

VPPGEDSKDVAAPHIRQPLTSSERIDKQRYILDGISALRKETCNKSNMCESSKEALAENNINLPKMAEKDG
CFQSGFNEETCLVKHHGLIEFEVYLEYLQNRJESSEEQARA VQMSTKVLJQFLQKKAKNLDAITTPIPTTN
ASLLTKLQANQWLQDMTHILILRSFKFELQSSLRALRQM (SEQ ID NO: 1)

FIG. 1

2/135

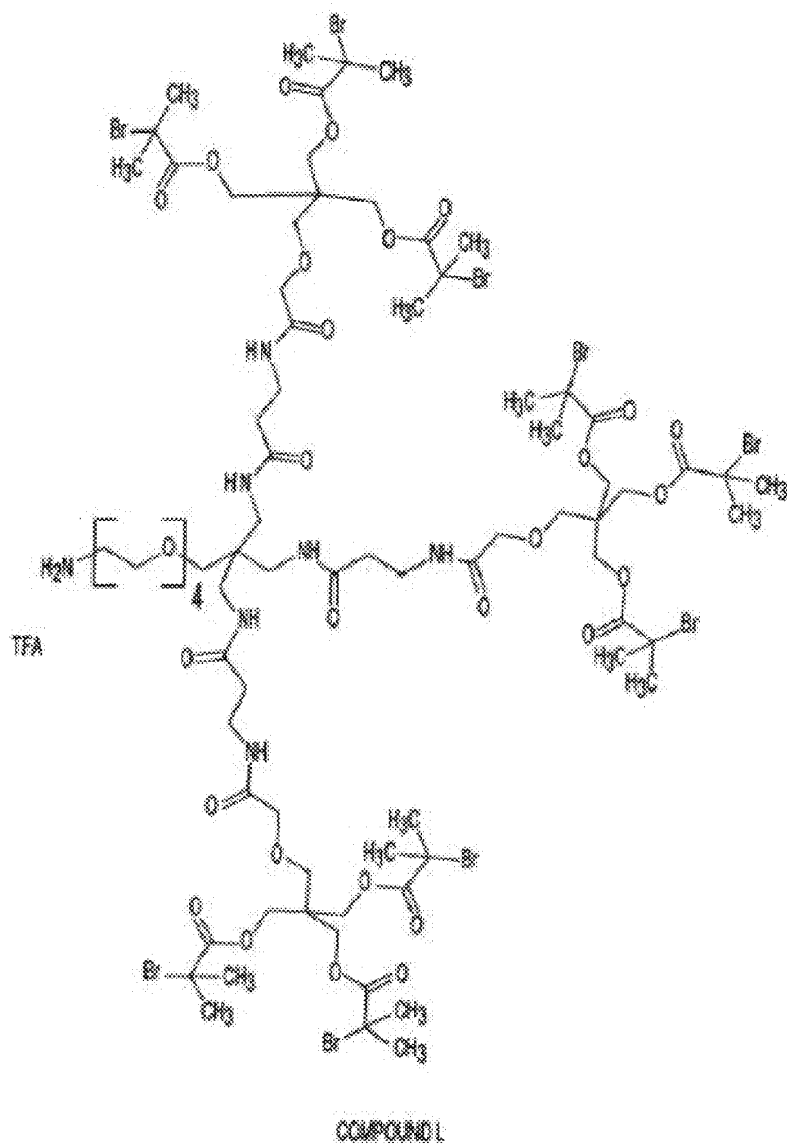
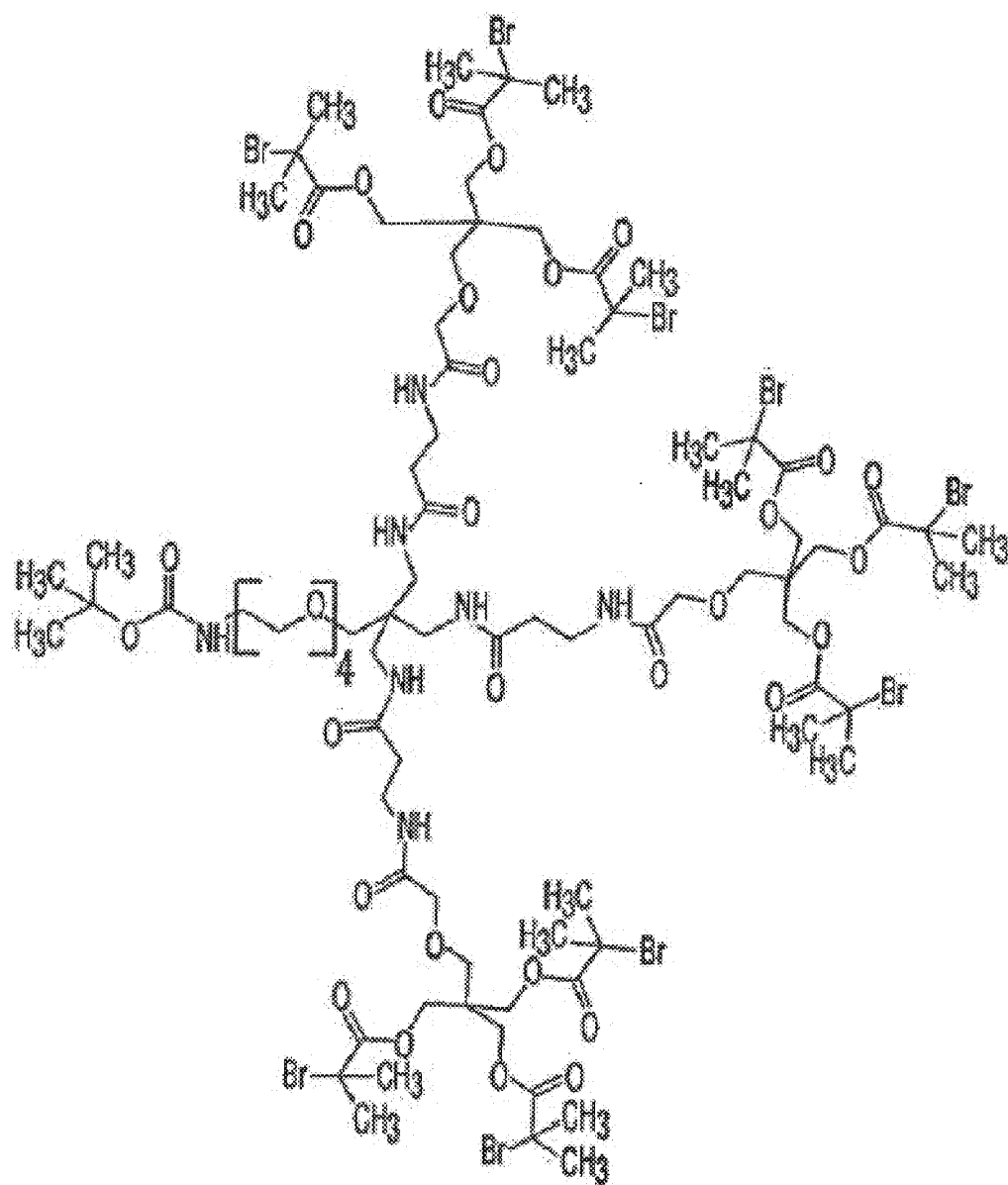


