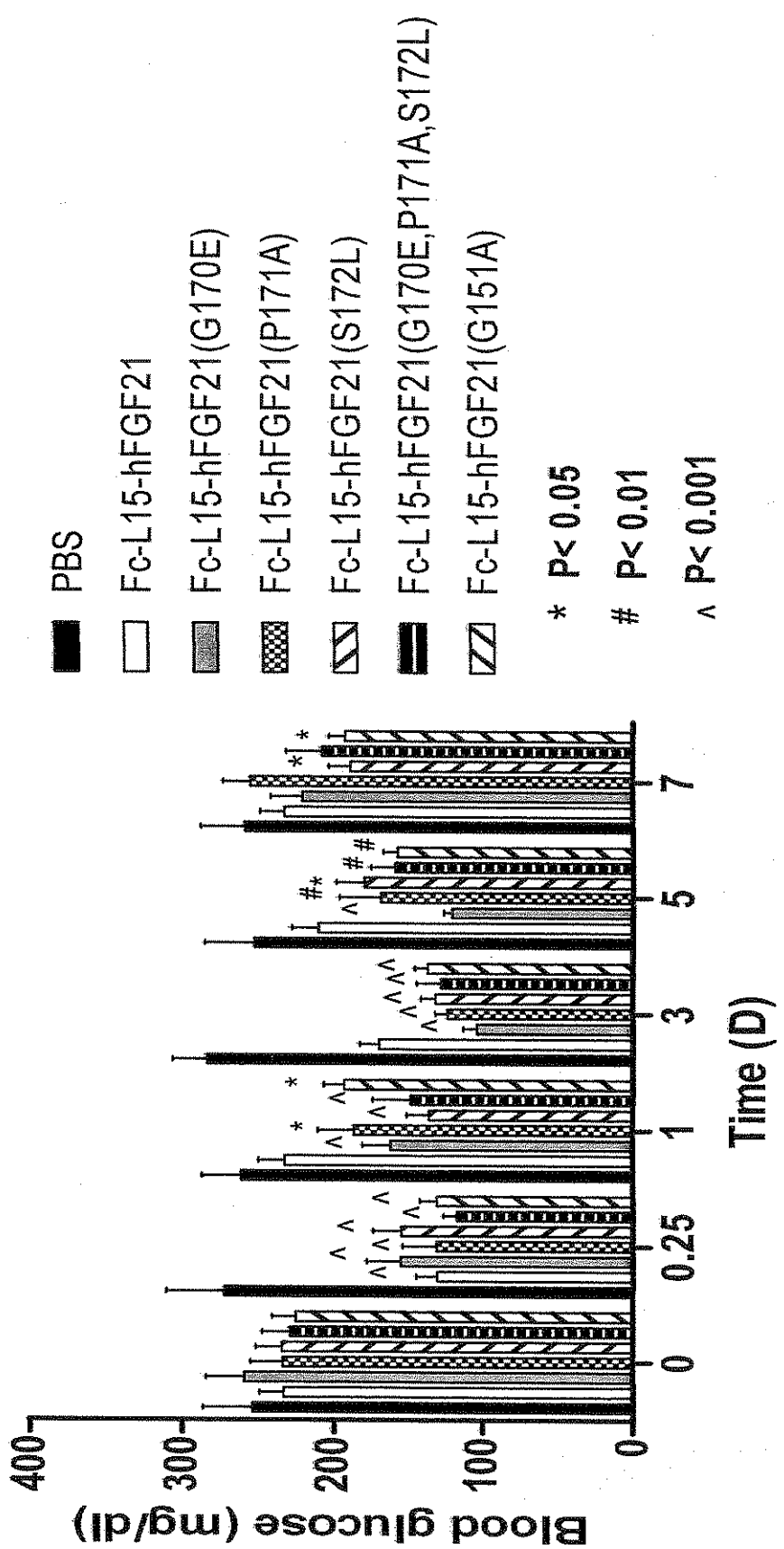

PBS
Fc-L15-hFGF21
Fc-L15-hFGF21(G170E)
Fc-L15-hFGF21(P171A)
Fc-L15-hFGF21(S172L)
Fc-L15-hFGF21(G170E,P171A,S172L)
Fc-L15-hFGF21(G151A)
* P< 0.05
# P< 0.01
^ P< 0.001
Blood glucose (mg/dl)
400
300
200
100
0
0
0.25
1
3
5
7
Time (D)

FIG. 12

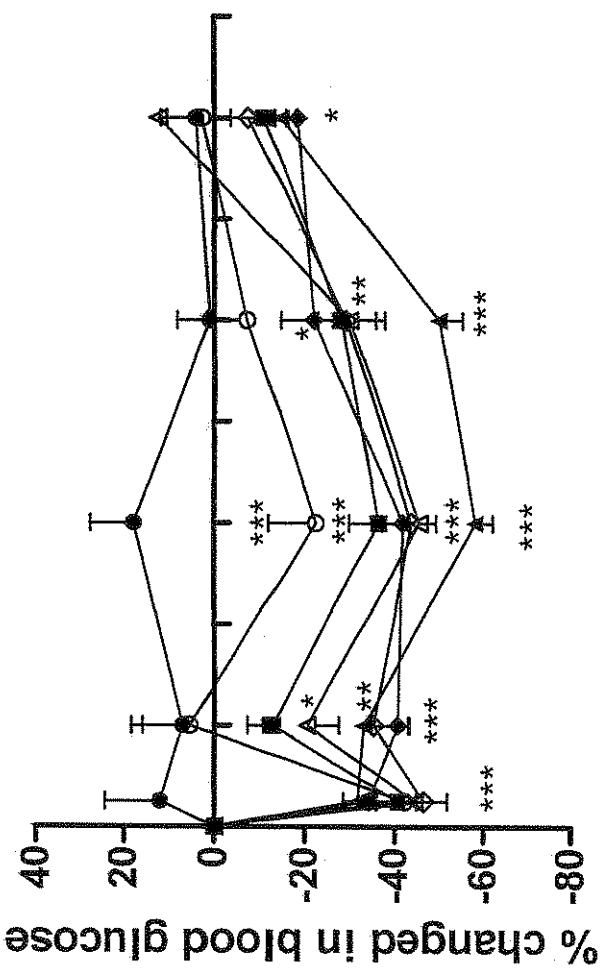

% changed in blood glucose
40
20
0
-20
-40
-60
-80
1
2
3
4
5
6
7
8
Time (D)
PBS
Fc-L15-hFGF21
Fc-L15-hFGF21(G170E)
Fc-L15-hFGF21(P171A)
Fc-L15-hFGF21(S172L)
Fc-L15-hFGF21(G170E,P171A,S172L)
Fc-L15-hFGF21(G151A)
* P< 0.05
** P< 0.01
*** P< 0.001

FIG. 13

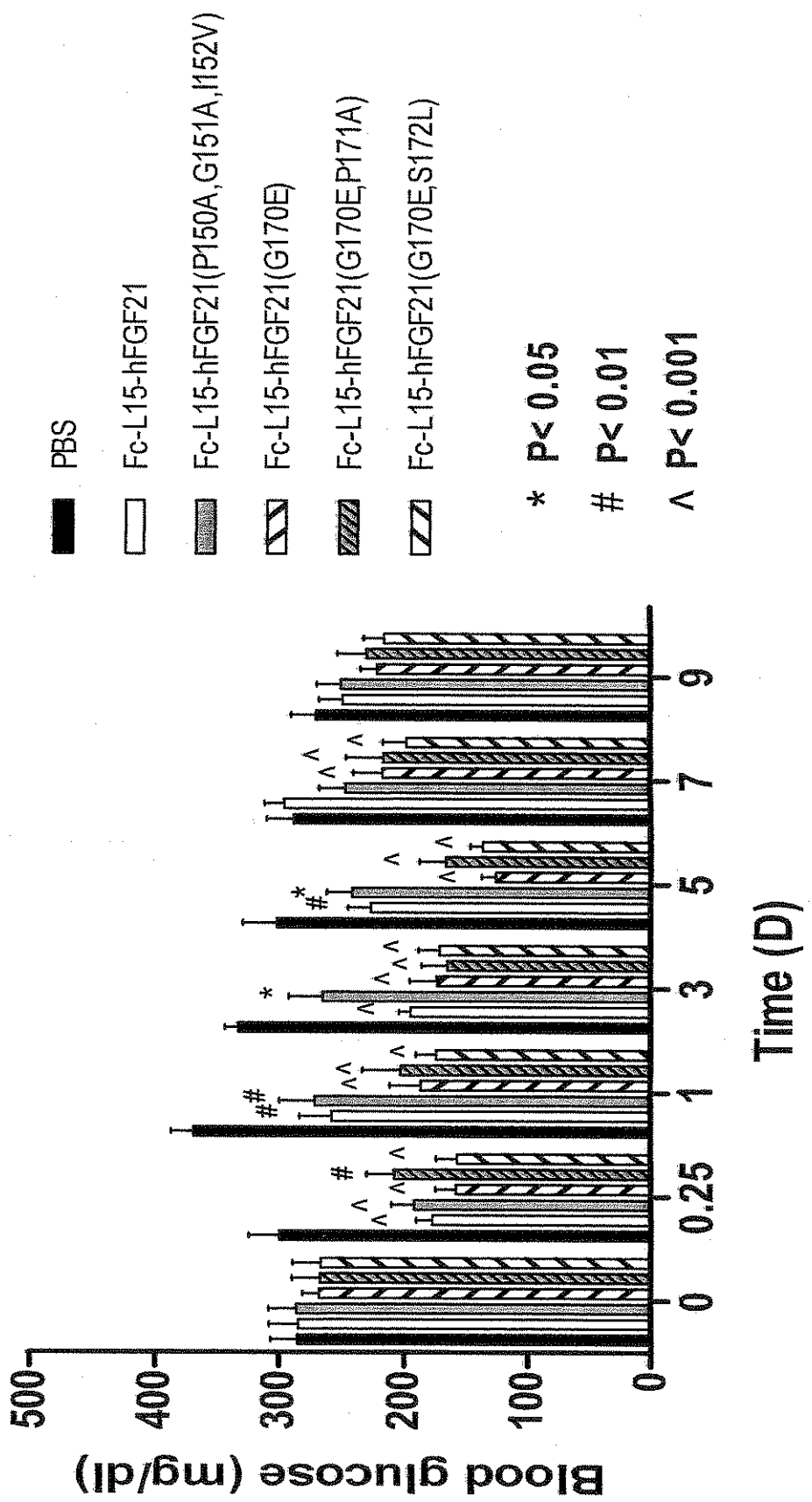

PBS
Fc-L15-hFGF21
Fc-L15-hFGF21(P150A,G151A,I152V)
Fc-L15-hFGF21(G170E)
Fc-L15-hFGF21(G170E,P171A)
Fc-L15-hFGF21(G170E,S172L)
* P< 0.05
# P< 0.01
^ P< 0.001
Blood glucose (mg/dl)
500
400
300
200
100
0
0
0.25
1
3
5
7
9
Time (D)

FIG. 14

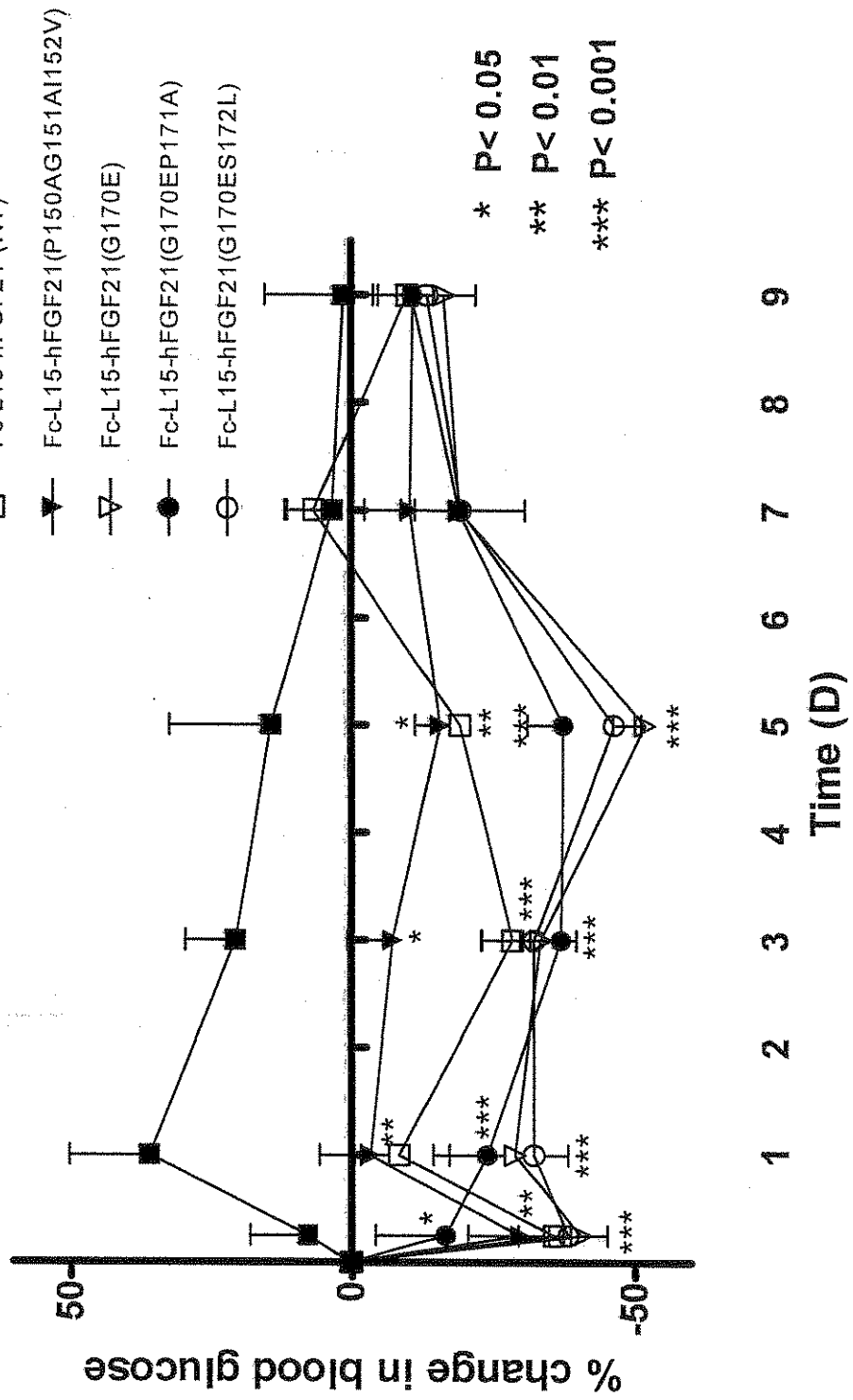

PBS
Fc-L15-hFGF21 (WT)
Fc-L15-hFGF21(P150AG151AI152V)
Fc-L15-hFGF21(G170E)
Fc-L15-hFGF21(G170EP171A)
Fc-L15-hFGF21(G170ES172L)
* P< 0.05
** P< 0.01
*** P< 0.001
% change in blood glucose
50
0
-50
1
2
3
4
5
6
7
8
9
Time (D)

FIG. 15

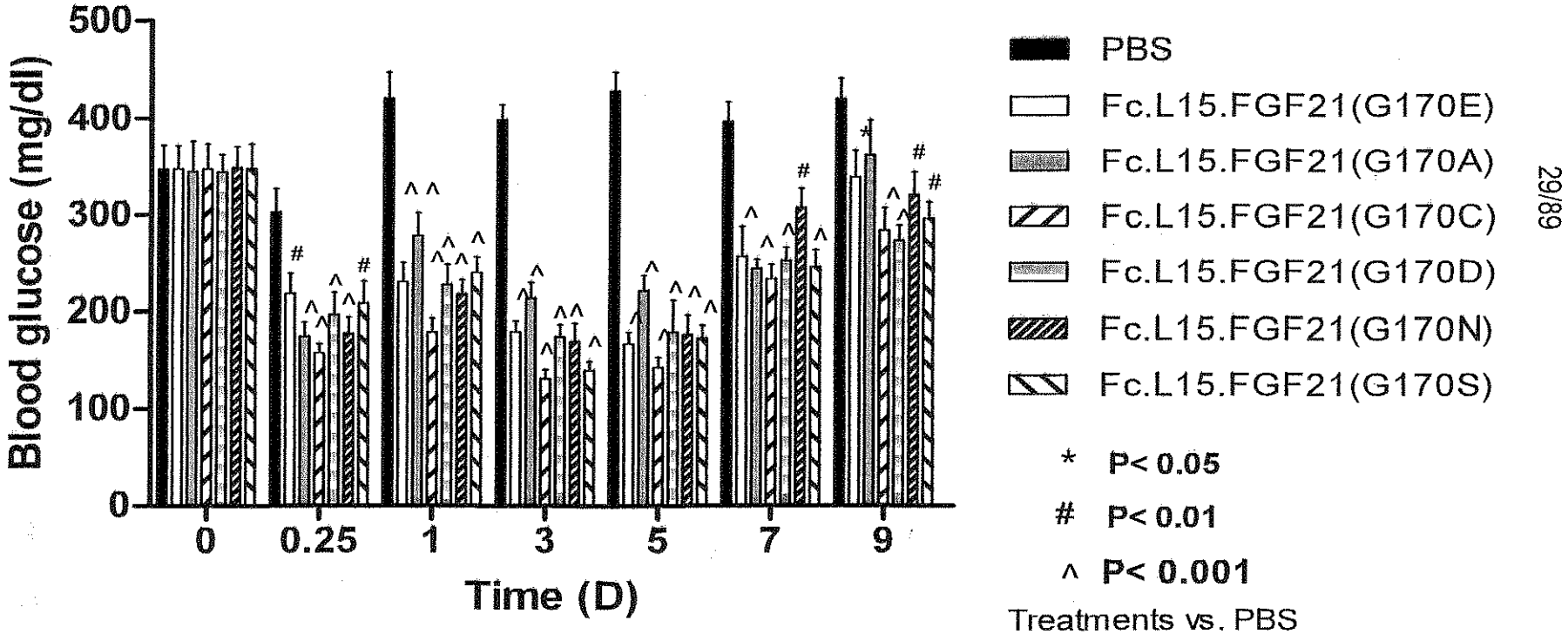

Blood glucose (mg/dl)
500
400
300
200
100
0
0
0.25
1
3
5
7
9
Time (D)
PBS
Fc.L15.FGF21(G170E)
Fc.L15.FGF21(G170A)
Fc.L15.FGF21(G170C)
Fc.L15.FGF21(G170D)
Fc.L15.FGF21(G170N)
Fc.L15.FGF21(G170S)
* P< 0.05
# P< 0.01
^ P< 0.001
Treatments vs. PBS

FIG. 16

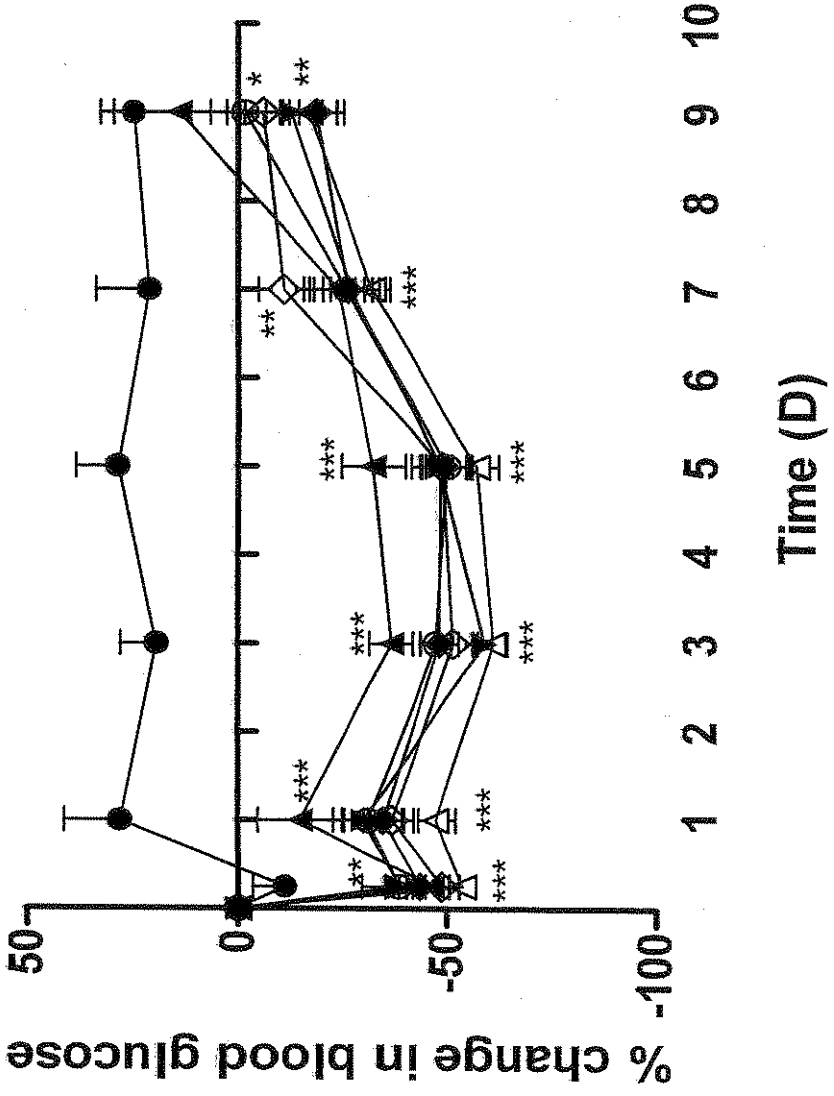

% change in blood glucose
50
0
-50
-100
1
2
3
4
5
6
7
8
9
10
Time (D)
PBS
Fc.L15.FGF21(G170E)
Fc.L15.FGF21(G170A)
Fc.L15.FGF21(G170C)
Fc.L15.FGF21(G170D)
Fc.L15.FGF21(G170N)
Fc.L15.FGF21(G170S)
* P< 0.05
** P< 0.01
*** P< 0.001
Treatments vs. PBS

FIG. 17

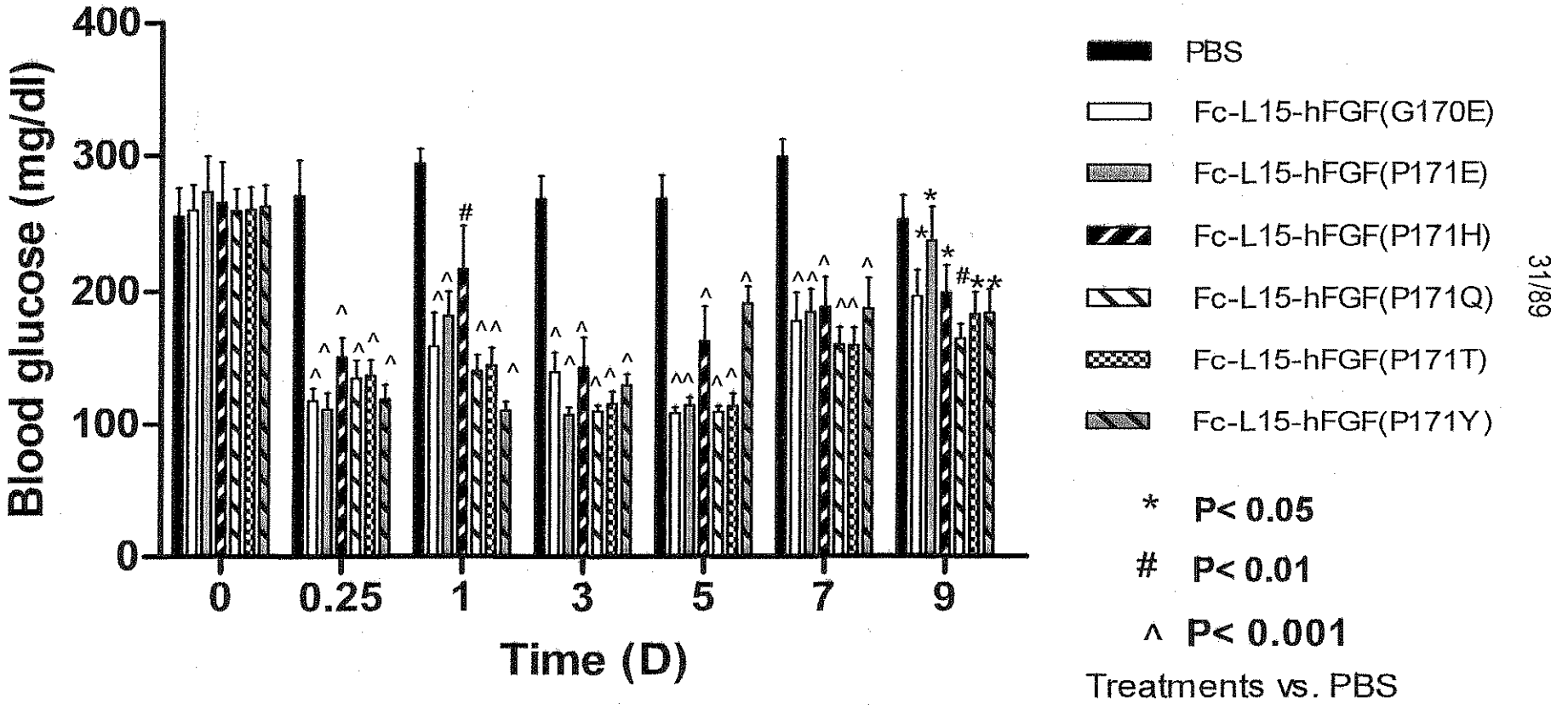

Blood glucose (mg/dl)
400
300
200
100
0
0
0.25
1
3
5
7
9
Time (D)
PBS
Fc-L15-hFGF(G170E)
Fc-L15-hFGF(P171E)
Fc-L15-hFGF(P171H)
Fc-L15-hFGF(P171Q)
Fc-L15-hFGF(P171T)
Fc-L15-hFGF(P171Y)
* P< 0.05
# P< 0.01
^ P< 0.001
Treatments vs. PBS

