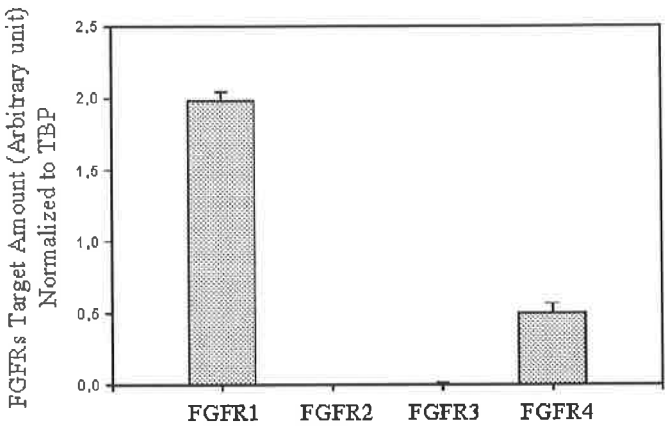
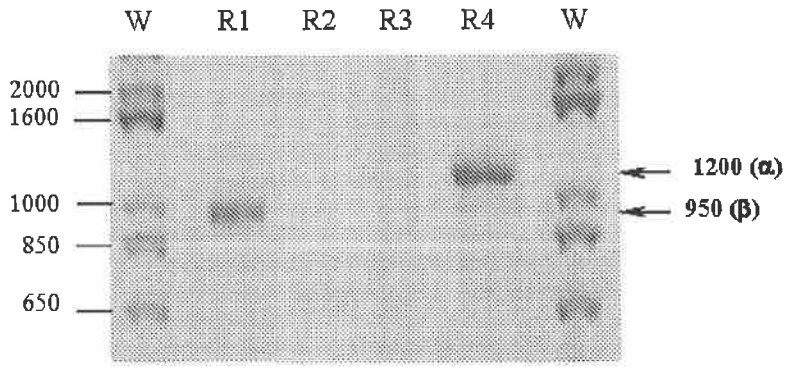
A


FGFRs Target Amount (Arbitrary unit)
Normalized to TBP
2,5
2,0
1,5
1,0
0,5
0,0
FGFR1
FGFR2
FGFR3
FGFR4

B


W
R1
R2
R3
R4
W
2000
1600
1000
850
650
1200 (α)
950 (β)

C

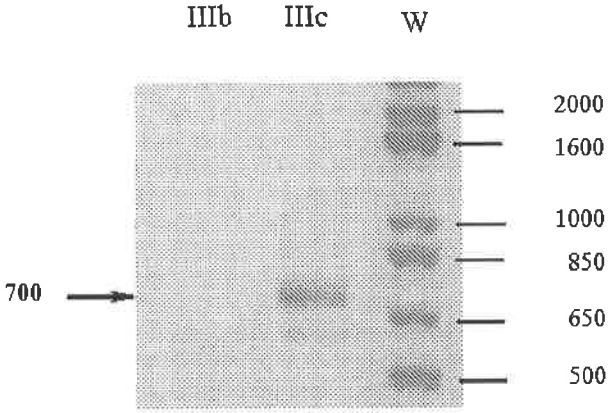
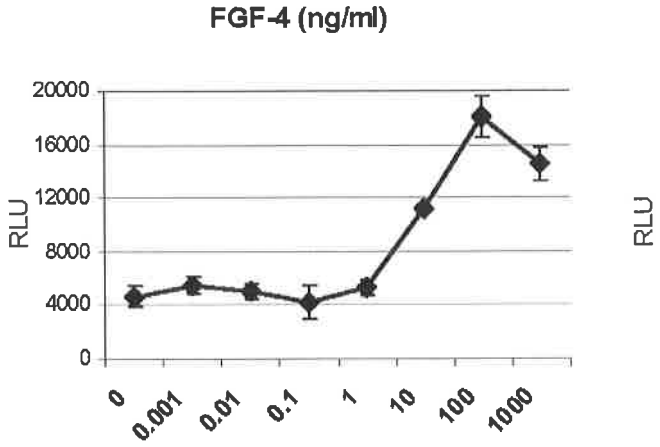

IIIb
IIIc
W
700
2000
1600
1000
850
650
500

Figure 1

A


FGF-4 (ng/ml)
RLU
20000
16000
12000
8000
4000
0
0
0.001
0.01
0.1
1
10
100
1000
RLU

B

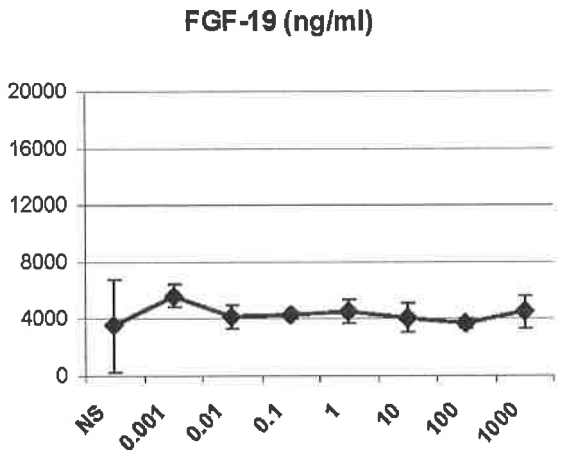

FGF-19 (ng/ml)
20000
16000
12000
8000
4000
0
NS
0.001
0.01
0.1
1
10
100
1000

Figure 2

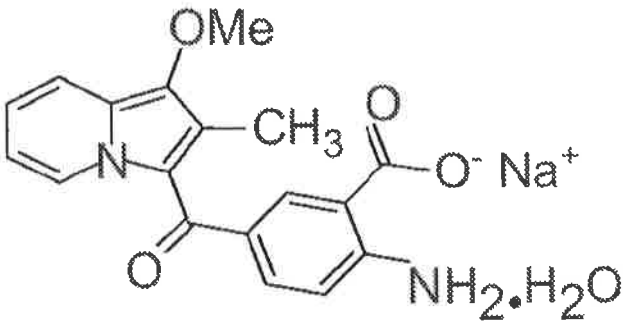
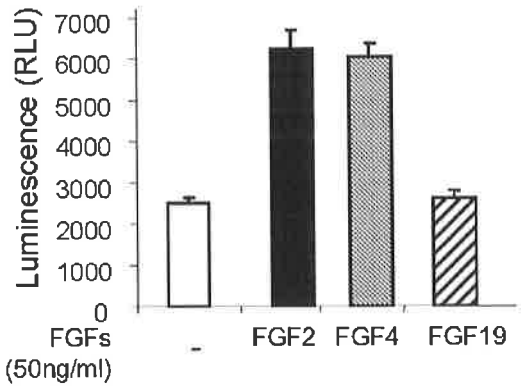


Figure 3

A


Luminescence (RLU)
7000
6000
5000
4000
3000
2000
1000
0
FGFs
(50ng/ml)
-
FGF2
FGF4
FGF19