FIG. 2A

3/135



COMPOUND K

FIG. 2B

4/135

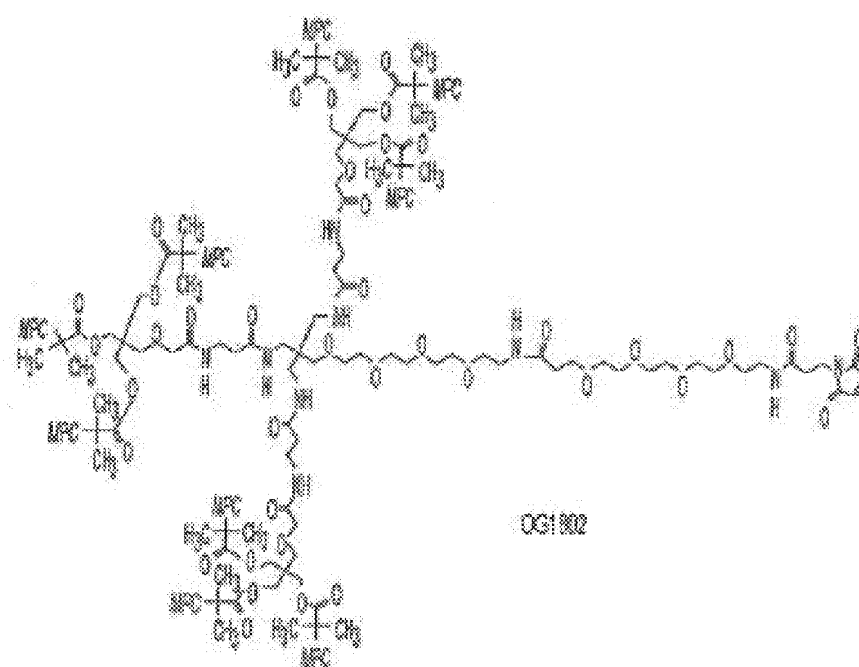
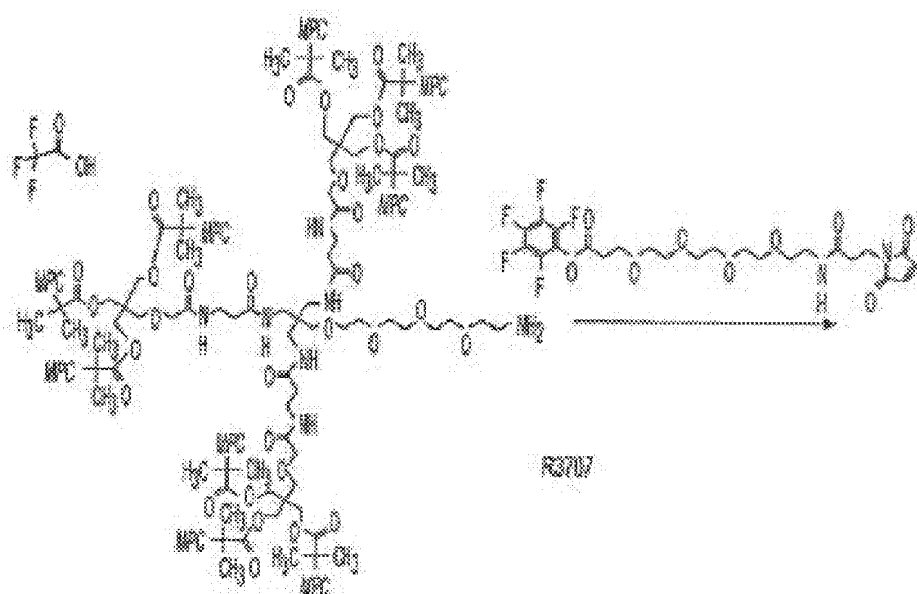
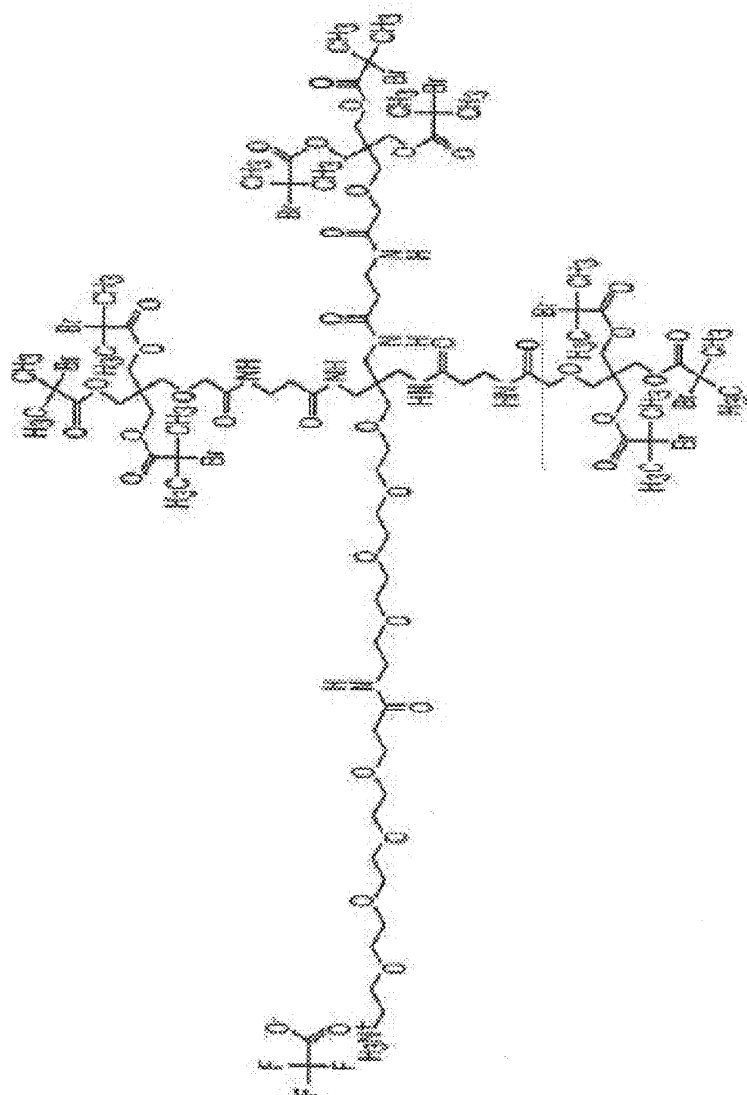


