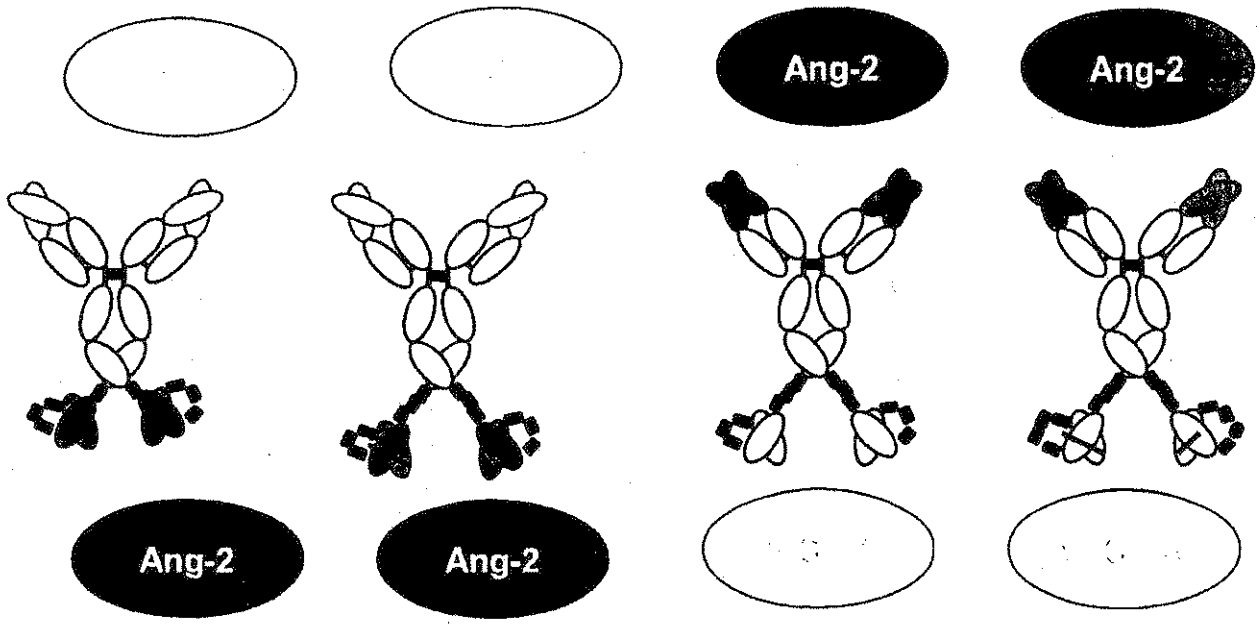
Figure 1B



TvAb5 C-Terminal Heavy Chain Fusion Format: 2310	TvAb6 C-Terminal Heavy Chain Fusion Format: 2331	TvAb9 C-Terminal Heavy Chain Fusion Format: 2330	TvAb15 C-Terminal Heavy Chain Fusion Format: 2431