B

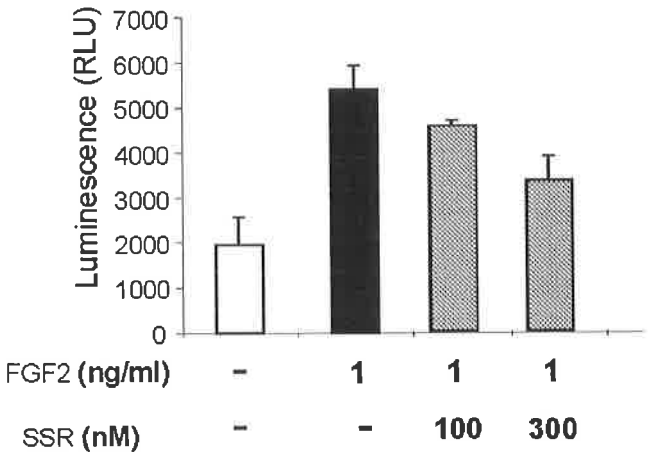
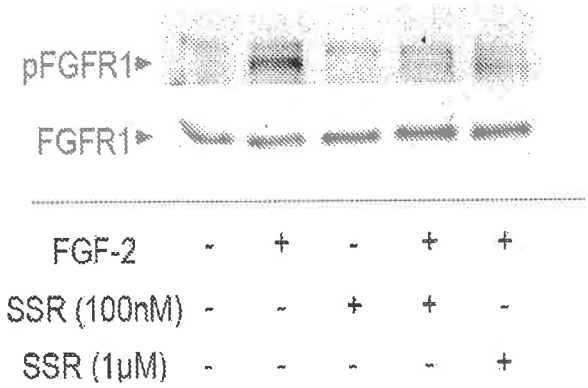

Luminescence (RLU)
7000
6000
5000
4000
3000
2000
1000
0
FGF2 (ng/ml)
-
1
1
1
SSR (nM)
-
-
100
300

Figure 4

C


pFGFR1
FGFR1
FGF-2 - + - + +
SSR (100nM) - - + + -
SSR (1µM) - - - - +

D

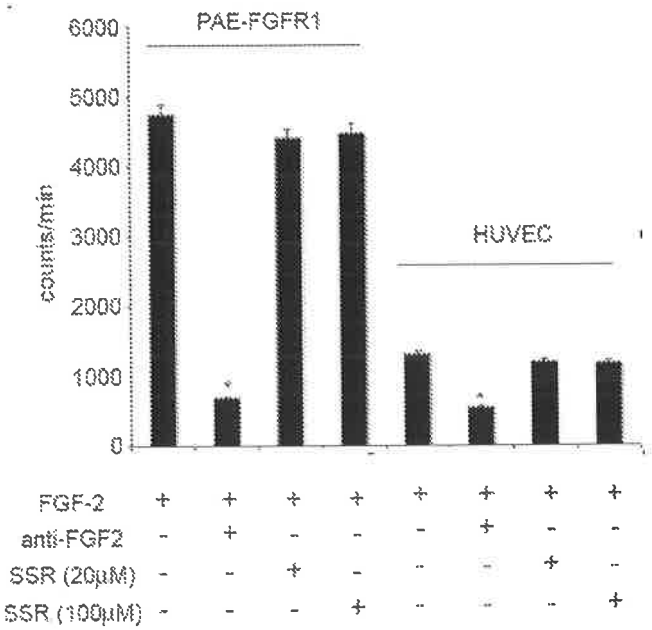
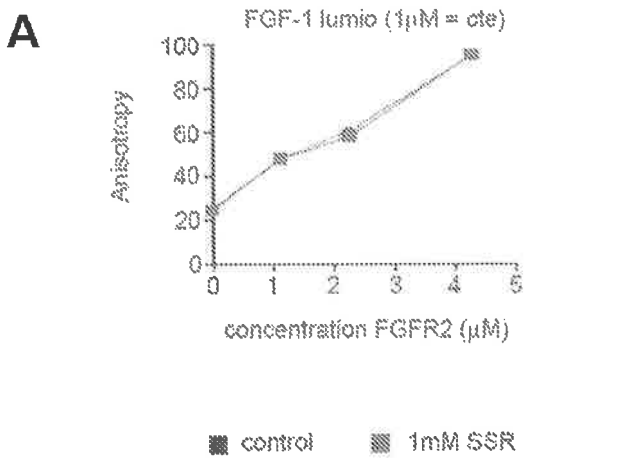
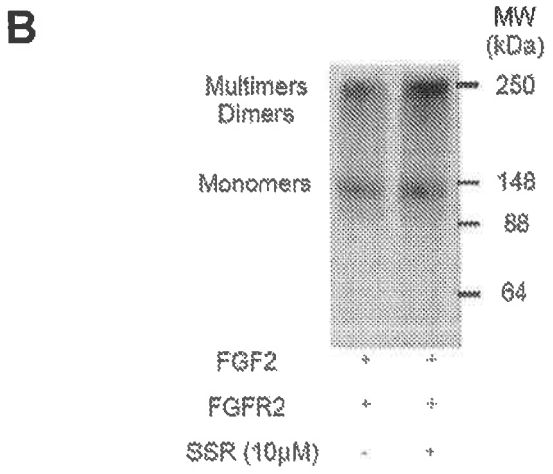

PAE-FGFR1
HUVEC
counts/min
6000
5000
4000
3000
2000
1000
0
FGF-2 + + + + + + + +
anti-FGF2 - + - - - + - -
SSR (20µM) - - + - - - + -
SSR (100µM) - - - + - - - +

Figure 4


A
FGF-1 lumio (1µM = cte)
Anisotropy
100
80
60
40
20
0
0
1
2
3
4
5
concentration FGFR2 (µM)
control
1mM SSR


B
MW
(kDa)
Multimers
Dimers
Monomers
250
148
88
64
FGF2
FGFR2
SSR (10µM)

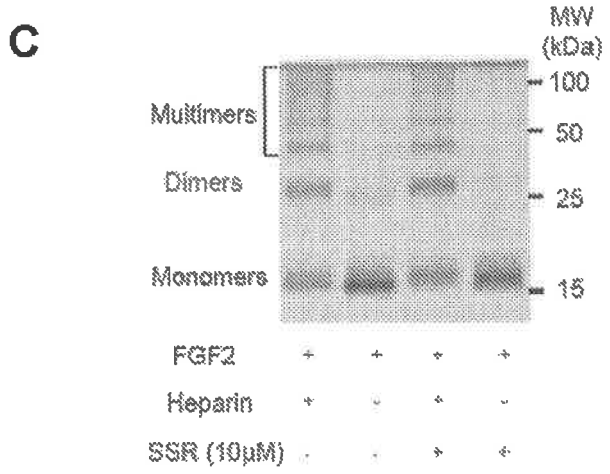
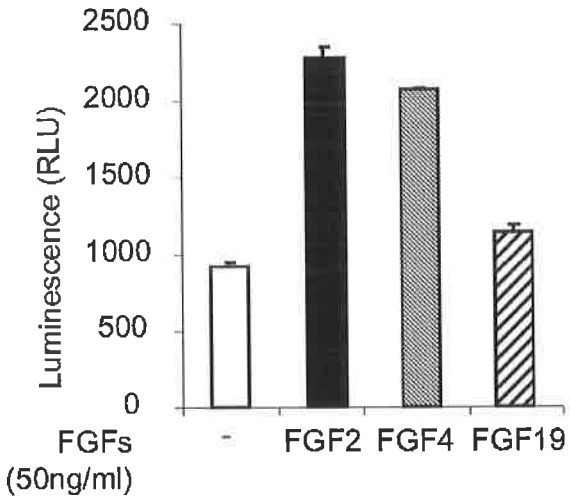

C
MW
(kDa)
Multimers
Dimers
Monomers
100
50
25
15
FGF2
Heparin
SSR (10µM)

