

Figure 1

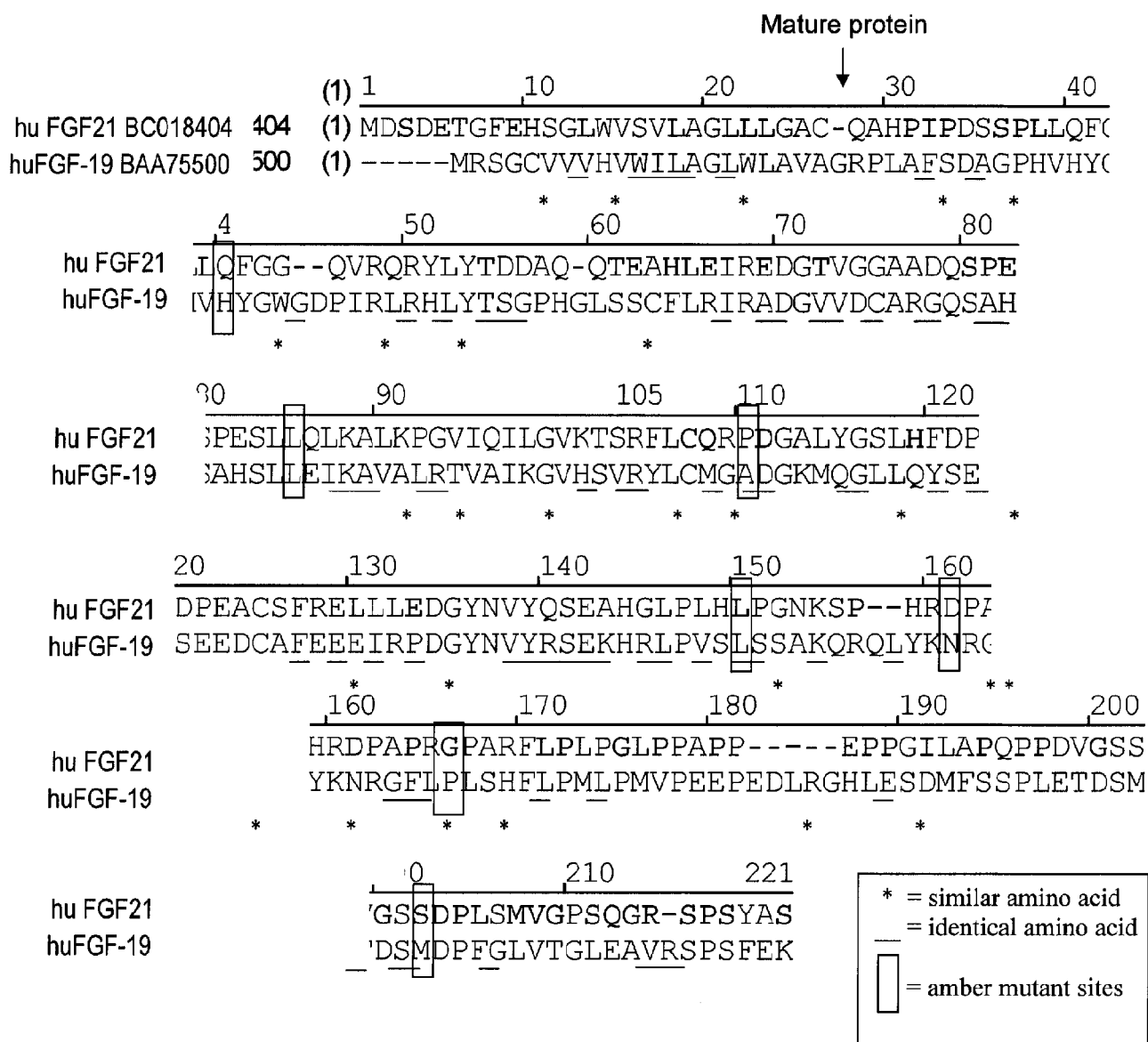


Figure 2

FGF 19

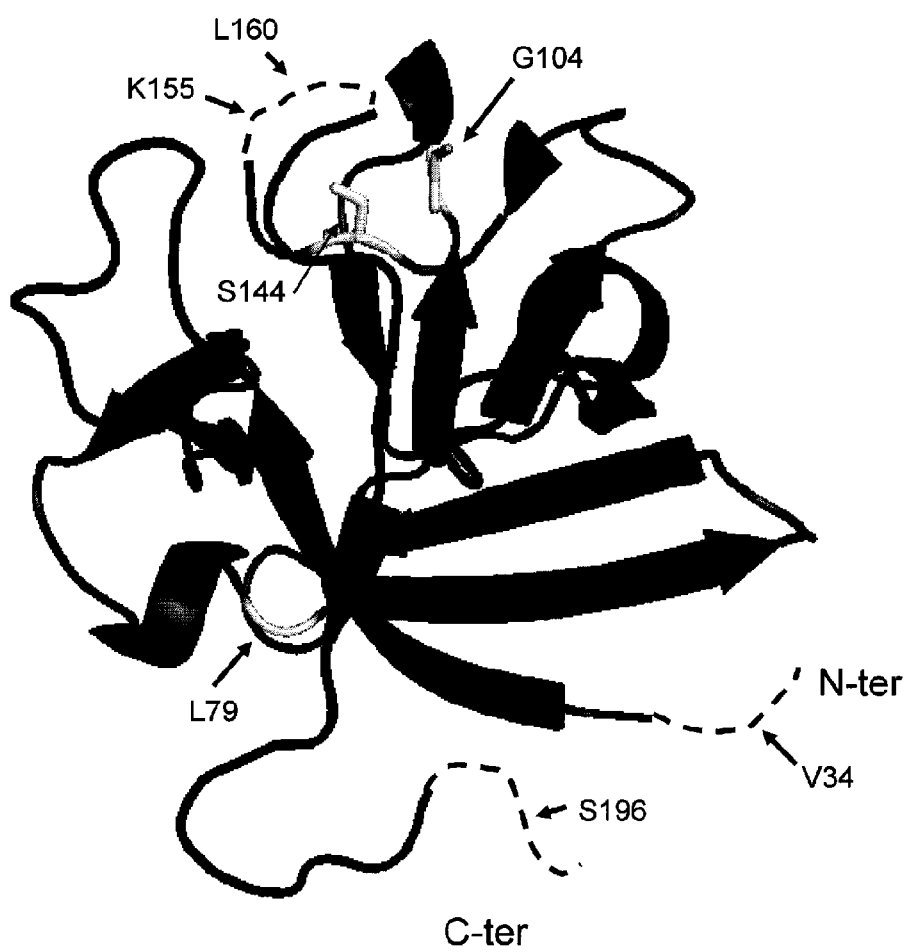


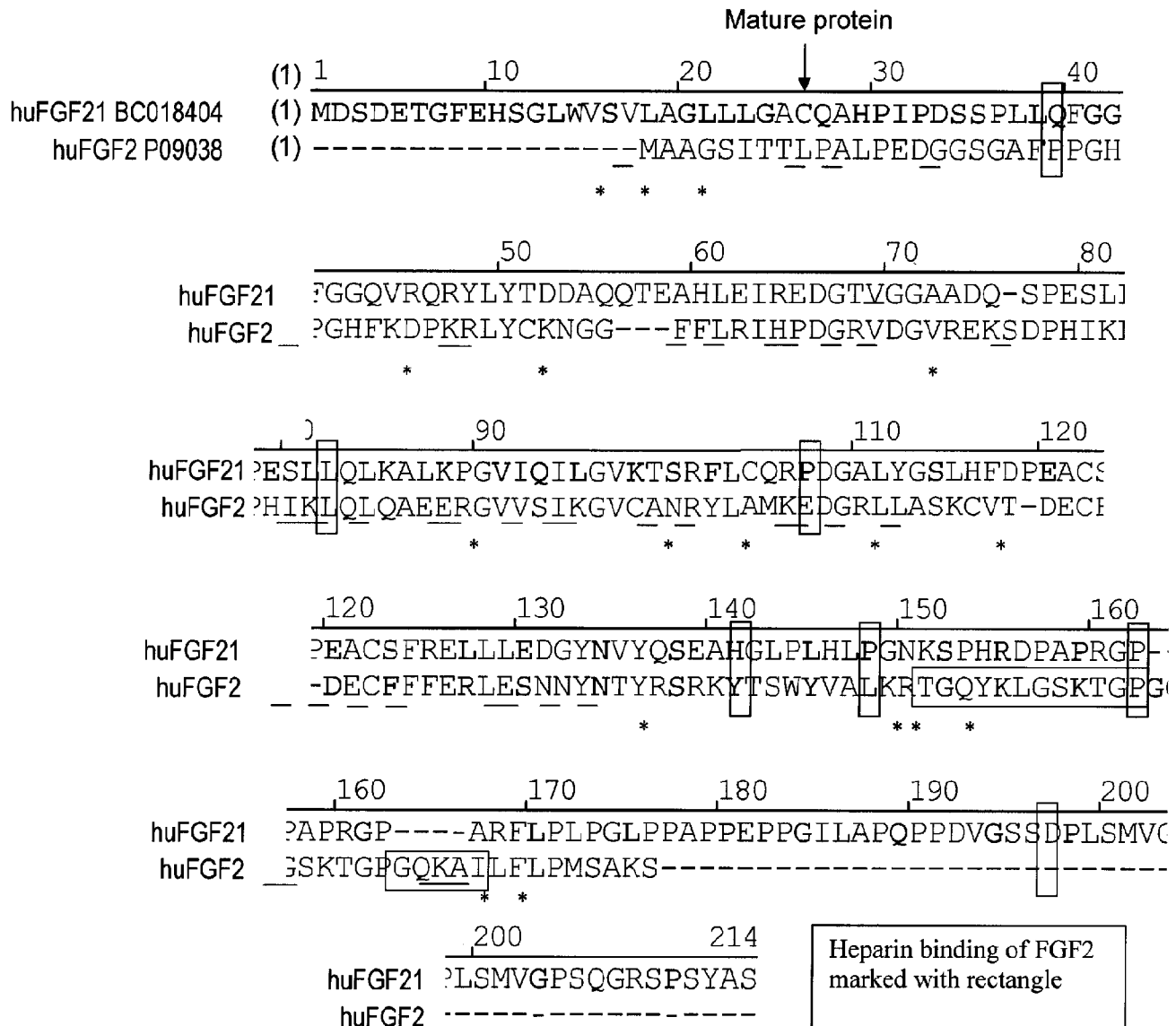
Figure 3

Figure 4

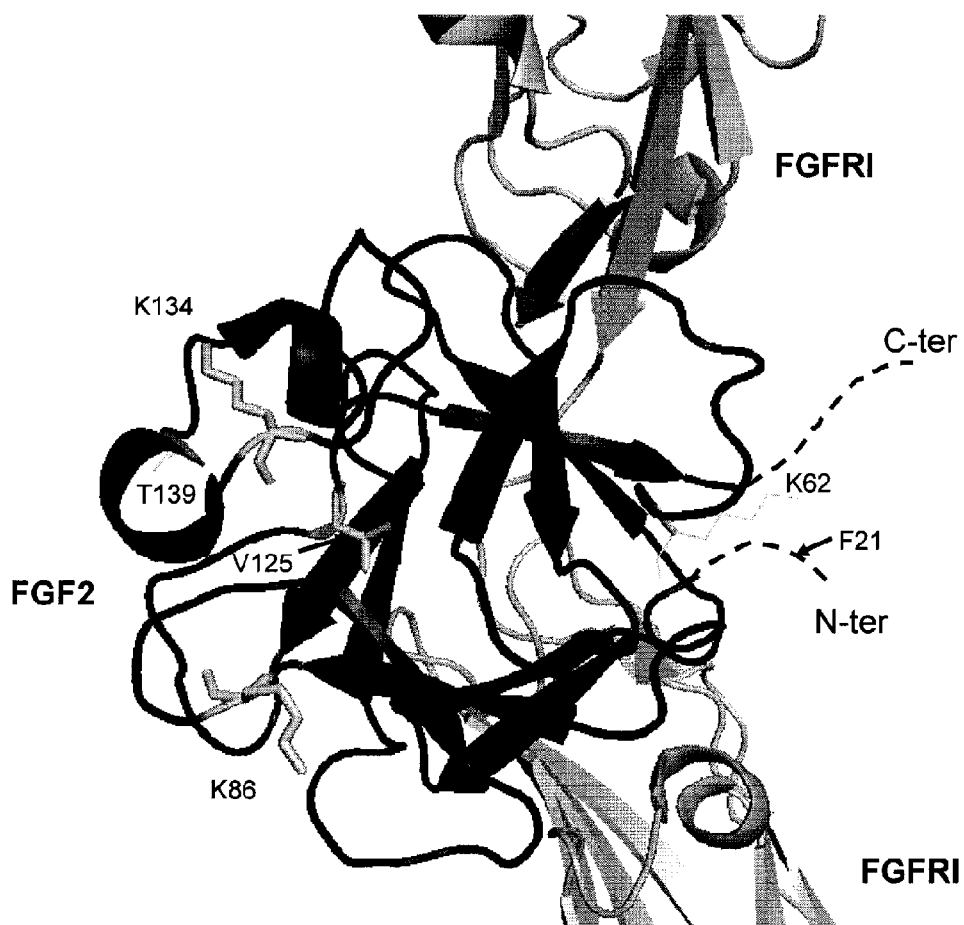


Figure 5