Figure 2 - part one

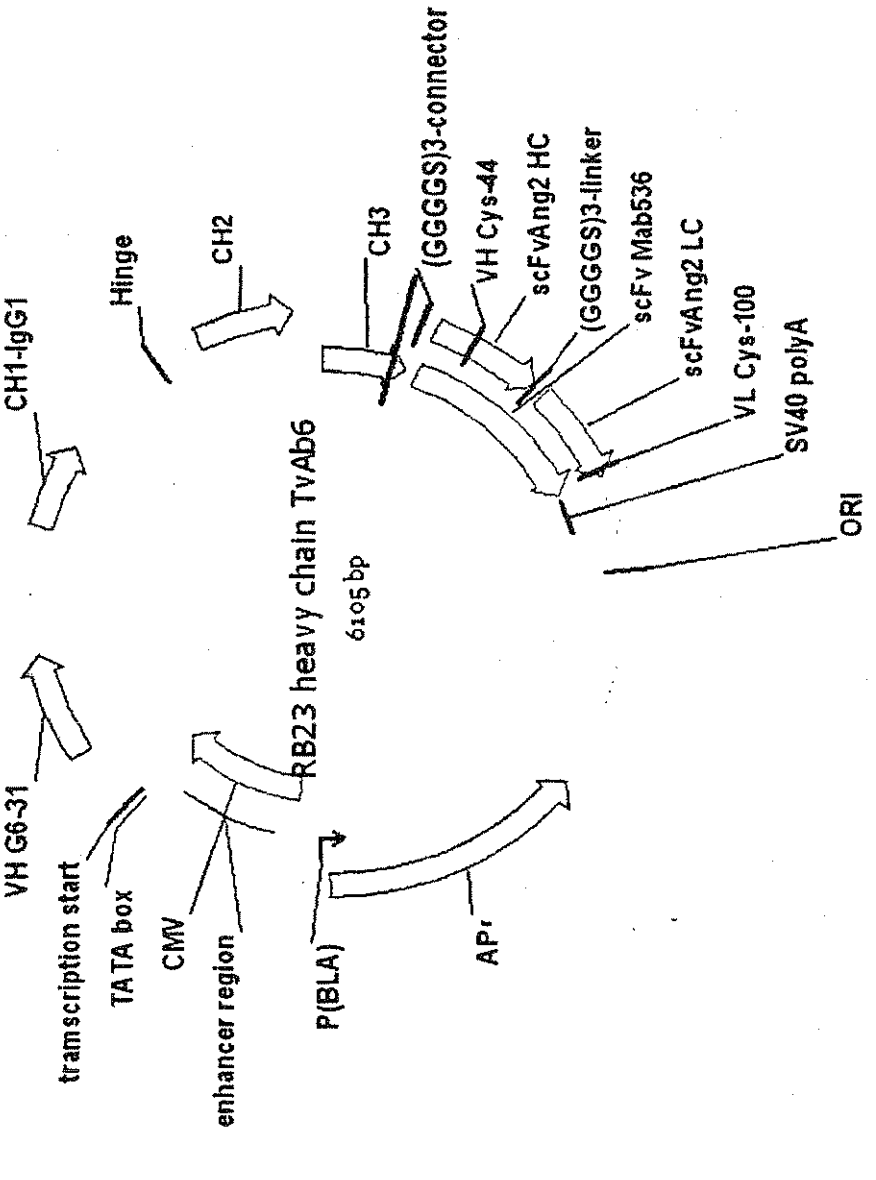


Figure 2b-part two

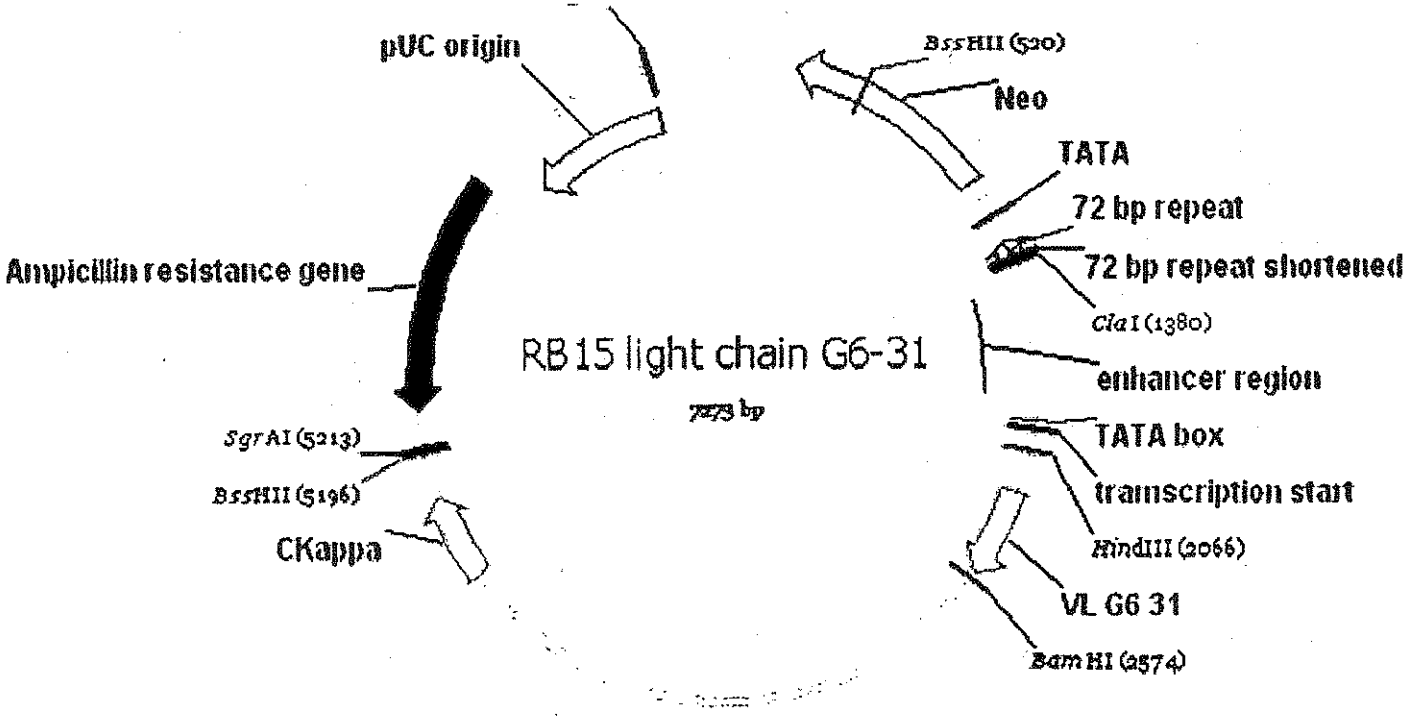


Fig. 4A

1. Protein A Pool

G6-31: 10 % aggregates

TvAb6: 25 % aggregates

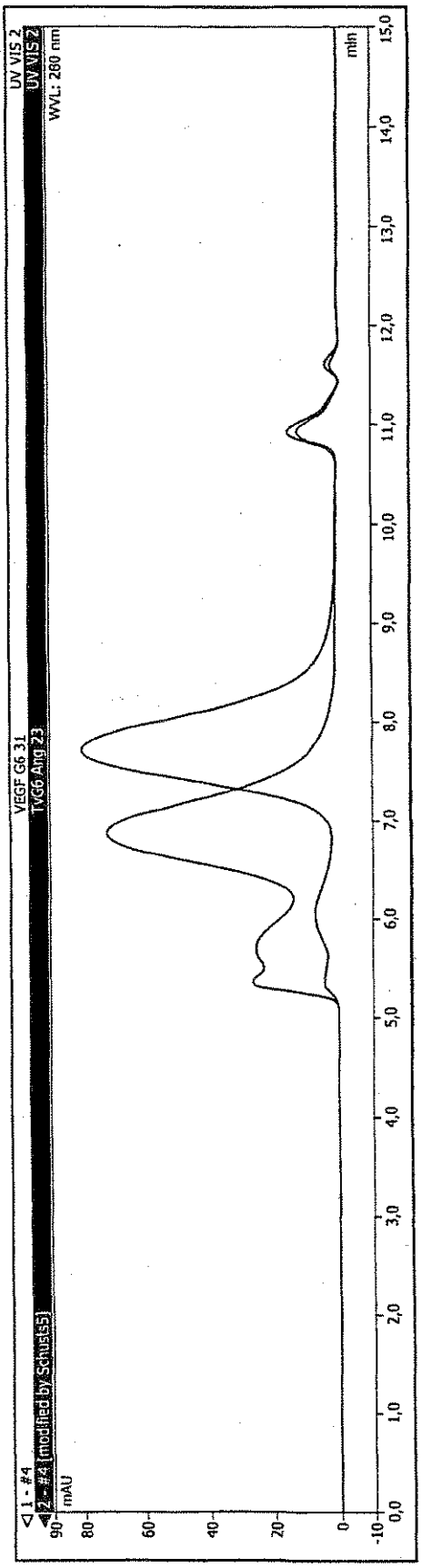


Fig. 4B

2. SEC Pool, after purification

G6-31: > 99 % monomer

TvAb6: > 99 % monomer

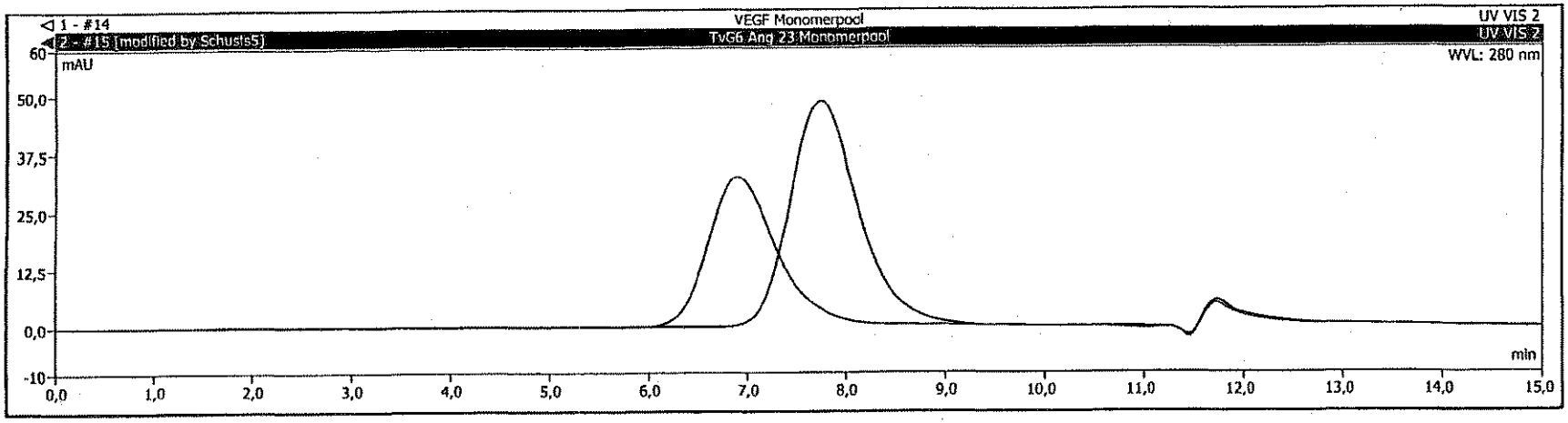


Fig. 4C

3. SEC Pool, after 24 h at 4 °C

G6-31: > 99 % monomer

TvAb6: > 99 % monomer

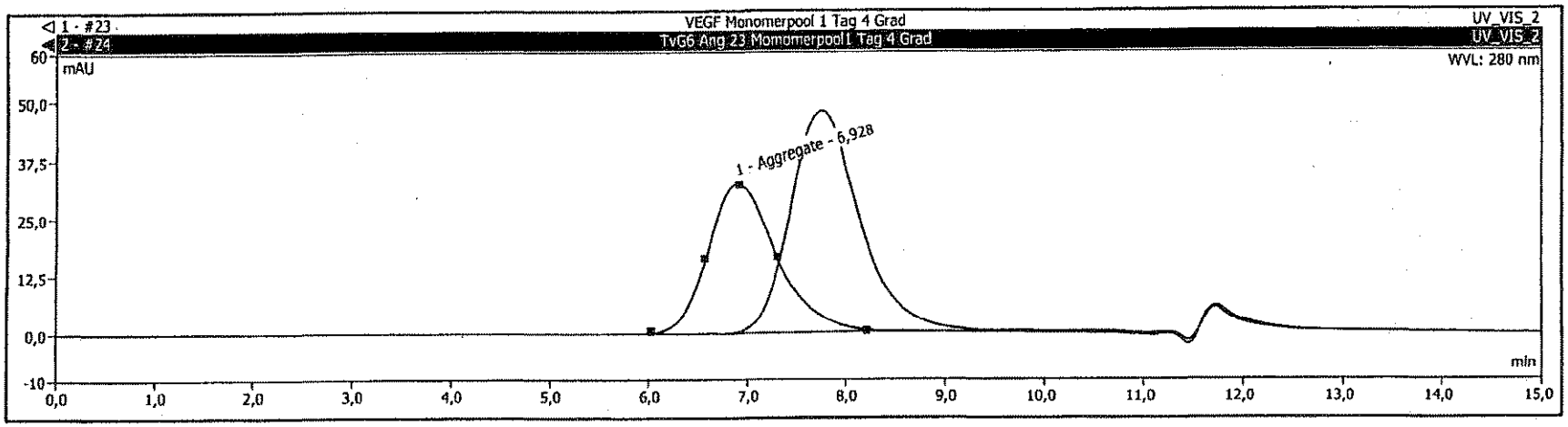


Figure 5 –part one

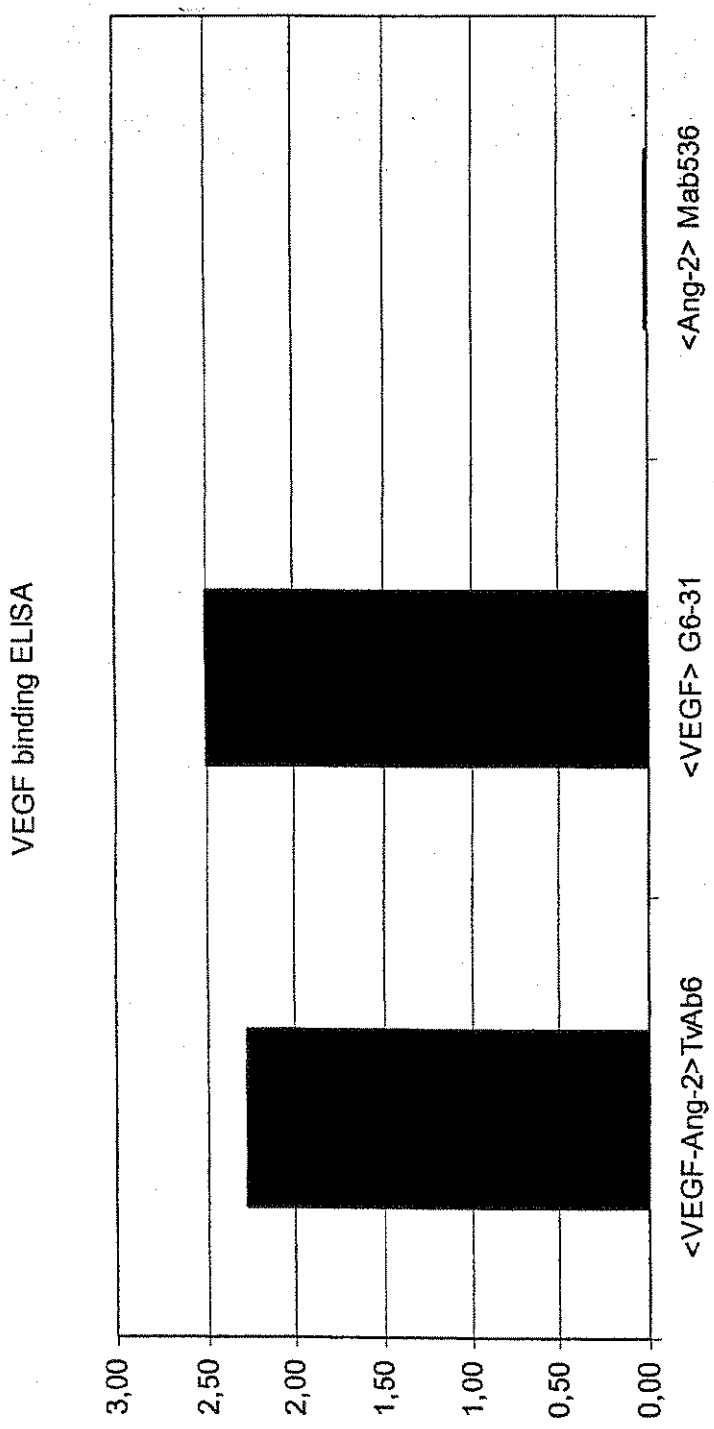


Figure 5–part two