FIG. 18

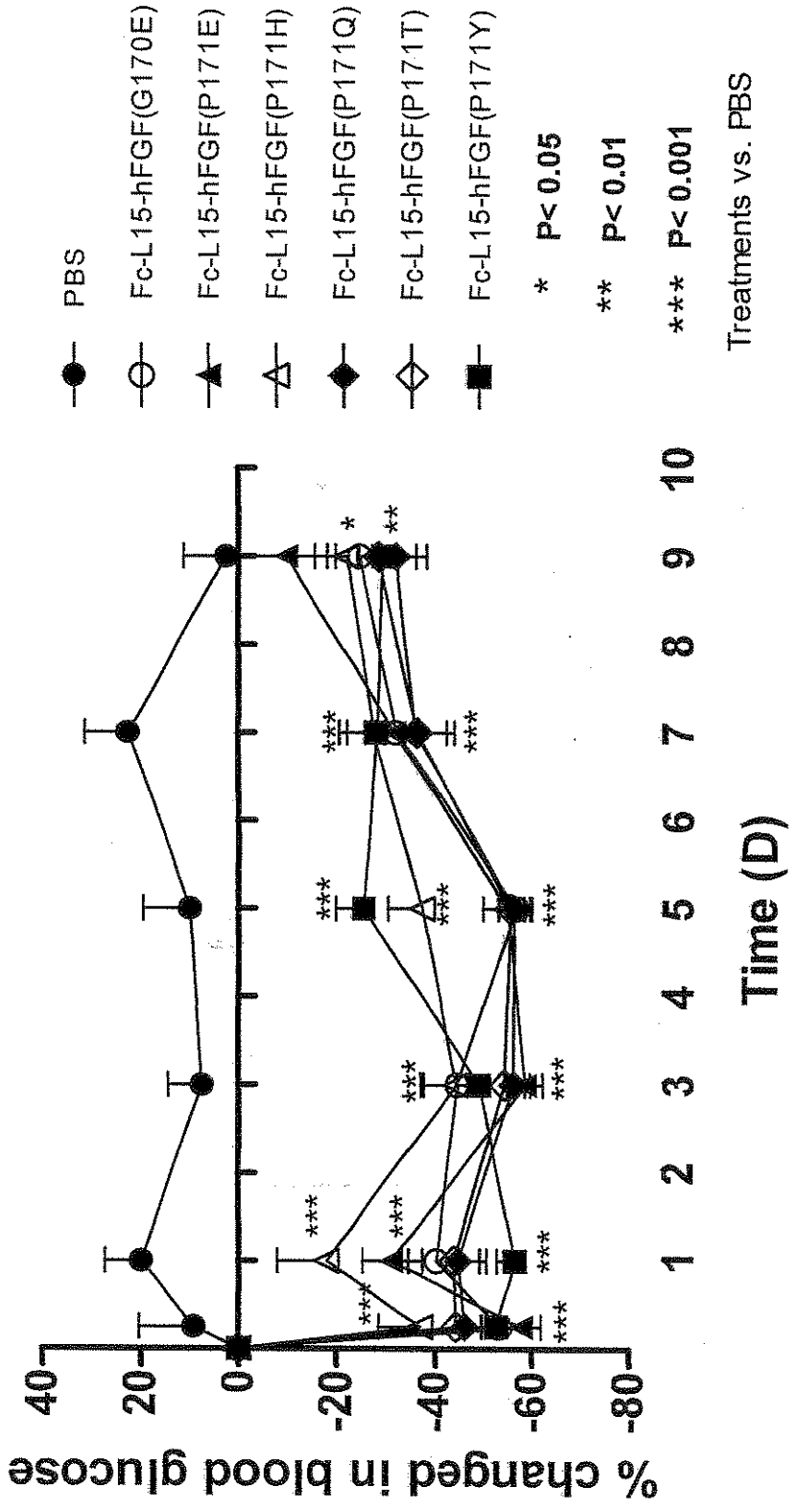

% changed in blood glucose
40
20
0
-20
-40
-60
-80
1
2
3
4
5
6
7
8
9
10
Time (D)
PBS
Fc-L15-hFGF(G170E)
Fc-L15-hFGF(P171E)
Fc-L15-hFGF(P171H)
Fc-L15-hFGF(P171Q)
Fc-L15-hFGF(P171T)
Fc-L15-hFGF(P171Y)
* P< 0.05
** P< 0.01
*** P< 0.001
Treatments vs. PBS

FIG. 19A

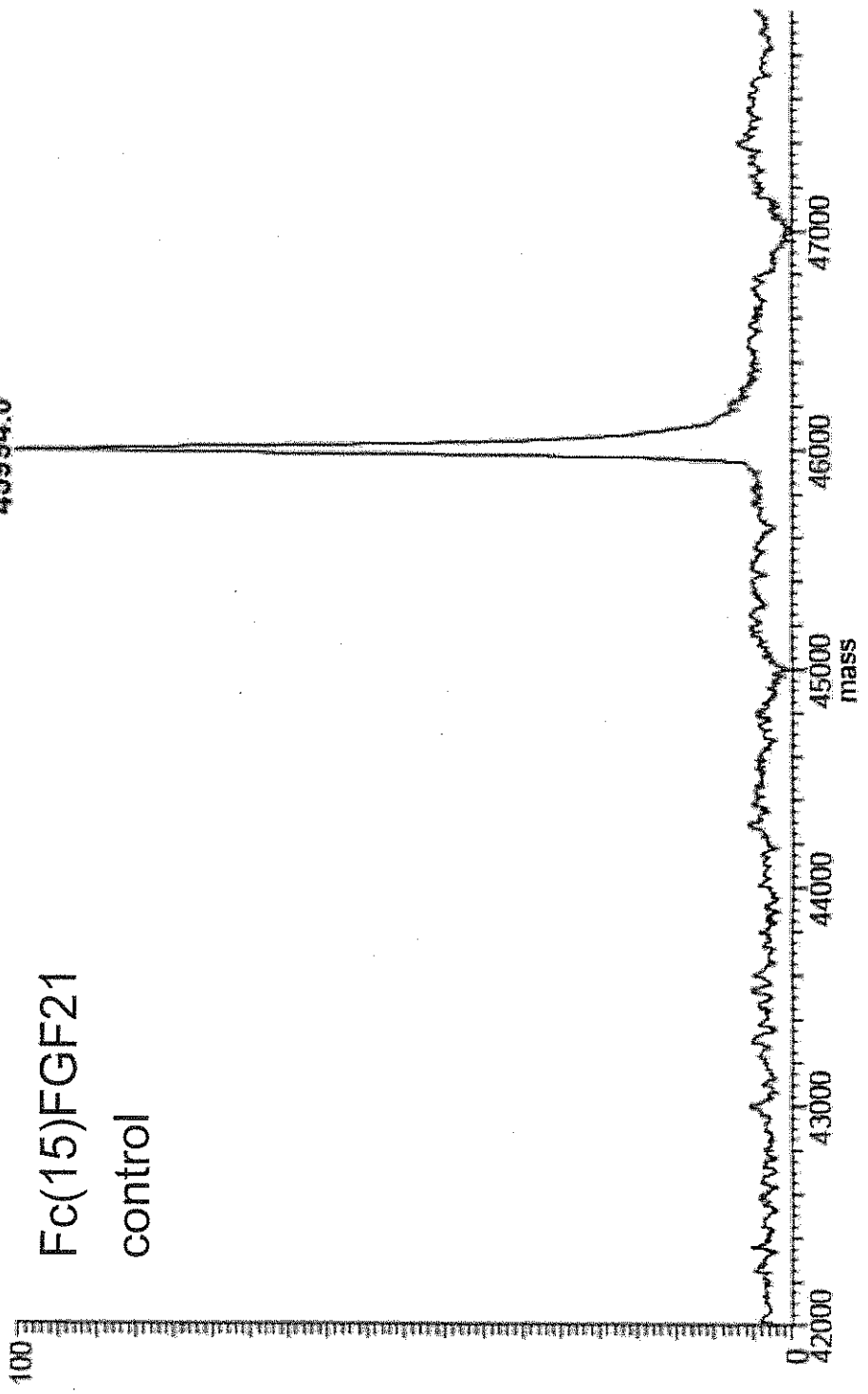

Fc(15)FGF21
control
[1-424]
45994.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 19B

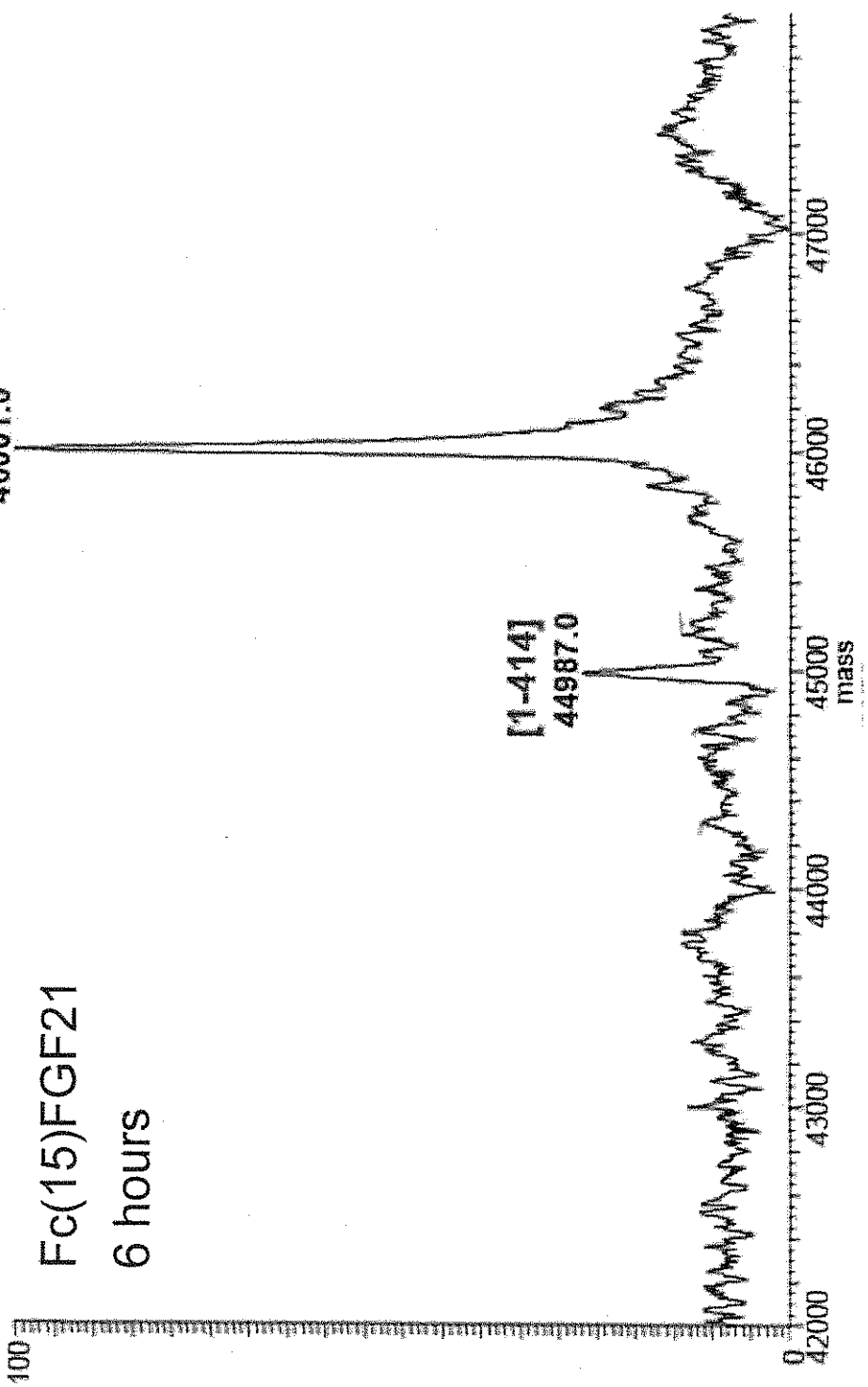

Fc(15)FGF21
6 hours
[1-424]
46001.0
[1-414]
44987.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 19C

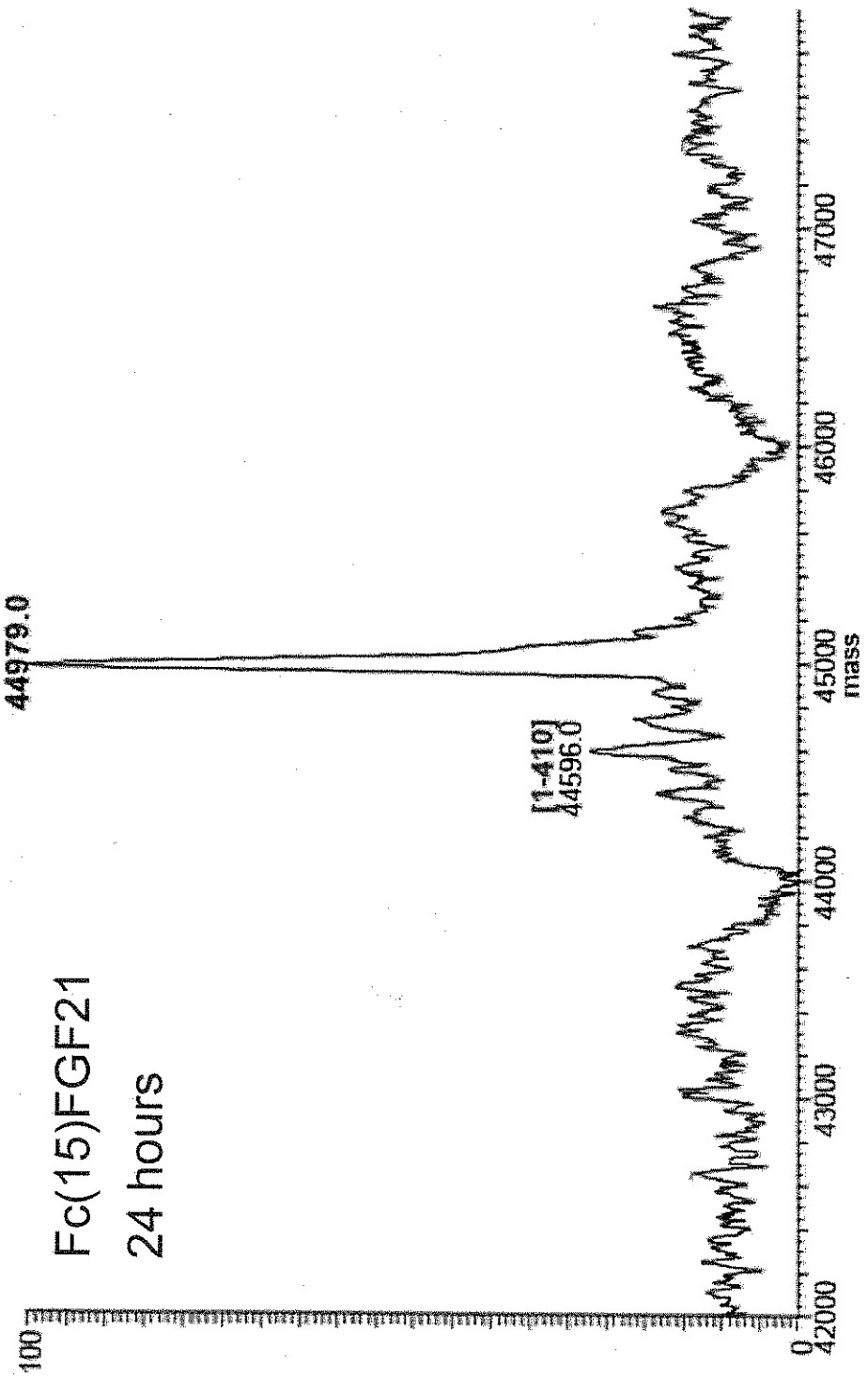

Fc(15)FGF21
24 hours
[1-414]
44979.0
[1-410]
44596.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 19D

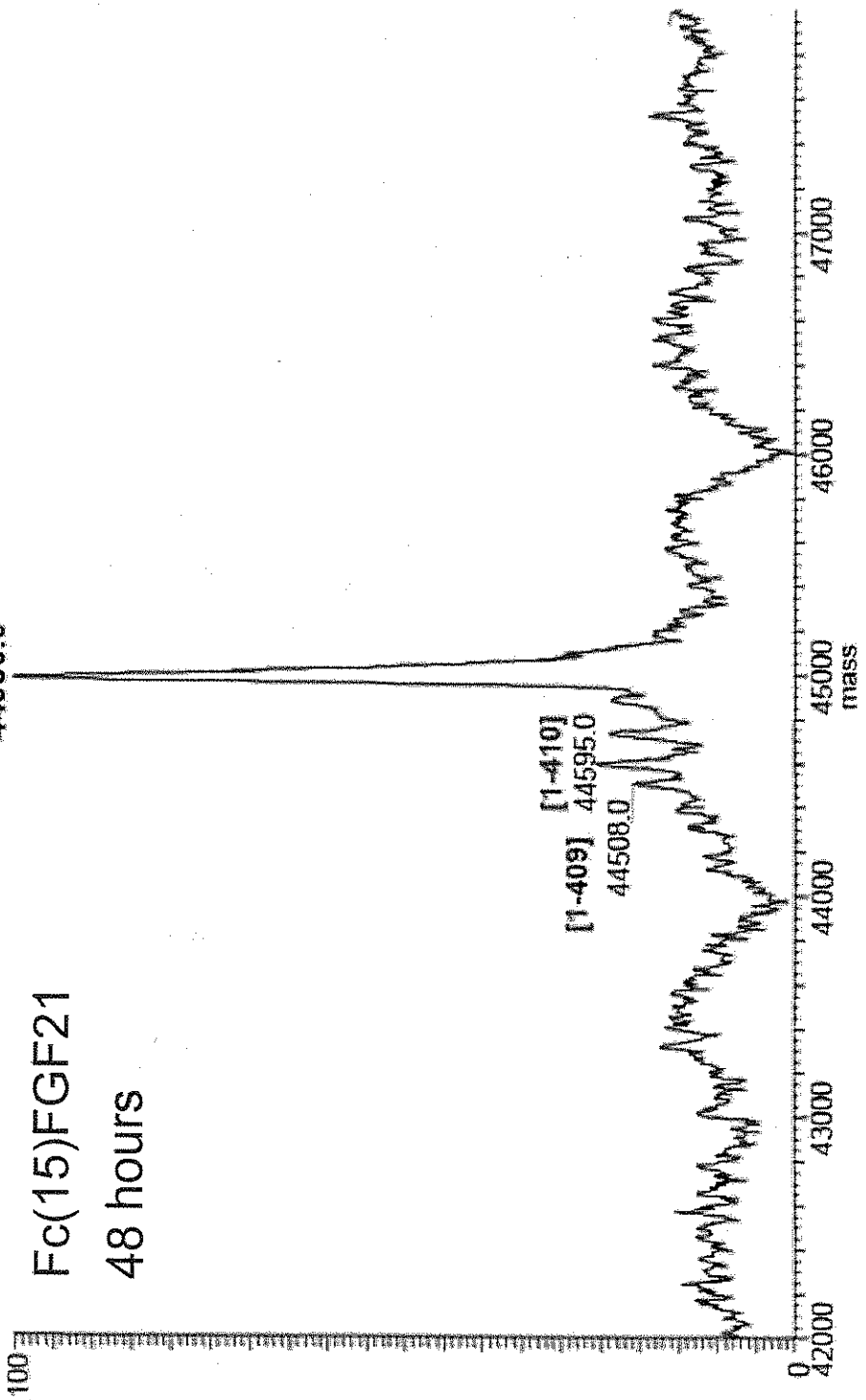

Fc(15)FGF21
48 hours
[1-414]
44980.0
[1-410]
44595.0
[1-409]
44508.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 20A

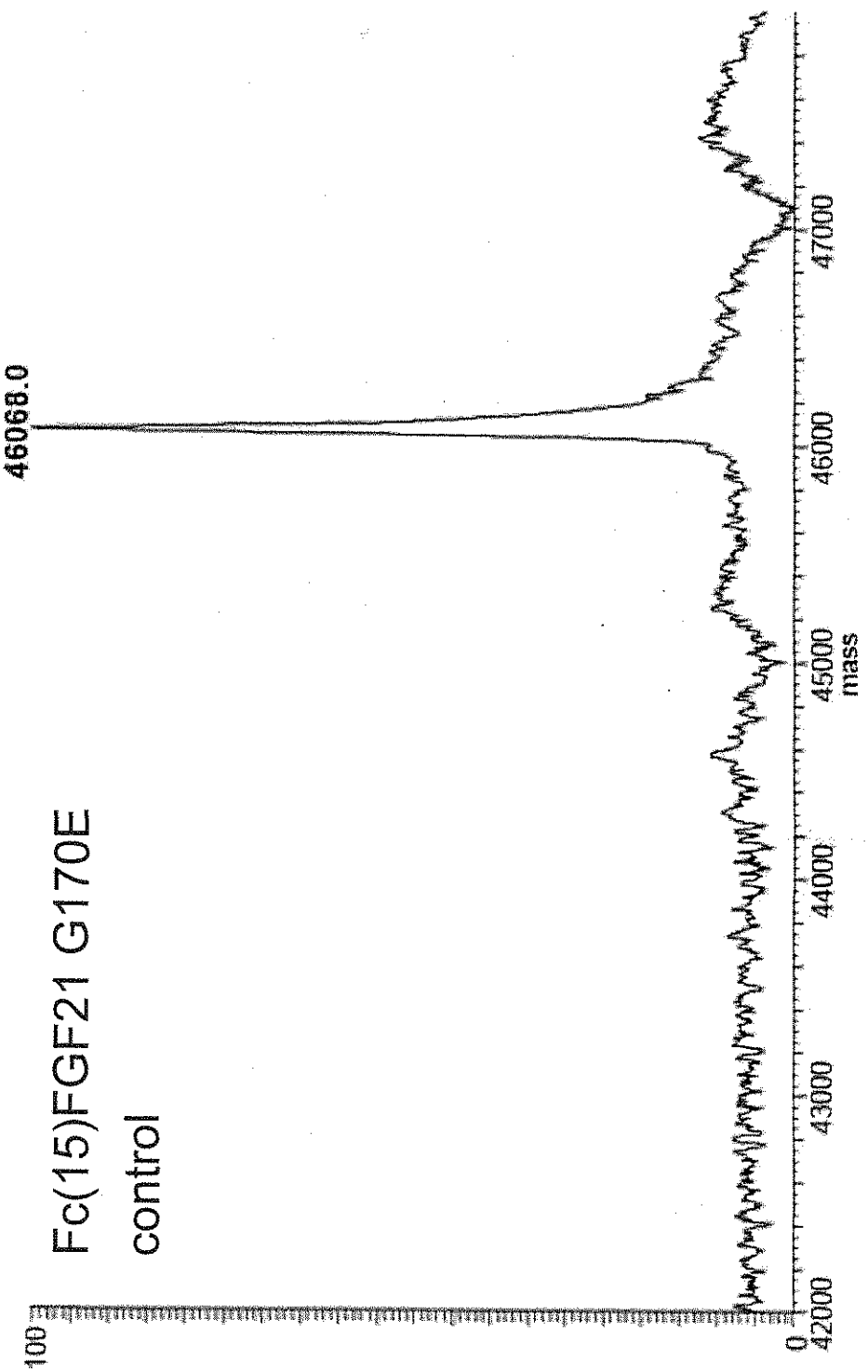

Fc(15)FGF21 G170E
control
[1-424]
46068.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 20B

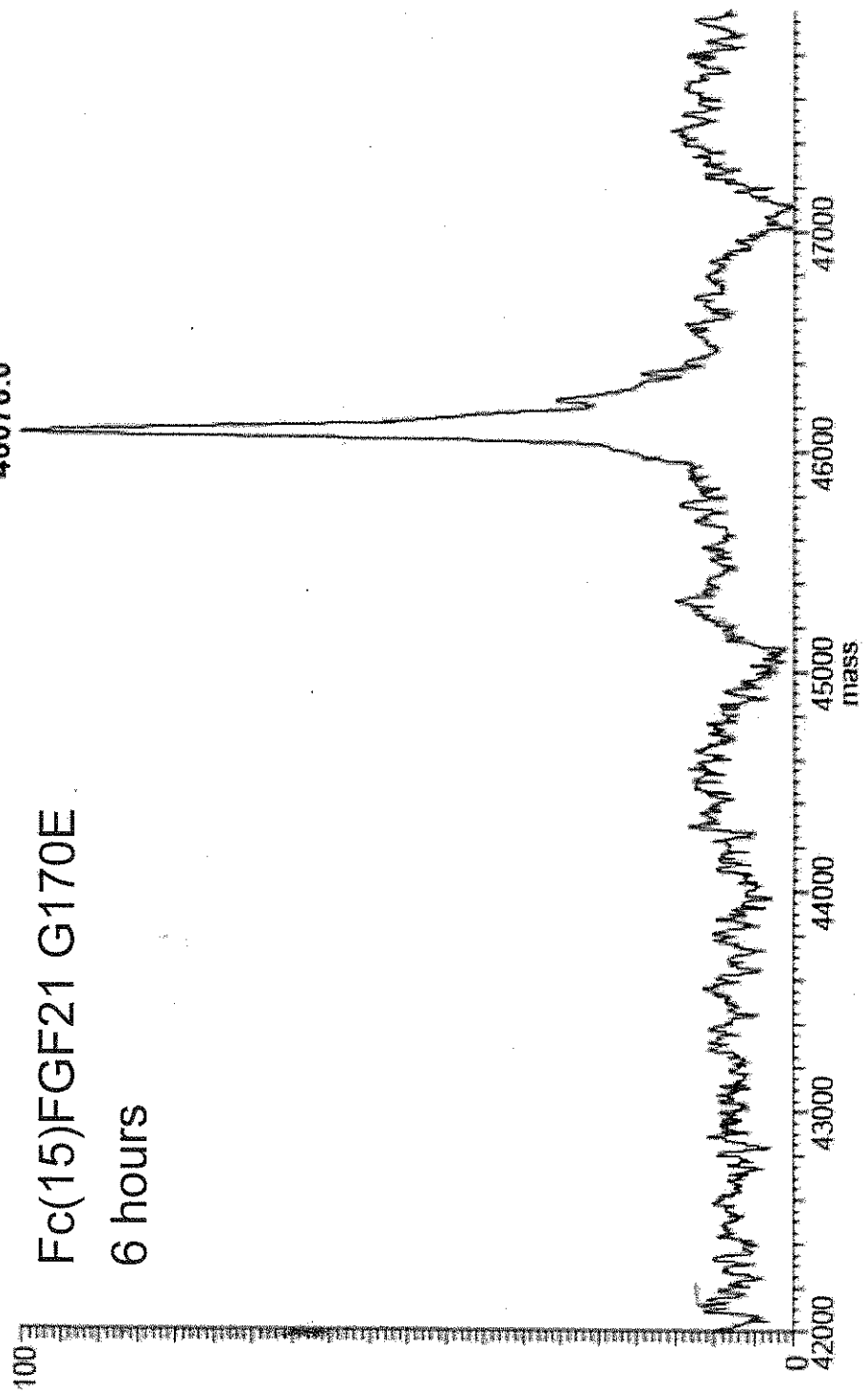

Fc(15)FGF21 G170E
6 hours
[1-4241]
46078.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 20C

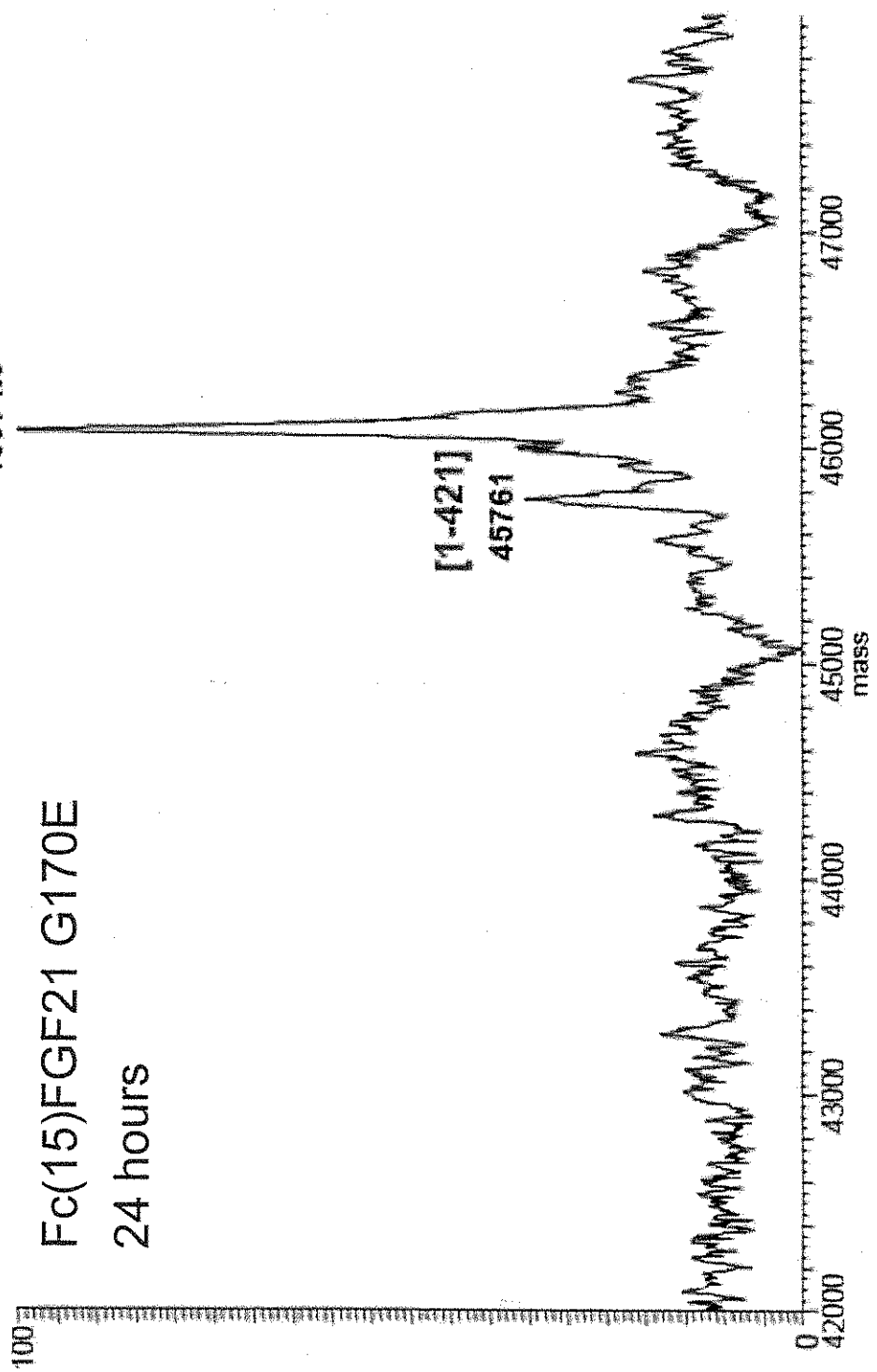

Fc(15)FGF21 G170E
24 hours
[1-424]
46074.0
[1-421]
45761
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 20D