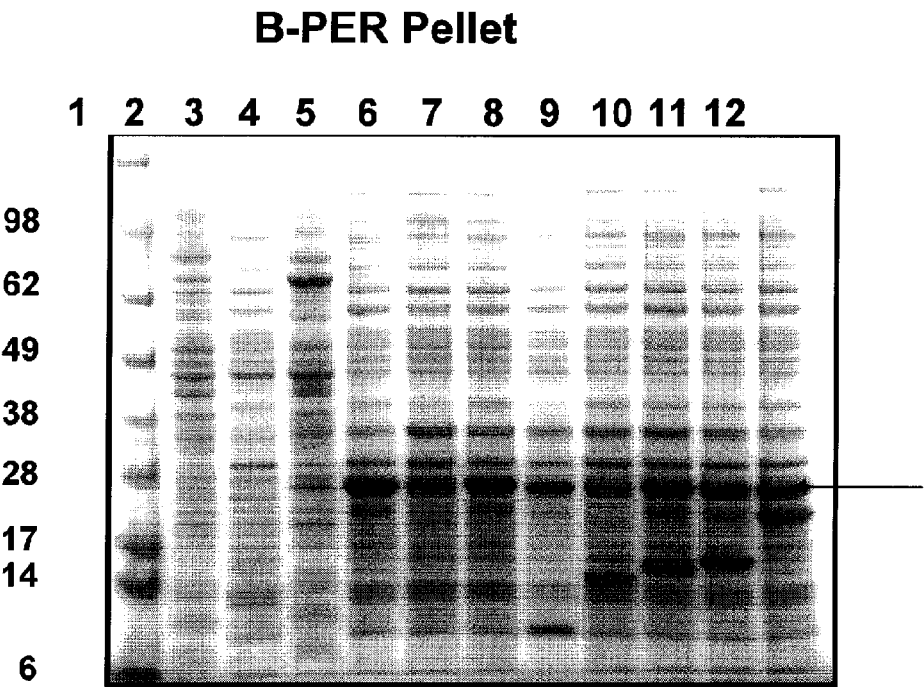


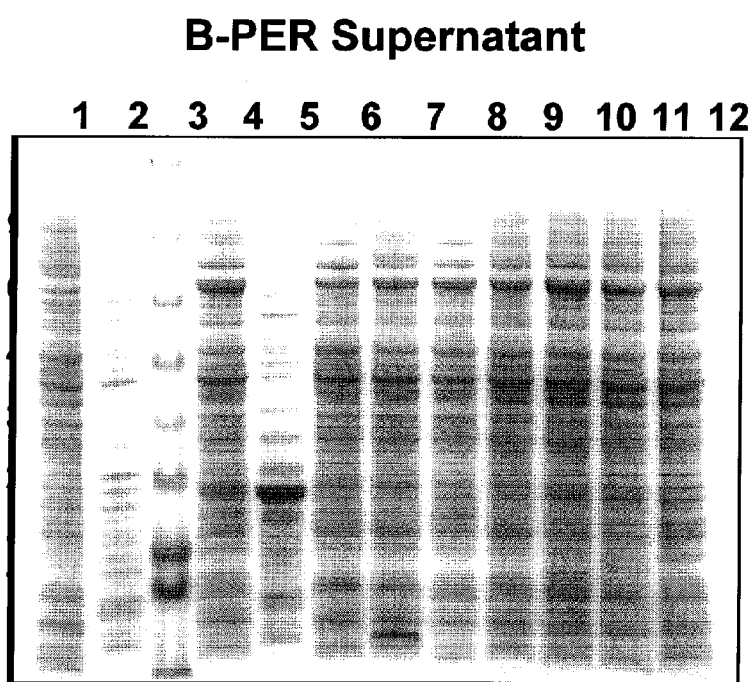
Figure 6

Figure 7a

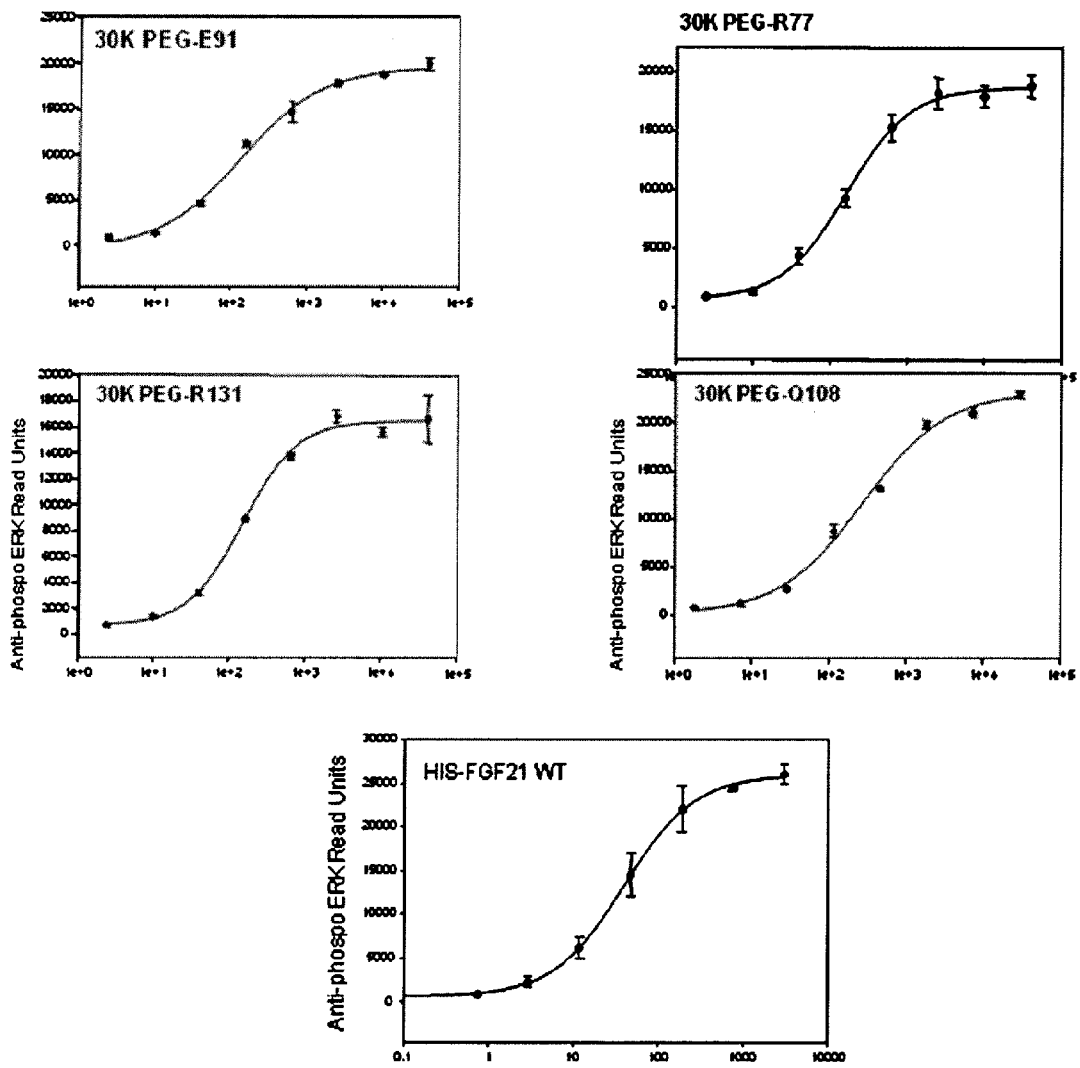
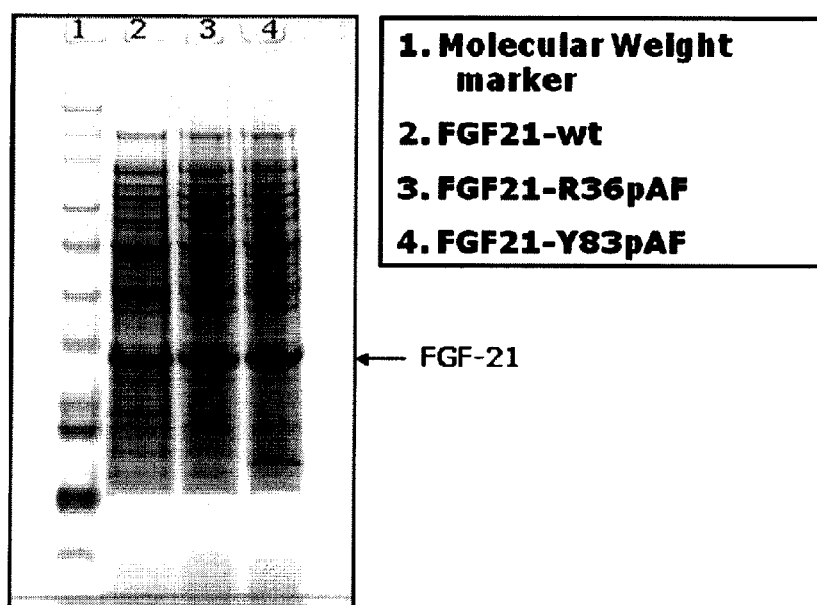
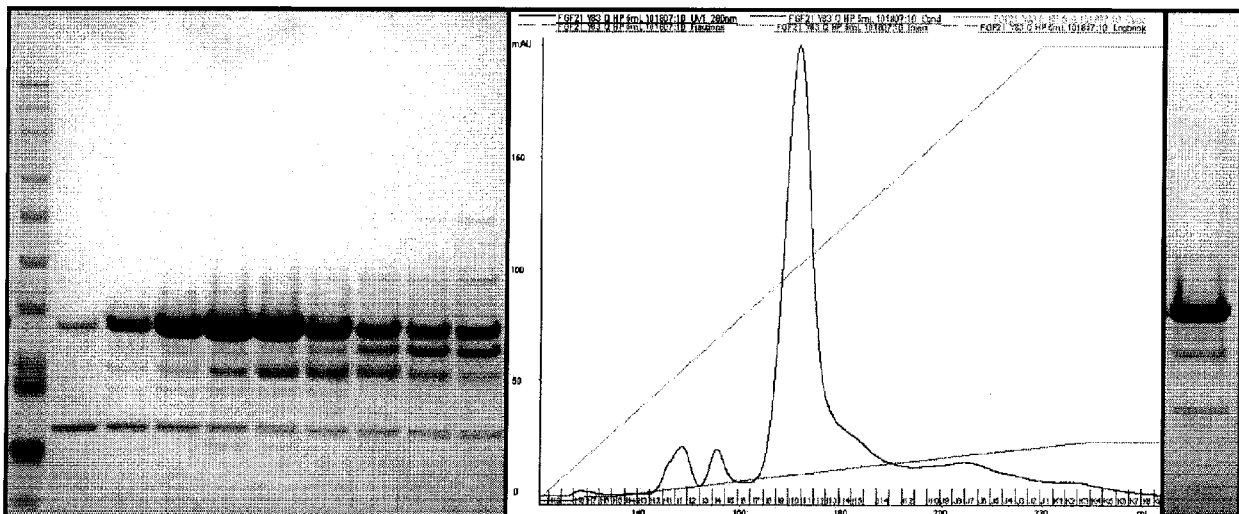