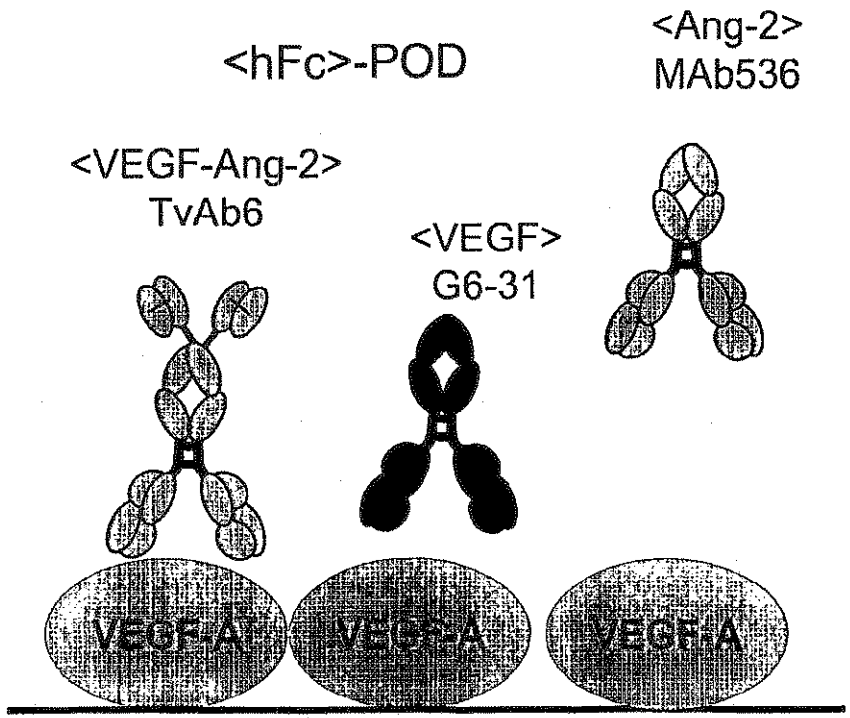


Figure 7–part one

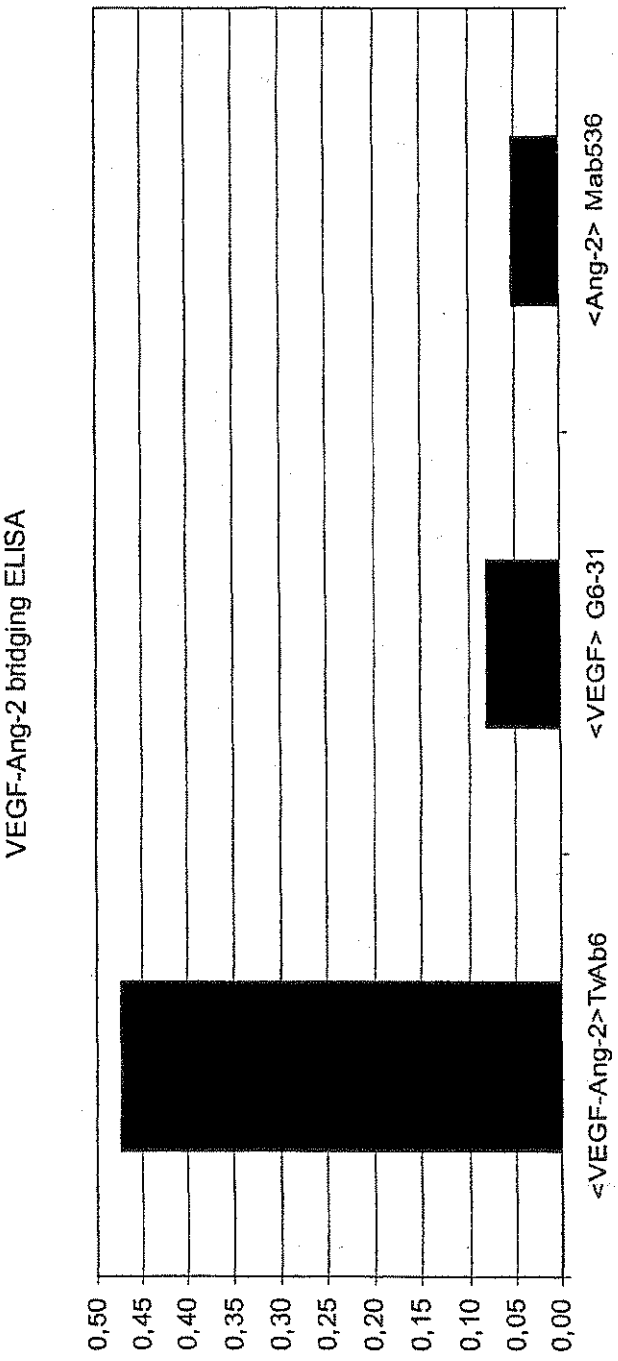


Figure 7–part two

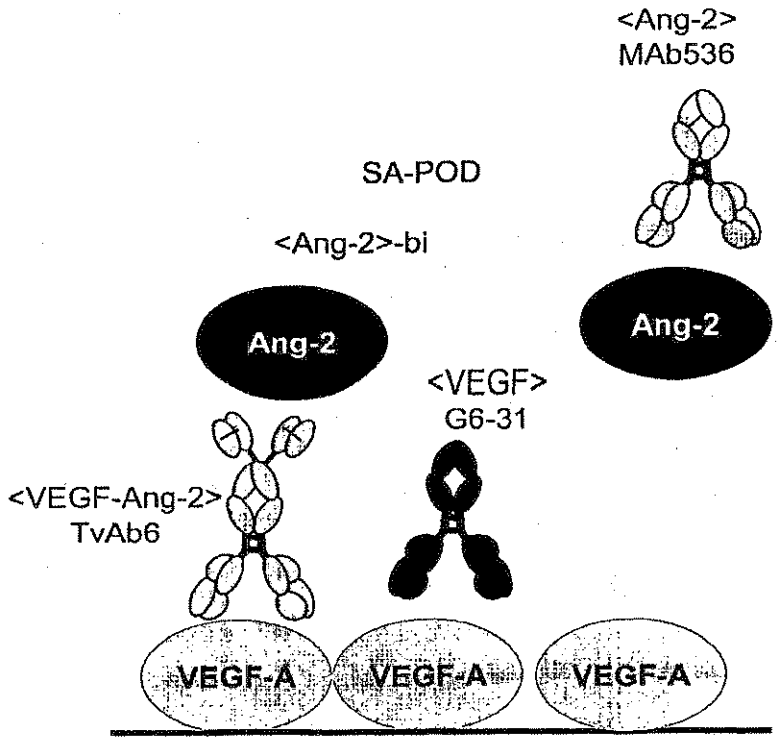


Figure 10A

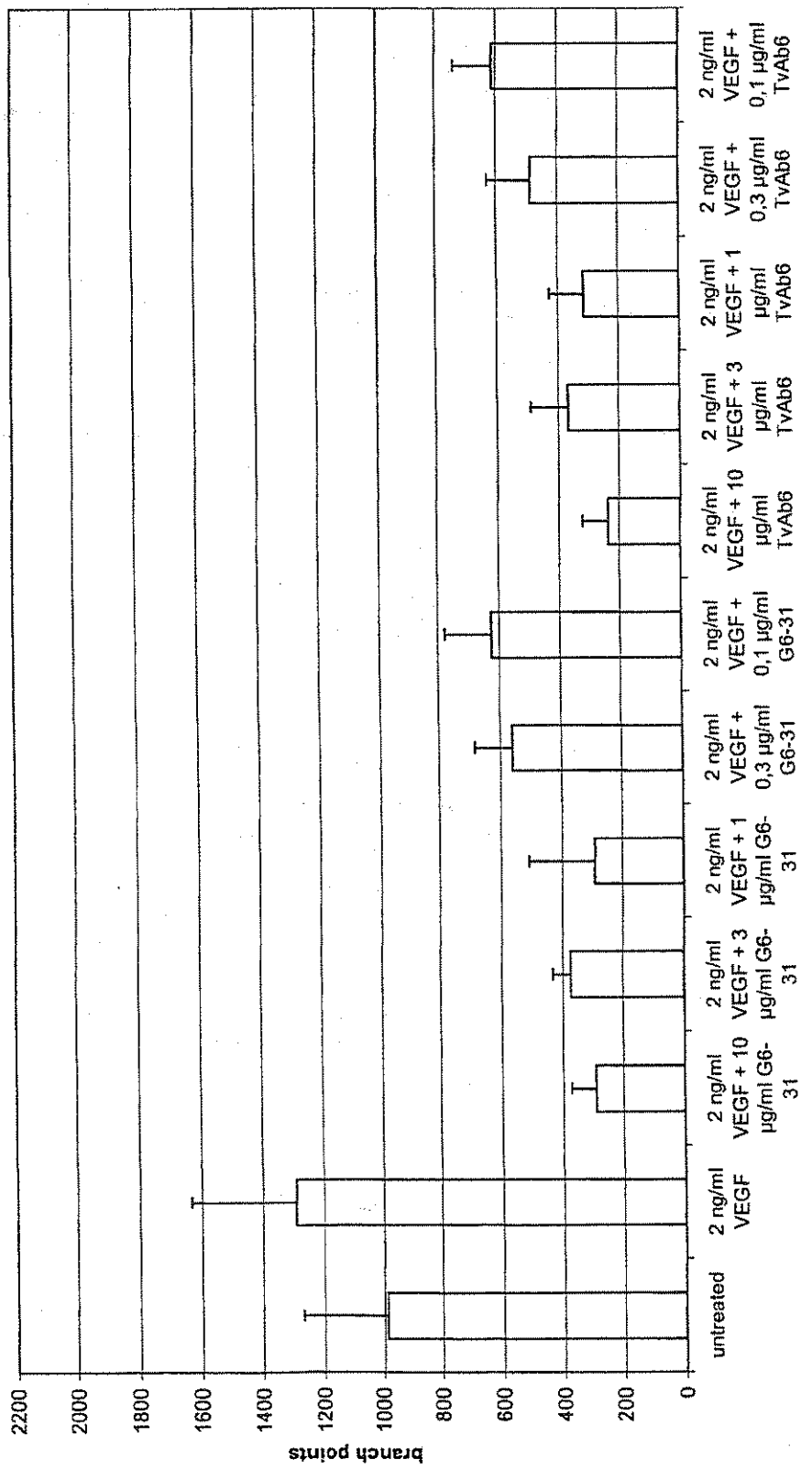

branch points
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
untreated
2 ng/ml VEGF
2 ng/ml VEGF + 10 µg/ml G6-31
2 ng/ml VEGF + 3 µg/ml G6-31
2 ng/ml VEGF + 1 µg/ml G6-31
2 ng/ml VEGF + 0,3 µg/ml G6-31
2 ng/ml VEGF + 0,1 µg/ml G6-31
2 ng/ml VEGF + 10 µg/ml TvAb6
2 ng/ml VEGF + 3 µg/ml TvAb6
2 ng/ml VEGF + 1 µg/ml TvAb6
2 ng/ml VEGF + 0,3 µg/ml TvAb6
2 ng/ml VEGF + 0,1 µg/ml TvAb6

Figure 10B