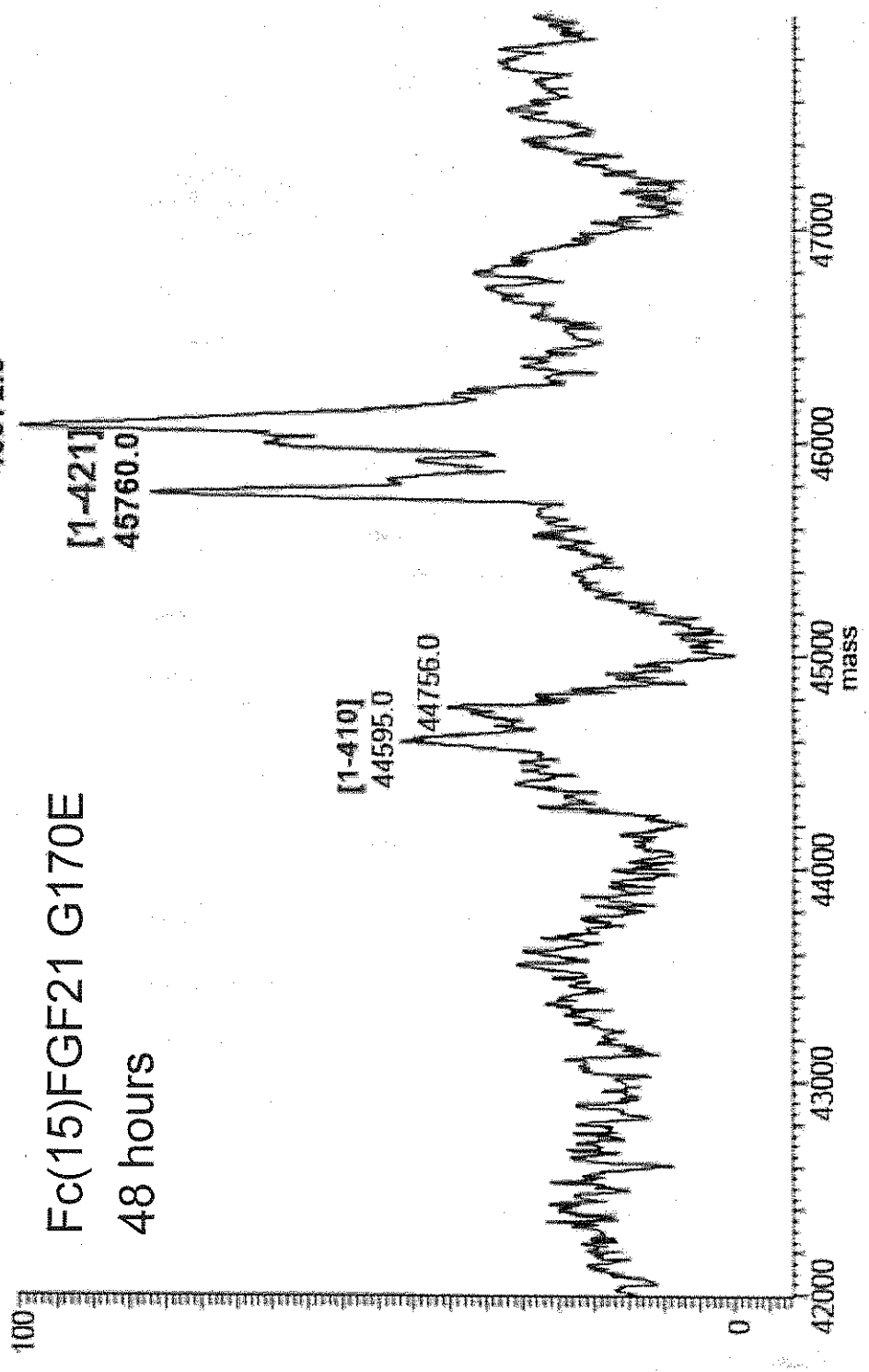

Fc(15)FGF21 G170E
48 hours
[1-424]
46072.0
[1-421]
45760.0
[1-410]
44595.0
44756.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 21A

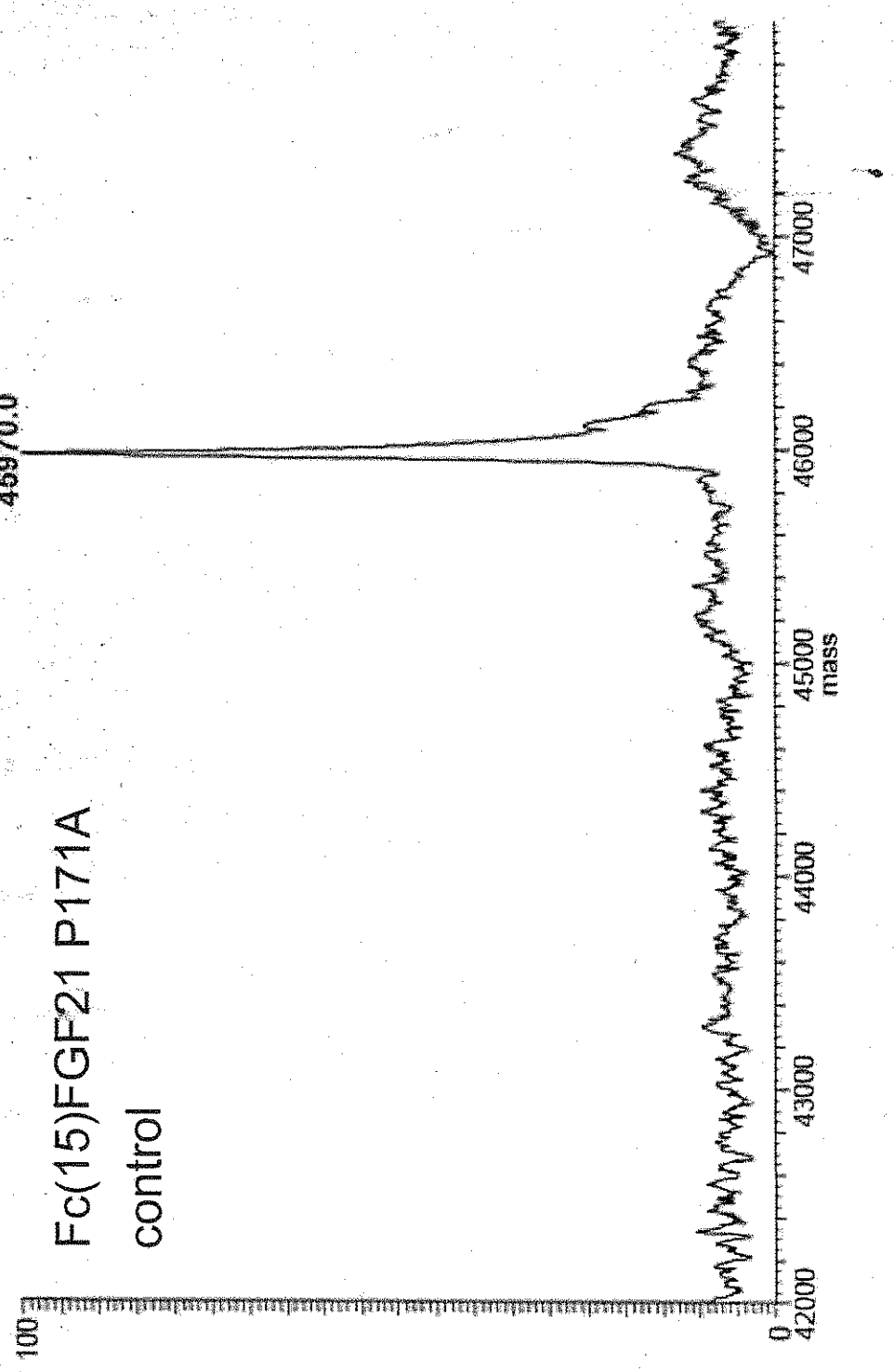

Fc(15)FGF21 P171A
control
[1-424]
46970.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 21B

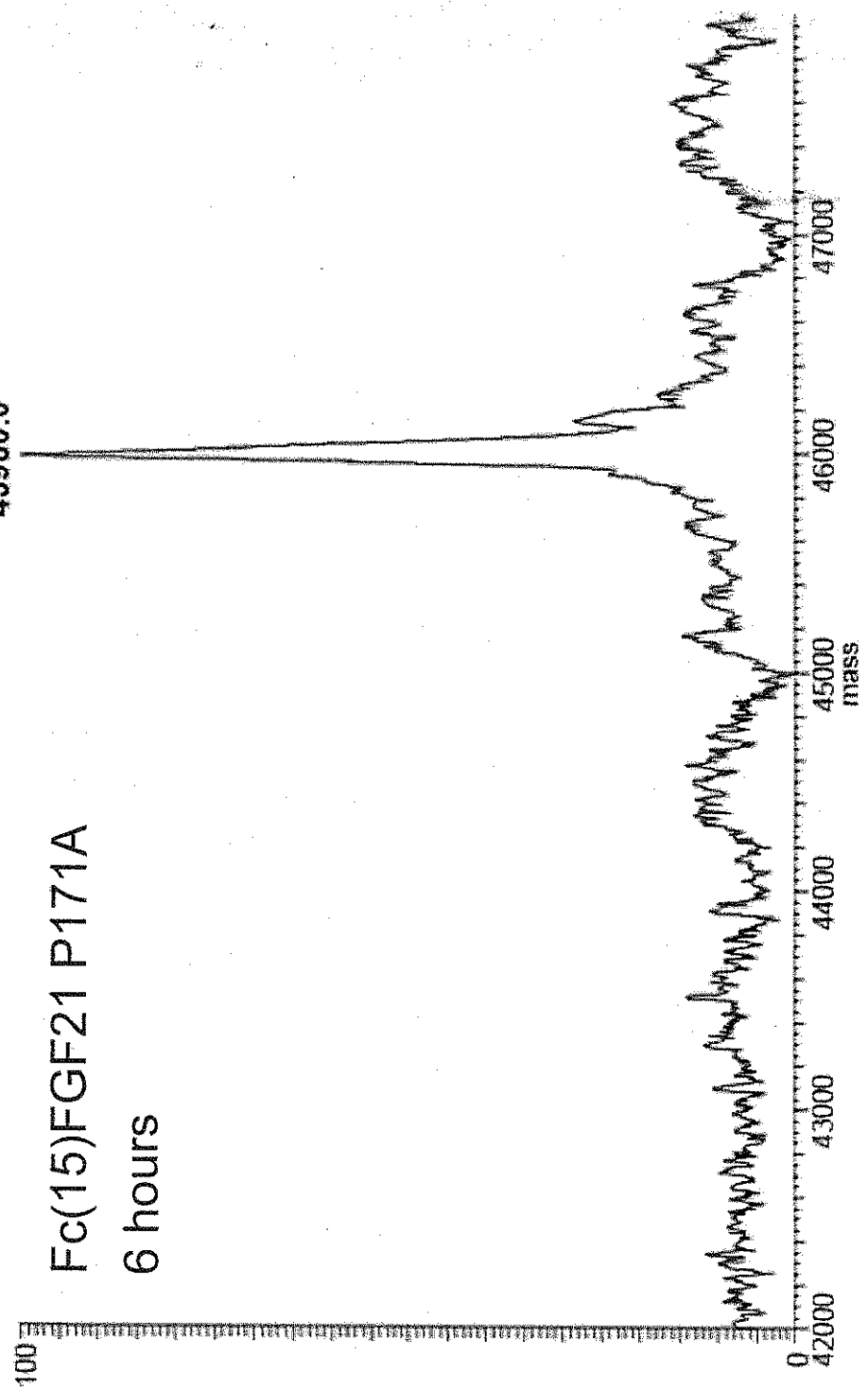

Fc(15)FGF21 P171A
6 hours
[1-424]
45980.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 21C

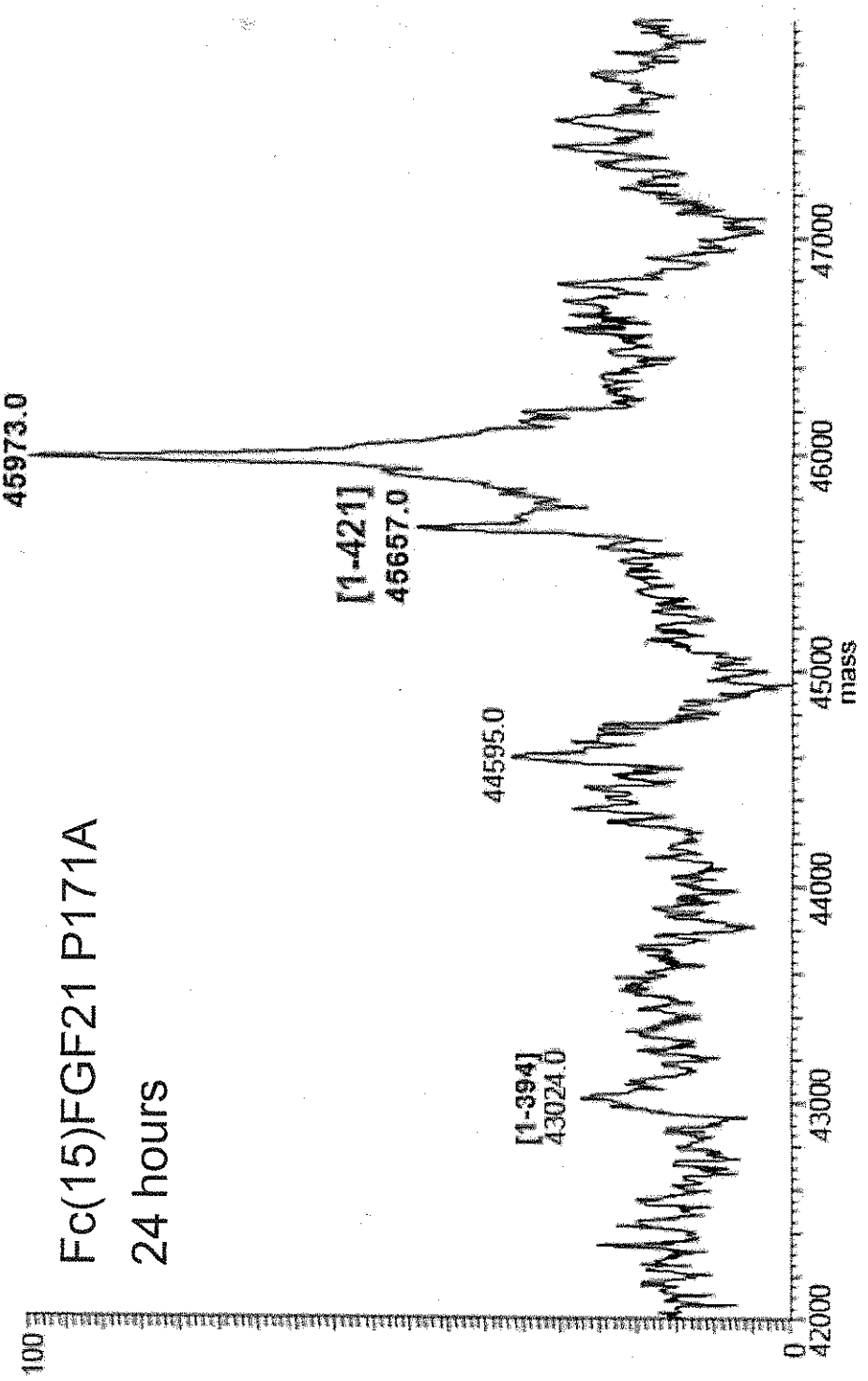

Fc(15)FGF21 P171A
24 hours
[1-424]
45973.0
[1-421]
45657.0
44595.0
[1-394]
43024.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 21D

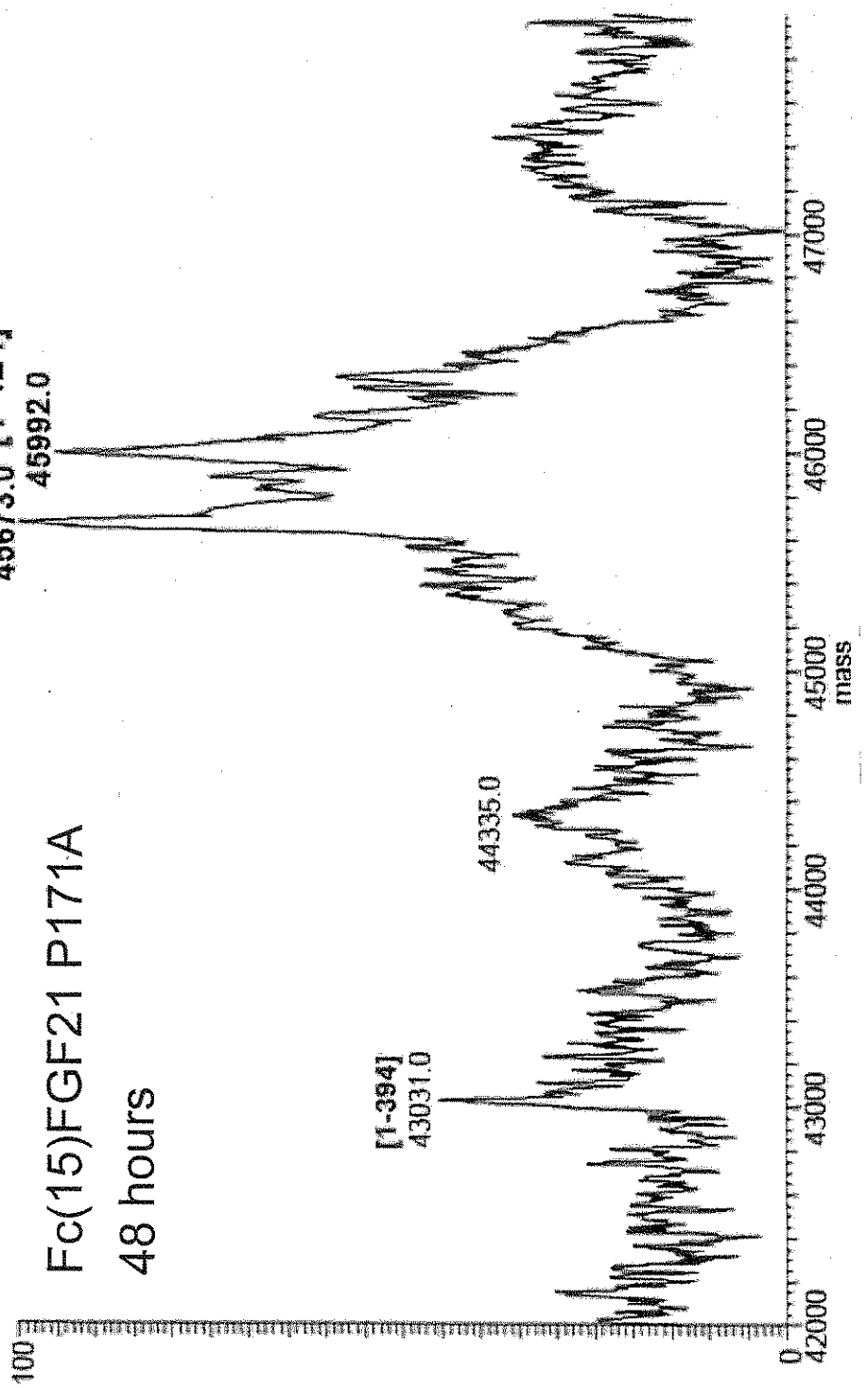

Fc(15)FGF21 P171A
48 hours
[1-421]
45673.0
[1-424]
45992.0
[1-394]
43031.0
44335.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 22A

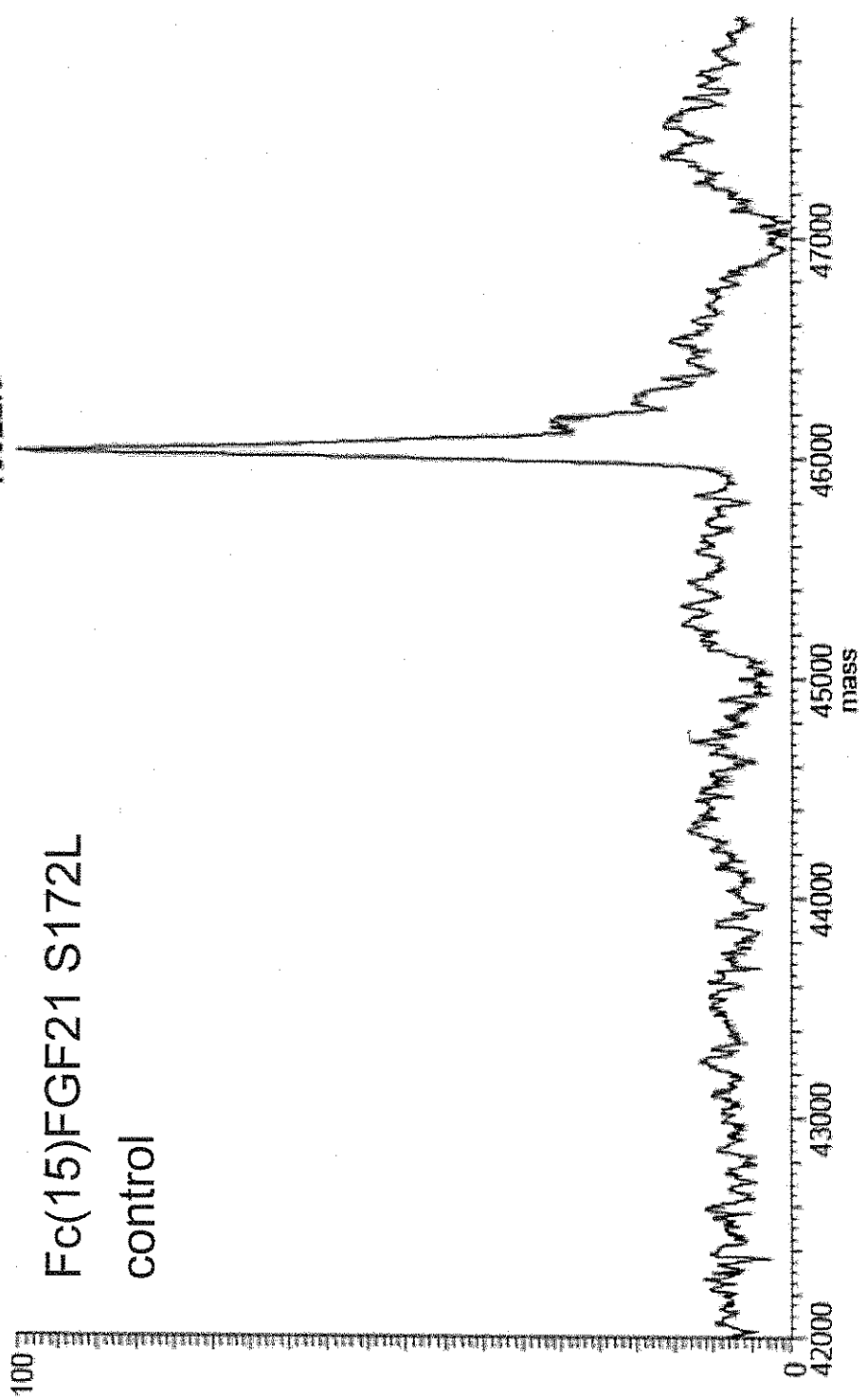

Fc(15)FGF21 S172L
control
[1-424]
46022.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 22B

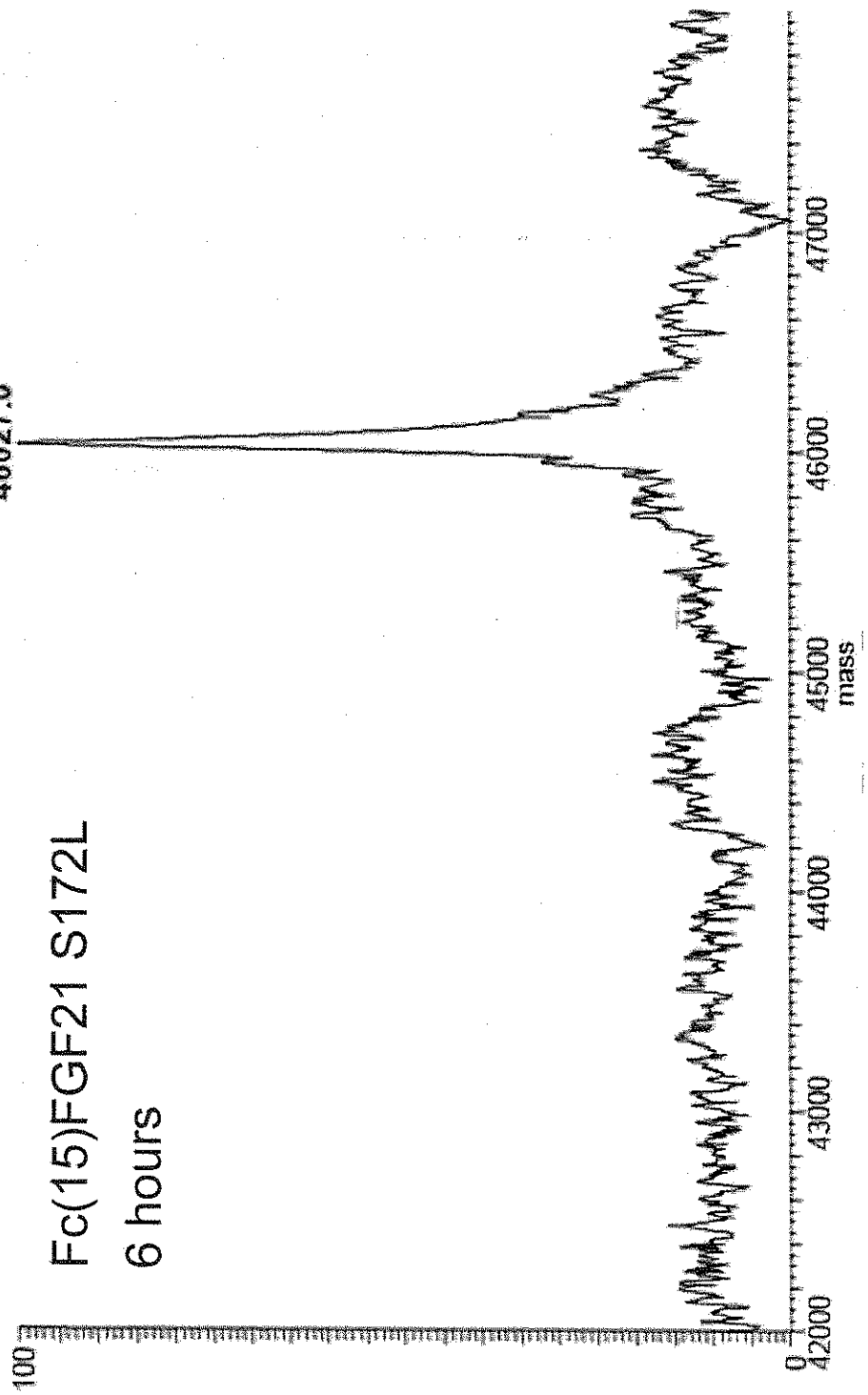

Fc(15)FGF21 S172L
6 hours
[1-424]
46027.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 22C