Figure 7b

Protein	Fold loss of activity
HIS-FGF21	1
30KPEG-E91	4
30KPEG R131	4
30KPEG-Q108	6
30KPEG R77	6
30KPEG-R72	14
30KPEG H87	19
30KPEG L86	10
30KPEG R126	11
30KPEG E110	16
30KPEG Y83	17
30KPEG-P146	22
30KPEG R135	26
30KPEG R96	47
30KPEG R36	47
30KPEG Y104	No agonist activity
30KPEG L99	No agonist activity
30KPEG K56	No agonist activity
30KPEG Y22	No agonist activity

Figure 8**Expression of Untagged FGF-21**

SDS-PAGE analysis of FGF-21 expressed in *E.coli*.

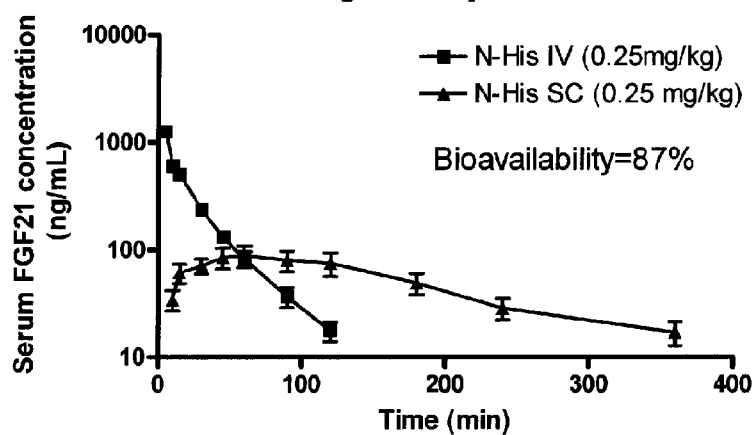
Figure 9**Purification: Untagged FGF-21-Y83pAF****A.****B.****C.**

Purification of untagged FGF-21-Y83pAF. **A.** Chromatogram of Q HP elution. **B.** SDS-PAGE analysis of FGF-21-Y83pAF elution fractions. **C.** SDS-PAGE analysis of FGF-21-Y83pAF Q HP elution pool.

Figure 10

N-His WT FGF21

**N-His WT FGF21 serum concentration
after single SC injection in rat**



**N-His WT FGF21 serum concentration
after single SC injection in rat**

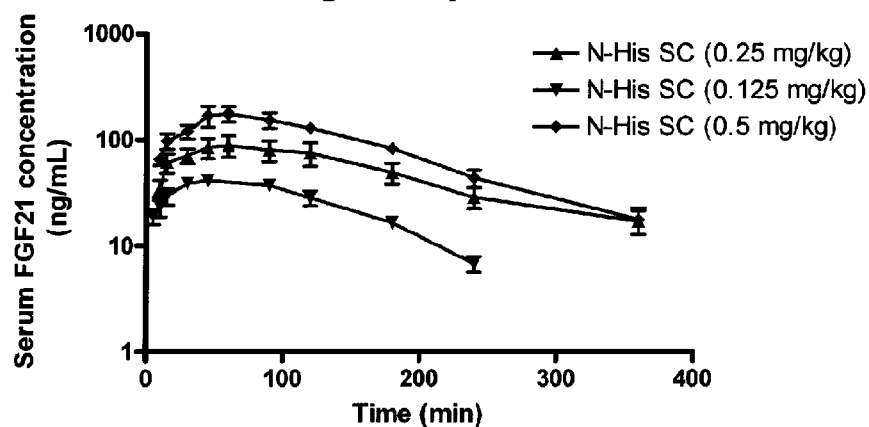


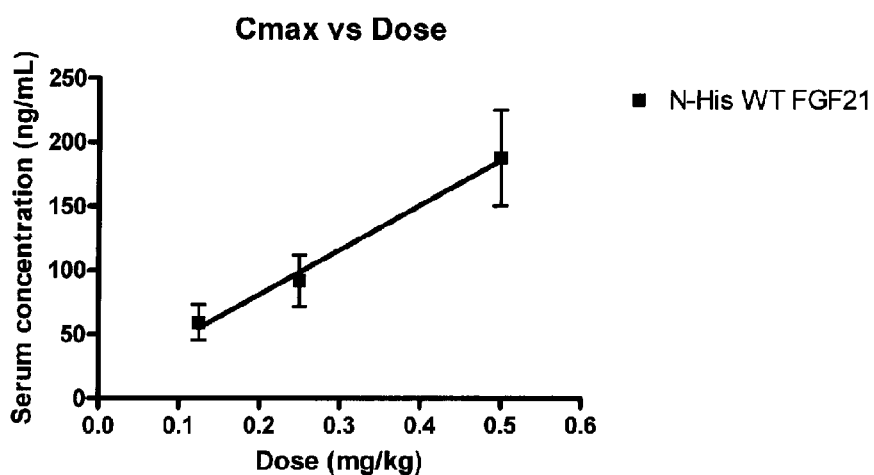
Figure 11**N-His WT FGF21****Best-fit values**Slope 348.5 ± 91.22 Y-intercept when $X=0.0$ 11.55 ± 30.17 X-intercept when $Y=0.0$ -0.03315 1/slope 0.002870 **95% Confidence Intervals**Slope 145.2 to 551.7 Y-intercept when $X=0.0$ -55.67 to 78.77 X-intercept when $Y=0.0$ -0.5647 to 0.1635 **Goodness of Fit** r^2 0.5934 Sy.x 49.27

Figure 12

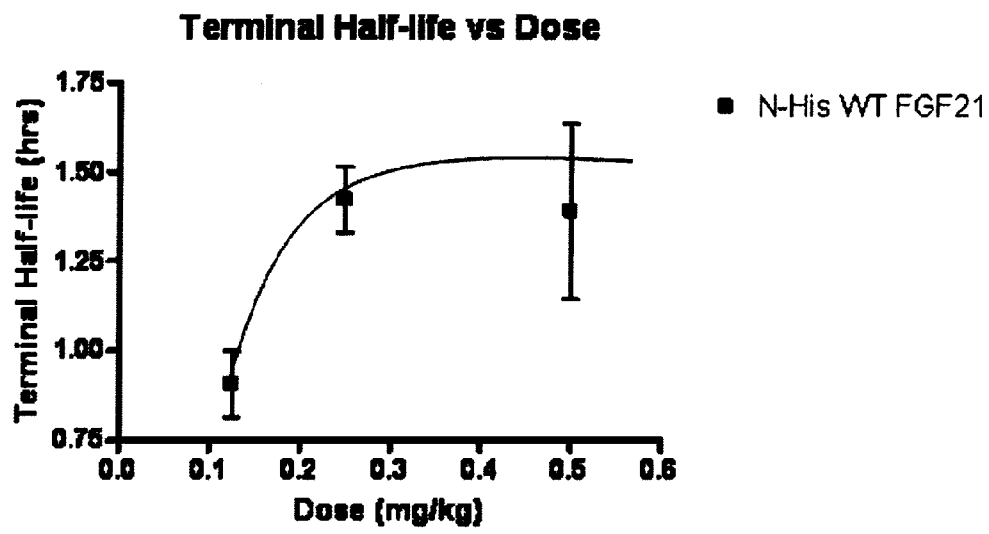
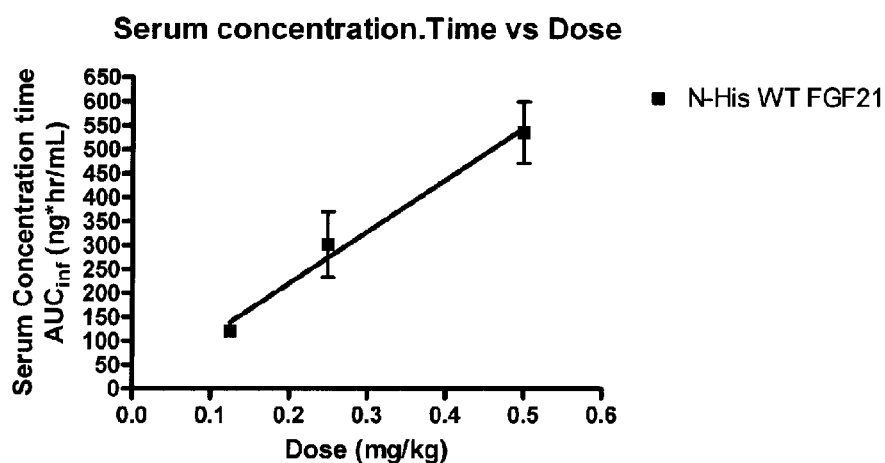