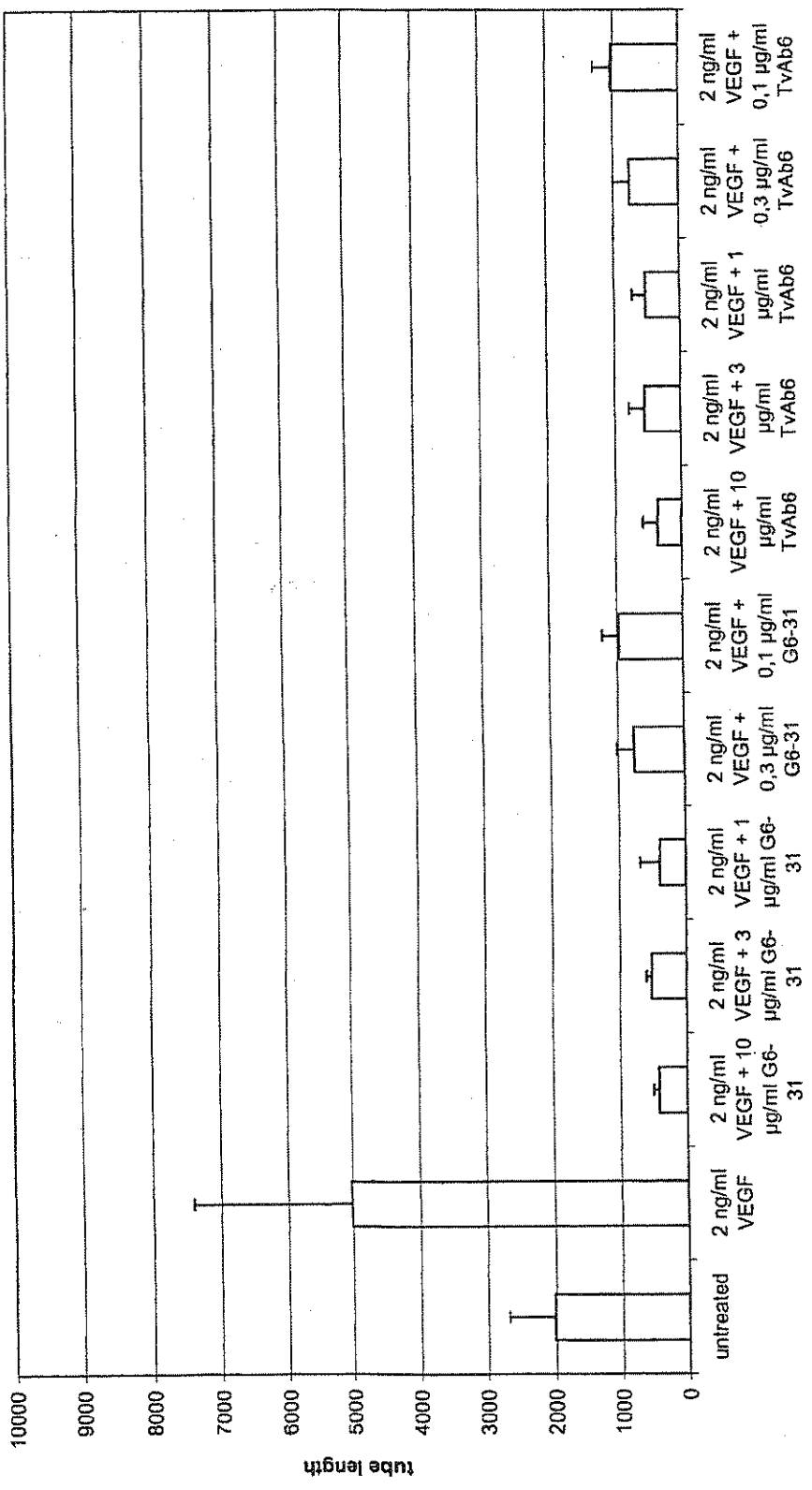

tube length per set
tube length
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
untreated
2 ng/ml VEGF
2 ng/ml VEGF + 10 µg/ml G6-31
2 ng/ml VEGF + 3 µg/ml G6-31
2 ng/ml VEGF + 1 µg/ml G6-31
2 ng/ml VEGF + 0,3 µg/ml G6-31
2 ng/ml VEGF + 0,1 µg/ml G6-31
2 ng/ml VEGF + 10 µg/ml TvAb6
2 ng/ml VEGF + 3 µg/ml TvAb6
2 ng/ml VEGF + 1 µg/ml TvAb6
2 ng/ml VEGF + 0,3 µg/ml TvAb6
2 ng/ml VEGF + 0,1 µg/ml TvAb6

Figure 11

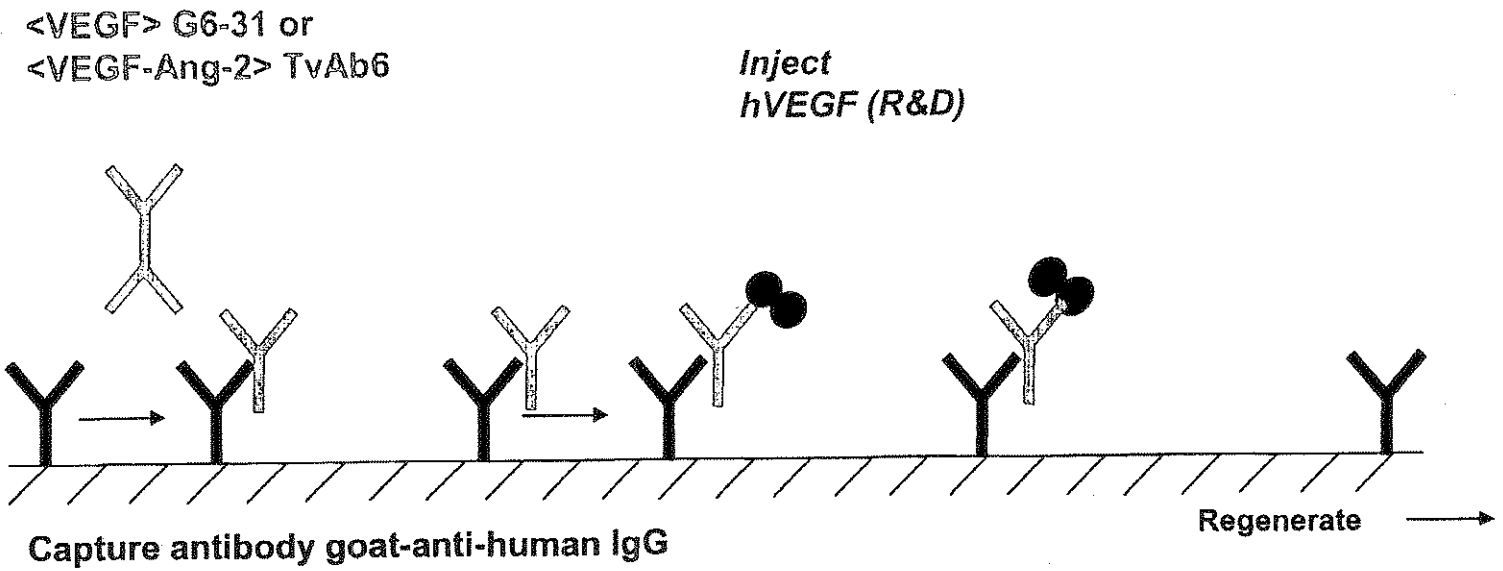

<VEGF> G6-31 or
<VEGF-Ang-2> TvAb6
Inject
hVEGF (R&D)
Capture antibody goat-anti-human IgG
Regenerate