Figure 5

A


2500
2000
1500
1000
500
0
Luminescence (RLU)
FGFs
(50ng/ml)
-
FGF2
FGF4
FGF19

B

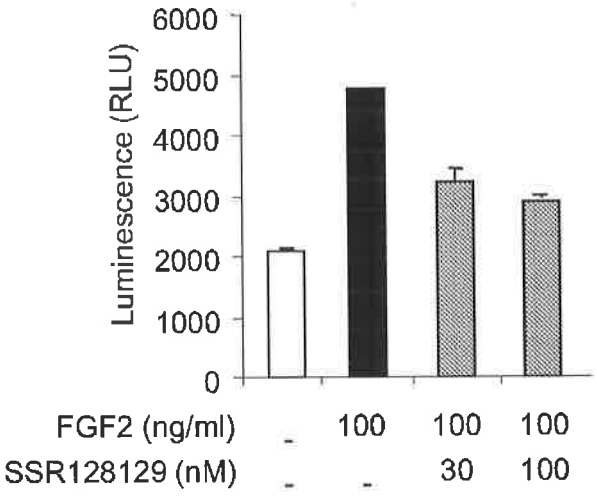
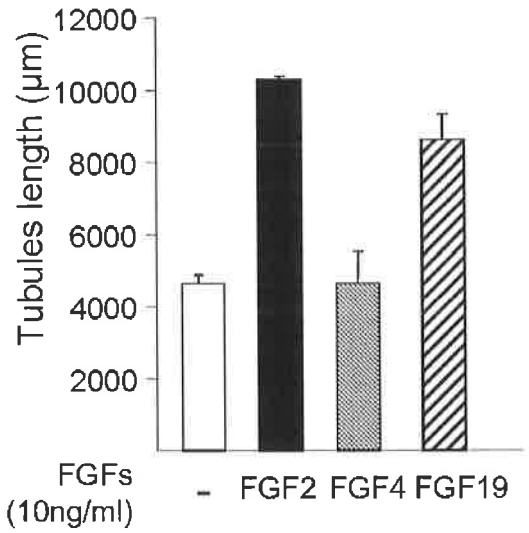

6000
5000
4000
3000
2000
1000
0
Luminescence (RLU)
FGF2 (ng/ml)
SSR128129 (nM)
-
100
100
100
-
-
30
100

Figure 6

A


Tubules length (µm)
12000
10000
8000
6000
4000
2000
FGFs
(10ng/ml)
-
FGF2
FGF4
FGF19

B

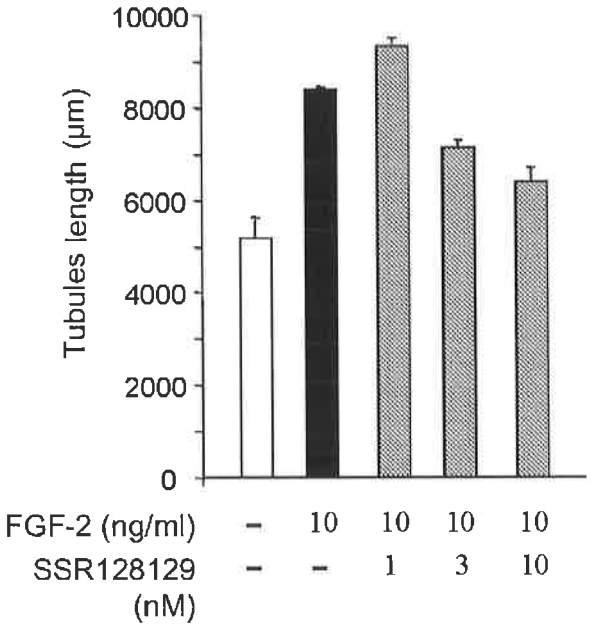
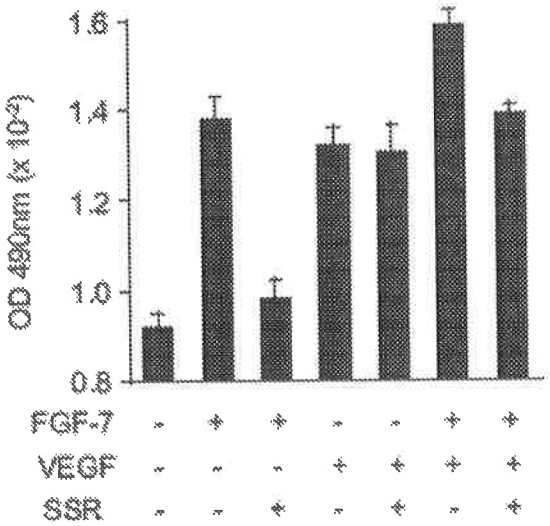

Tubules length (µm)
10000
8000
6000
4000
2000
0
FGF-2 (ng/ml) - 10 10 10 10
SSR128129 (nM) - - 1 3 10

Figure 7

A


1.6
1.4
1.2
1.0
0.8
OD 490nm (x 10-2)
FGF-7 - + + - - + +
VEGF - - - + + + +
SSR - - + - + - +

B

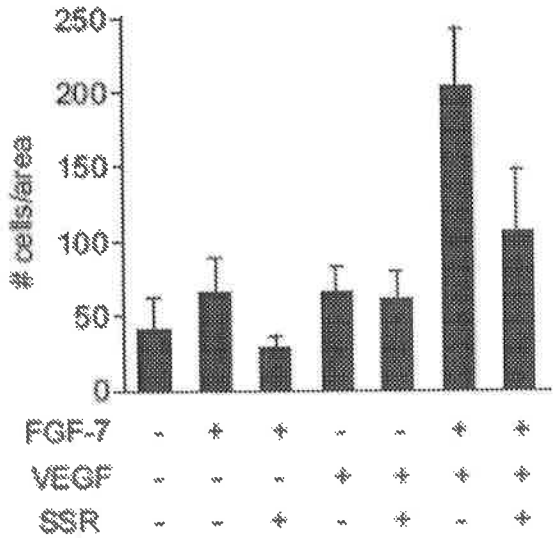

250
200
150
100
50
0
cells/area
FGF-7 - + + - - + +
VEGF - - - + + + +
SSR - - + - + - +

Figure 8

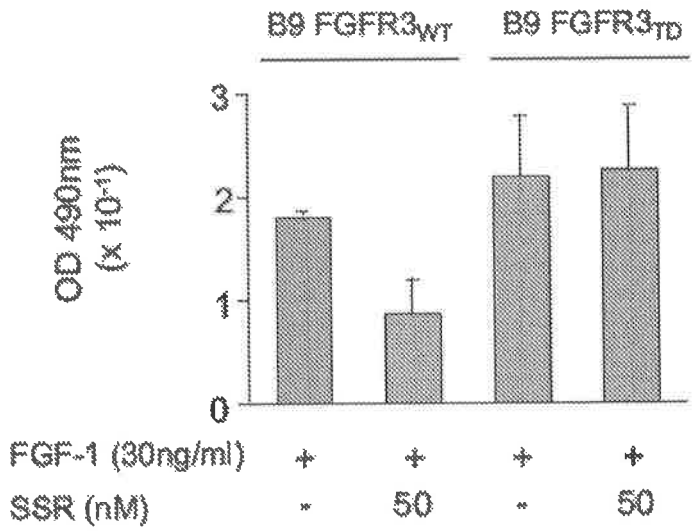

B9 FGFR3WT
B9 FGFR3TD
OD 490nm (x 10-1)
3
2
1
0
FGF-1 (30ng/ml)
+
+
+
+
SSR (nM)
-
50
-
50