Figure 13

N-His WT FGF21

Best-fit values

Slope 1079 ± 194.1

Y-intercept when $X=0.0$ 4.274 ± 64.19

X-intercept when $Y=0.0$ -0.003959

1/slope 0.0009265

95% Confidence Intervals

Slope 646.9 to 1512

Y-intercept when $X=0.0$ -138.7 to 147.3

X-intercept when $Y=0.0$ -0.2567 to 0.1357

Goodness of Fit

r^2 0.7556

Sy.x 104.8

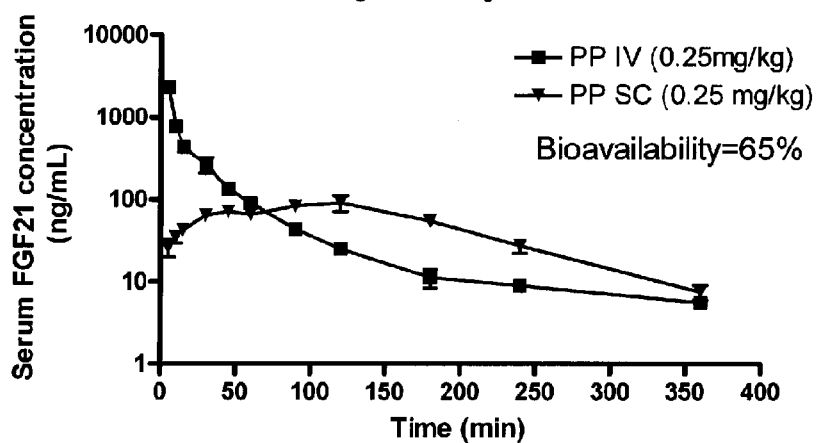
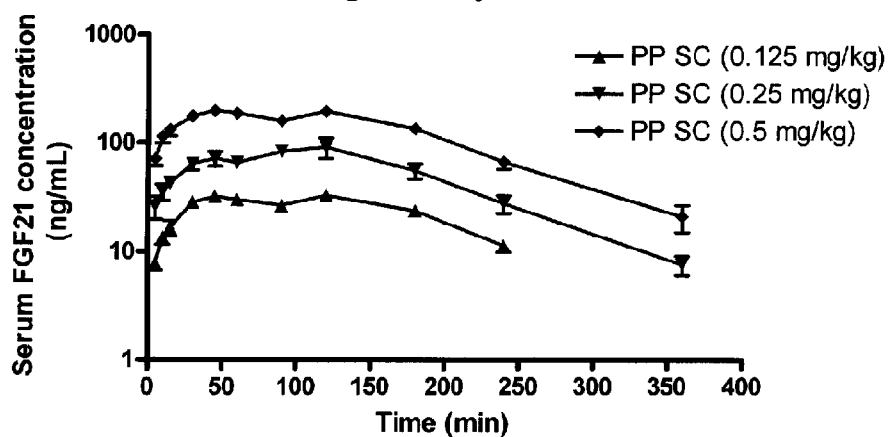
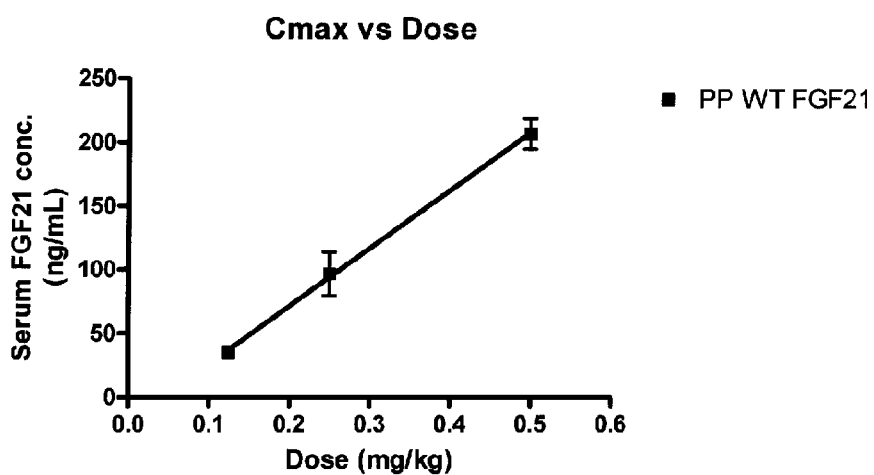
Figure 14**Periplasmic-derived WT FGF21****PP WT FGF21 serum concentration
after single SC injection in rat****PP WT FGF21 serum concentration
after single SC injection in rat**

Figure 15

PP WT FGF21

Best-fit values

Slope 454.2 ± 42.42

Y-intercept when $X=0.0$ -19.66 ± 14.03

X-intercept when $Y=0.0$ 0.04329

$1/\text{slope}$ 0.002202

95% Confidence Intervals

Slope 359.6 to 548.7

Y-intercept when $X=0.0$ -50.92 to 11.60

X-intercept when $Y=0.0$ -0.05351 to 0.1176

Goodness of Fit

r^2 0.9197

$Sy.x$ 22.91

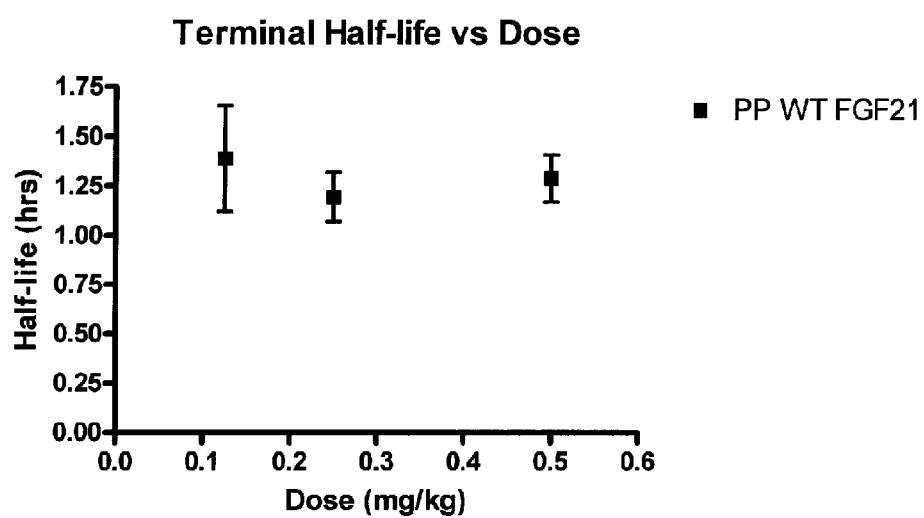
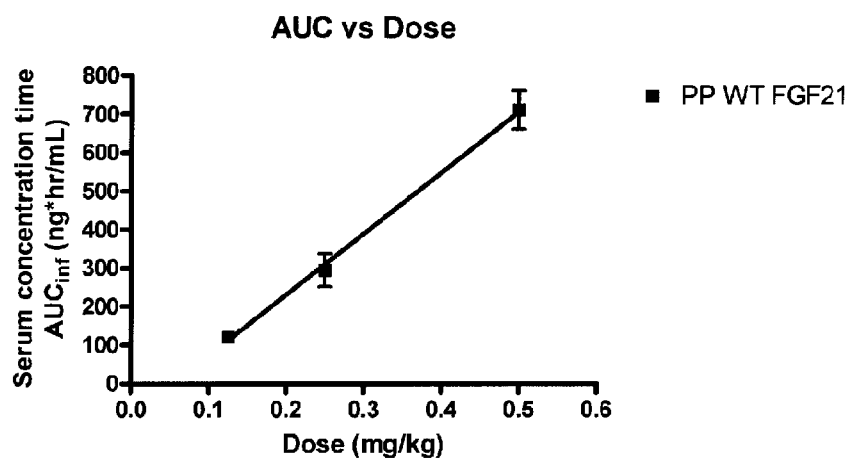
Figure 16

Figure 17

PP WT FGF21

Best-fit values

Slope 1585 ± 137.1

Y-intercept when $X=0.0$ -86.76 ± 45.33

X-intercept when $Y=0.0$ 0.05474

$1/\text{slope}$ 0.0006309

95% Confidence Intervals

Slope 1280 to 1890

Y-intercept when $X=0.0$ -187.8 to 14.25

X-intercept when $Y=0.0$ -0.03184 to 0.1230

Goodness of Fit

r^2 0.9304

Syx 74.03

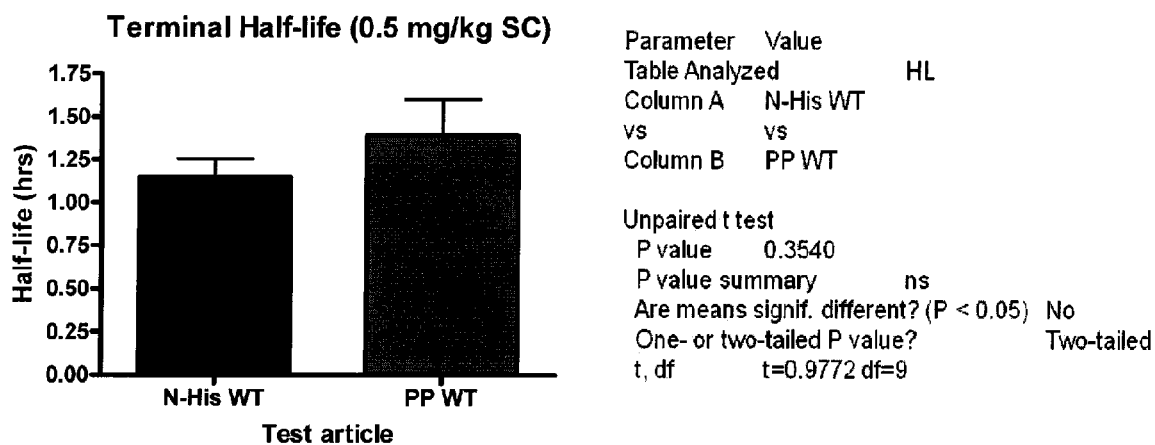
Figure 18**FGF-R-003
WT head-to-head comparison**

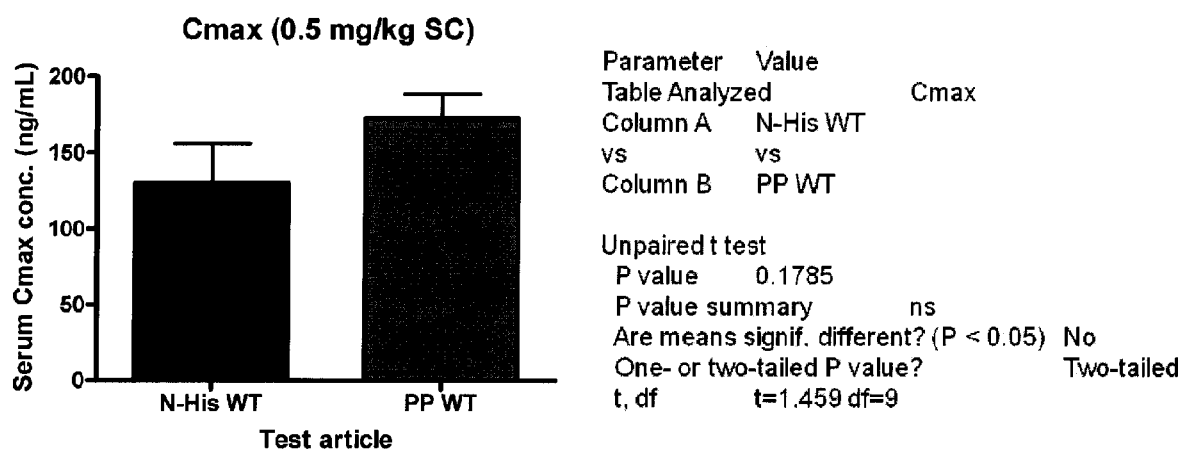
Figure 19**FGF-R-003
WT head-to-head comparison**