Figure 12

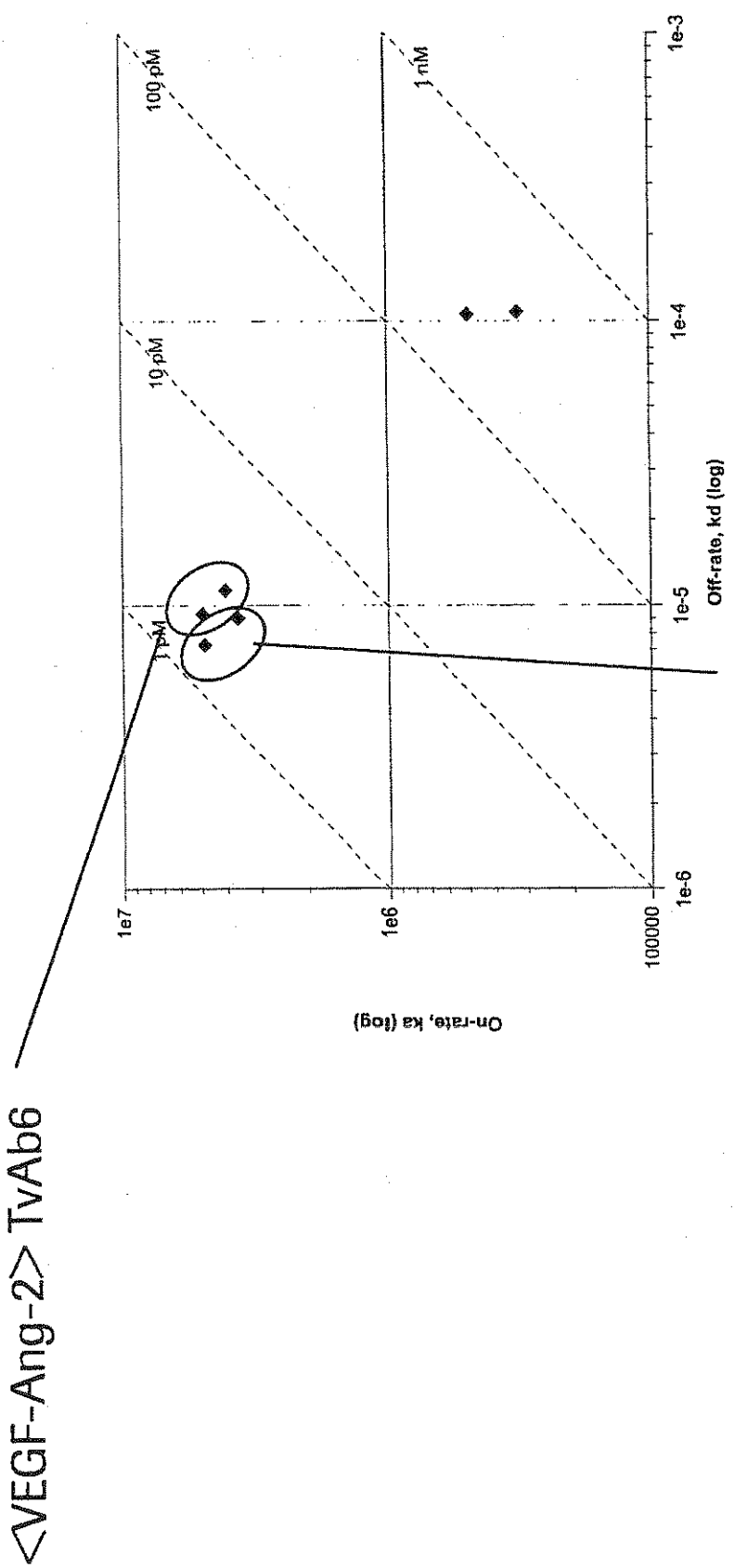

100 pM
1 nM
10 pM
1 pM
1e7
1e6
100000
1e-3
1e-4
1e-5
1e-6
On-rate, ka (log)
Off-rate, kd (log)
<VEGF-Ang-2> TvAb6
<VEGF> G6-31

Figure 13

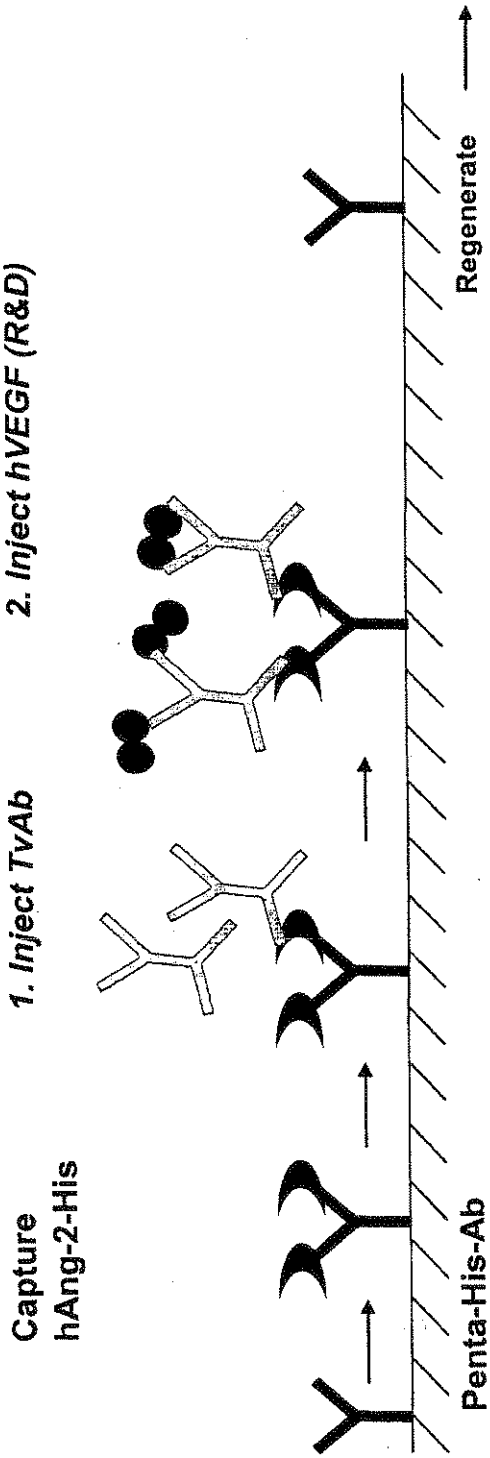

Capture
hAng-2-His
1. Inject TvAb
2. Inject hVEGF (R&D)
Regenerate
Penta-His-Ab
(Qiagen 34660)
CM5-Chip