Figure 9

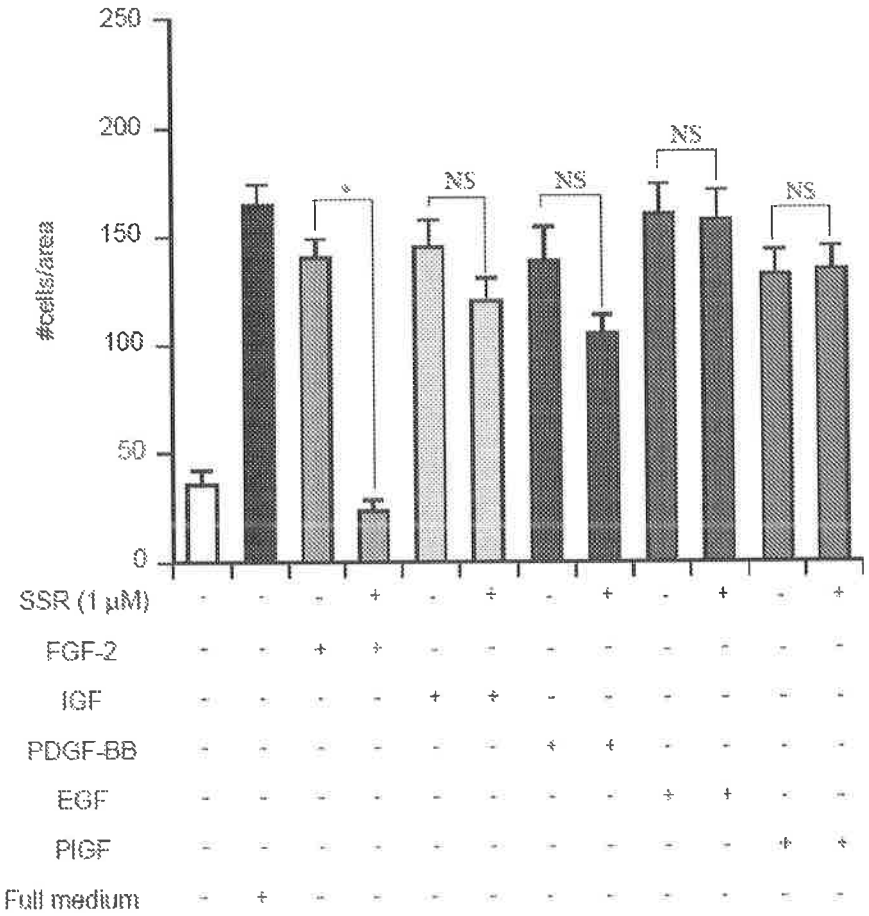
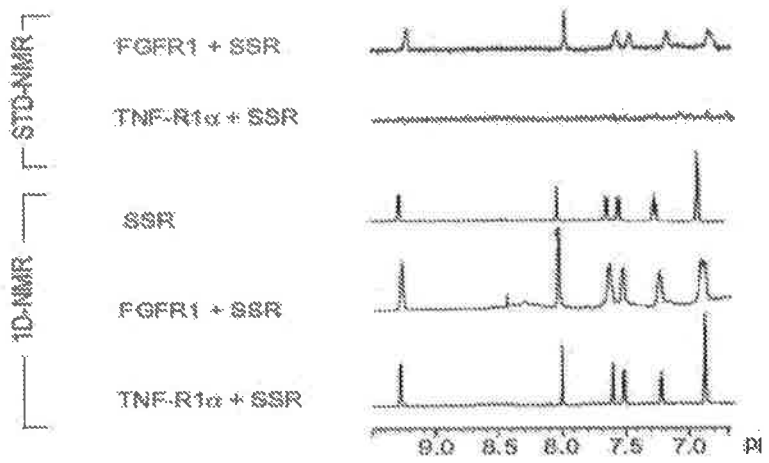

250
200
150
100
50
0
#cells/area
*
NS
NS
NS
NS
SSR (1 µM)
FGF-2
IGF
PDGF-BB
EGF
PlGF
Full medium

Figure 10

A


STD-NMR
1D-NMR
FGFR1 + SSR
TNF-R1α + SSR
SSR
FGFR1 + SSR
TNF-R1α + SSR
9.0
8.5
8.0
7.5
7.0
ppm

B

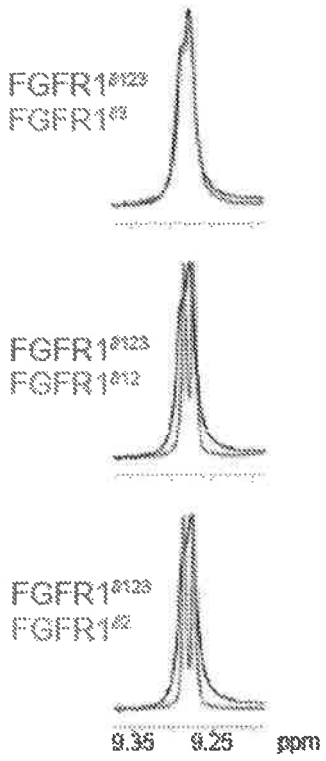
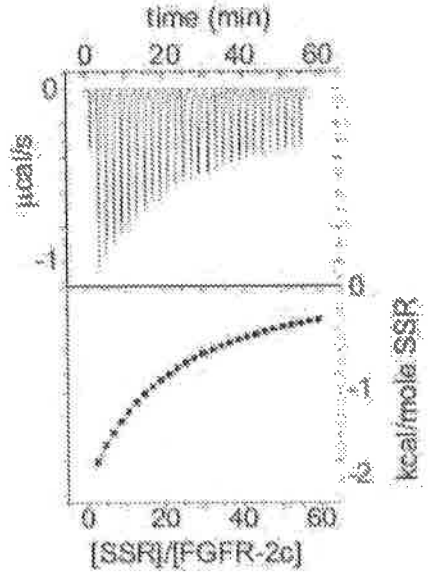

FGFR1
FGFR1
FGFR1
FGFR1
FGFR1
FGFR1
9.35
9.25
ppm

Figure 11

C


time (min)
0
20
40
60
0
µcal/s
-1
0
-1
-2
kcal/mole SSR
0
20
40
60
[SSR]/[FGFR-2c]

D

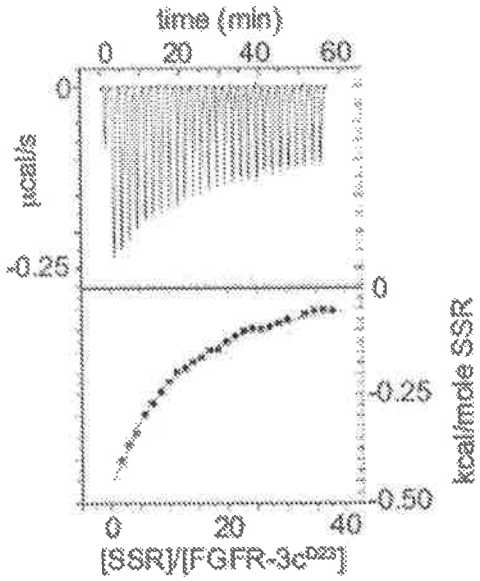
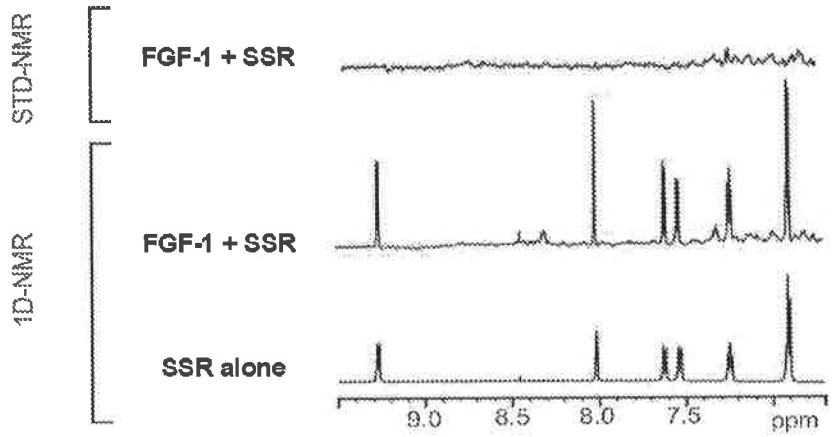

time (min)
0
20
40
60
0
µcal/s
-0.25
0
-0.25
-0.50
kcal/mole SSR
0
20
40
[SSR]/[FGFR-3c^{b2b}]