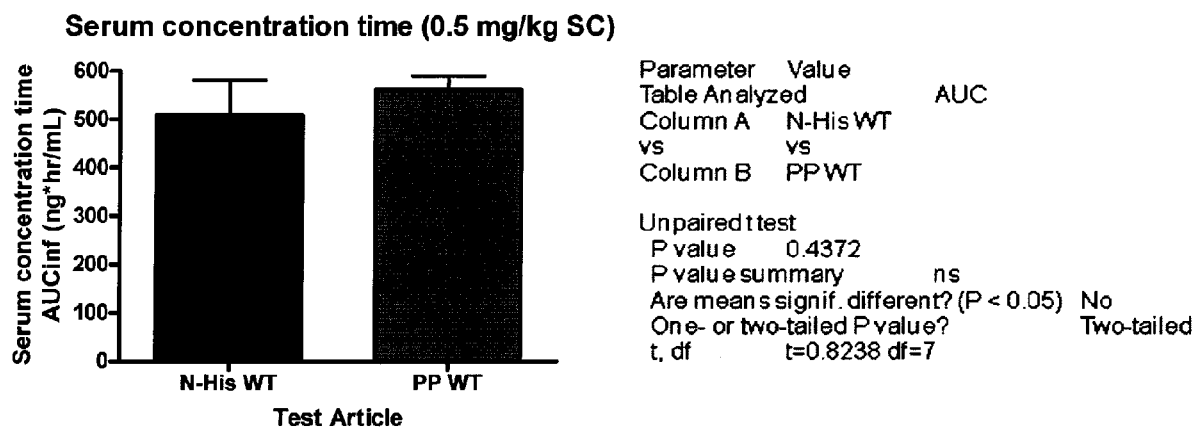
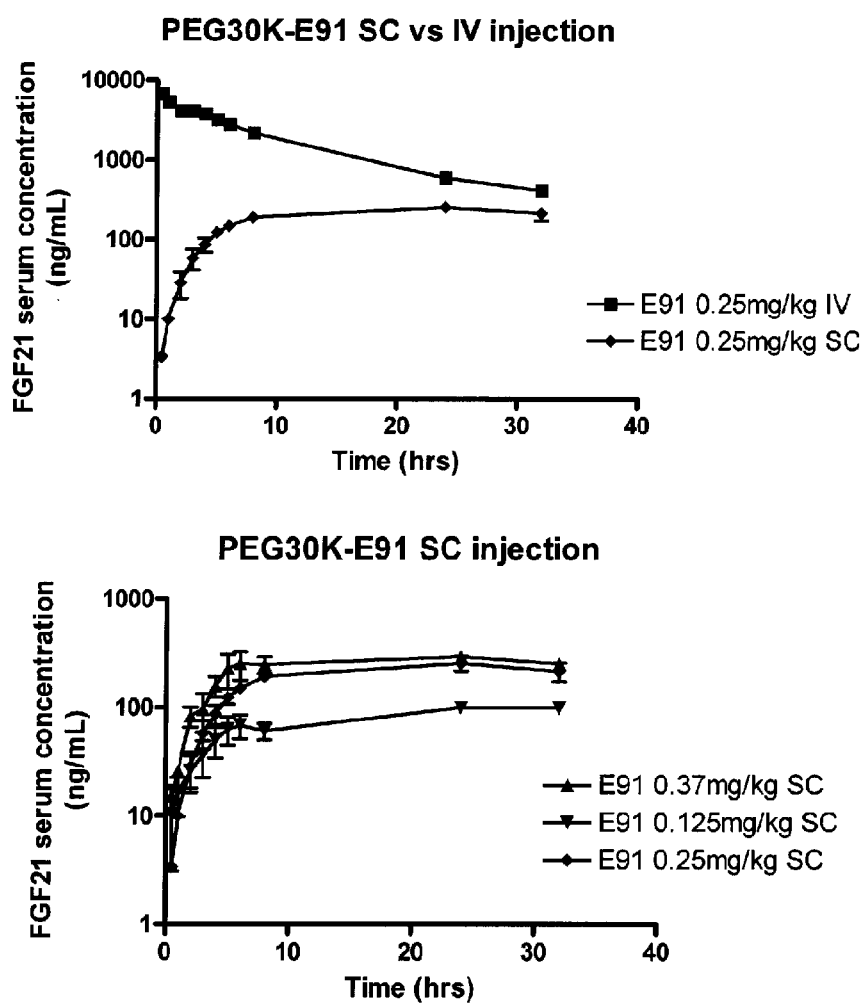
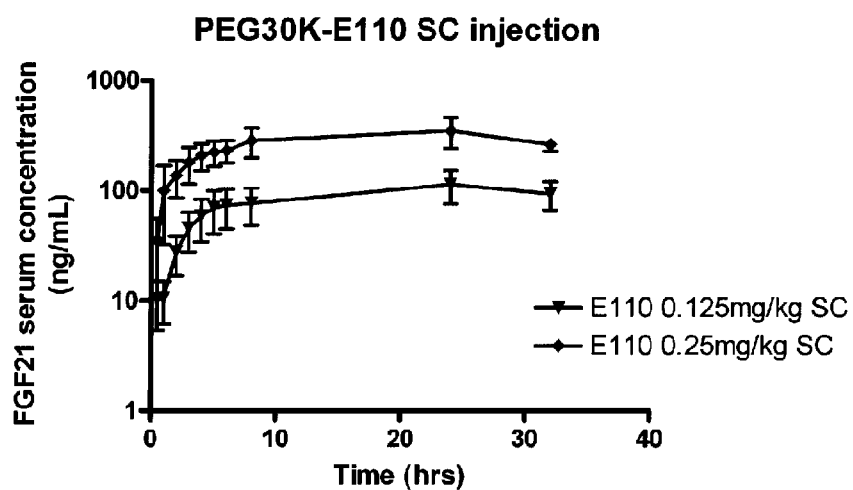
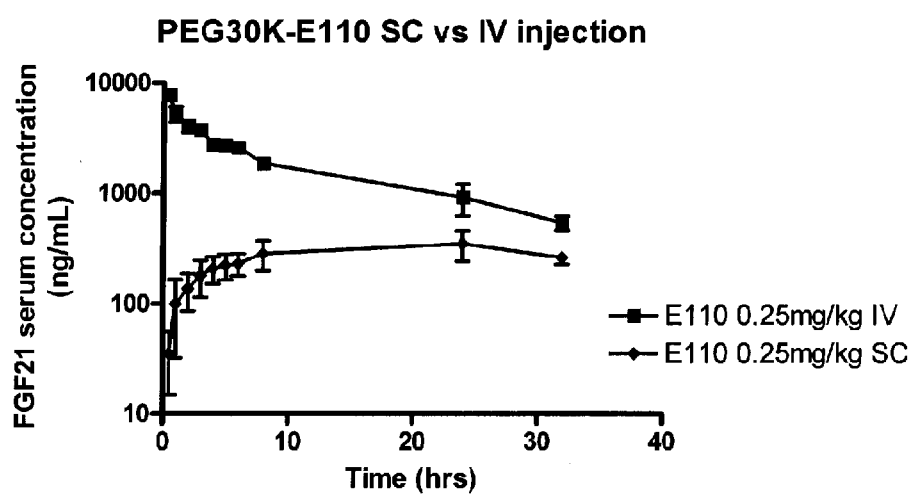
Figure 20**FGF-R-003
WT head-to-head comparison**