Figure 14

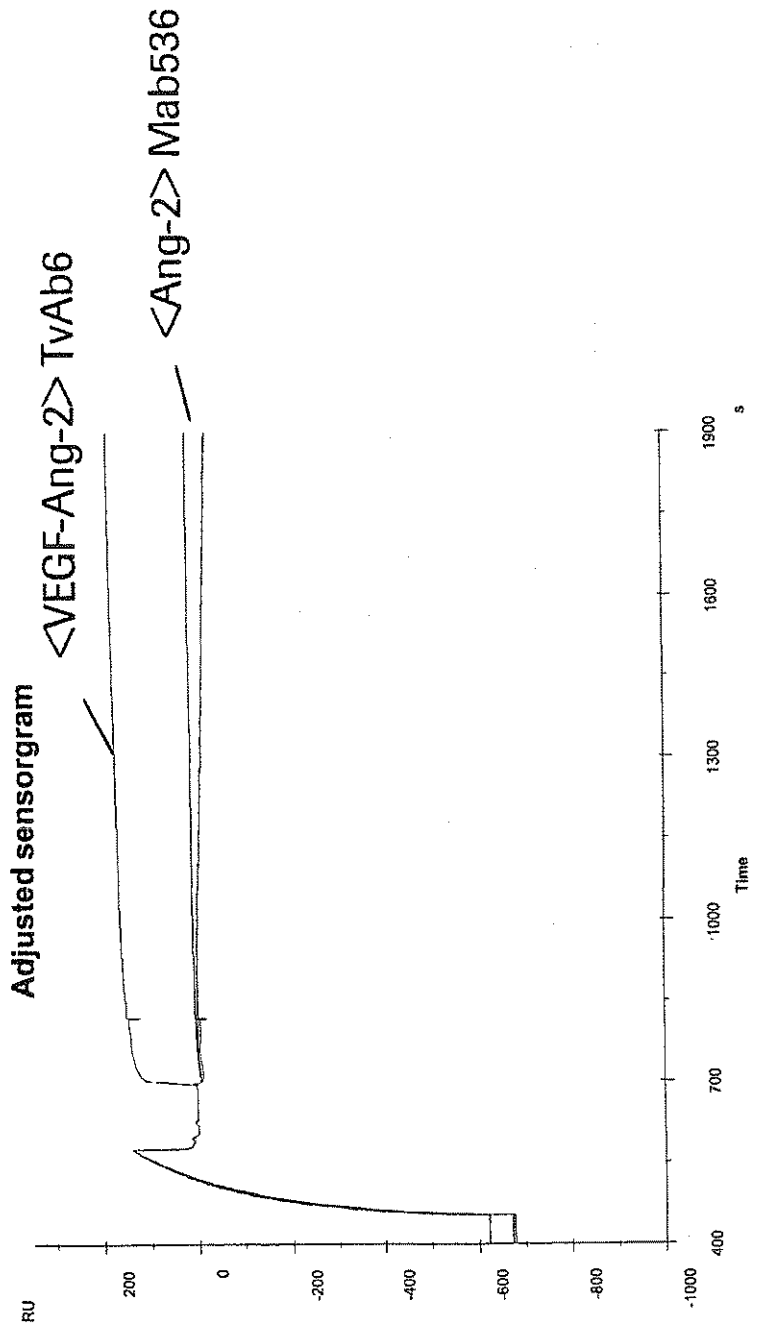

Adjusted sensorgram
<VEGF-Ang-2> TvAb6
<Ang-2> Mab536
RU
200
0
-200
-400
-600
-800
-1000
400
700
1000
1300
1600
1900
Time
s

Fig 15A

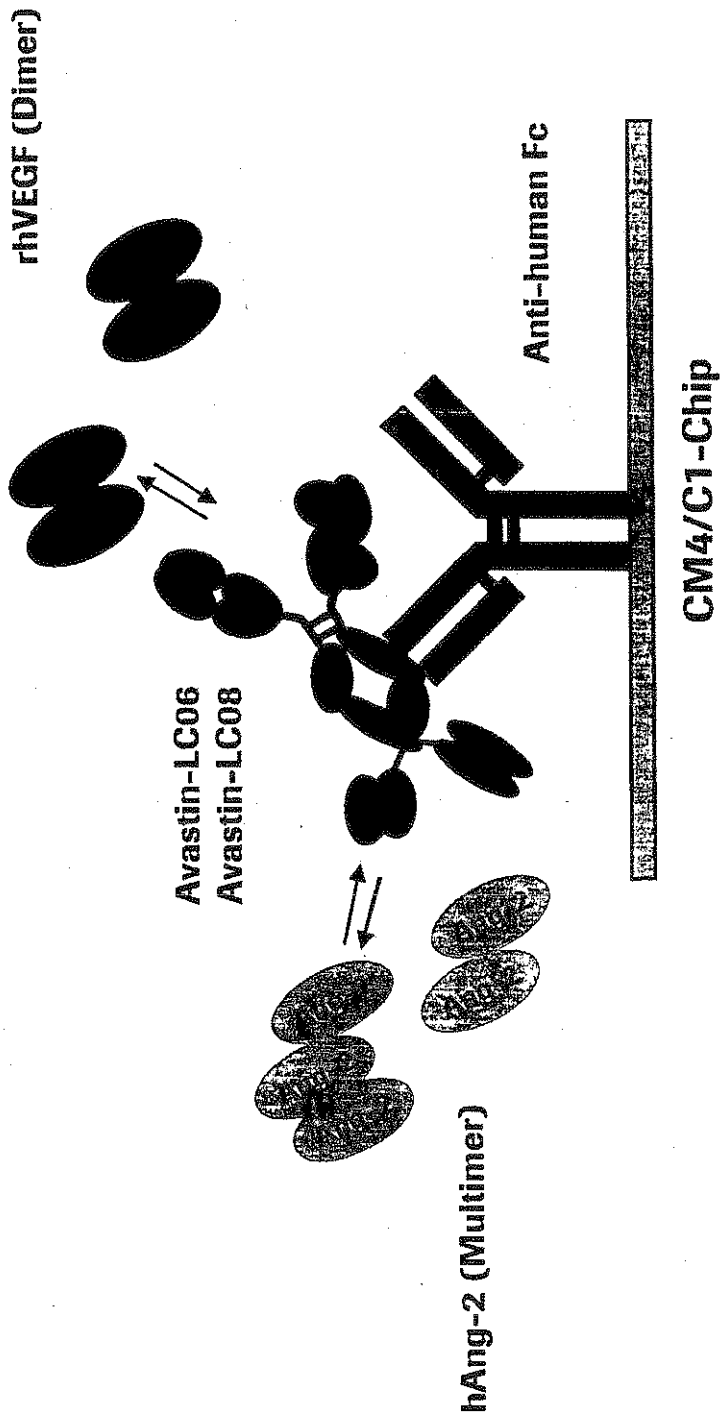

rhVEGF (Dimer)
Avastin-LC06
Avastin-LC08
Anti-human Fc
CM4/C1-Chip
hAng-2 (Multimer)

Fig 15B

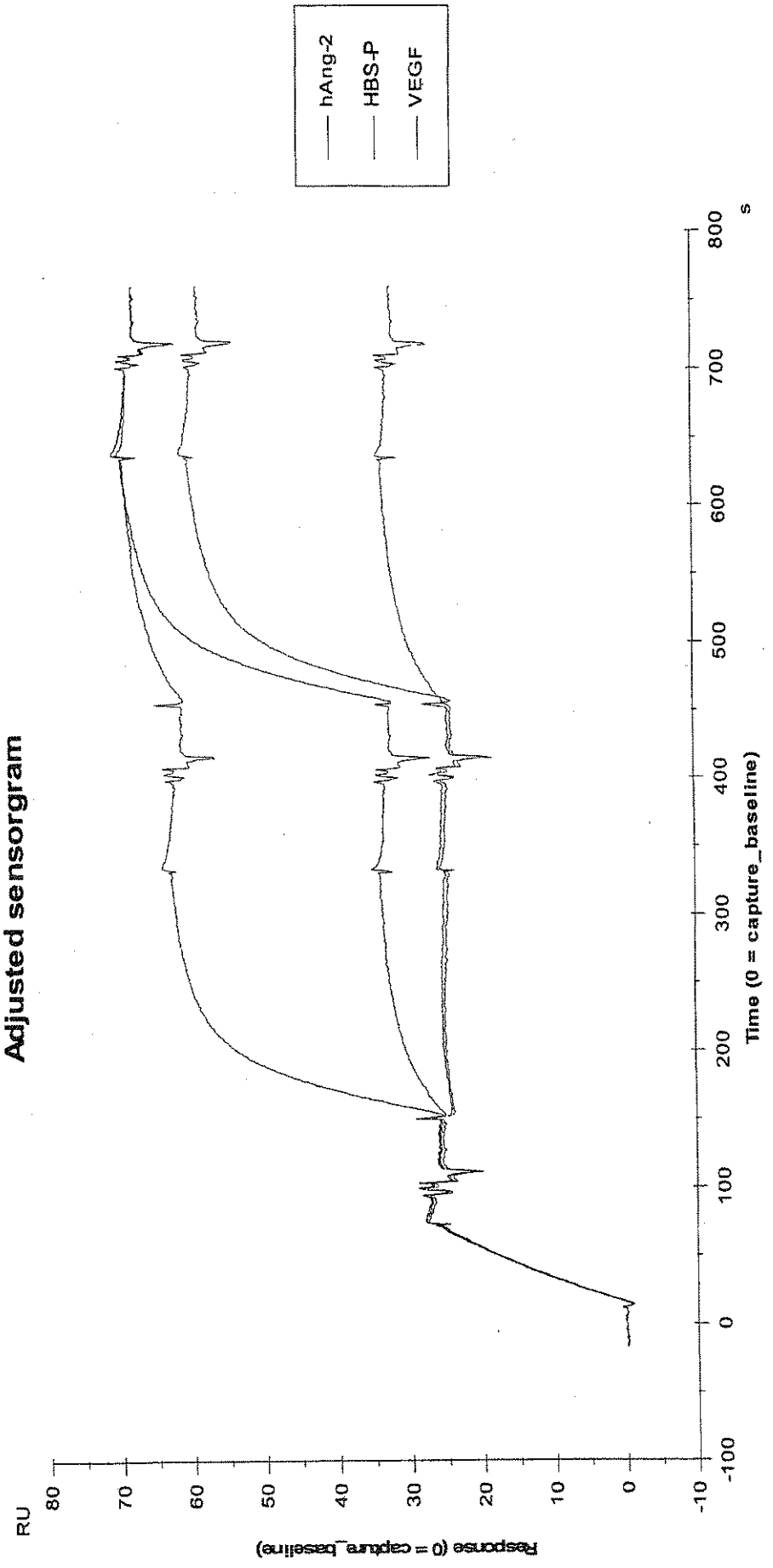

Adjusted sensorgram
RU
Response (0 = capture_baseline)
80
70
60
50
40
30
20
10
0
-10
-100
0
100
200
300
400
500
600
700
800
s
Time (0 = capture_baseline)
hAng-2
HBS-P
VEGF