FIG. 2C

5/135



CG1786

FIG. 2D

6/135

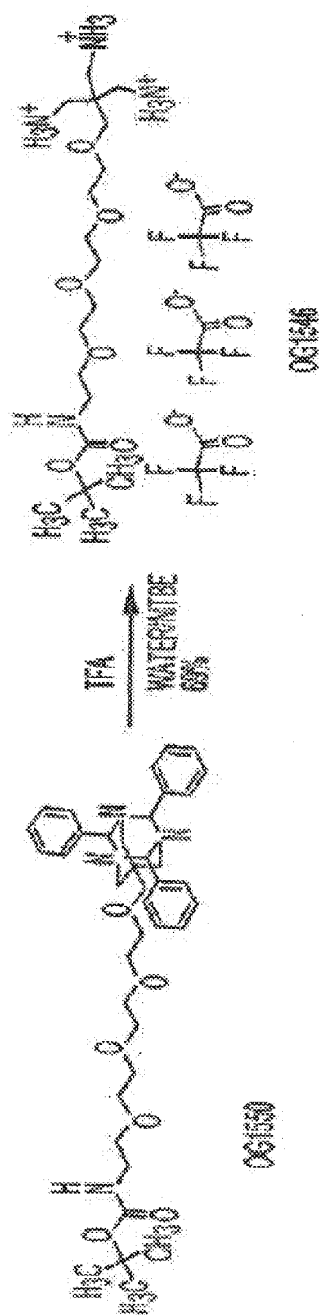


FIG. 2E