Figure 21**FGF-R-004 PEG PK part 1**

***Diminished Bioavailability**

Figure 22**FGF-R-004 PEG PK part 1**

***Diminished Bioavailability**

Figure 23
PEG PK comparison part 2

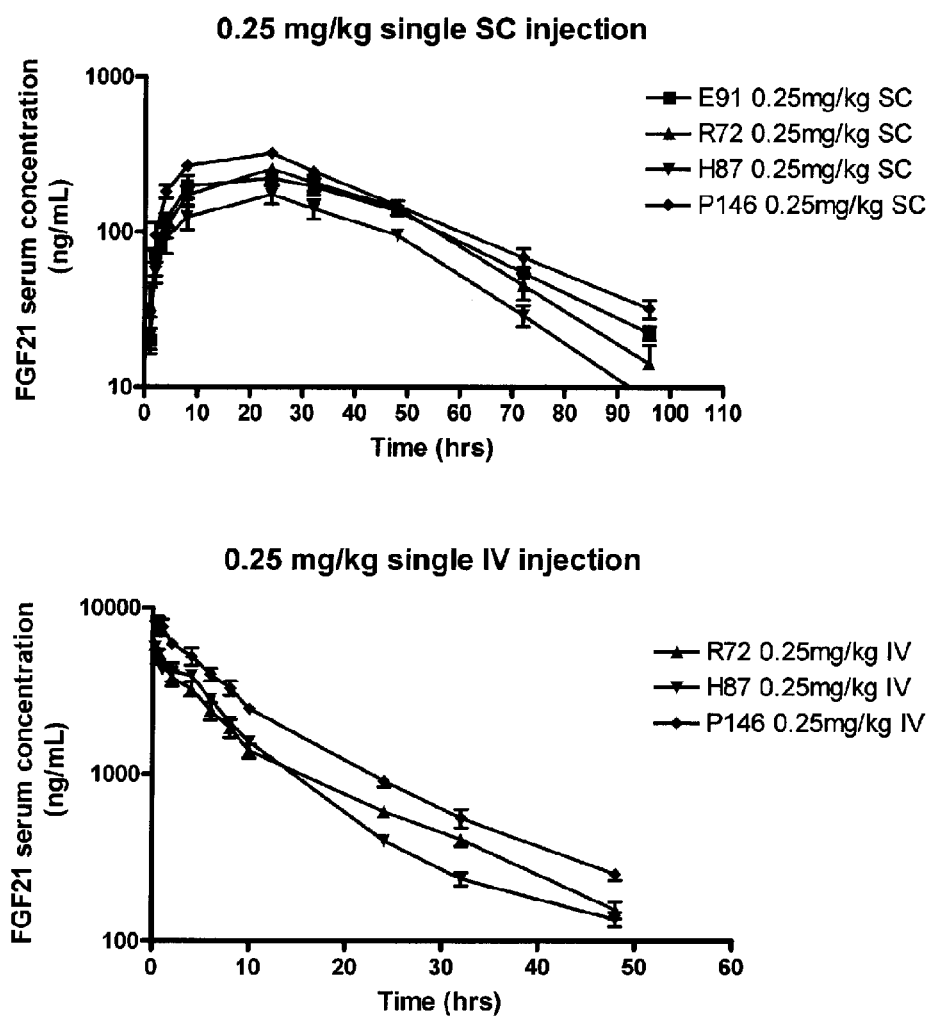


Figure 24

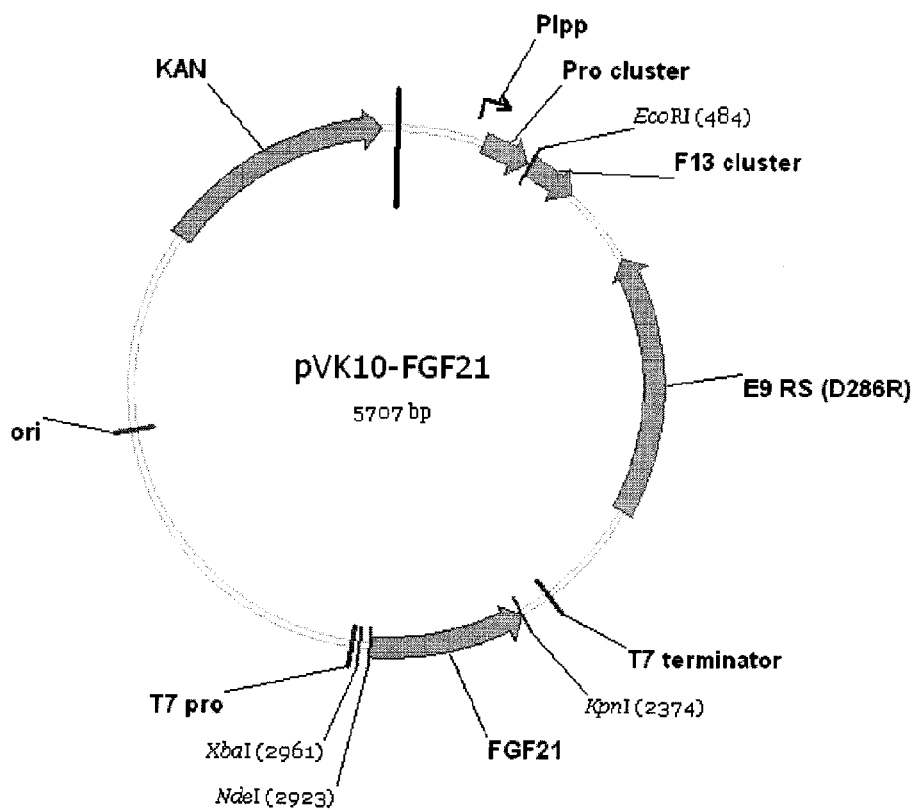


Figure 26

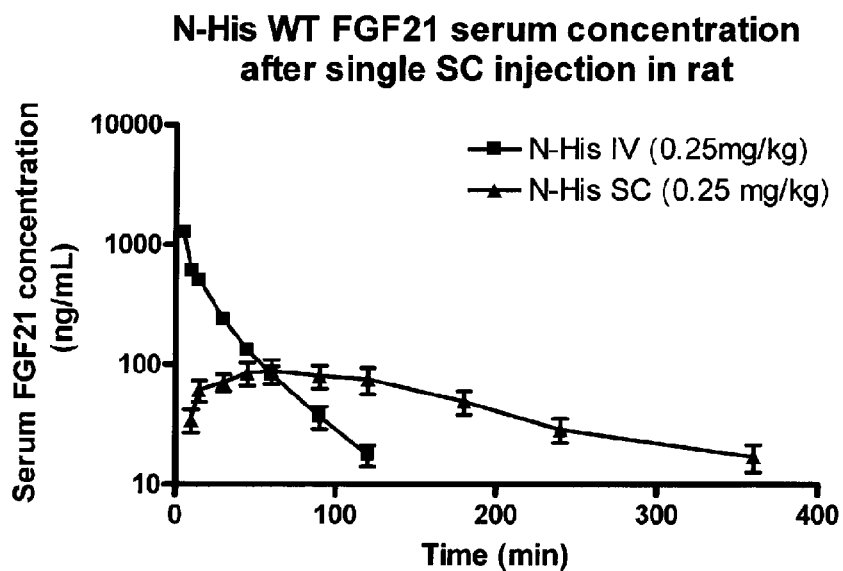
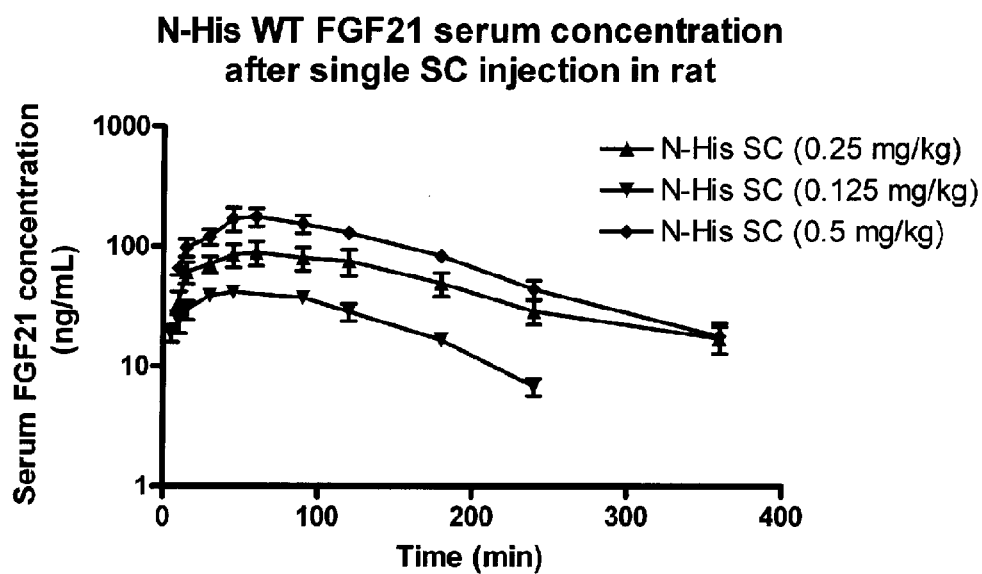
Pharmacokinetic evaluation of Wild-type (WT) N-His 6 tagged FGF21

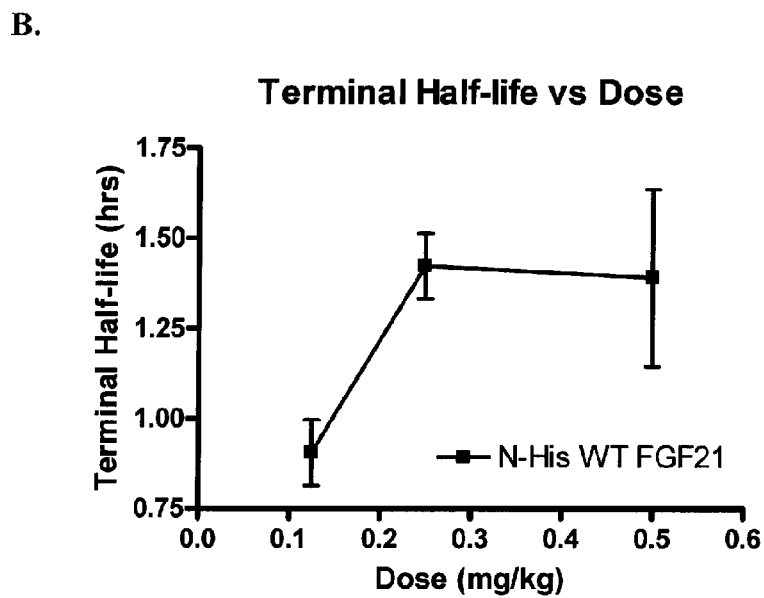
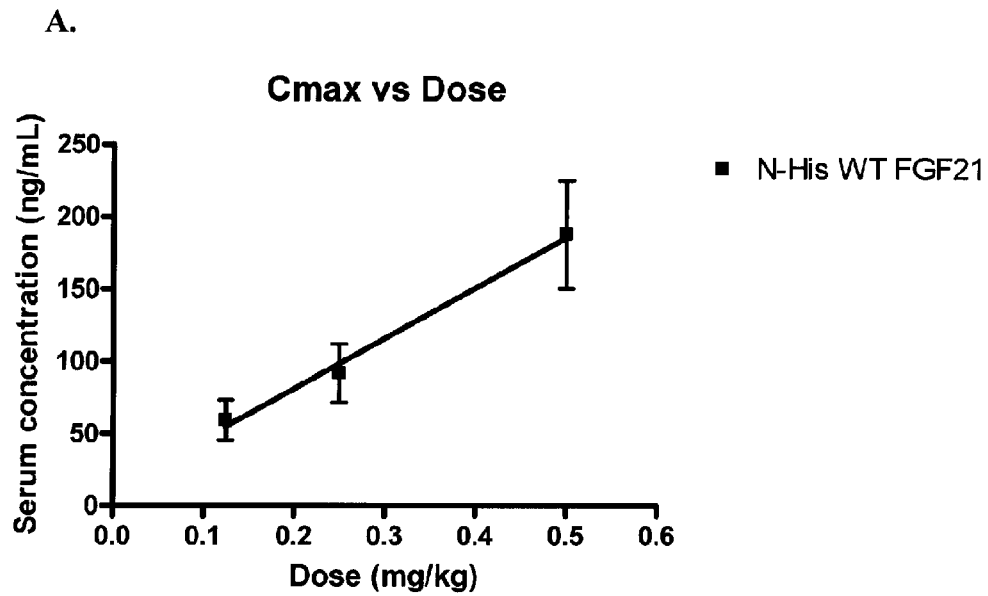
Figure 27

Figure 27 (continued)

C.