Figure 11

A


STD-NMR
FGF-1 + SSR
1D-NMR
FGF-1 + SSR
SSR alone
9.0
8.5
8.0
7.5
ppm

B

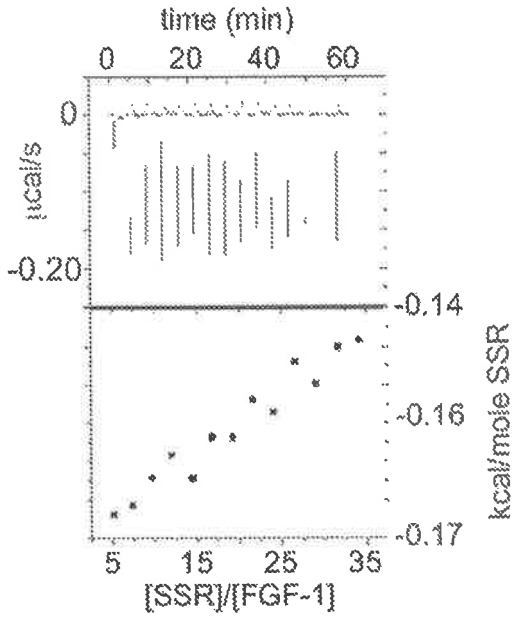
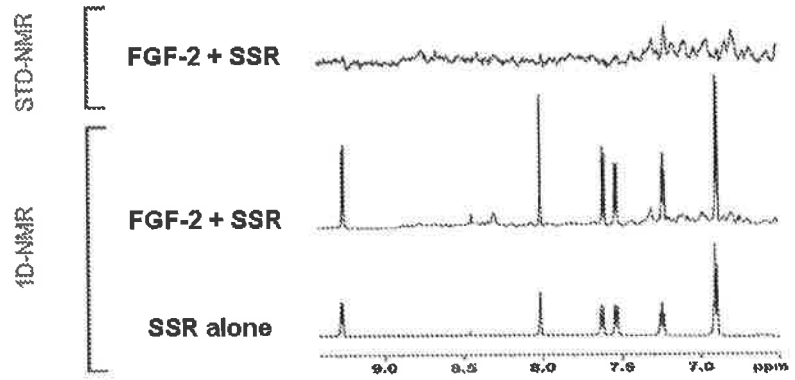

time (min)
0
20
40
60
0
µcal/s
-0.20
-0.14
-0.16
-0.17
kcal/mole SSR
5
15
25
35
[SSR]/[FGF-1]

Figure 12

C


STD-NMR
FGF-2 + SSR
1D-NMR
FGF-2 + SSR
SSR alone
9.0
8.5
8.0
7.5
7.0
ppm

D

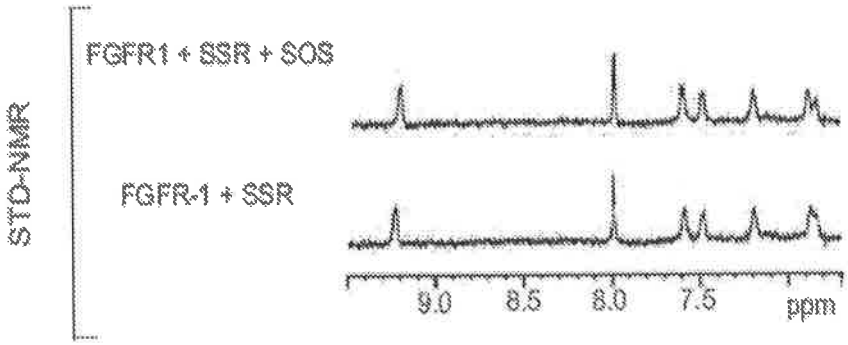
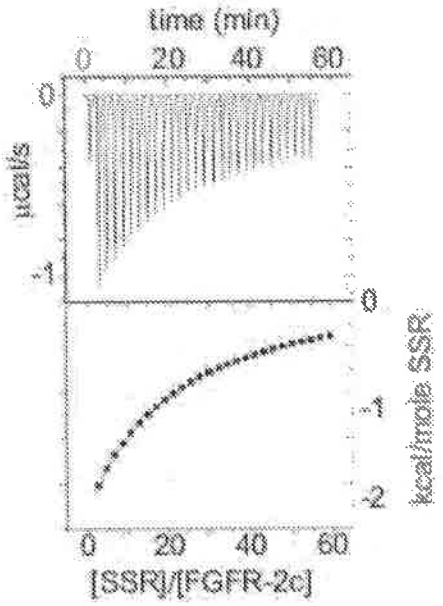

STD-NMR
FGFR1 + SSR + SOS
FGFR-1 + SSR
9.0
8.5
8.0
7.5
ppm

Figure 12

A


time (min)
0
20
40
60
0
µcal/s
-1
0
-1
-2
kcal/mole SSR
0
20
40
60
[SSR]/[FGFR-2c]

B

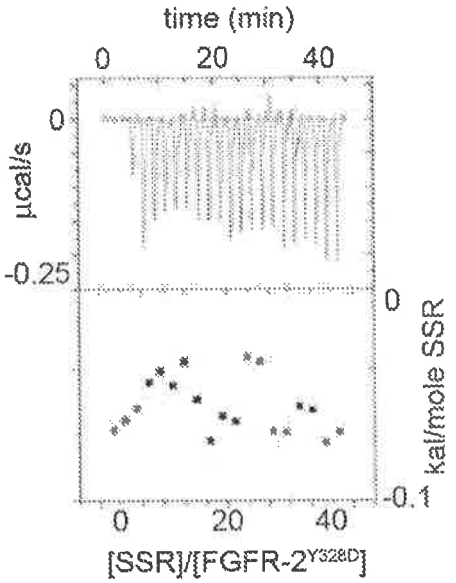

time (min)
0
20
40
0
µcal/s
-0.25
0
-0.1
kal/mole SSR
0
20
40
[SSR]/[FGFR-2Y328D]