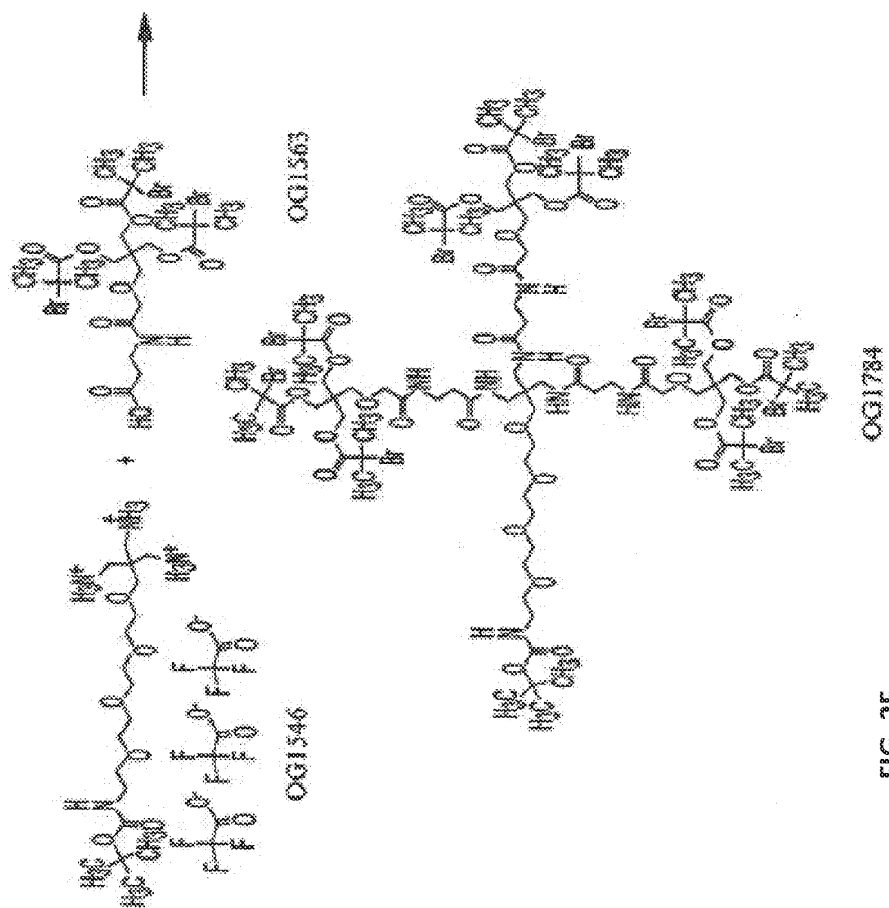


FIG. 2F

8/135

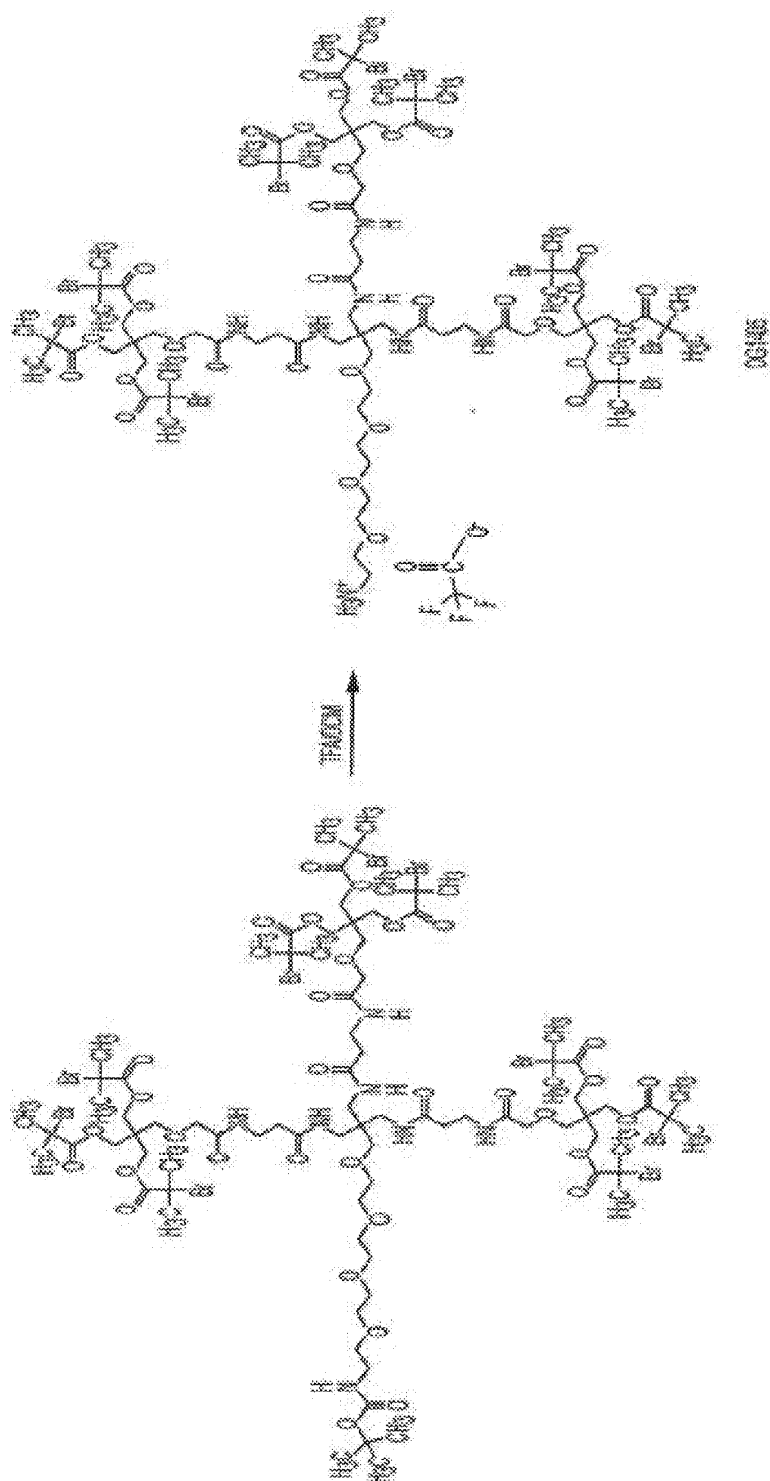


FIG. 2G