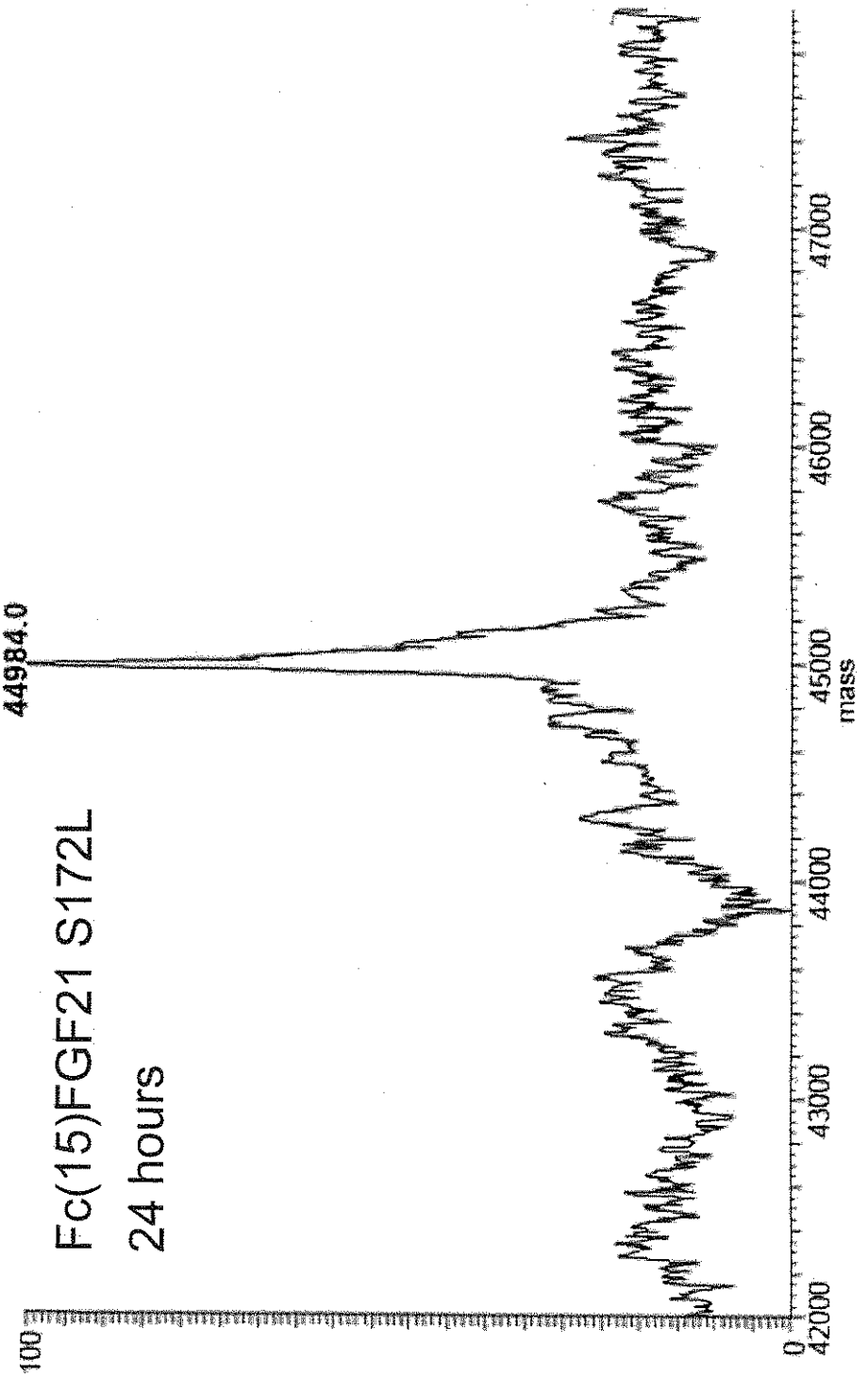

Fc(15)FGF21 S172L
24 hours
[1-414]
44984.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 22D

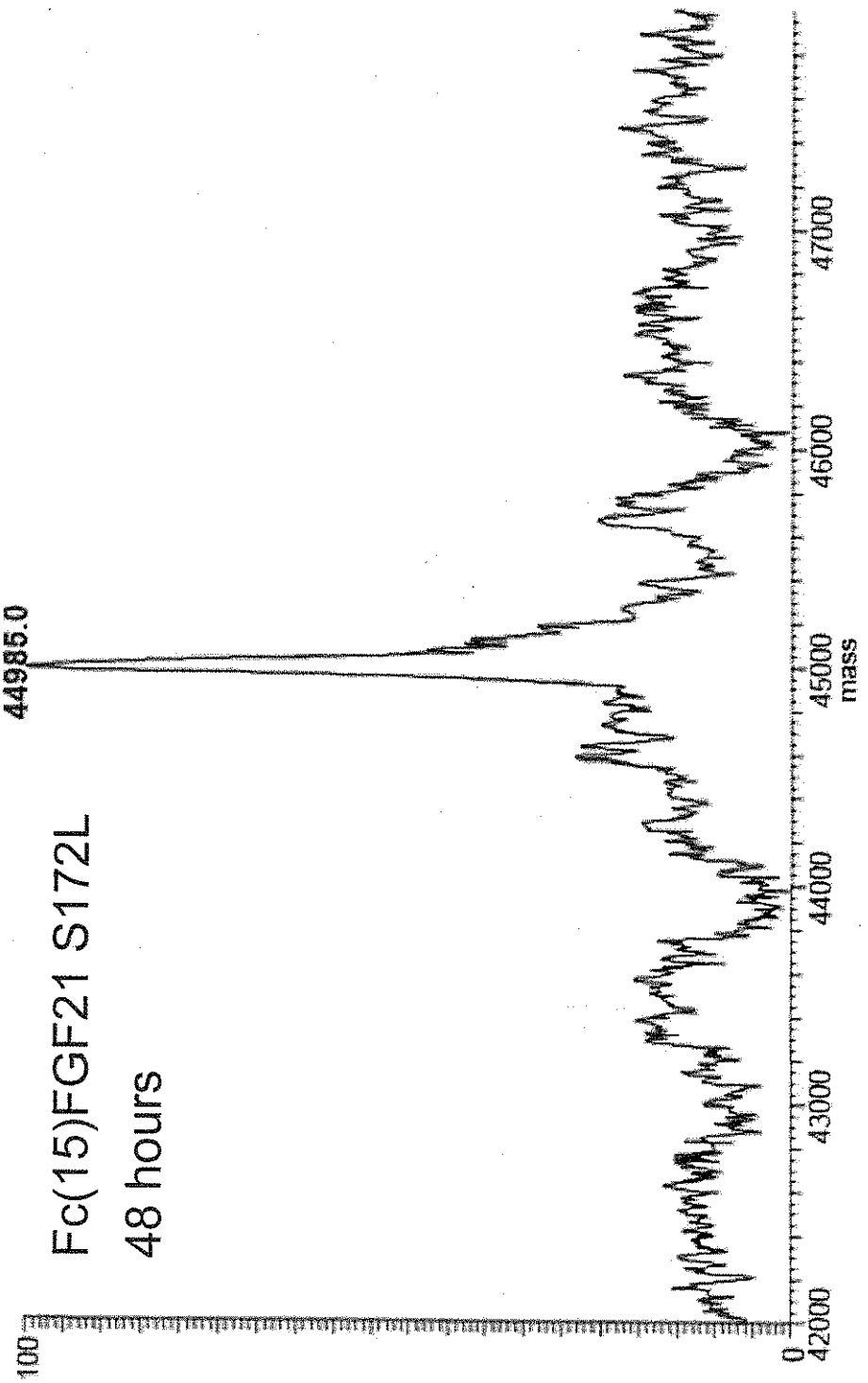

Fc(15)FGF21 S172L
48 hours
[1-414]
44985.0
100
0
42000
43000
44000
45000
46000
47000
mass

FIG. 23A

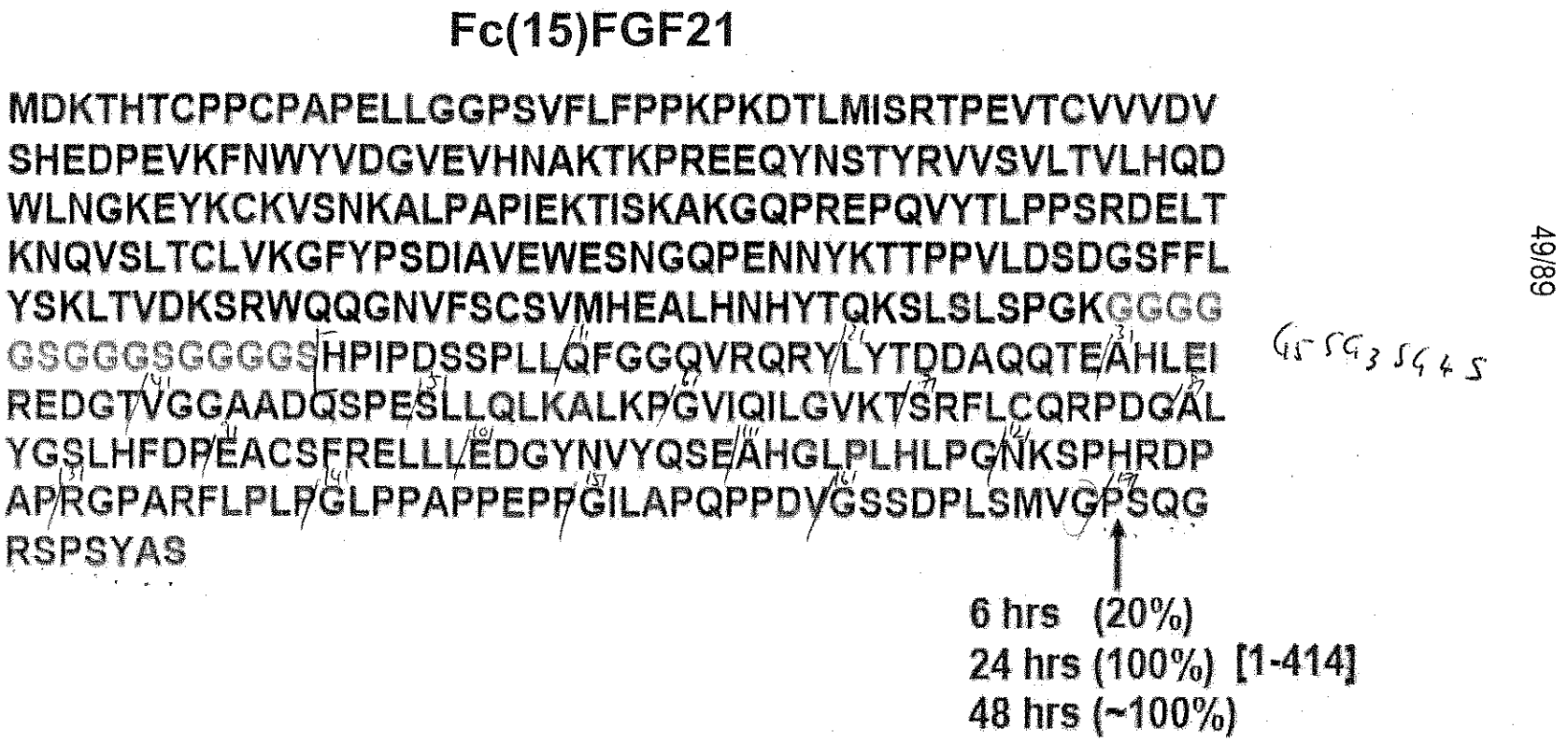

Fc(15)FGF21
MDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGG
GSGGGSGGGGSHPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEI
REDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQRPDGAL
YGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDP
APRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGPSQG
RSPSYAS
6 hrs (20%)
24 hrs (100%) [1-414]
48 hrs (~100%)

FIG. 23B

## Fc(15)FGF21 G170E

MDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGG
GSGGGSGGGGSHPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEI
REDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQRPDGAL
YGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDP
APRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVEPSQG
RSPSYAS

6 hrs (0%)
24 hrs (20%) [1-421]
48 hrs (~40%)

G4S G3S G4S

FIG. 23C

## Fc(15)FGF21 P171A

MDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGG
GSGGGSGGGGSHPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEI
REDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQRPDGAL
YGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDP
APRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGASQG
RSPSYAS

6 hrs (0%)
24 hrs (~30%) [1-421]
48 hrs (~50%)

FIG. 23D

## Fc(15)FGF21 S172L

MDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGG
GSGGGSGGGGSHPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEI
REDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQRPDGAL
YGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDP
APRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGPLQG
RSPSYAS

[1-414] 6 hrs (0%)
24 hrs (100%)
48 hrs (100%)

GSSGSGS

FIG. 24A

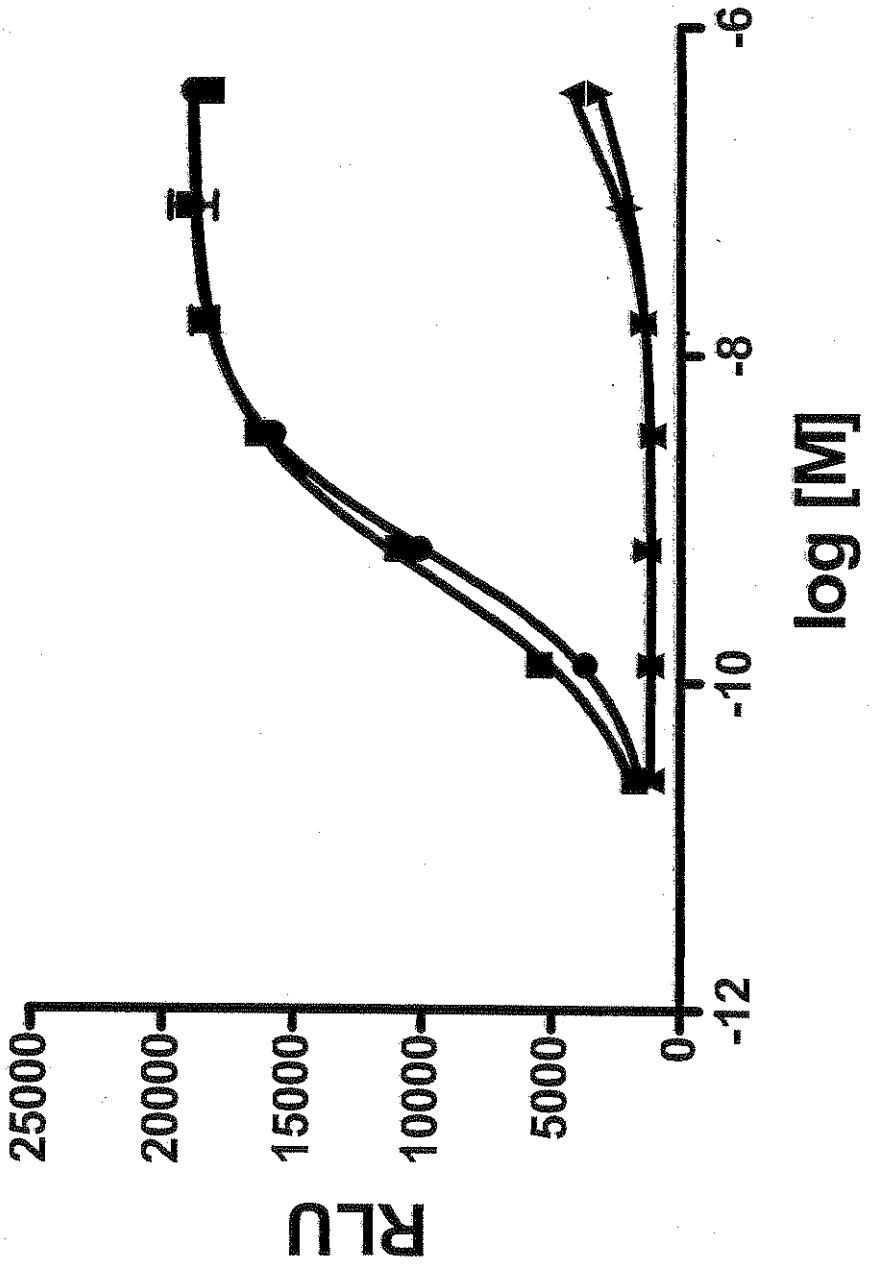

huFGF21
FGF21 L99R
FGF21 L99D
FGF21 A111T
RLU
25000
20000
15000
10000
5000
0
-12
-10
-8
-6
log [M]

FIG. 24B

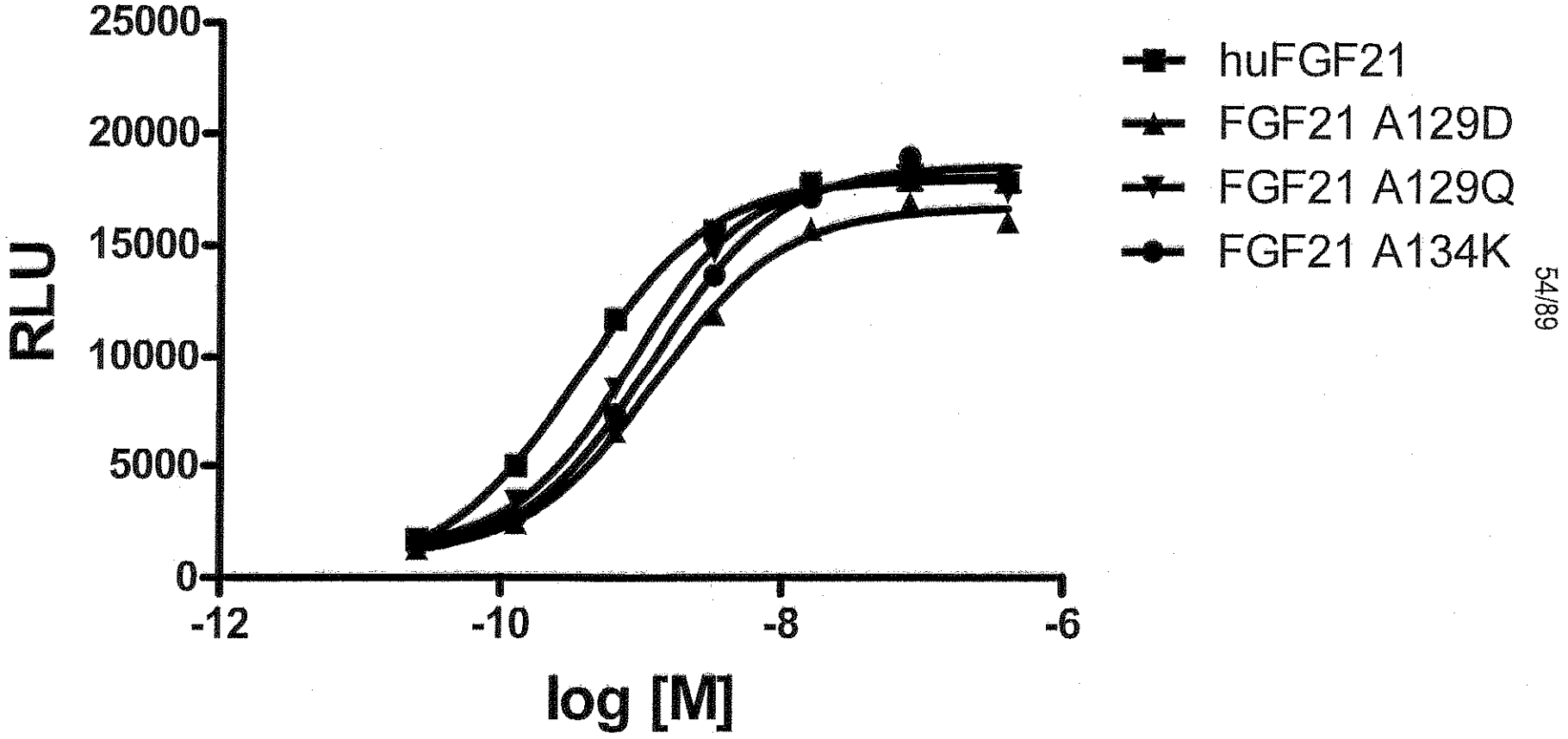

25000
20000
15000
10000
5000
0
RLU
-12
-10
-8
-6
log [M]
huFGF21
FGF21 A129D
FGF21 A129Q
FGF21 A134K

FIG. 24C

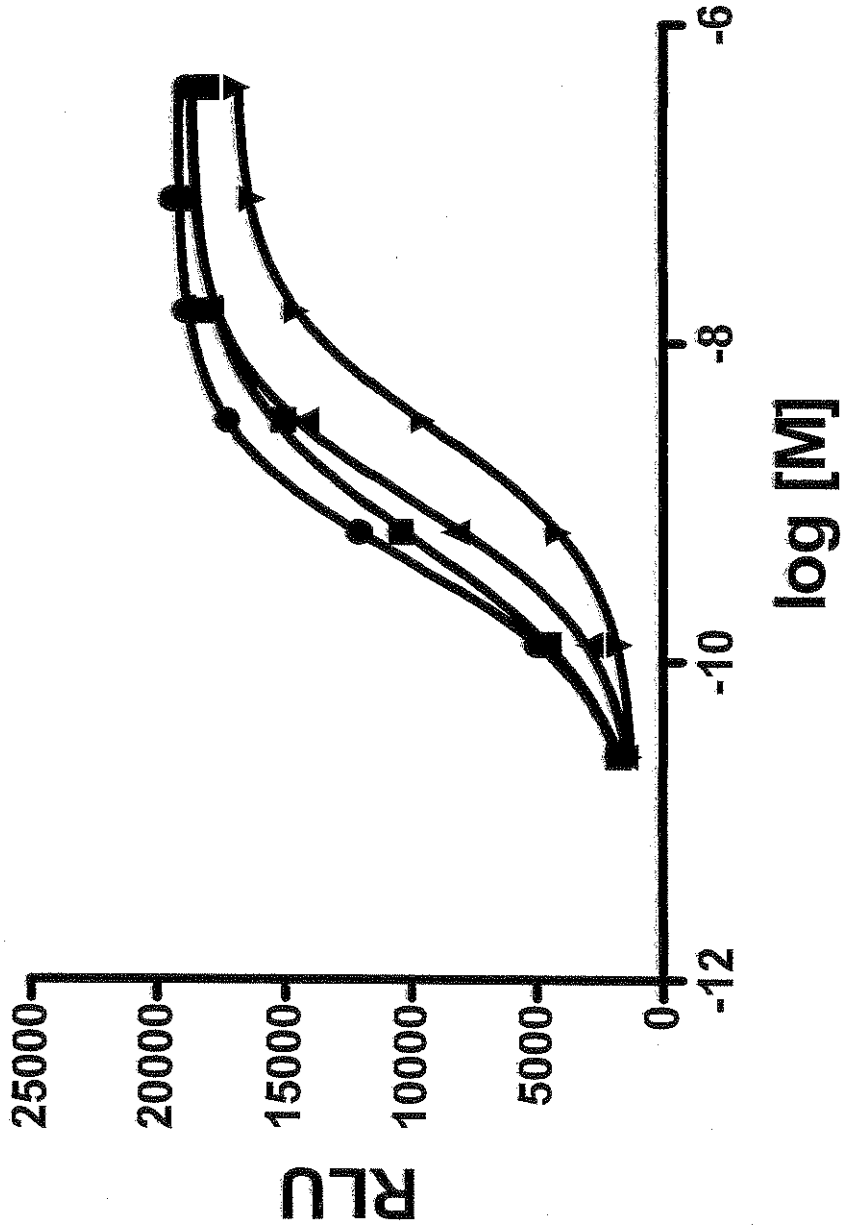

huFGF21
FGF21 A134Y
FGF21 A134E
FGF21 A129K
RLU
25000
20000
15000
10000
5000
0
-12
-10
-8
-6
log [M]

FIG. 25A

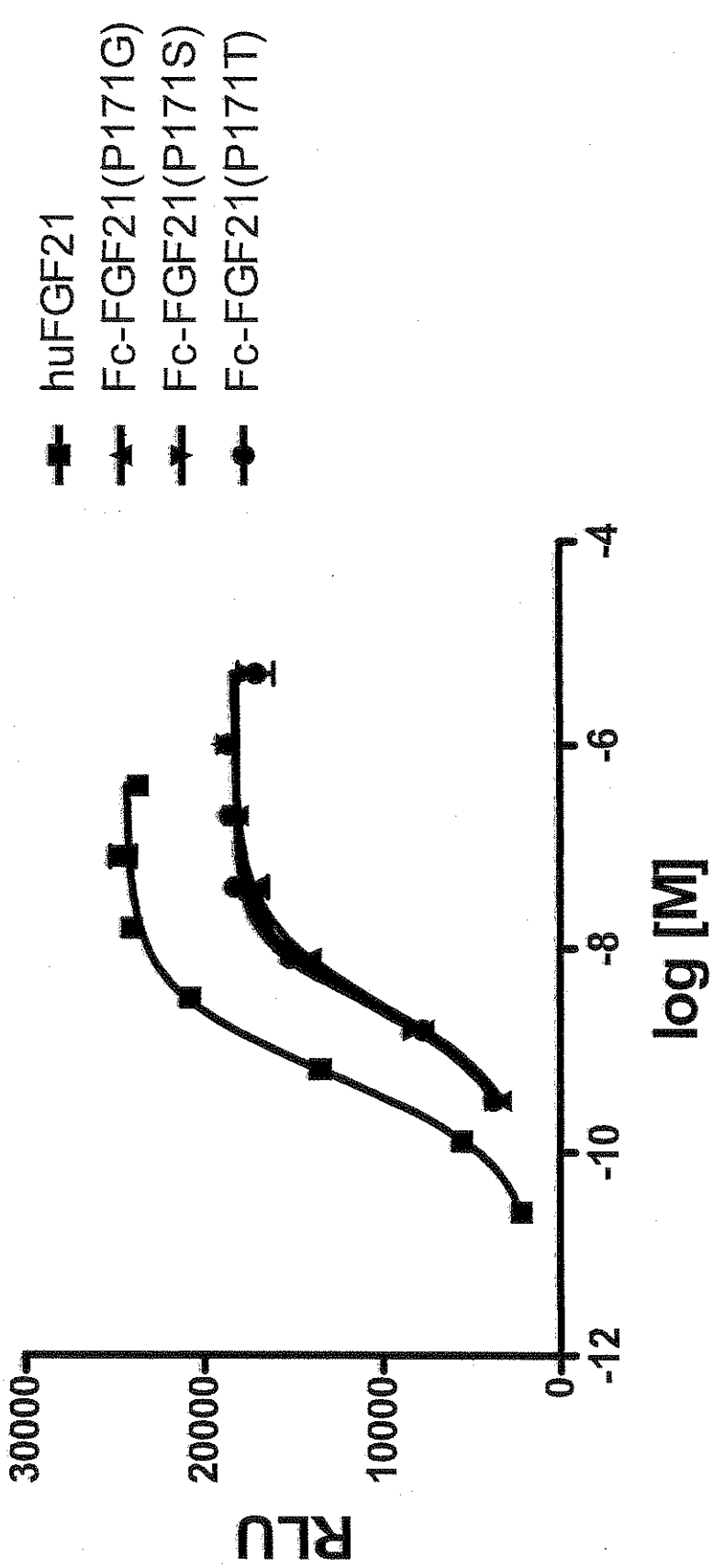

huFGF21
Fc-FGF21(P171G)
Fc-FGF21(P171S)
Fc-FGF21(P171T)
RLU
30000
20000
10000
0
-12
-10
-8
-6
-4
log [M]