Figure 13

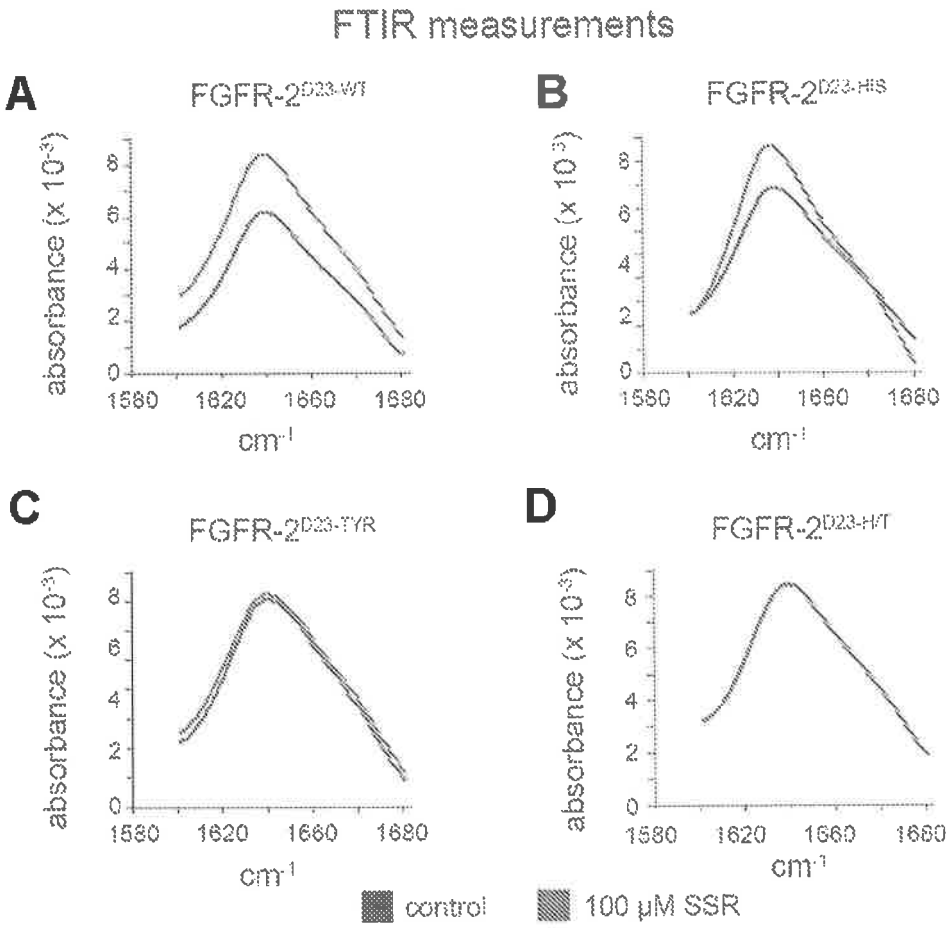
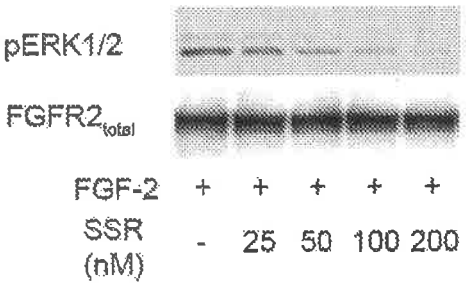

FTIR measurements
A
FGFR-2D23-WT
B
FGFR-2D23-HIS
C
FGFR-2D23-TYR
D
FGFR-2D23-H/T
absorbance (x 10-3)
cm-1
1580
1620
1660
1680
control
100 µM SSR

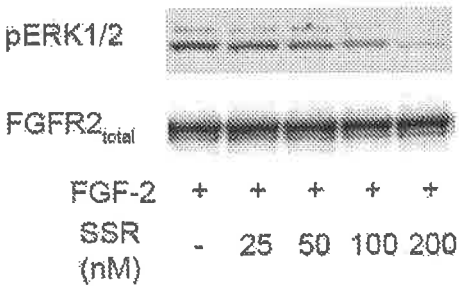
Figure 14

A



IC50 = 28nM ± 12

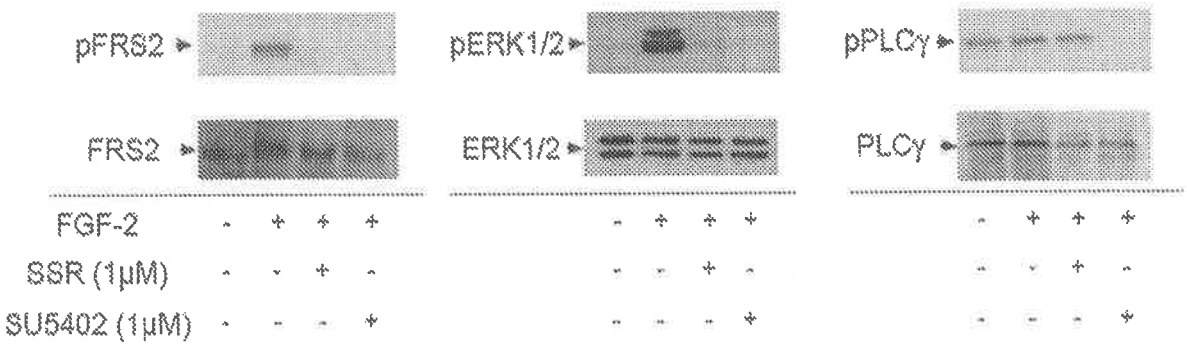
B



IC50 = 121nM ± 30

Figure 15

A


pFRS2
pERK1/2
pPLCγ
FRS2
ERK1/2
PLCγ
FGF-2
SSR (1μM)
SU5402 (1μM)

B

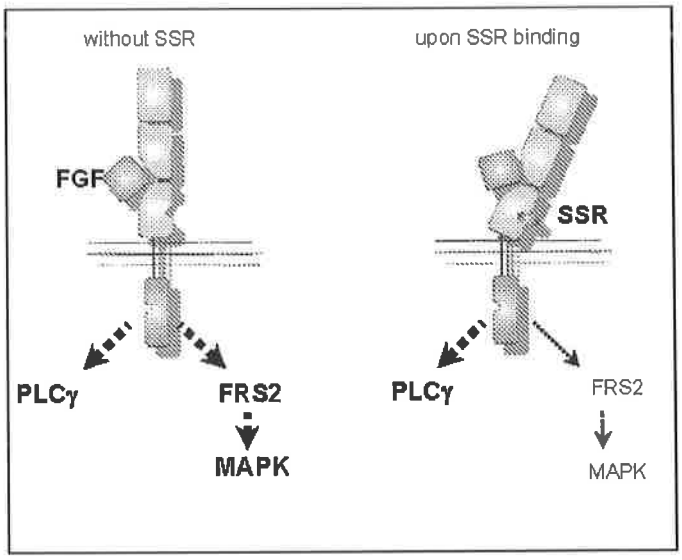
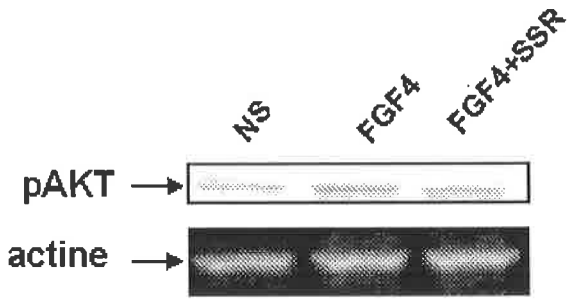