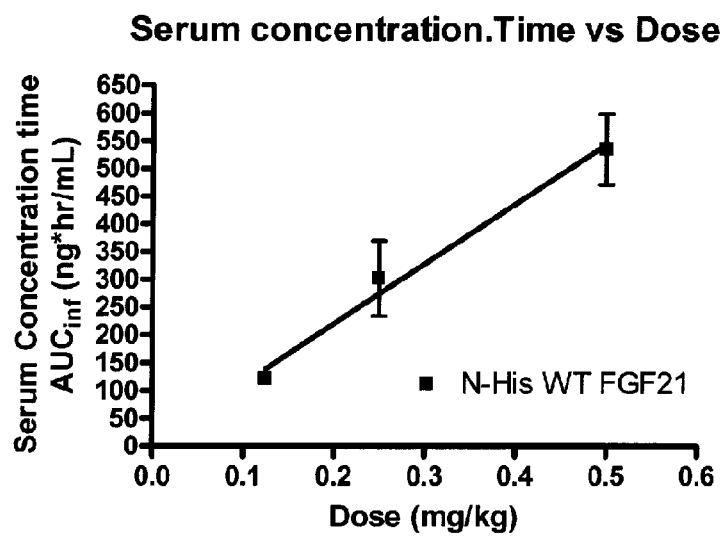
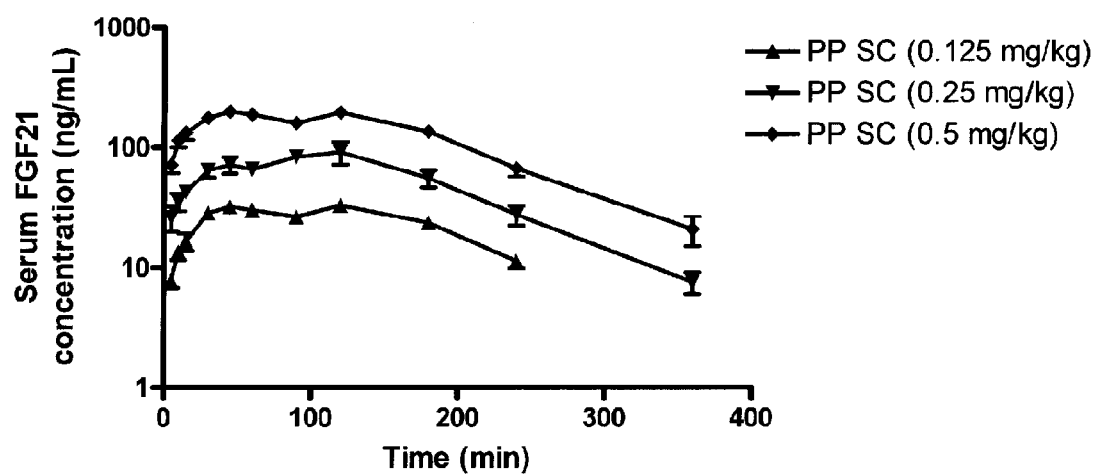


Figure 28

A.

**PP WT FGF21 serum concentration
after single SC injection in rat**

B.

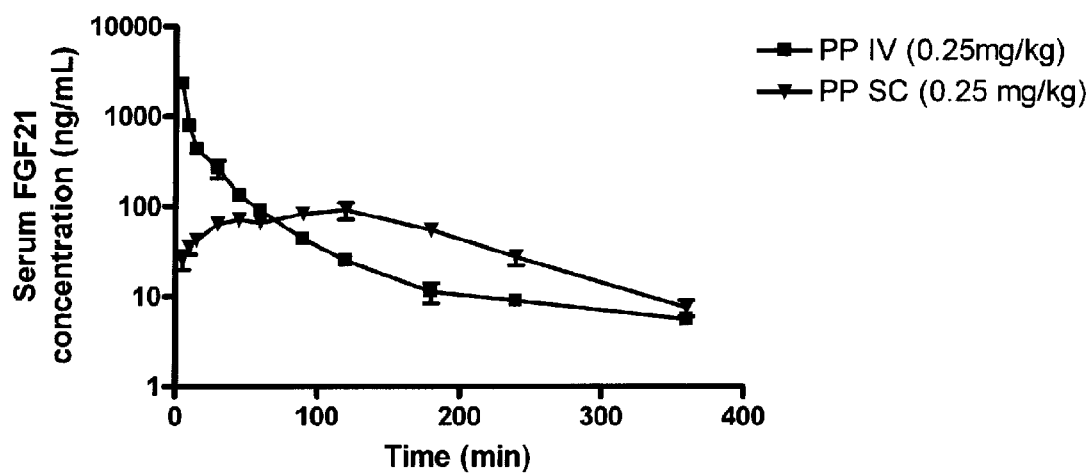
**PP WT FGF21 serum concentration
after single injection in rat**

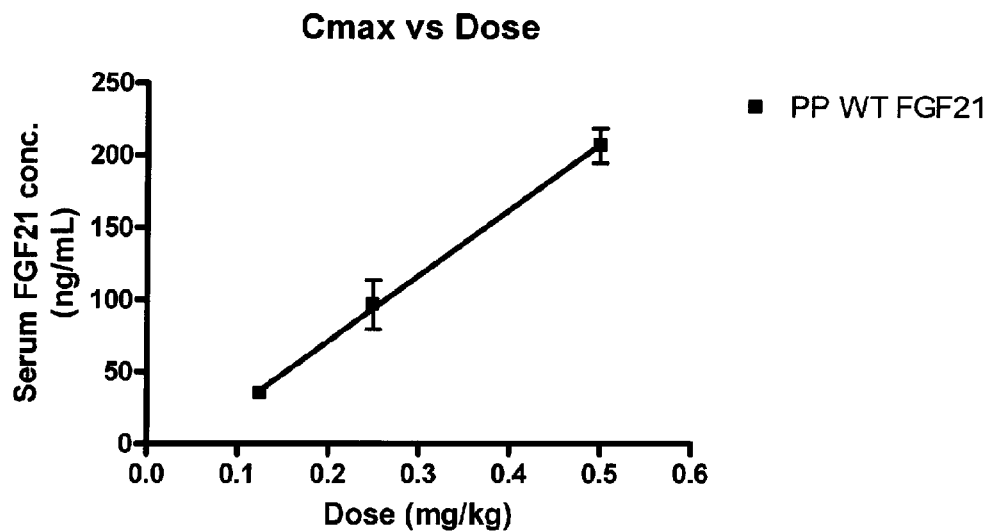
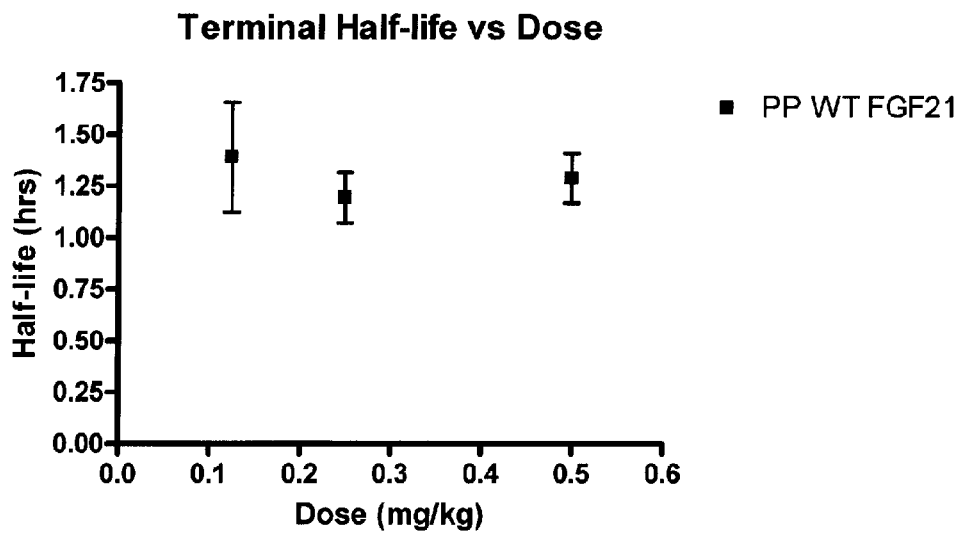
Figure 29**A.****B.**

Figure 29 (continued)

C.

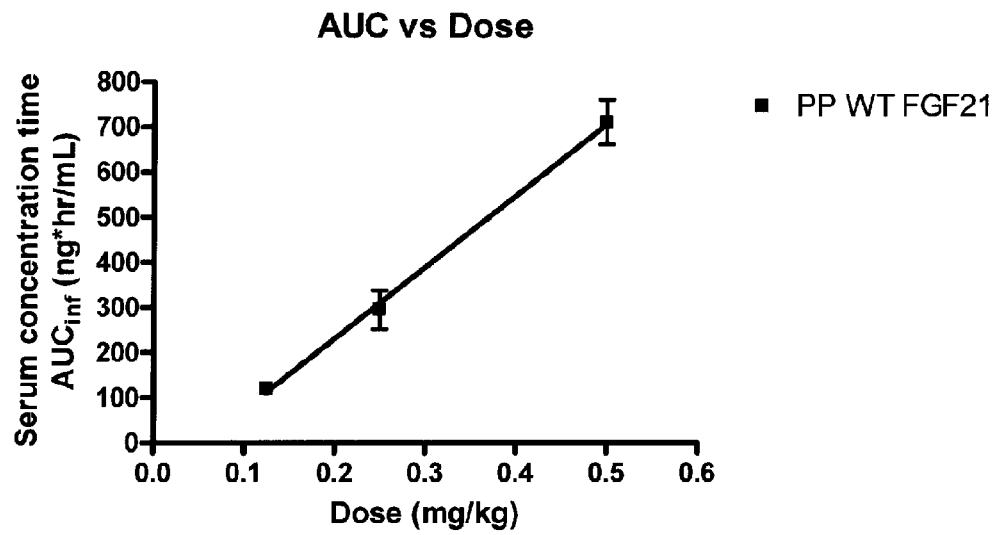


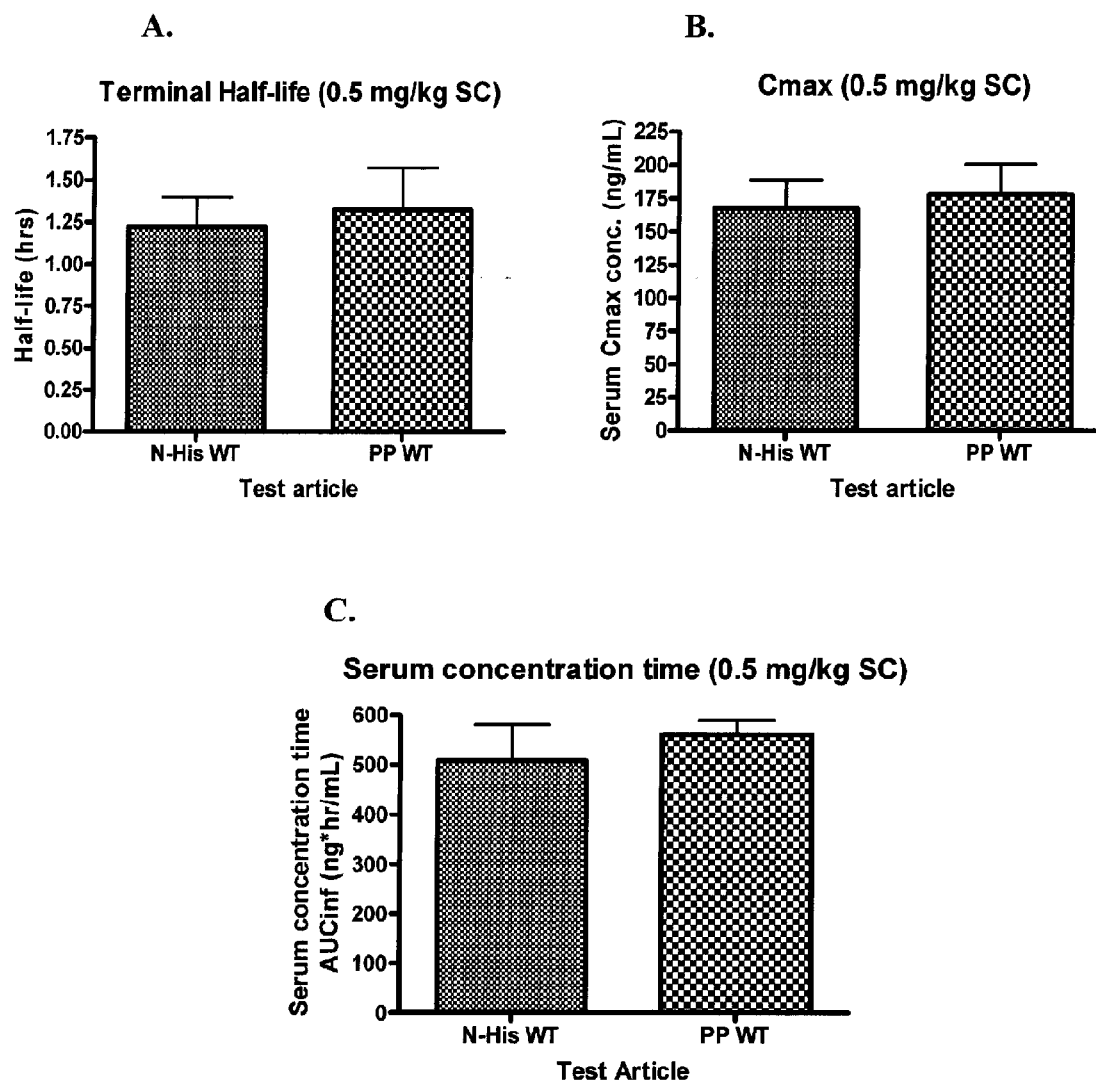
Figure 30

Figure 31

A.