FIG. 25B

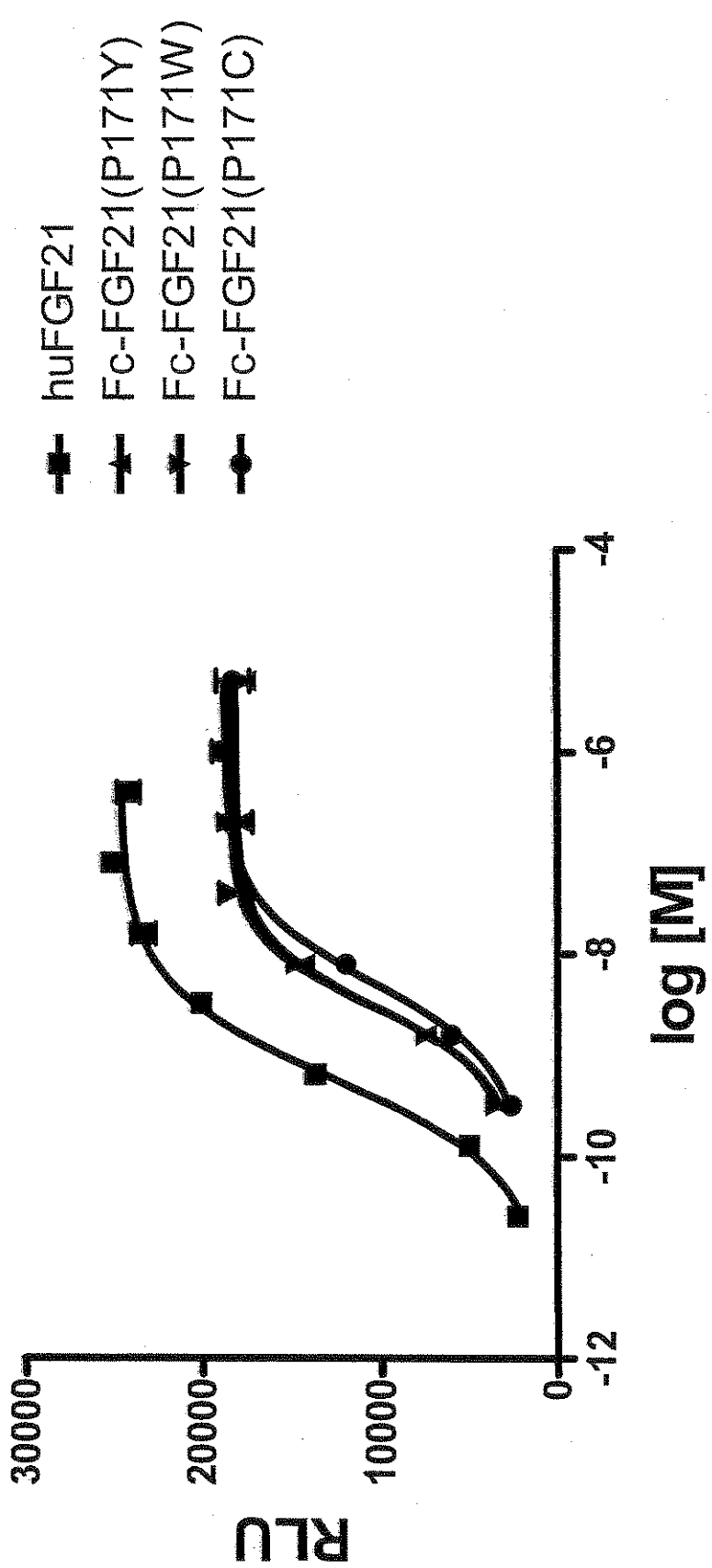

huFGF21
Fc-FGF21(P171Y)
Fc-FGF21(P171W)
Fc-FGF21(P171C)
RLU
30000
20000
10000
0
-12
-10
-8
-6
-4
log [M]

FIG. 25C

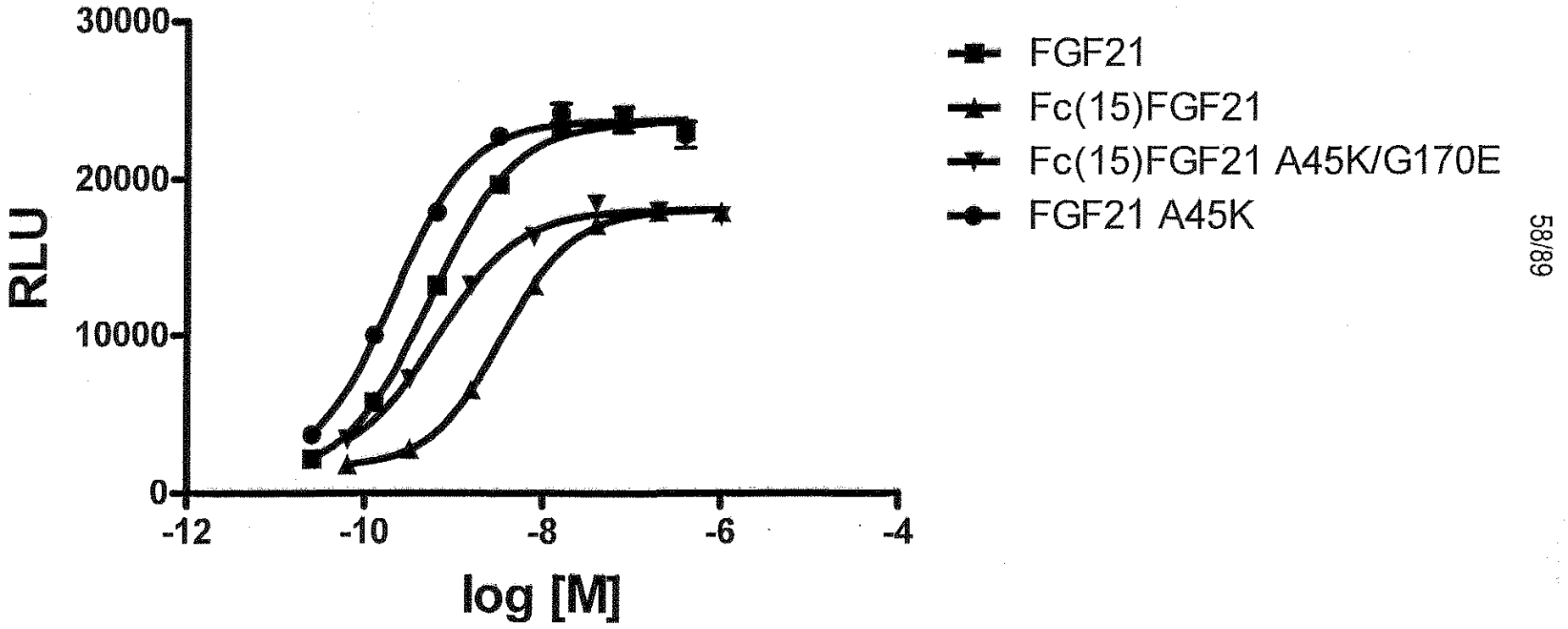

30000
20000
10000
0
RLU
-12
-10
-8
-6
-4
log [M]
FGF21
Fc(15)FGF21
Fc(15)FGF21 A45K/G170E
FGF21 A45K

FIG. 25D

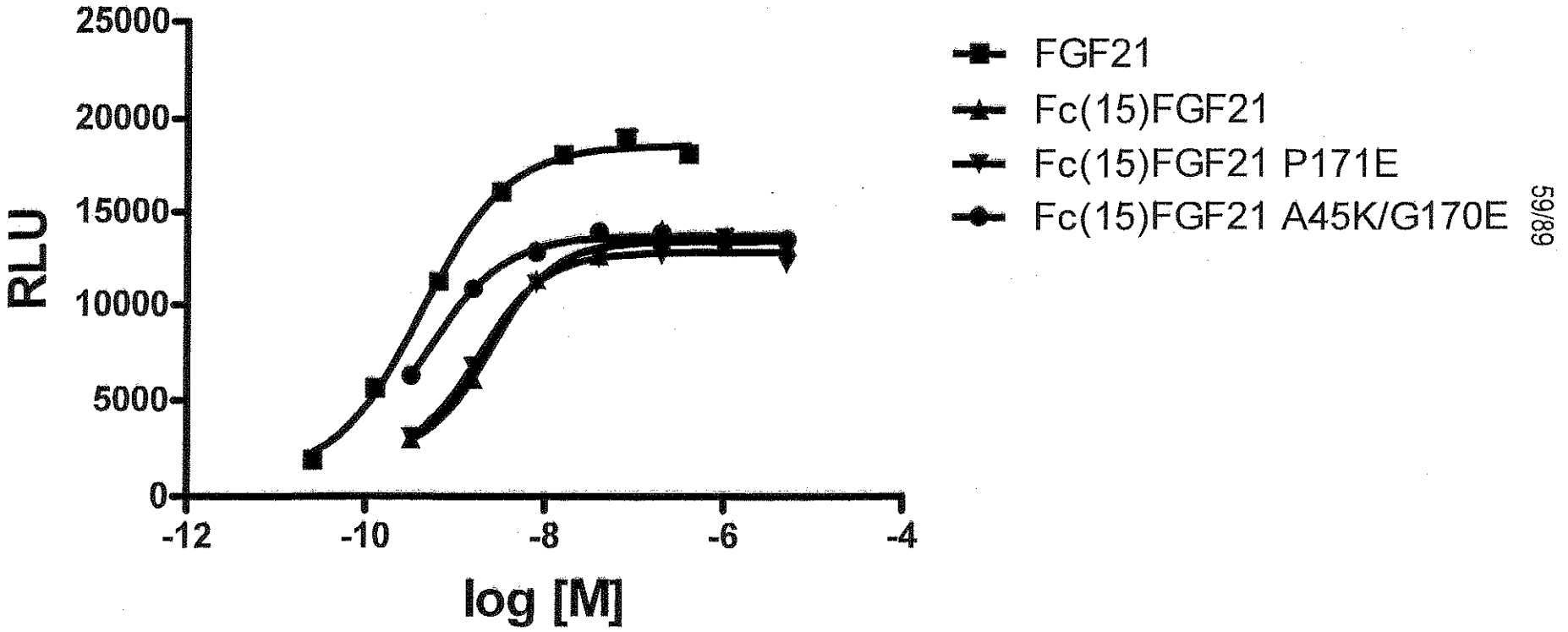

25000
20000
15000
10000
5000
0
RLU
-12
-10
-8
-6
-4
log [M]
FGF21
Fc(15)FGF21
Fc(15)FGF21 P171E
Fc(15)FGF21 A45K/G170E

FIG. 26A

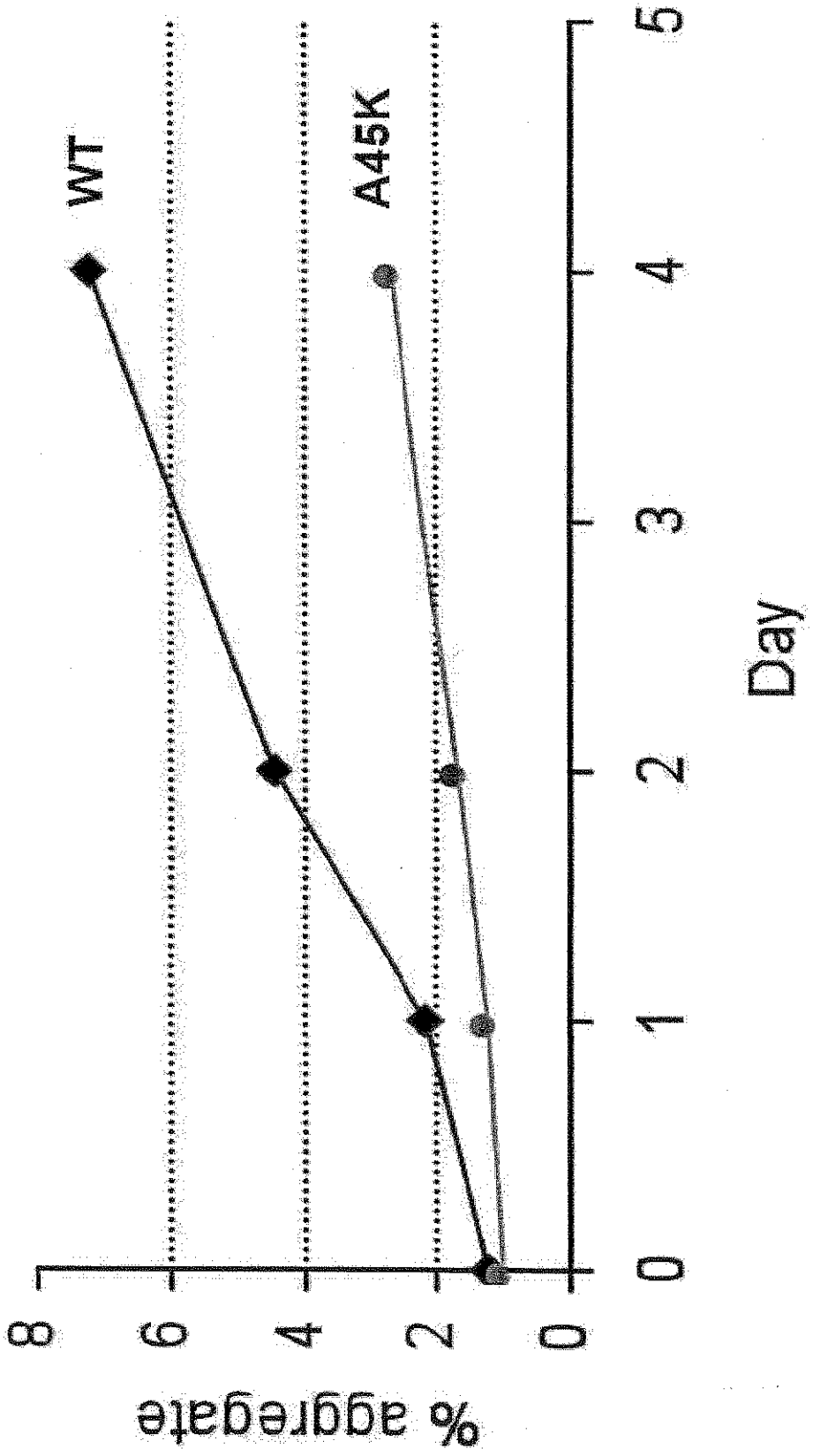


FIG. 26B

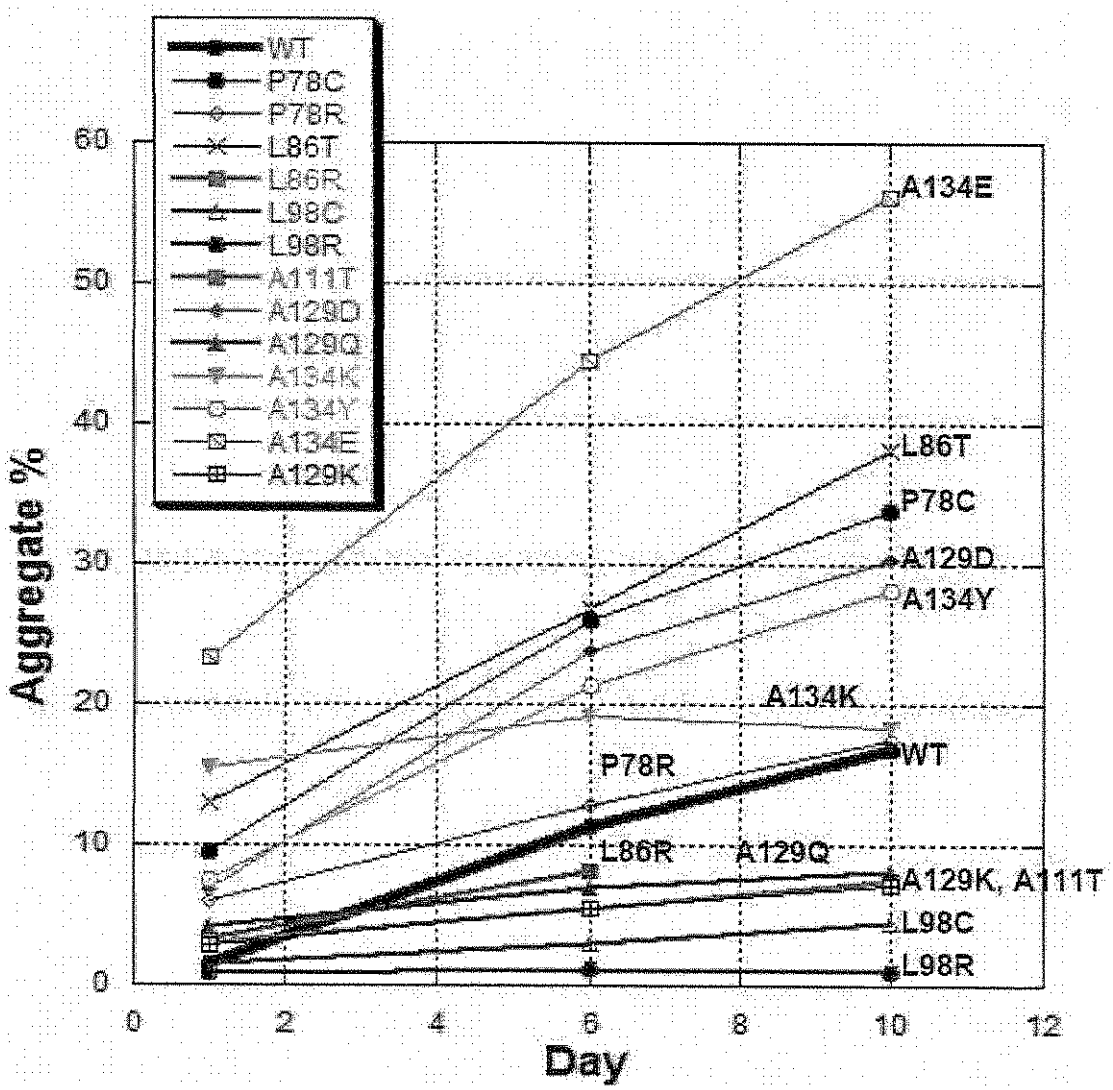

WT
P78C
P78R
L86T
L86R
L98C
L98R
A111T
A129D
A129Q
A134K
A134Y
A134E
A129K
Aggregate %
Day
0
10
20
30
40
50
60
0
2
4
6
8
10
12
A134E
L86T
P78C
A129D
A134Y
A134K
WT
P78R
L86R
A129Q
A129K, A111T
L98C
L98R

FIG. 27

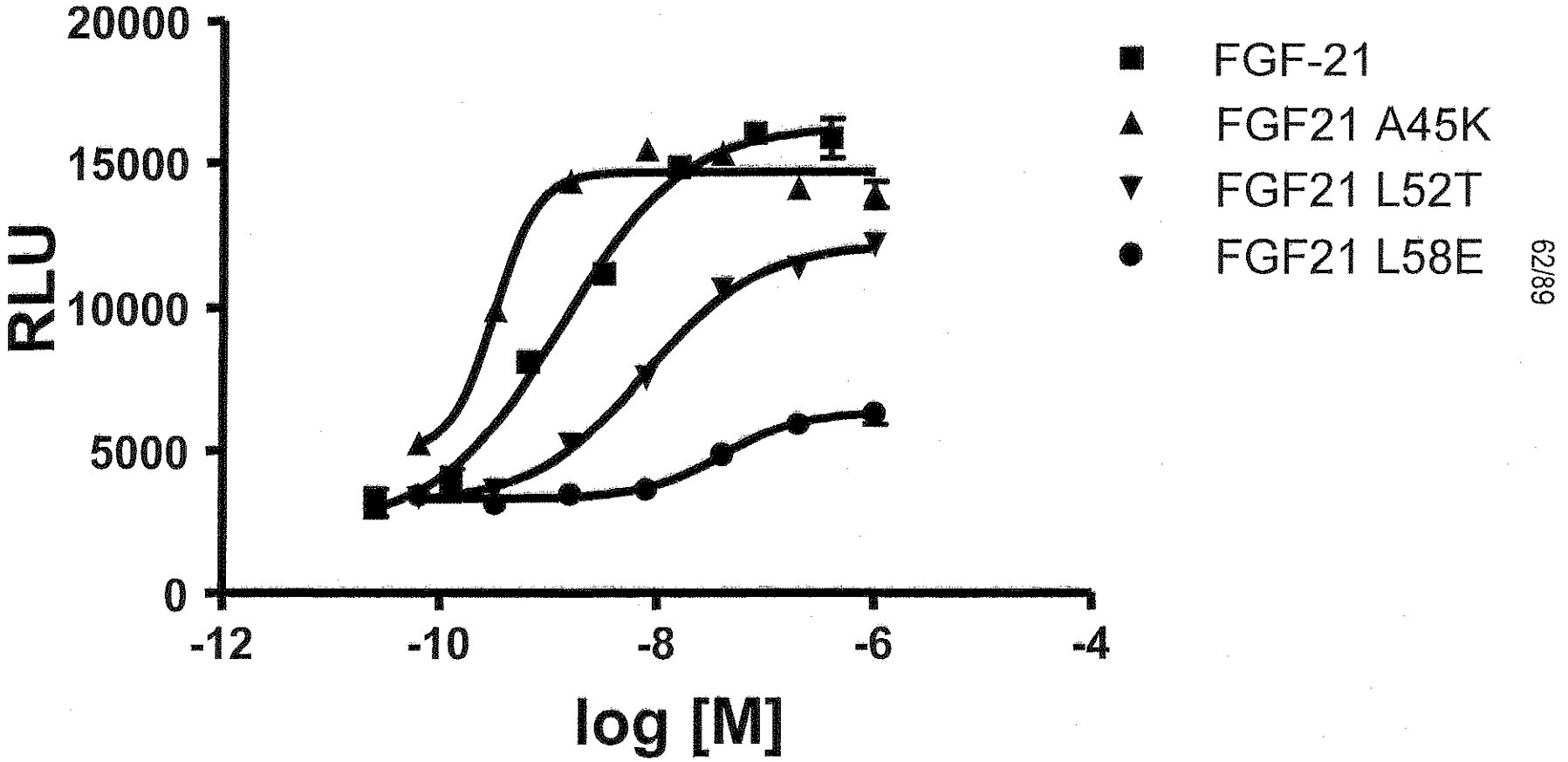

20000
15000
10000
5000
0
RLU
-12
-10
-8
-6
-4
log [M]
FGF-21
FGF21 A45K
FGF21 L52T
FGF21 L58E

FIG. 28A

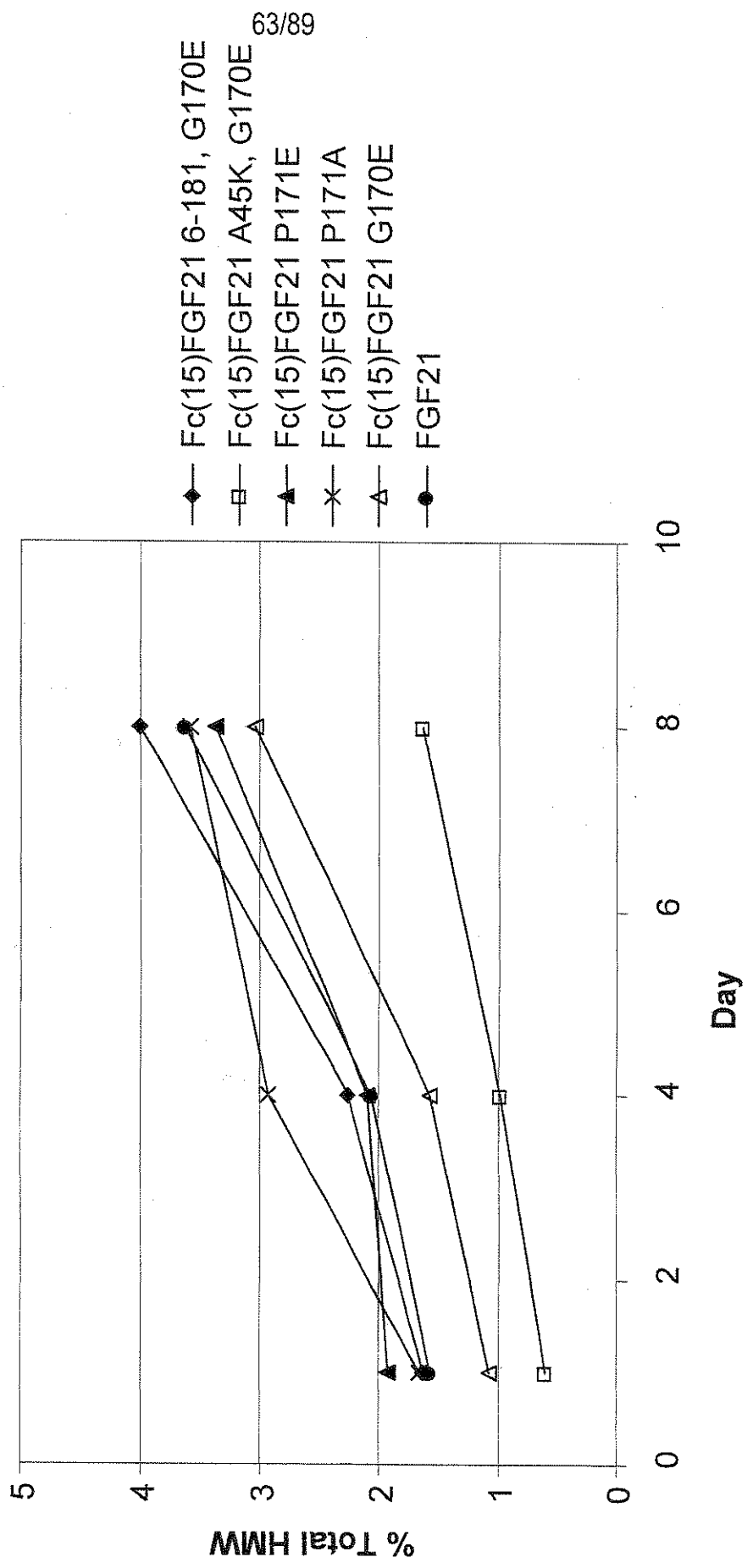

Fc(15)FGF21 6-181, G170E
Fc(15)FGF21 A45K, G170E
Fc(15)FGF21 P171E
Fc(15)FGF21 P171A
Fc(15)FGF21 G170E
FGF21
% Total HMW
Day
0
1
2
3
4
5
0
2
4
6
8
10