Fig 16A

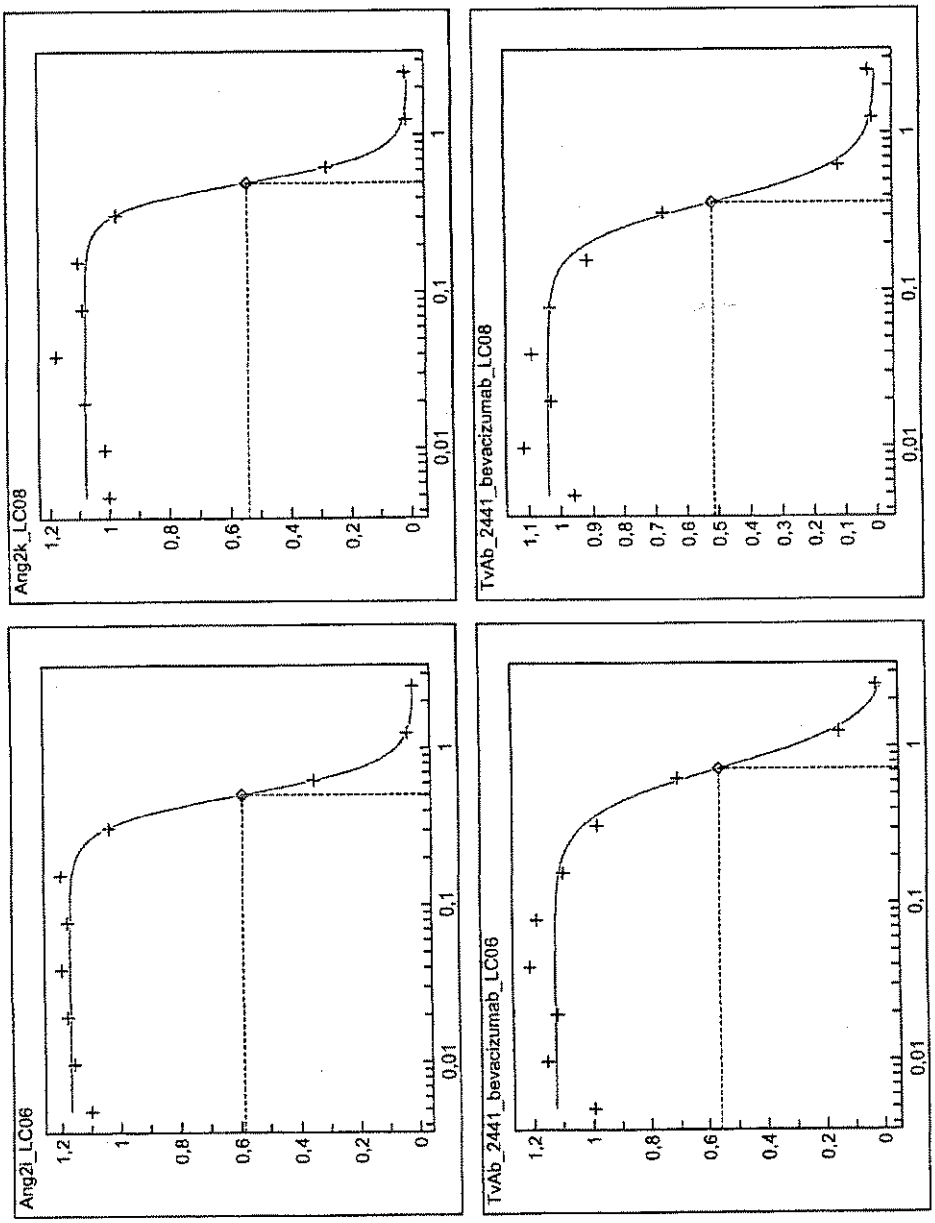

Ang2k_LC08
Ang2i_LC06
TvAb_2441_bevacizumab_LC08
TvAb_2441_bevacizumab_LC06

Fig 16B

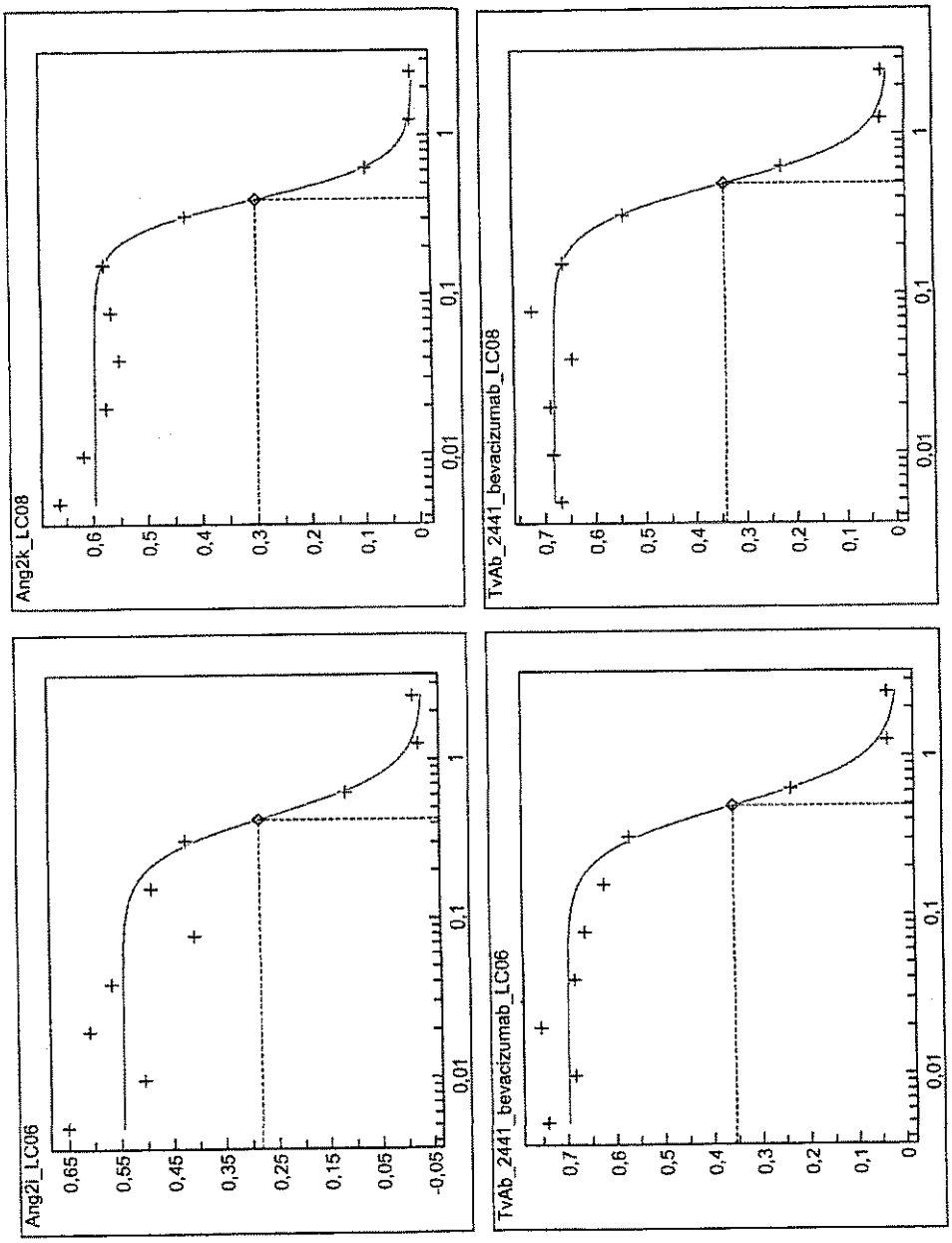

Ang2k_LC08
TvAb_2441_bevacizumab_LC08
Ang2l_LC06
TvAb_2441_bevacizumab_LC06

Fig 17

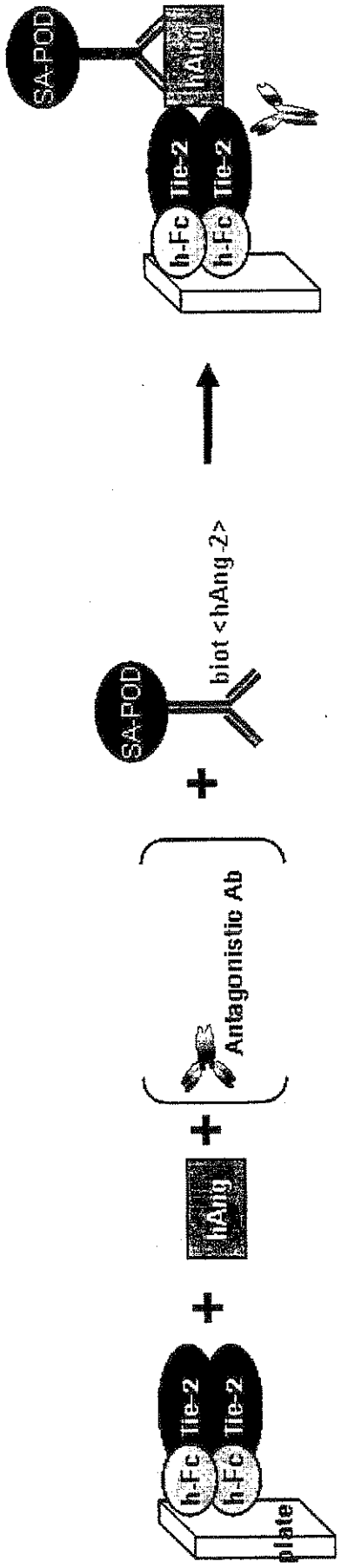

SA-POD
hAng
Tie-2
Tie-2
h-Fc
h-Fc
plate
hAng
Antagonistic Ab
SA-POD
biot <hAng-2>
SA-POD
hAng
Tie-2
Tie-2
h-Fc
h-Fc