without SSR
upon SSR binding
FGF
SSR
PLCγ
FRS2
MAPK
PLCγ
FRS2
MAPK

Figure 16

A


NS
FGF4
FGF4+SSR
pAKT
actine

B

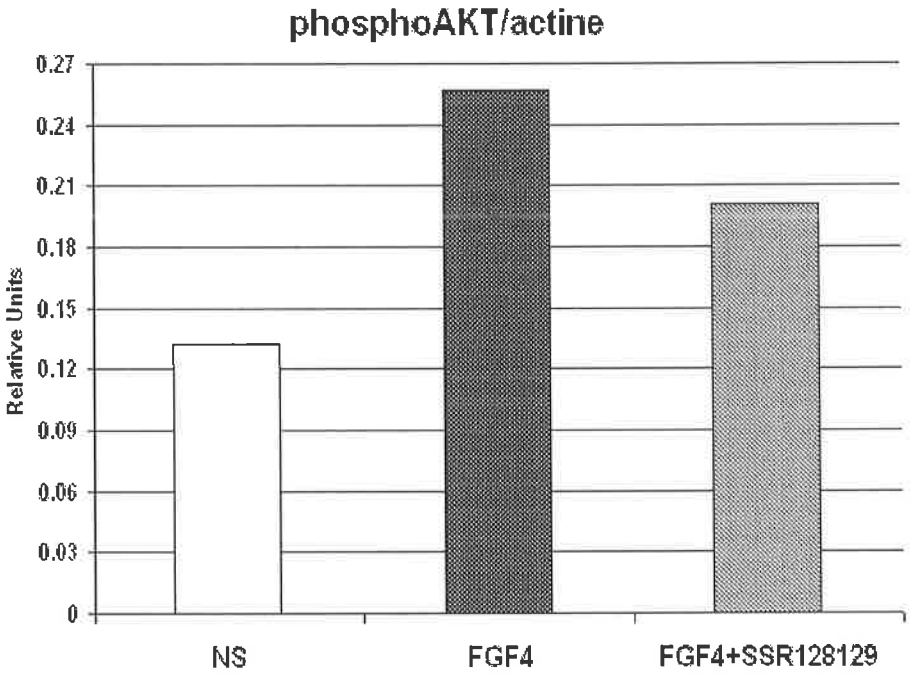
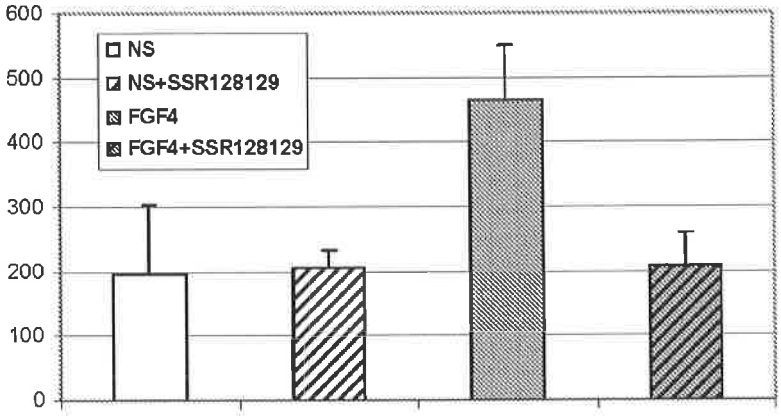

phosphoAKT/actine
Relative Units
0.27
0.24
0.21
0.18
0.15
0.12
0.09
0.06
0.03
0
NS
FGF4
FGF4+SSR128129

Figure 17

C


600
500
400
300
200
100
0
NS
NS+SSR128129
FGF4
FGF4+SSR128129

D

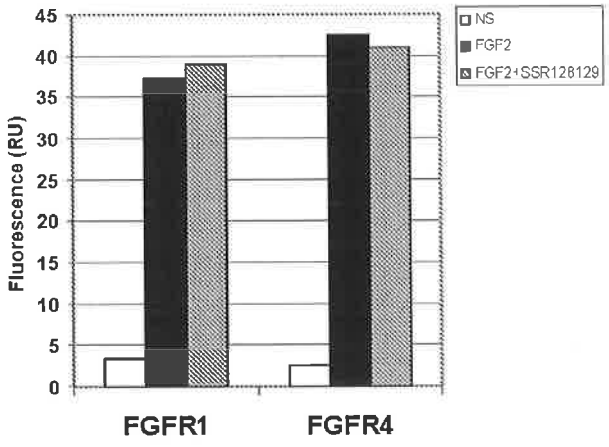

45
40
35
30
25
20
15
10
5
0
Fluorescence (RU)
FGFR1
FGFR4
NS
FGF2
FGF2+SSR128129

Figure 17

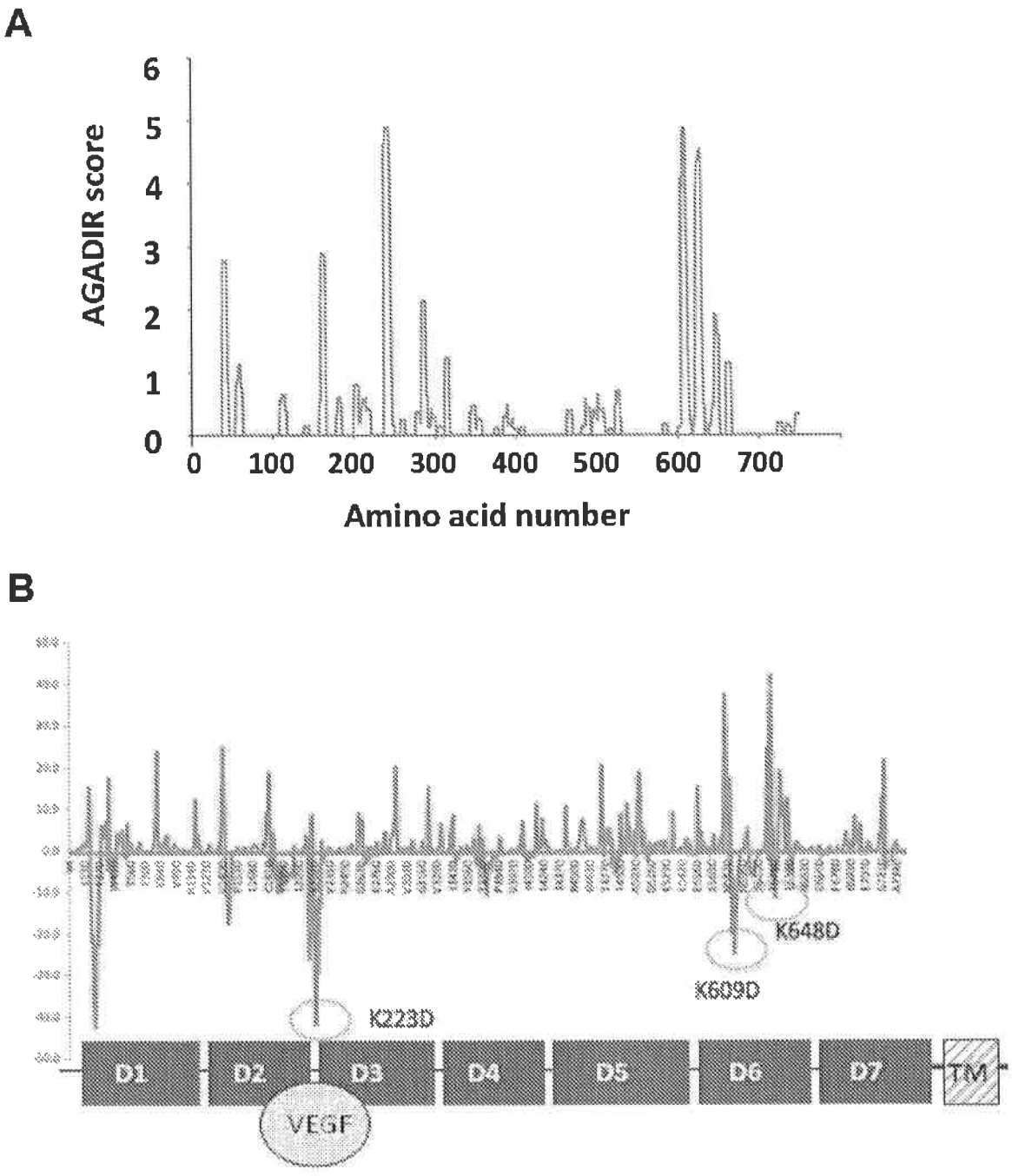
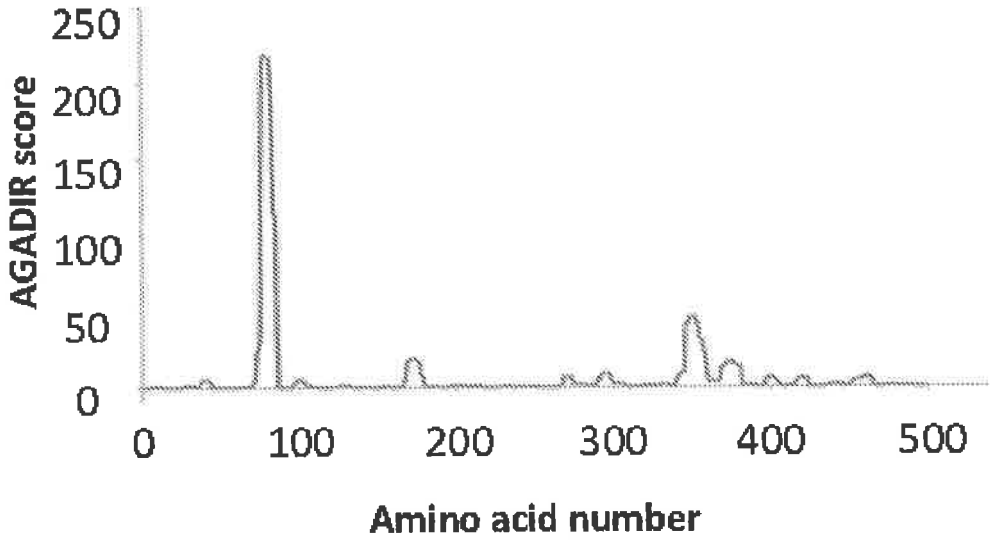