FIG. 28B

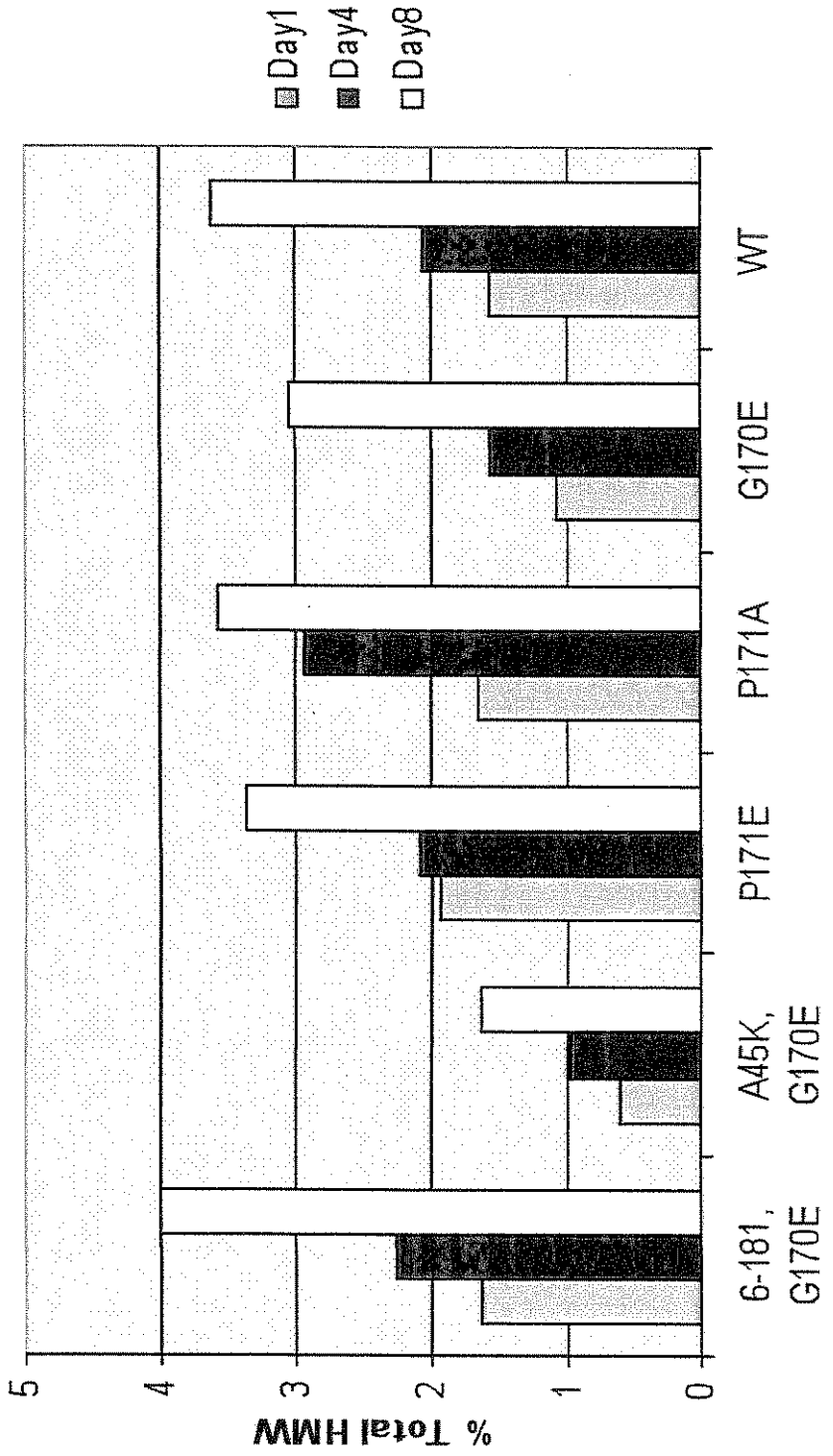

Day1
Day4
Day8
% Total HMW
0
1
2
3
4
5
WT
G170E
P171A
P171E
A45K, G170E
6-181, G170E

FIG. 29

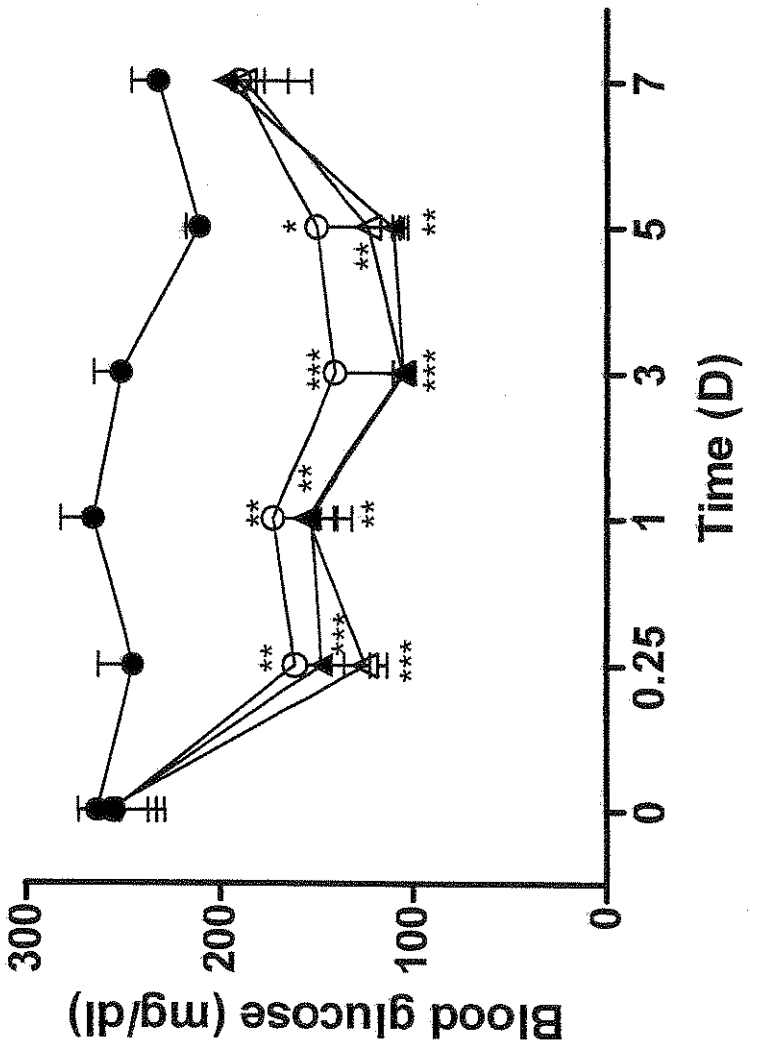
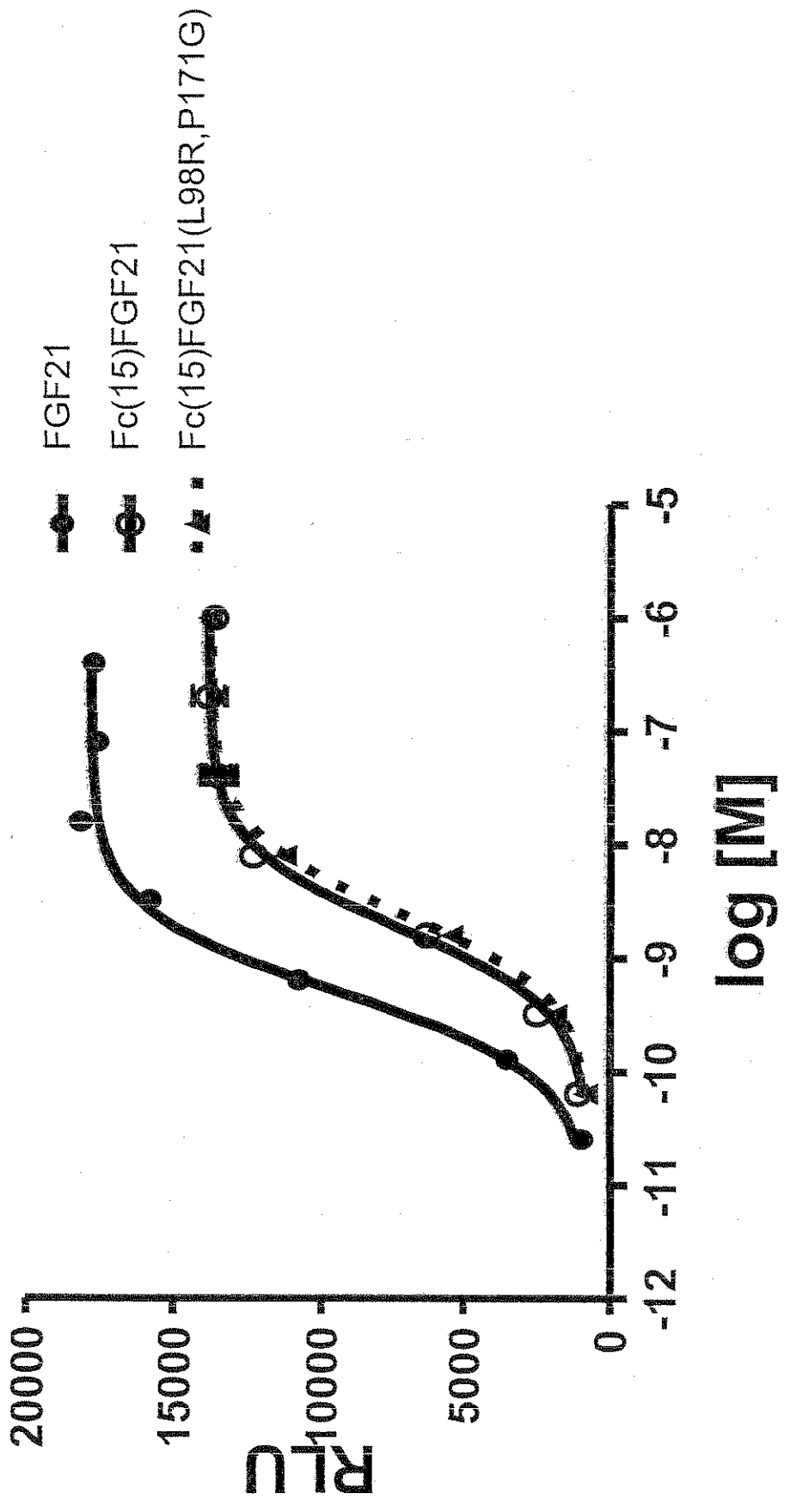

Blood glucose (mg/dl)
300
200
100
0
0
0.25
1
3
5
7
Time (D)
Vehicle
Fc-L15-hFGF(A45K,G170E)
Fc-L15-hFGF(A45K,P171G)
Fc-L15-hFGF(L98R,P171G)
* P< 0.05
** P< 0.01
*** P< 0.001
Treatments vs. Veh

Fig. 30


FGF21
Fc(15)FGF21
Fc(15)FGF21(L98R,P171G)
RLU
20000
15000
10000
5000
0
-12
-11
-10
-9
-8
-7
-6
-5
log [M]

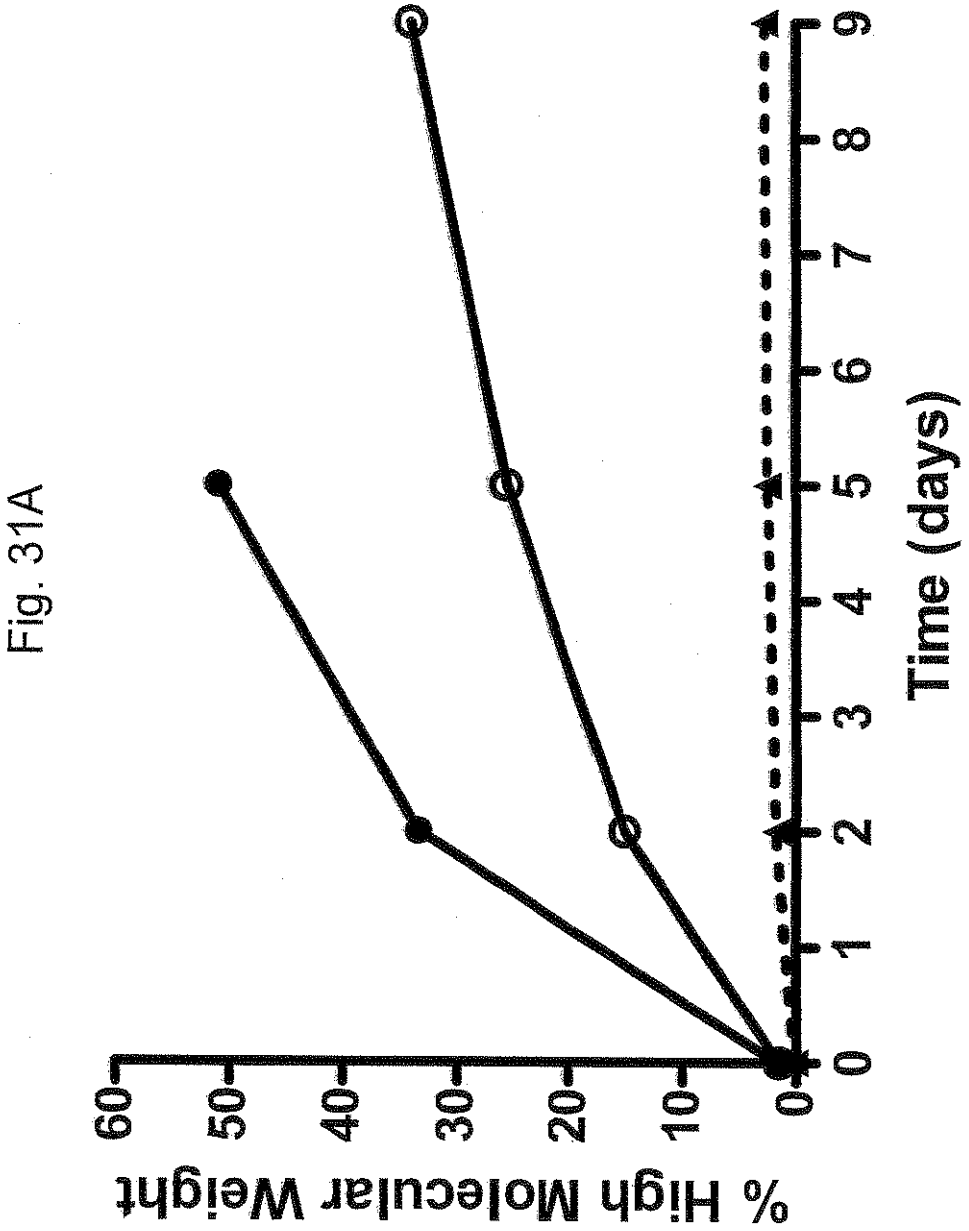

% High Molecular Weight
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
Time (days)

Fig. 31A

Fig. 31B

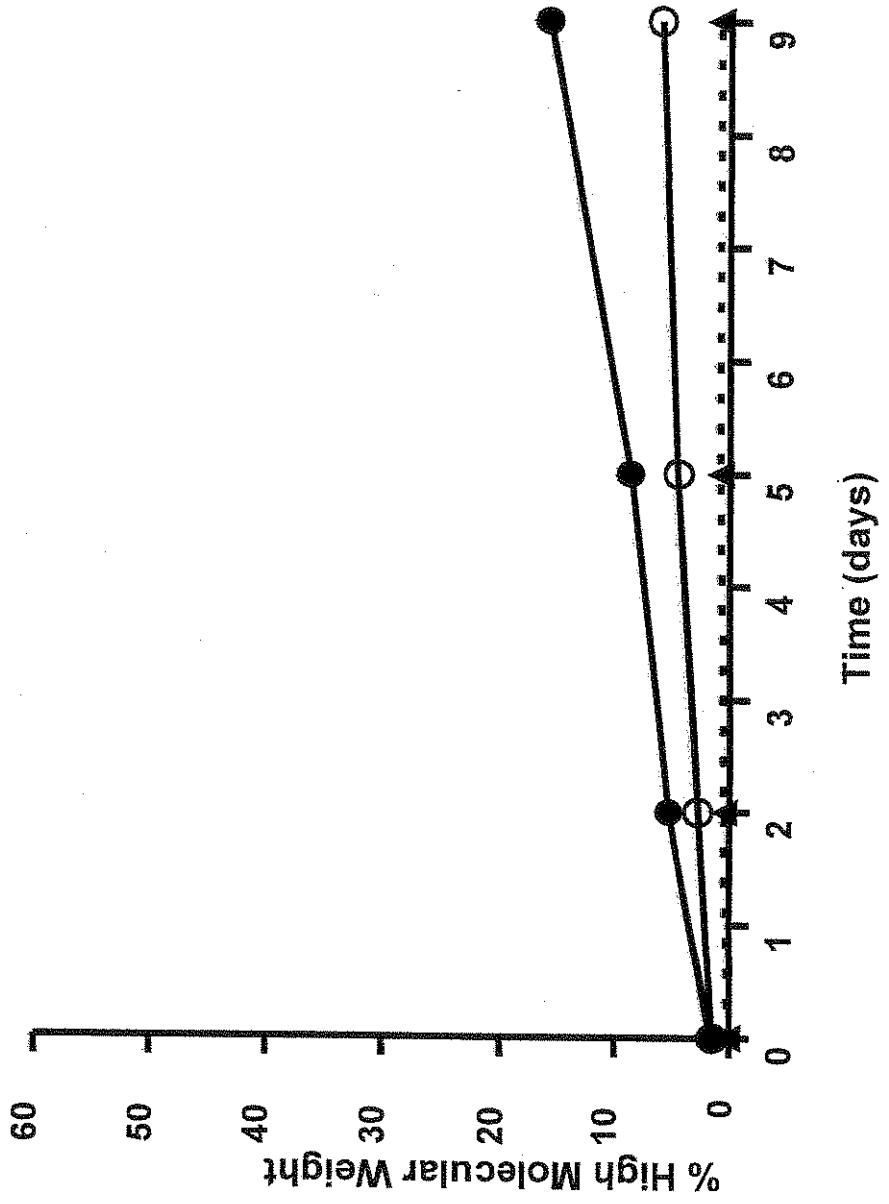

% High Molecular Weight
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
Time (days)

Fig. 32

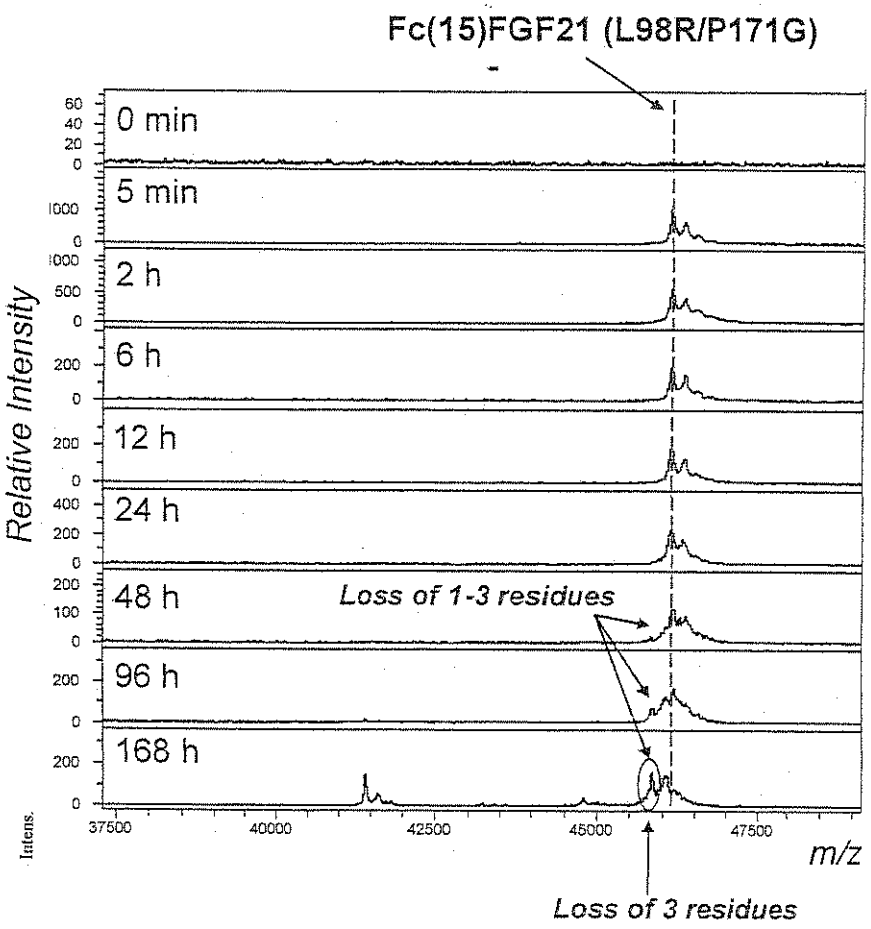

Fc(15)FGF21 (L98R/P171G)
0 min
5 min
2 h
6 h
12 h
24 h
48 h
96 h
168 h
Loss of 1-3 residues
Loss of 3 residues
Relative Intensity
Intens.
m/z
37500
40000
42500
45000
47500

FIG. 33

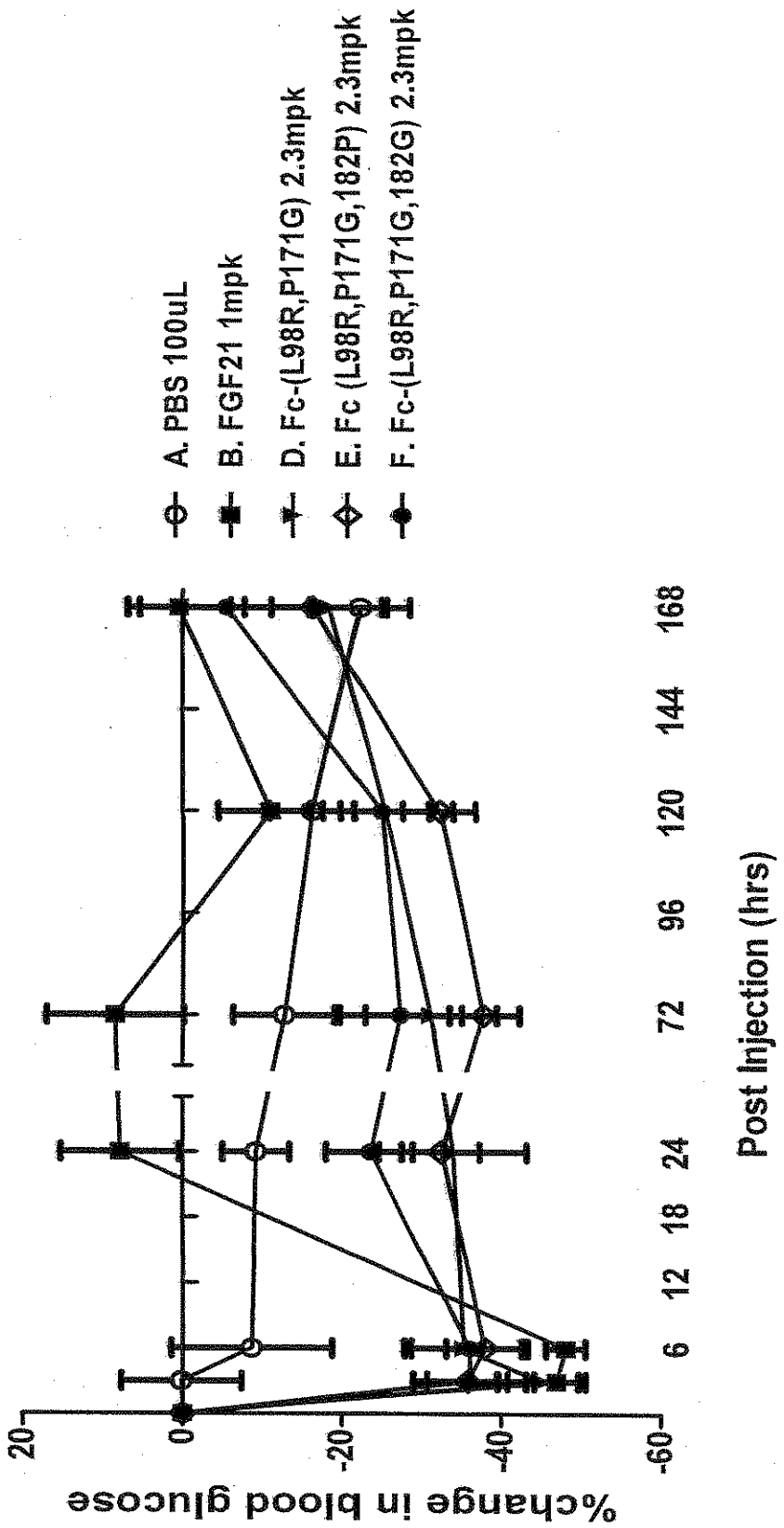

A. PBS 100uL
B. FGF21 1mpk
D. Fc-(L98R,P171G) 2.3mpk
E. Fc (L98R,P171G,182P) 2.3mpk
F. Fc-(L98R,P171G,182G) 2.3mpk
%change in blood glucose
20
0
-20
-40
-60
6
12
18
24
72
96
120
144
168
Post Injection (hrs)

FIG. 34

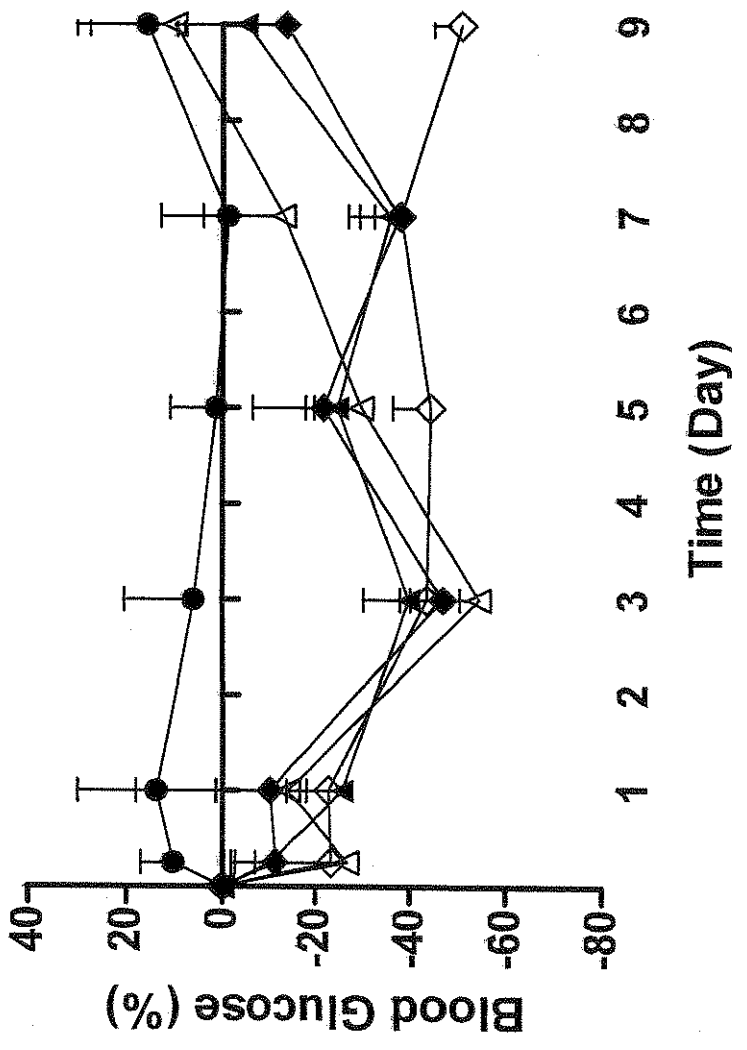

Veh
FcFGF21(L98R,P171G)
FcFGF21(L98R,P171G.182G.183G )
FcFGF21(L98R,P171G.182G)
FcFGF21(L98R,P171G.182P)
Blood Glucose (%)
40
20
0
-20
-40
-60
-80
1
2
3
4
5
6
7
8
9
Time (Day)