Fig 18

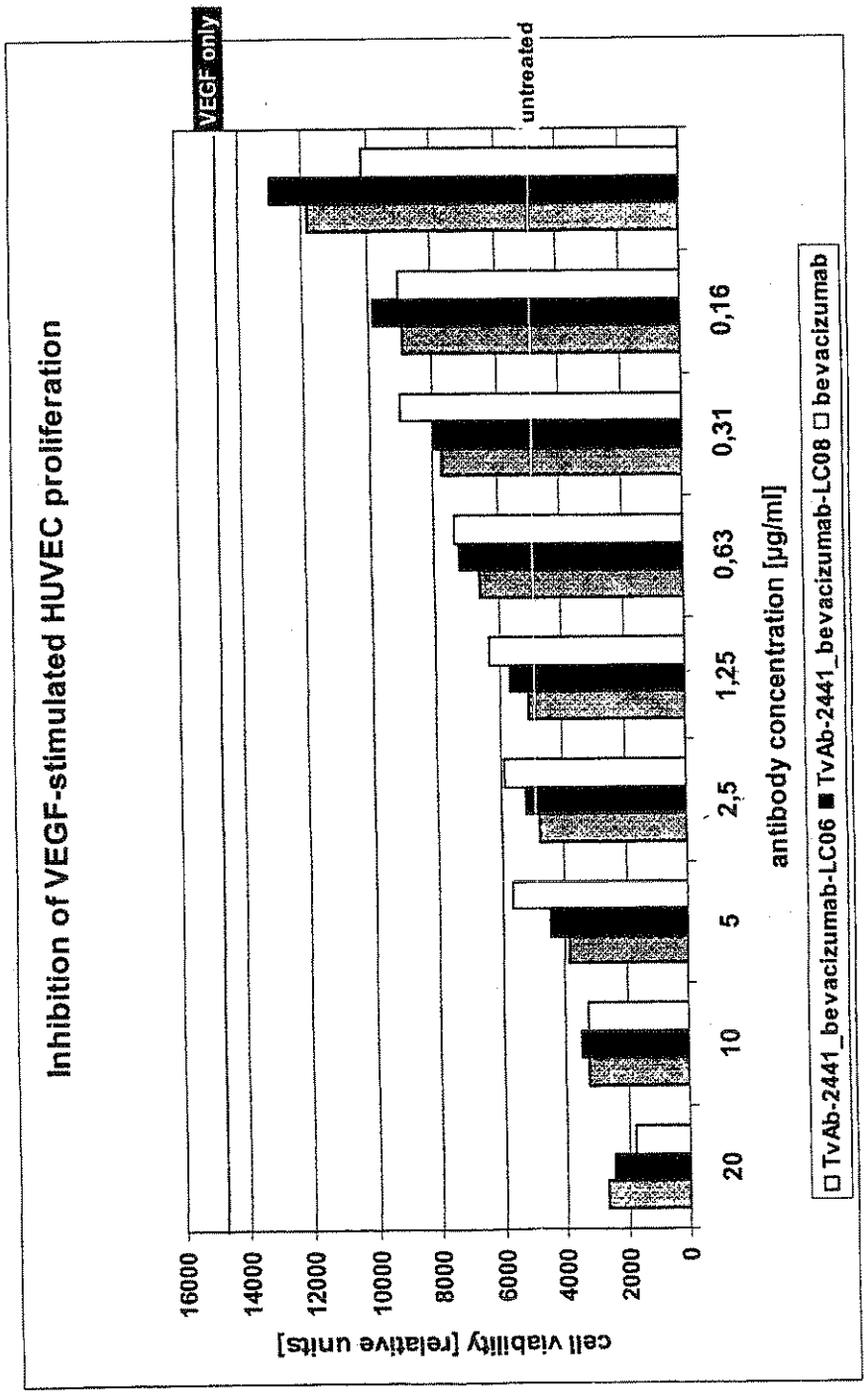
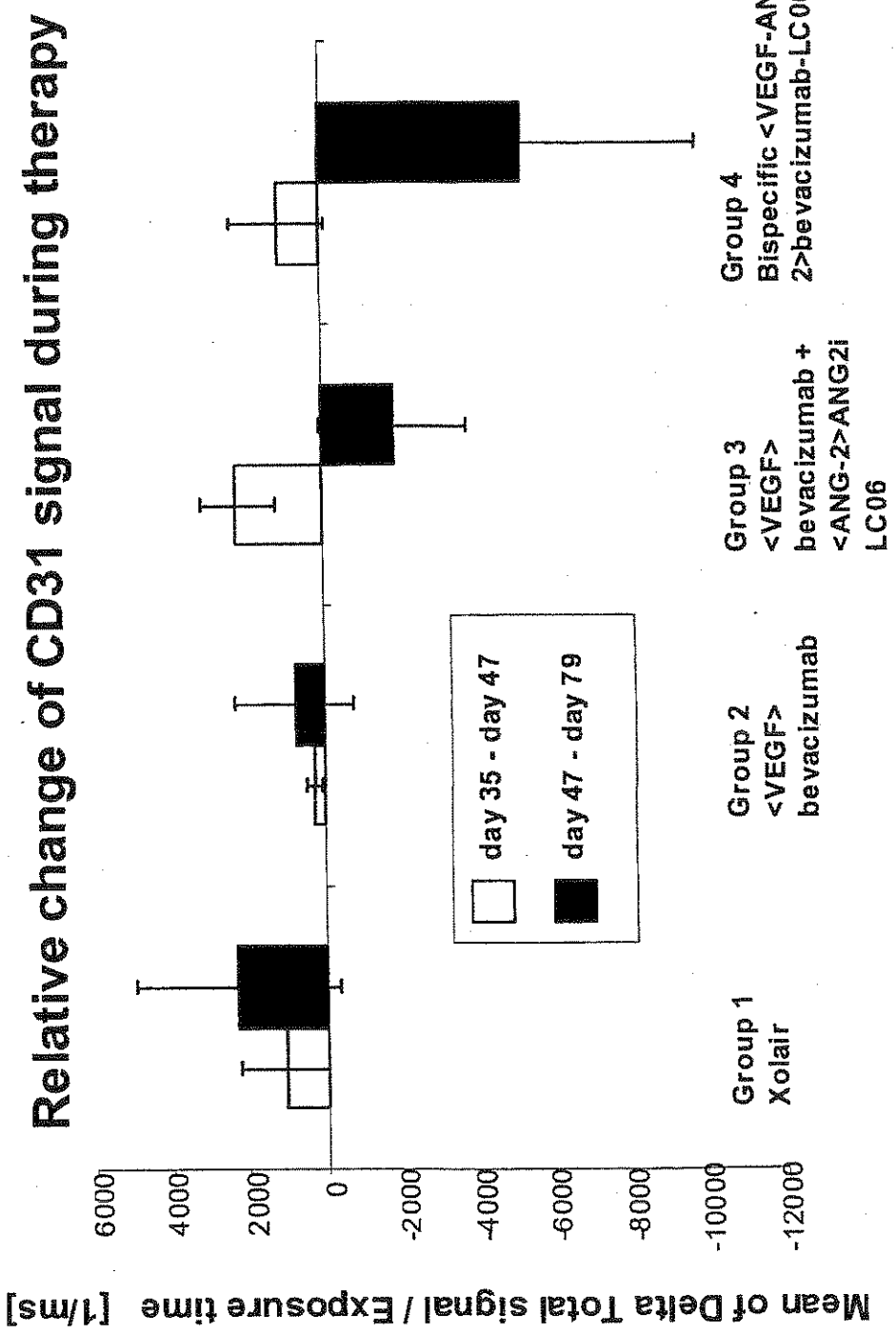

Inhibition of VEGF-stimulated HUVEC proliferation
VEGF only
untreated
cell viability [relative units]
16000
14000
12000
10000
8000
6000
4000
2000
0
20
10
5
2,5
1,25
0,63
0,31
0,16
antibody concentration [µg/ml]
TvAb-2441_bevacizumab-LC06
TvAb-2441_bevacizumab-LC08
bevacizumab

Fig 19


Relative change of CD31 signal during therapy
Mean of Delta Total signal / Exposure time [1/ms]
6000
4000
2000
0
-2000
-4000
-6000
-8000
-10000
-12000
day 35 - day 47
day 47 - day 79
Group 1
Xolair
Group 2
<VEGF>
bevacizumab
Group 3
<VEGF>
bevacizumab +
<ANG-2>ANG2i
LC06
Group 4
Bispecific <VEGF-ANG-2>bevacizumab-LC06