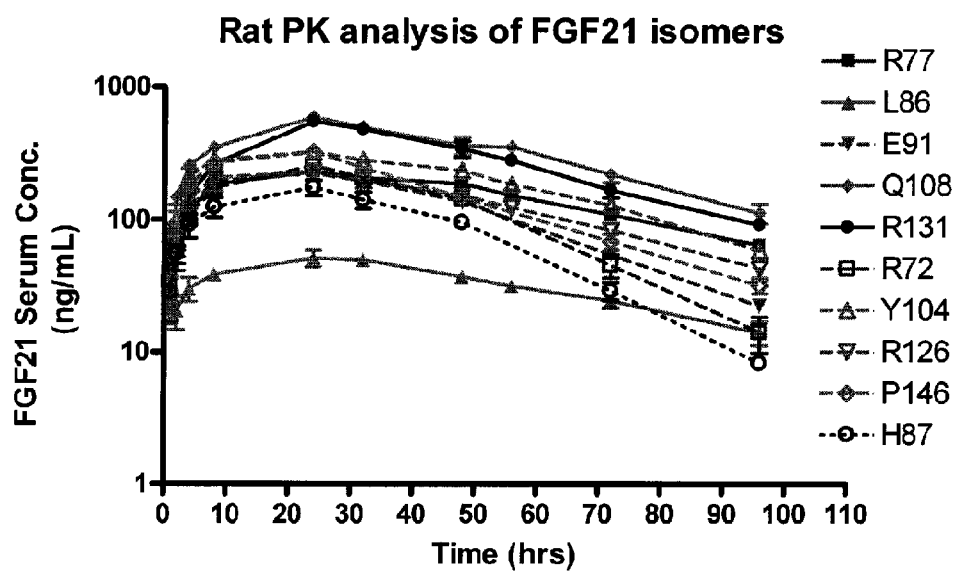


Figure 31 (Continued)

B.

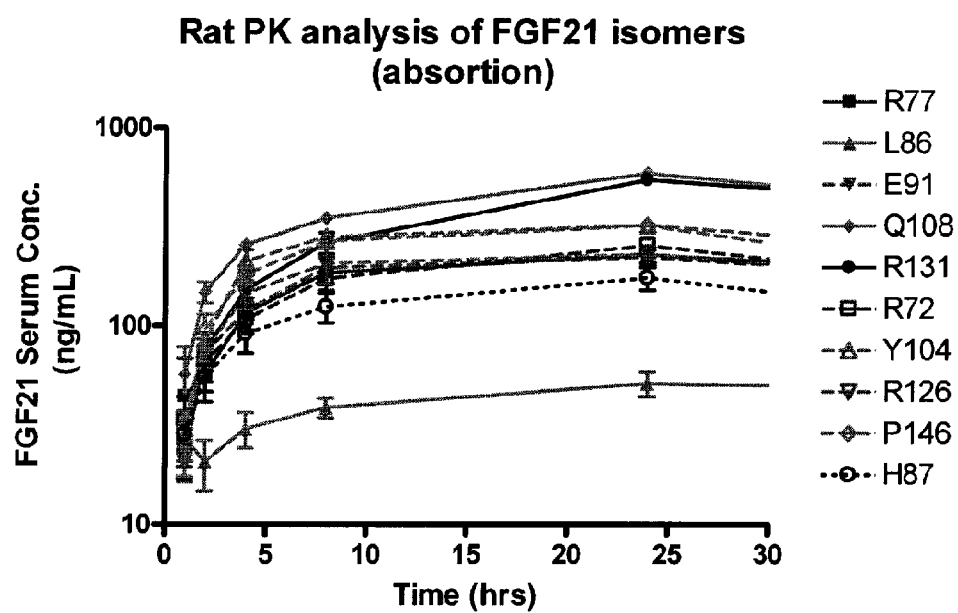


Figure 31 (continued)

C.

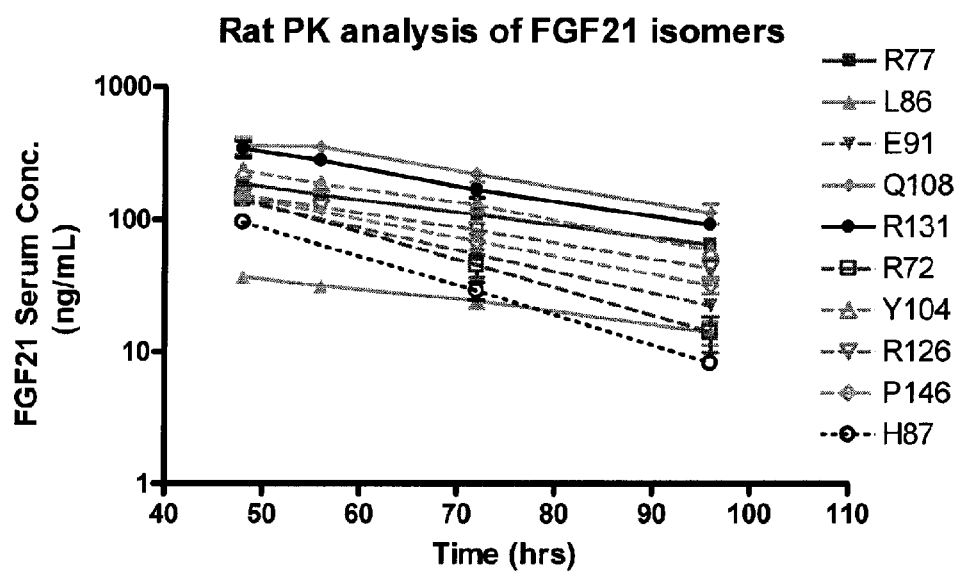


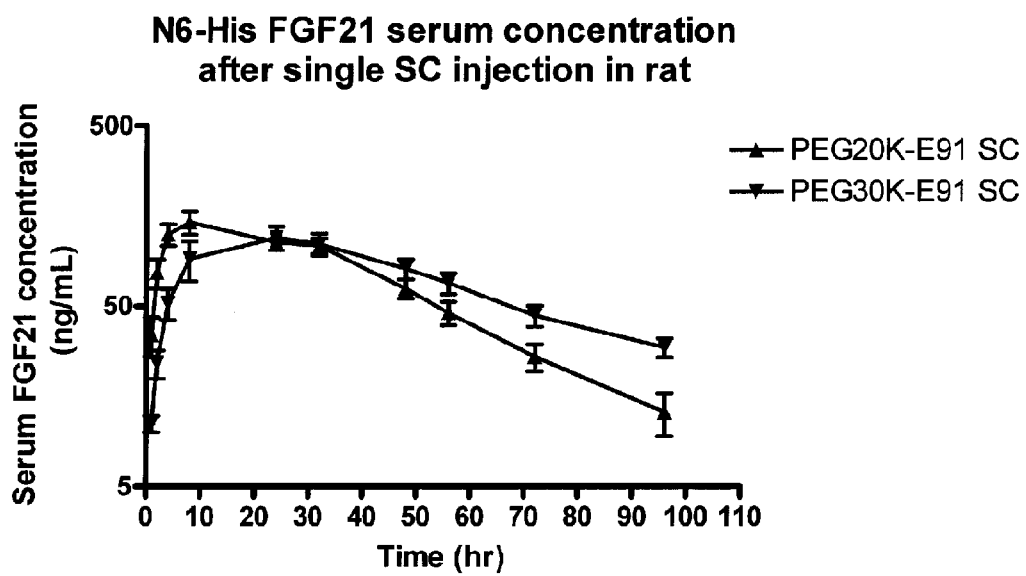
Figure 32

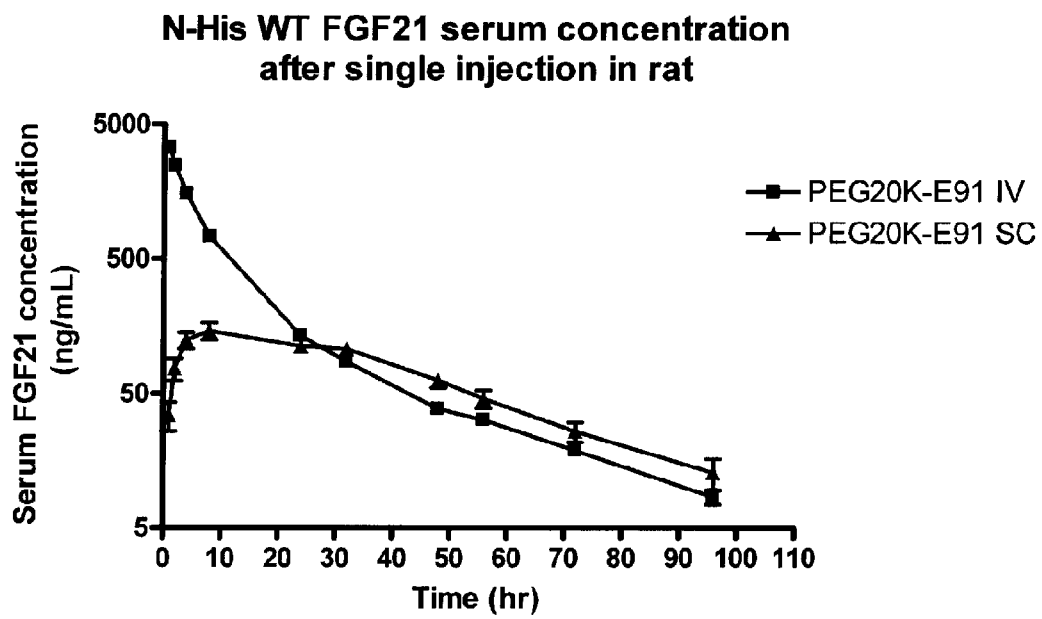
Figure 33

FIGURE 34**Secretion of FGF21 in e.coli**