FIG. 35

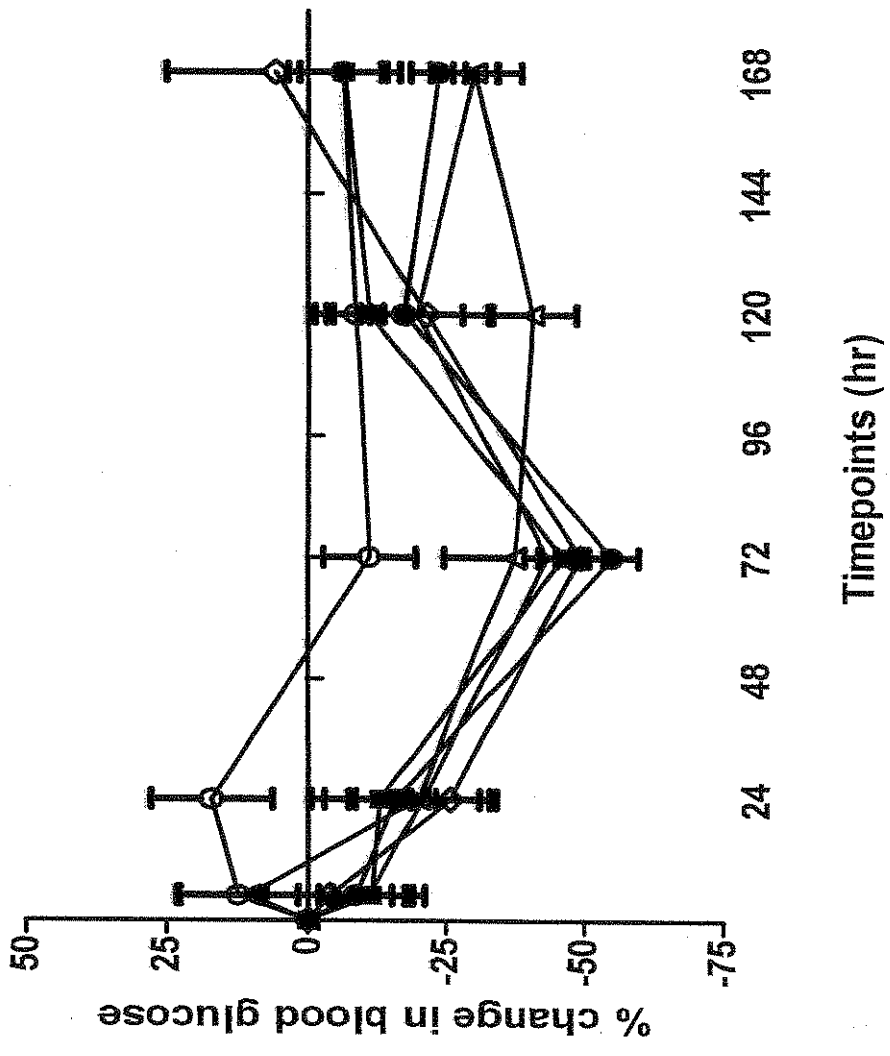

PBS
Fc(L98RP171G) 2.3mpk
Fc(L98RP171GY179S) 2.3mpk
Fc(L98RP171GY179A) 2.3mpk
Fc(L98RP171GA180S) 2.3mpk
Fc(L98RP171GA180G) 2.3mpk
% change in blood glucose
50
25
0
-25
-50
-75
24
48
72
96
120
144
168
Timepoints (hr)

FIG. 36

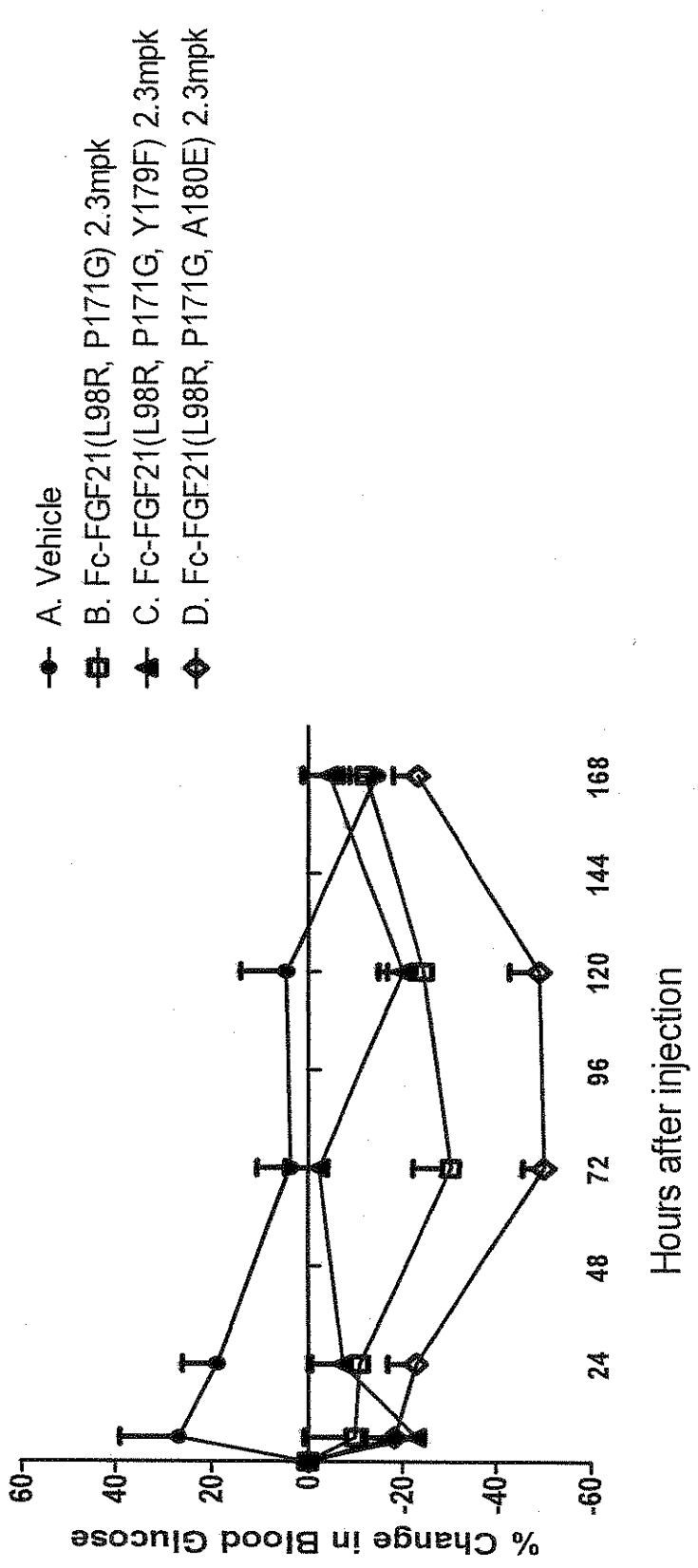

A. Vehicle
B. Fc-FGF21(L98R, P171G) 2.3mpk
C. Fc-FGF21(L98R, P171G, Y179F) 2.3mpk
D. Fc-FGF21(L98R, P171G, A180E) 2.3mpk
% Change in Blood Glucose
60
40
20
0
-20
-40
-60
24
48
72
96
120
144
168
Hours after injection

FIG. 37

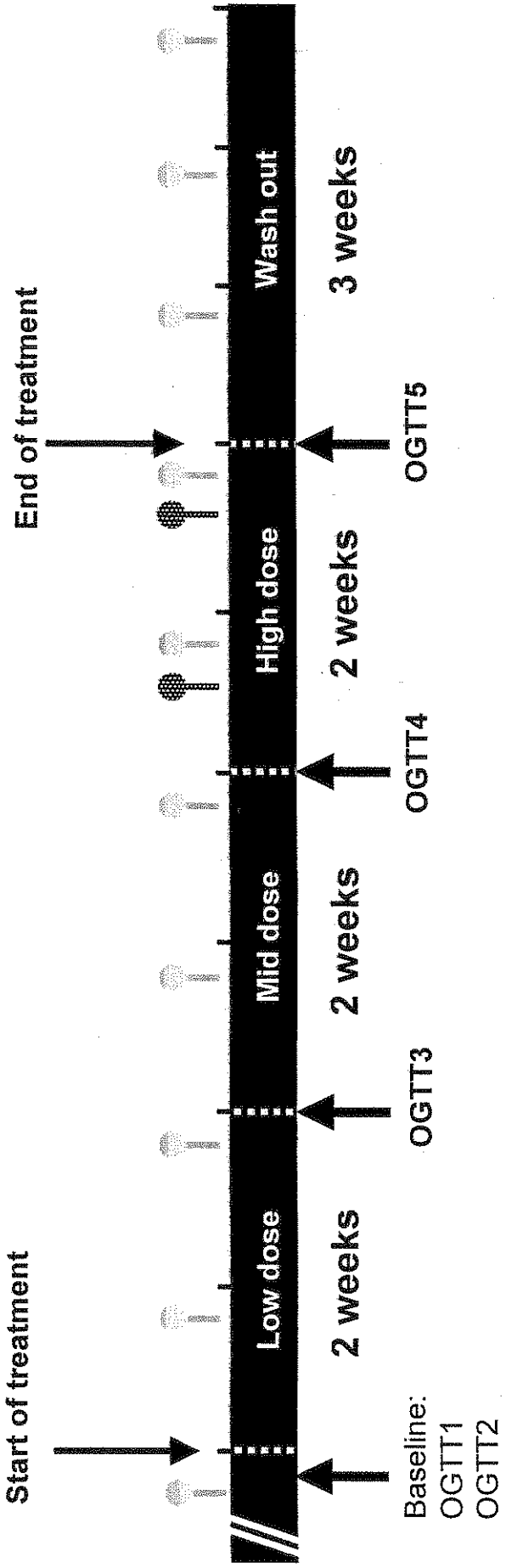

Start of treatment
End of treatment
Low dose
Mid dose
High dose
Wash out
2 weeks
2 weeks
2 weeks
3 weeks
Baseline:
OGTT1
OGTT2
OGTT3
OGTT4
OGTT5

FIG. 38A

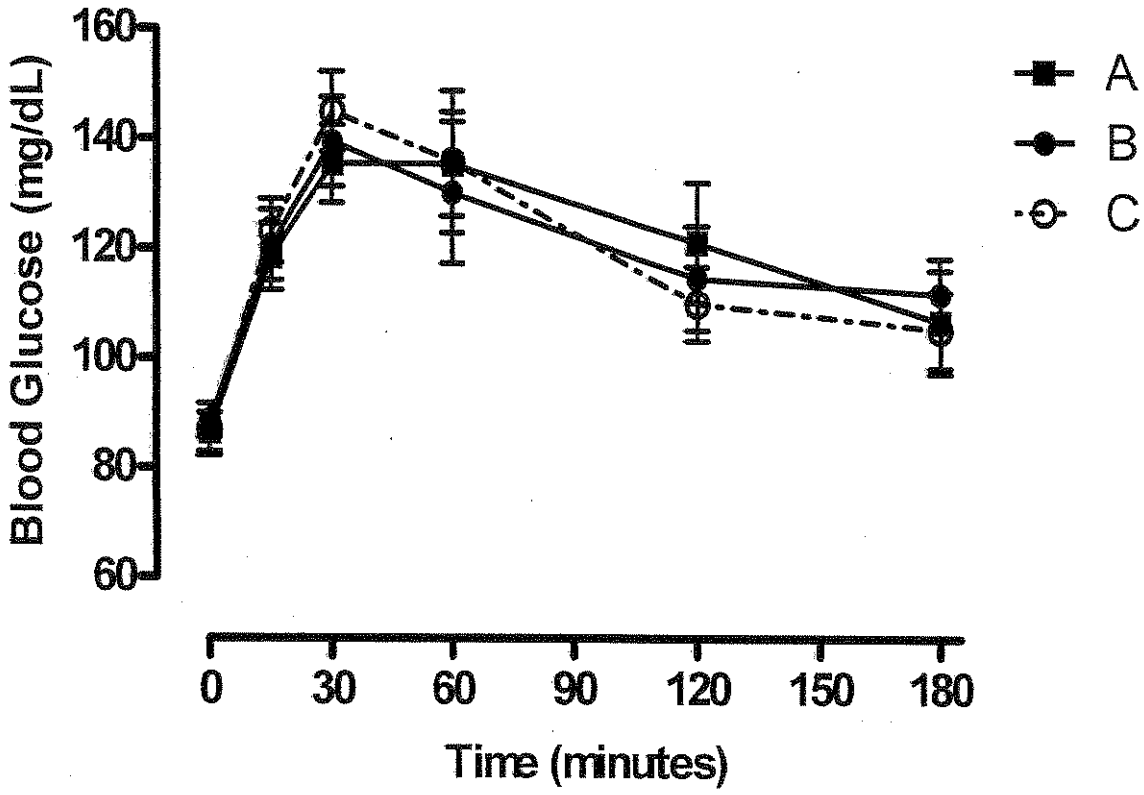
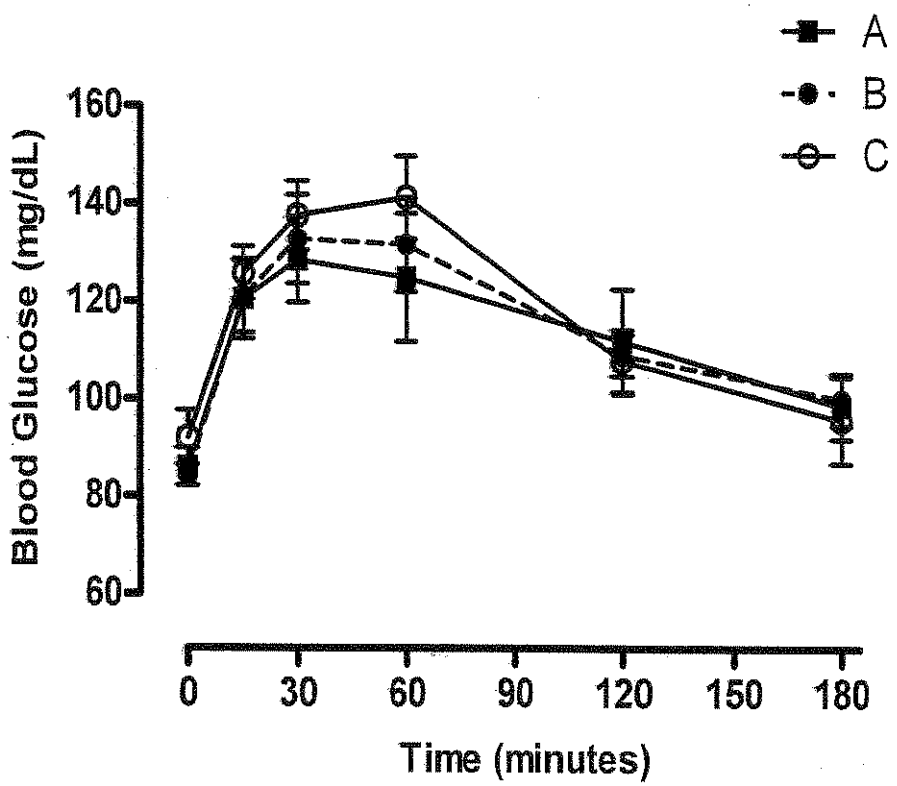

160
140
120
100
80
60
Blood Glucose (mg/dL)
0
30
60
90
120
150
180
Time (minutes)
A
B
C

FIG. 38B


A
B
C
160
140
120
100
80
60
Blood Glucose (mg/dL)
0
30
60
90
120
150
180
Time (minutes)

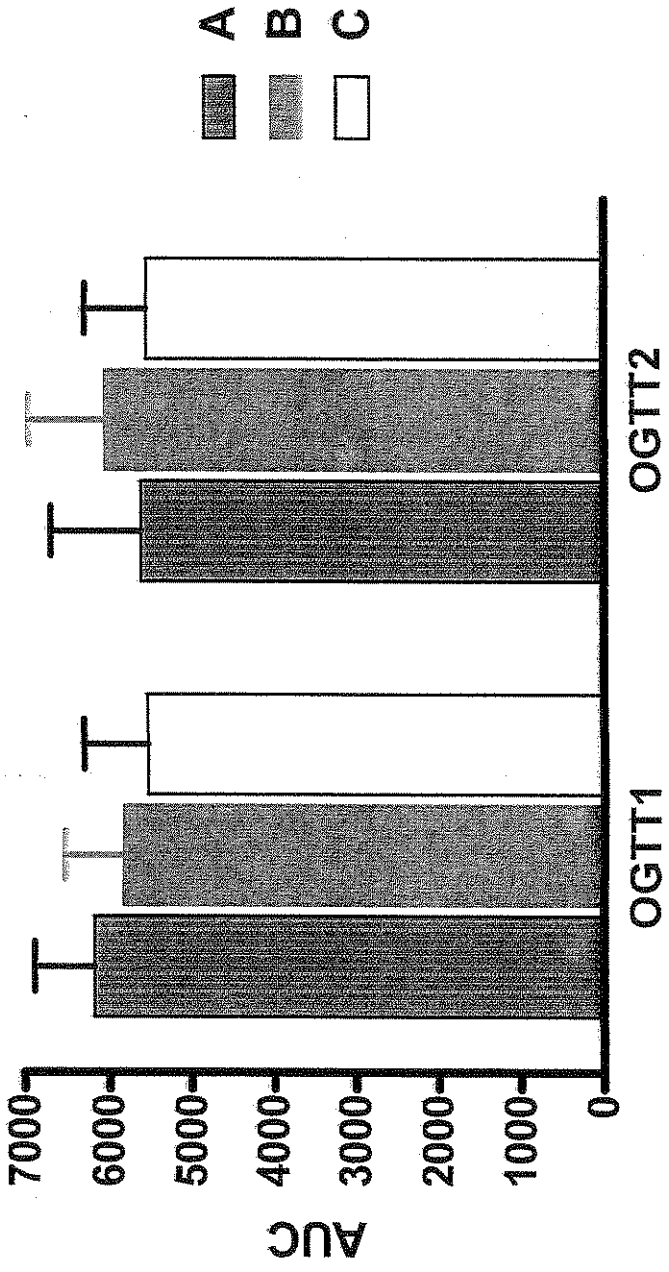



FIG. 38C

FIG. 38D

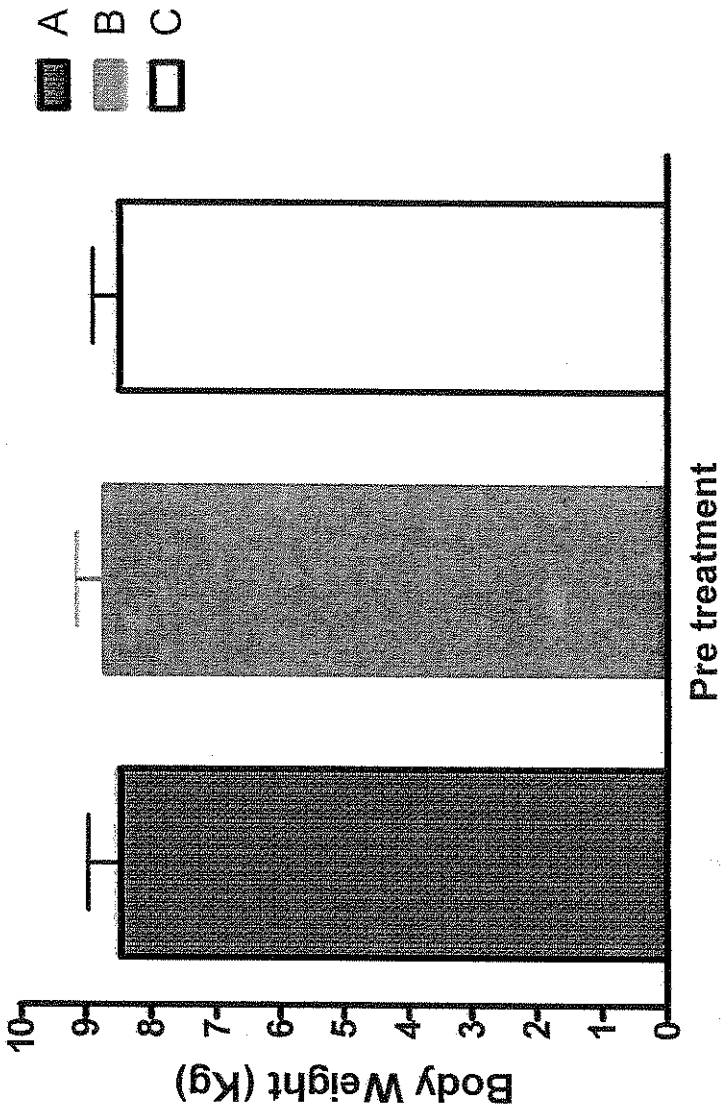


FIG. 39

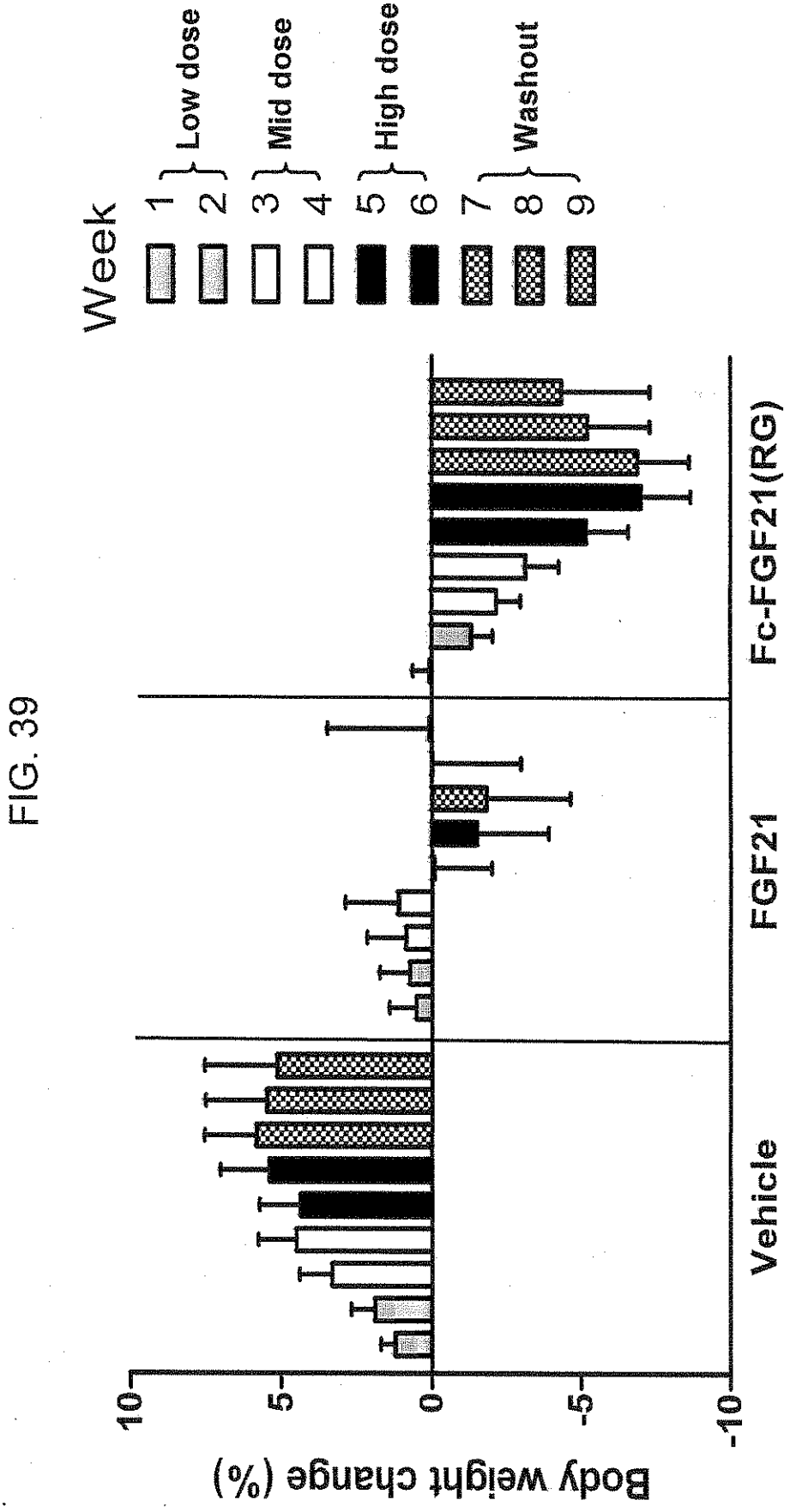

Week
1
2
3
4
5
6
7
8
9
Low dose
Mid dose
High dose
Washout
Body weight change (%)
10
5
0
-5
-10
Vehicle
FGF21
Fc-FGF21(RG)

FIG. 40

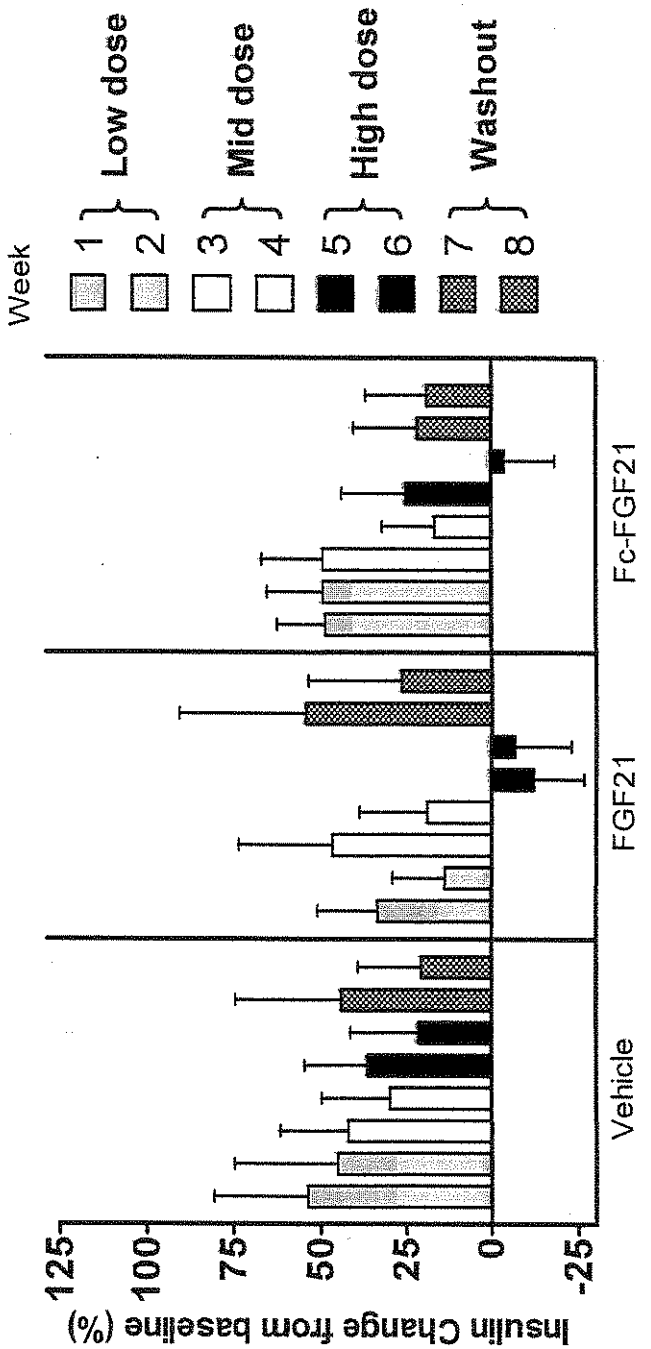

Insulin Change from baseline (%)
125
100
75
50
25
0
-25
Vehicle
FGF21
Fc-FGF21
Week
1
2
3
4
5
6
7
8
Low dose
Mid dose
High dose
Washout