A
AGADIR score
0
1
2
3
4
5
6
0
100
200
300
400
500
600
700
Amino acid number
B
K648D
K609D
K223D
D1
D2
D3
D4
D5
D6
D7
TM
VEGF

Figure 18

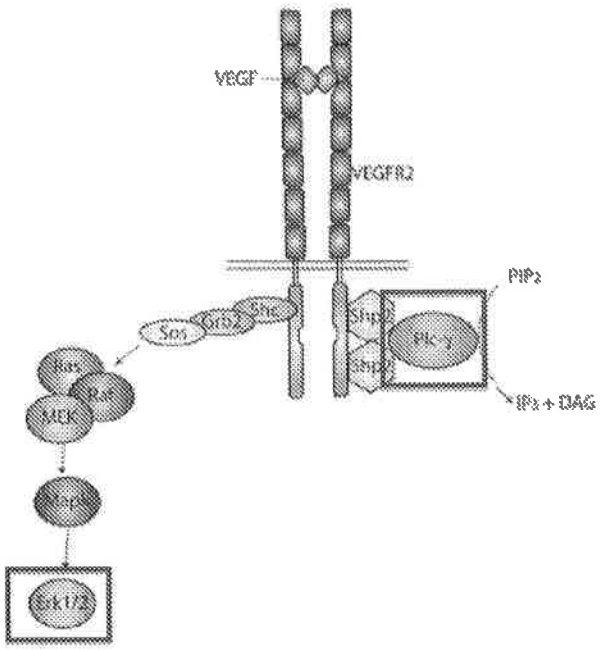


Change in agadir score when mutating residue to Aspartate (D)

hPDGFRbeta_K387D	-515.11
hPDGFRbeta_L383D	-485.6

Figure 19

A


VEGF
VEGFR2
PIP2
Grb2
Shc
Sos
Ras
Raf
MEK
Erk1/2
IP3 + DAG

B

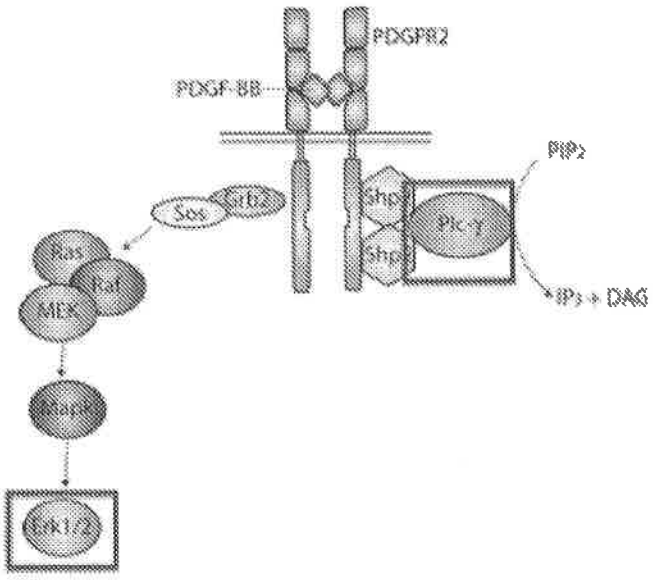
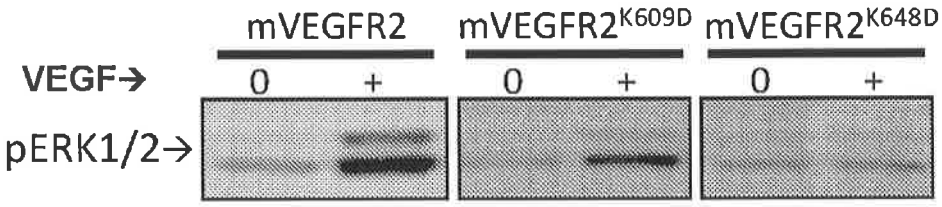
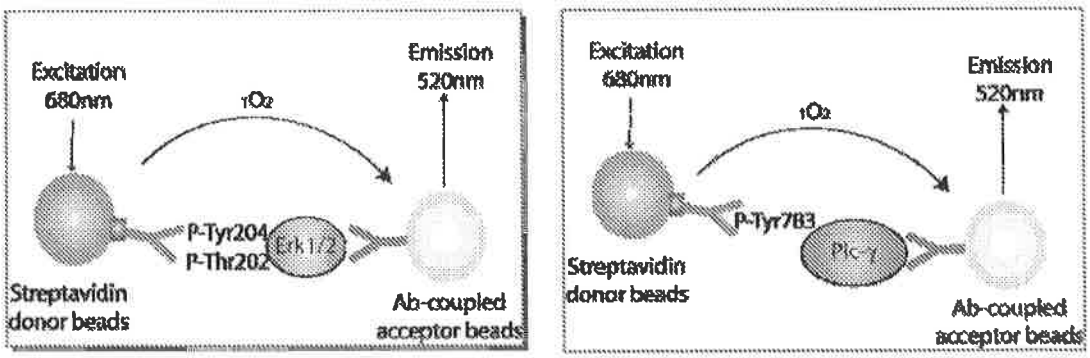

PDGFR2
PDGF-BB
PIP2
Grb2
Sos
Ras
Raf
MEK
Erk1/2
IP3 + DAG

Figure 20

A



B



C

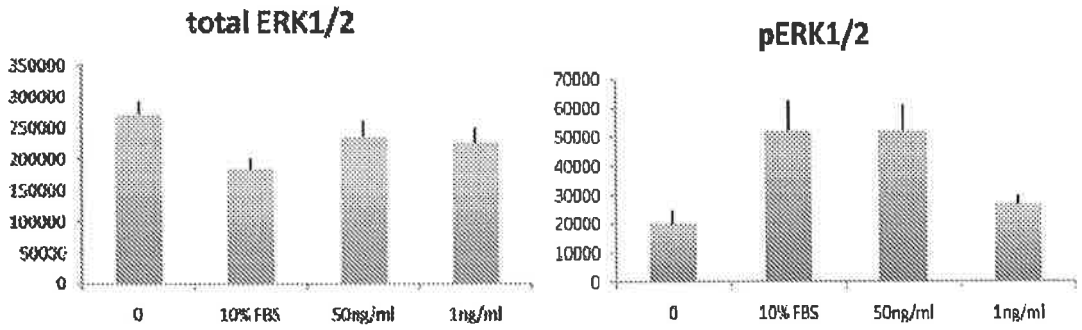


Figure 21