FIG. 41

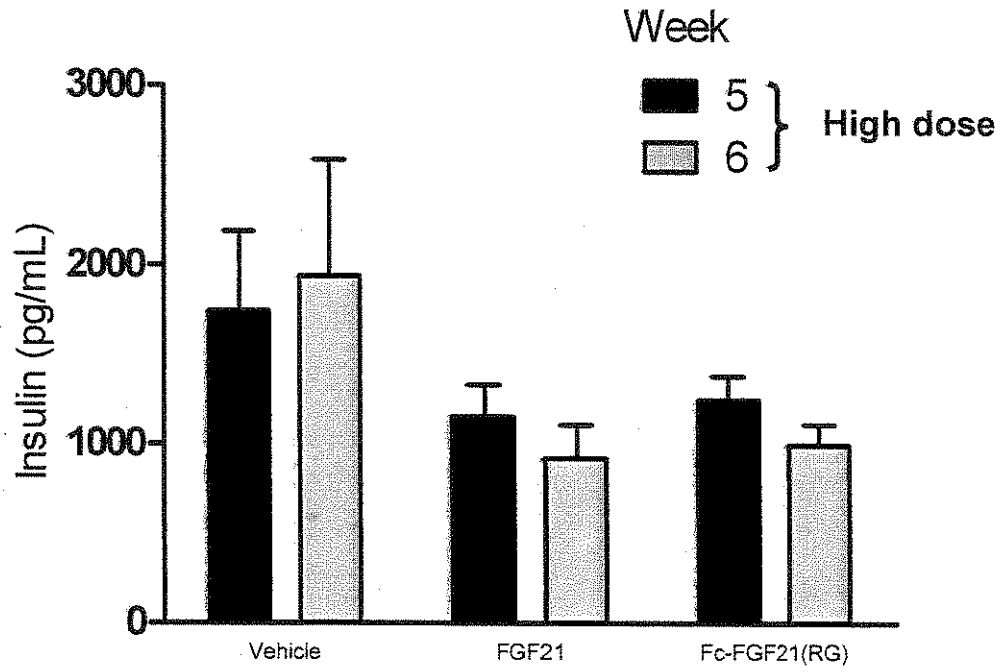

Week
5
6
High dose
3000
2000
1000
0
Insulin (pg/mL)
Vehicle
FGF21
Fc-FGF21(RG)

FIG. 42

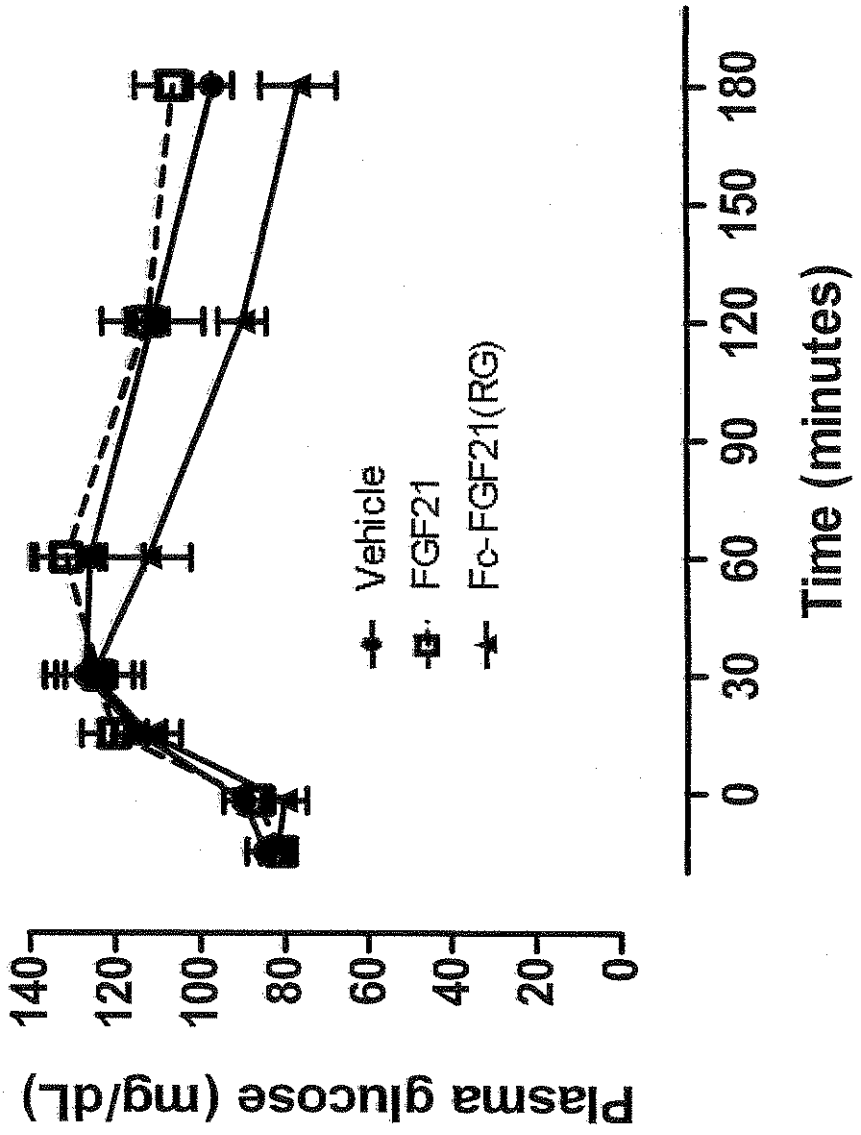

Plasma glucose (mg/dL)
140
120
100
80
60
40
20
0
Vehicle
FGF21
Fc-FGF21(RG)
0
30
60
90
120
150
180
Time (minutes)

FIG. 43

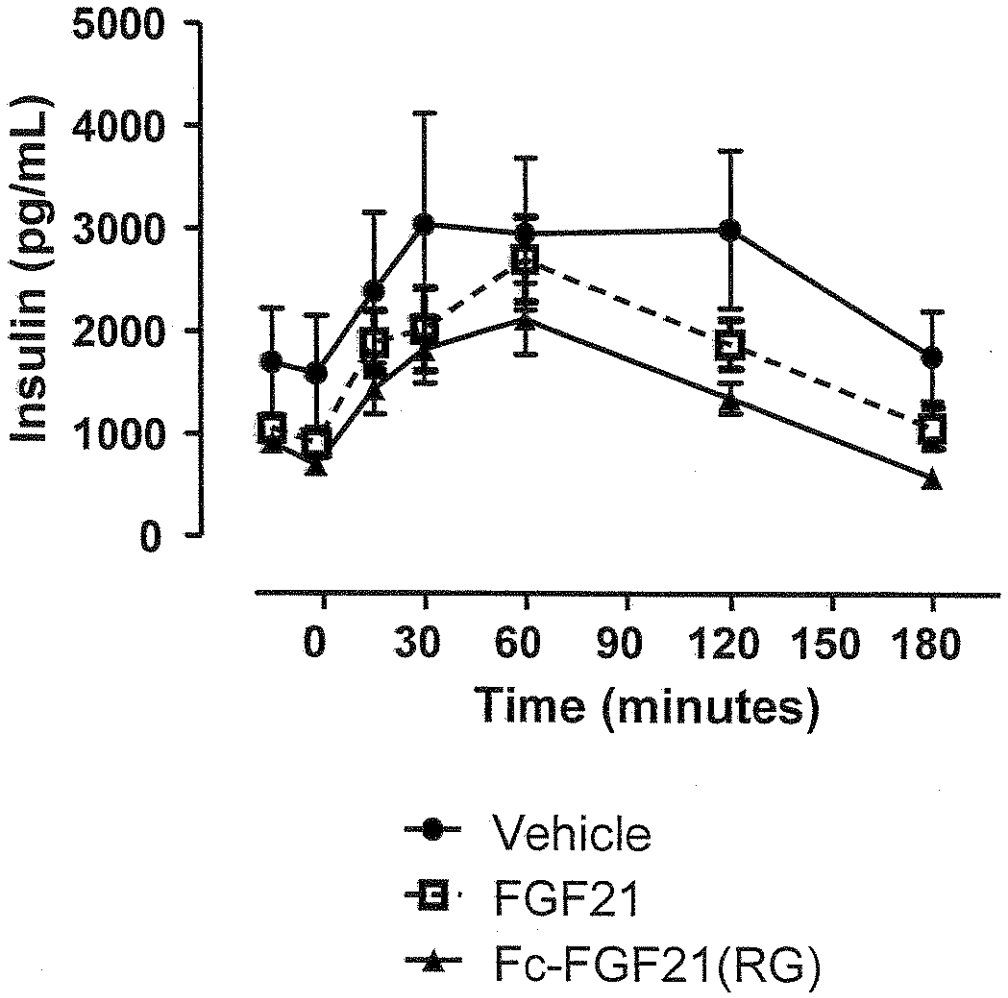

5000
4000
3000
2000
1000
0
Insulin (pg/mL)
0
30
60
90
120
150
180
Time (minutes)
Vehicle
FGF21
Fc-FGF21(RG)

FIG. 44

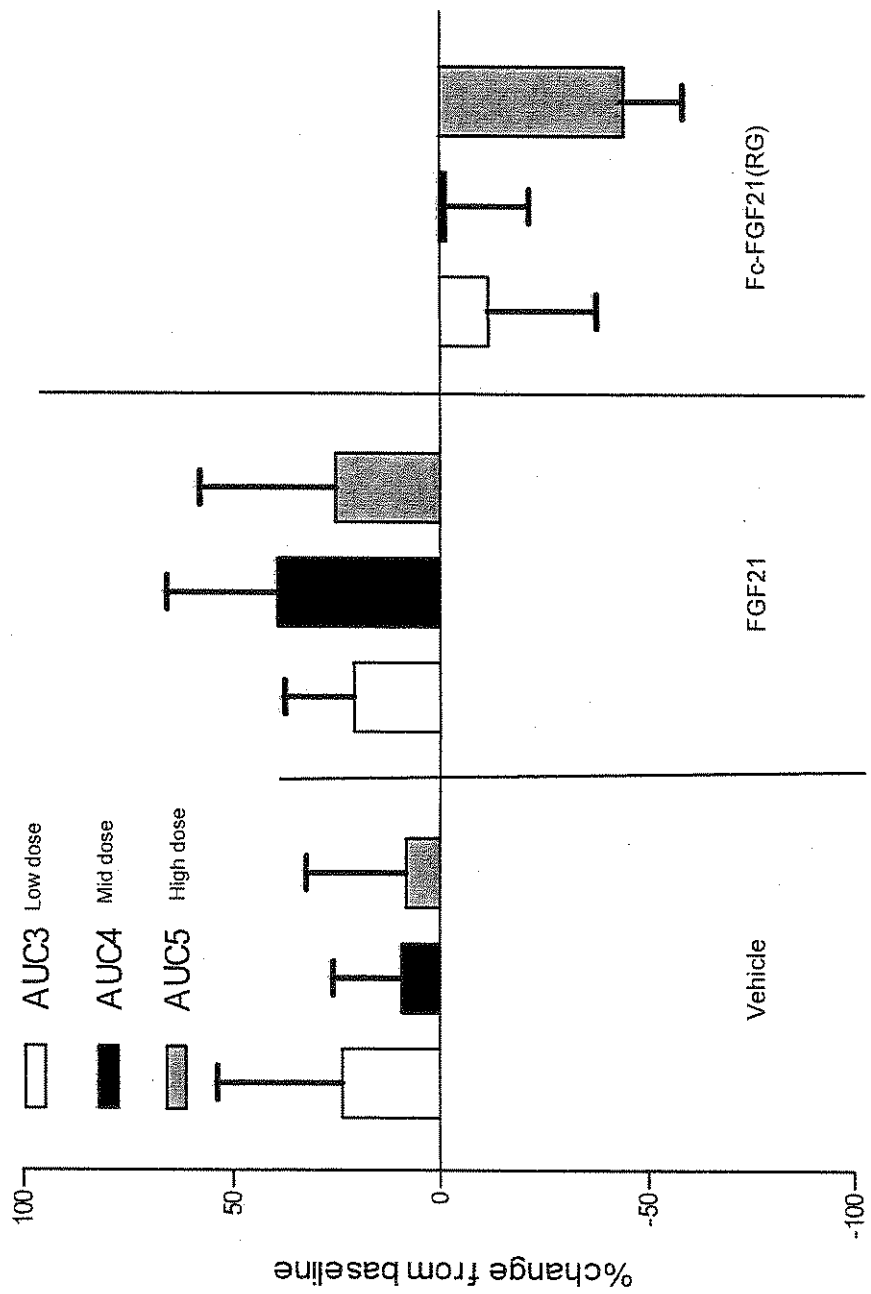

AUC3 Low dose
AUC4 Mid dose
AUC5 High dose
100
50
0
-50
-100
%change from baseline
Vehicle
FGF21
Fc-FGF21(RG)

FIG. 45

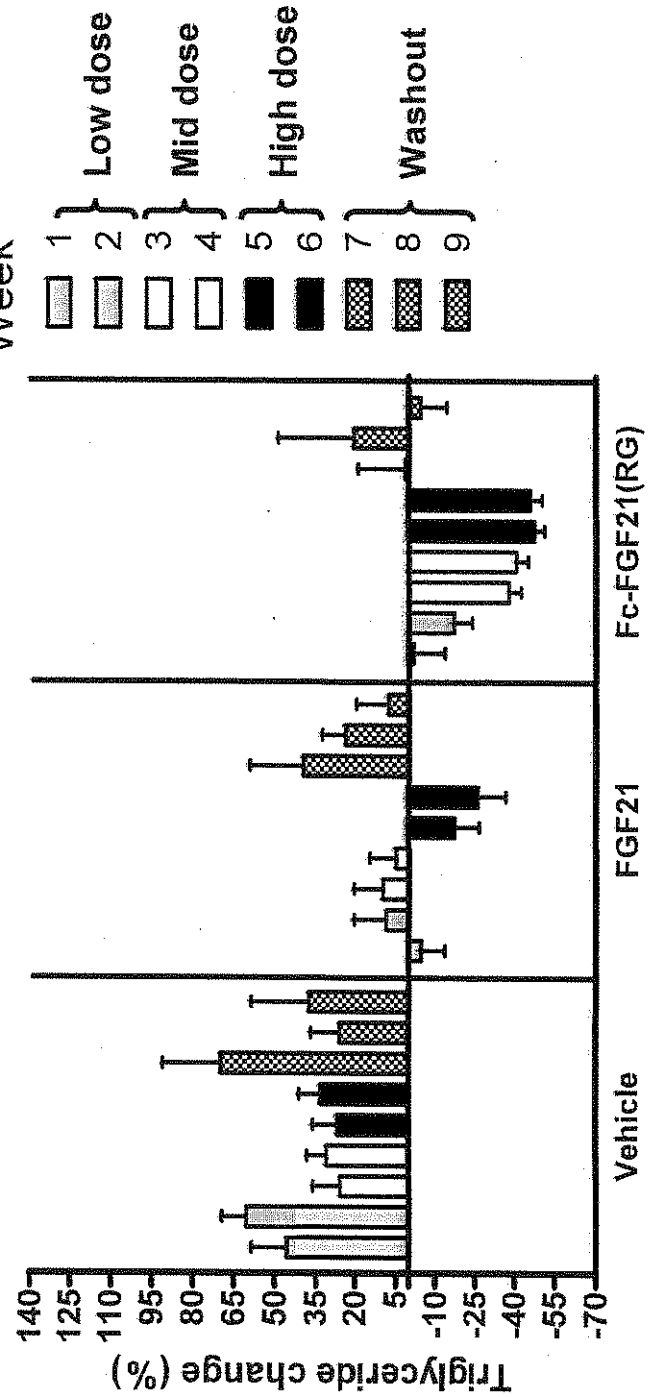

Week
1
2
3
4
5
6
7
8
9
Low dose
Mid dose
High dose
Washout
Triglyceride change (%)
140
125
110
95
80
65
50
35
20
5
-10
-25
-40
-55
-70
Vehicle
FGF21
Fc-FGF21(RG)

FIG. 46

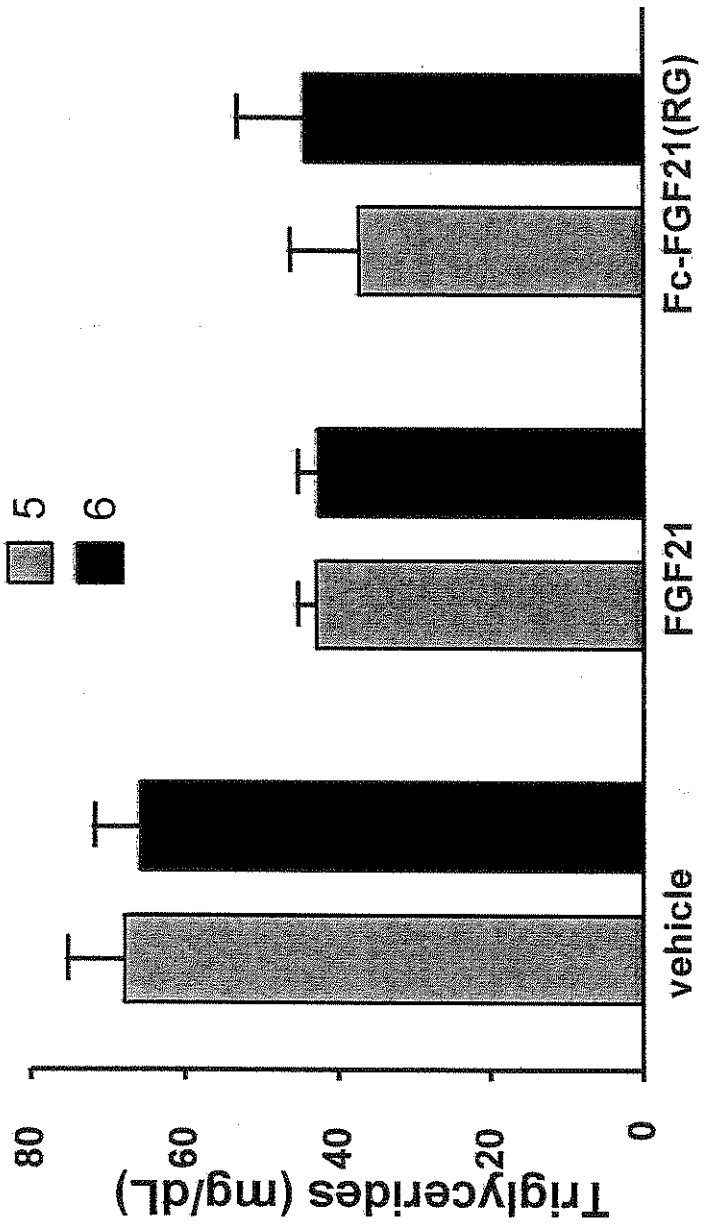

Triglycerides (mg/dL)
0
20
40
60
80
Week
5
6
vehicle
FGF21
Fc-FGF21(RG)

FIG. 47

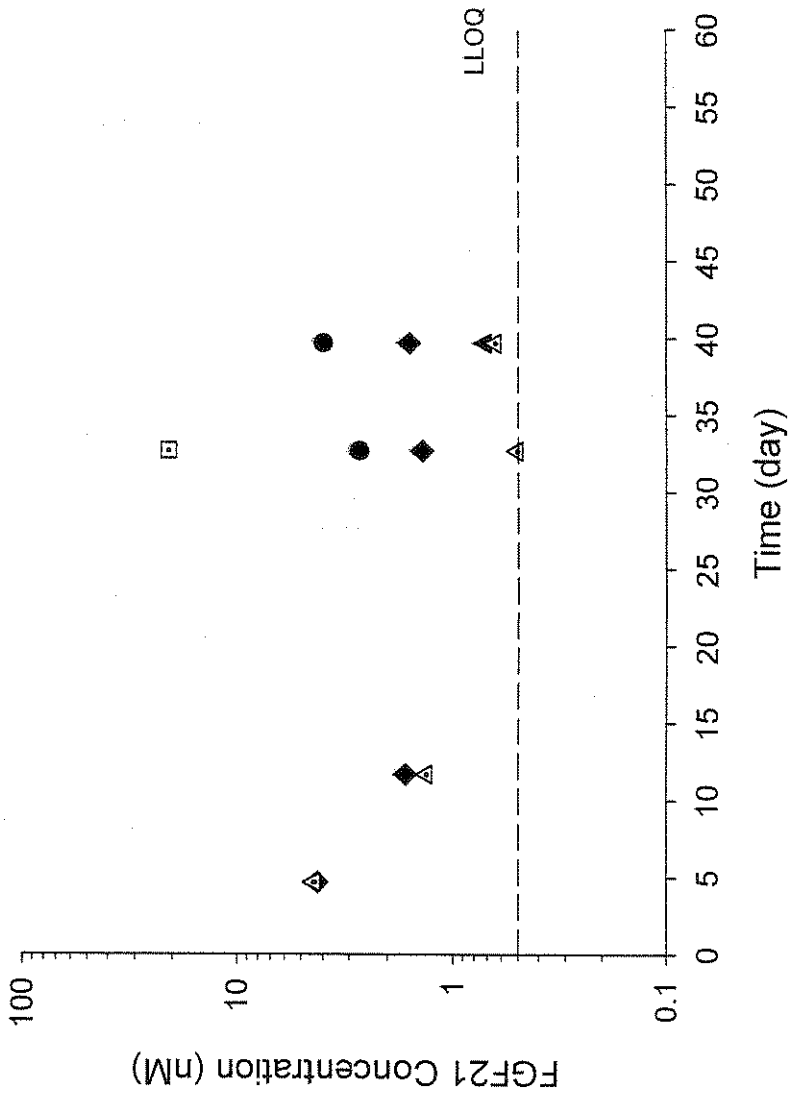

FGF21 Concentration (nM)
100
10
1
0.1
0
5
10
15
20
25
30
35
40
45
50
55
60
Time (day)
LLOQ

FIG. 48

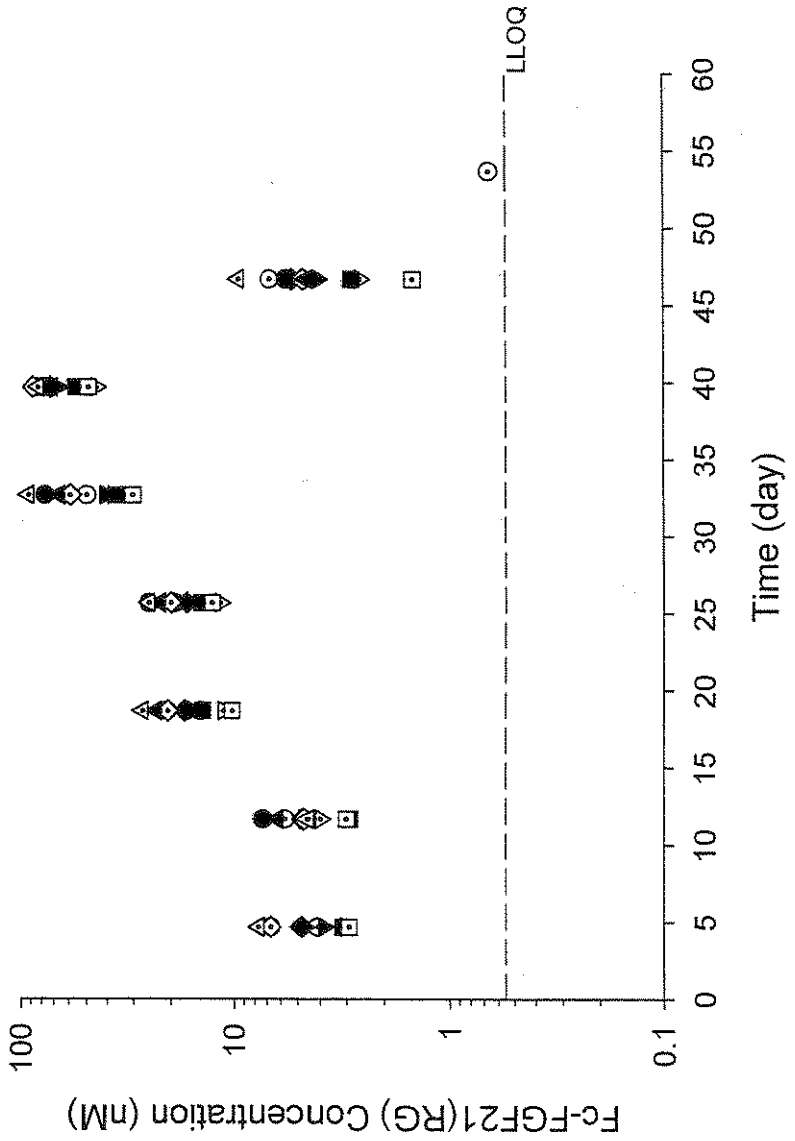
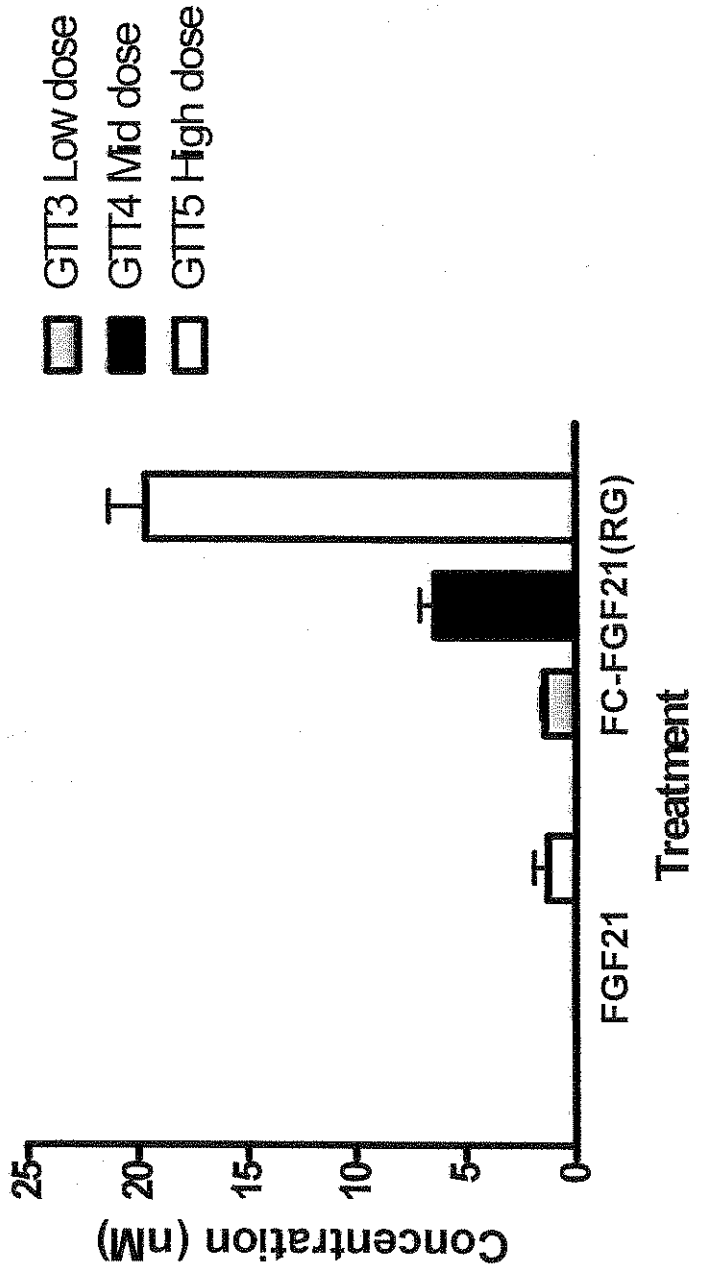

Fc-FGF21(RG) Concentration (nM)
100
10
1
0.1
0
5
10
15
20
25
30
35
40
45
50
55
60
Time (day)
LLOQ

FIG. 49


GTT3 Low dose
GTT4 Mid dose
GTT5 High dose
Concentration (nM)
25
20
15
10
5
0
FGF21
FC-FGF21(RG)
Treatment