9/135

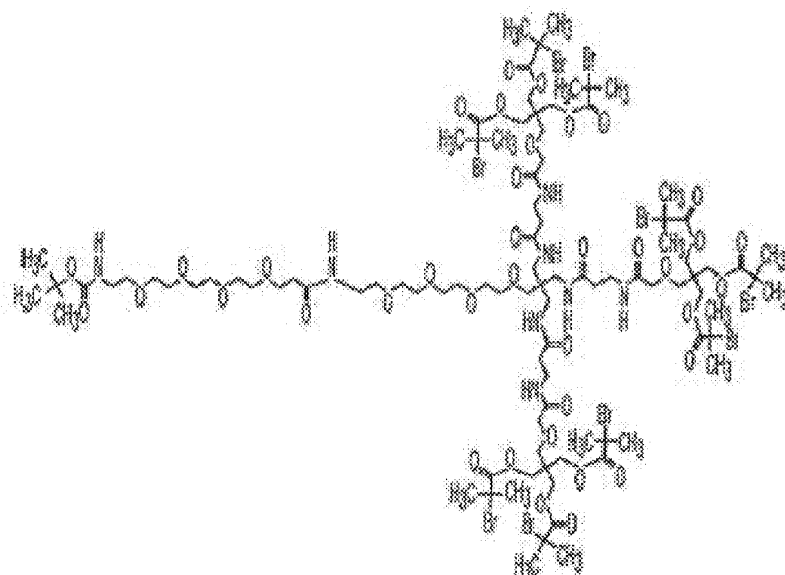
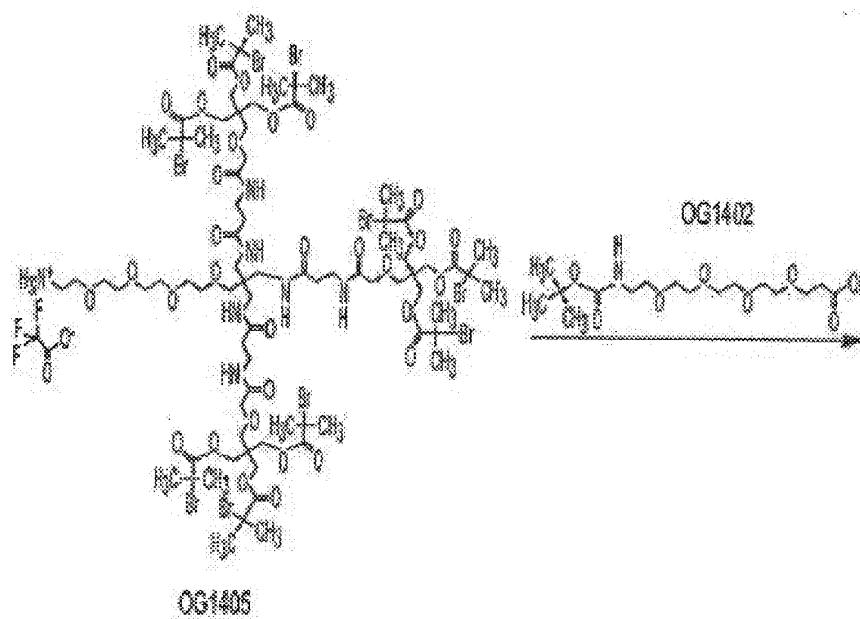


FIG. 2H

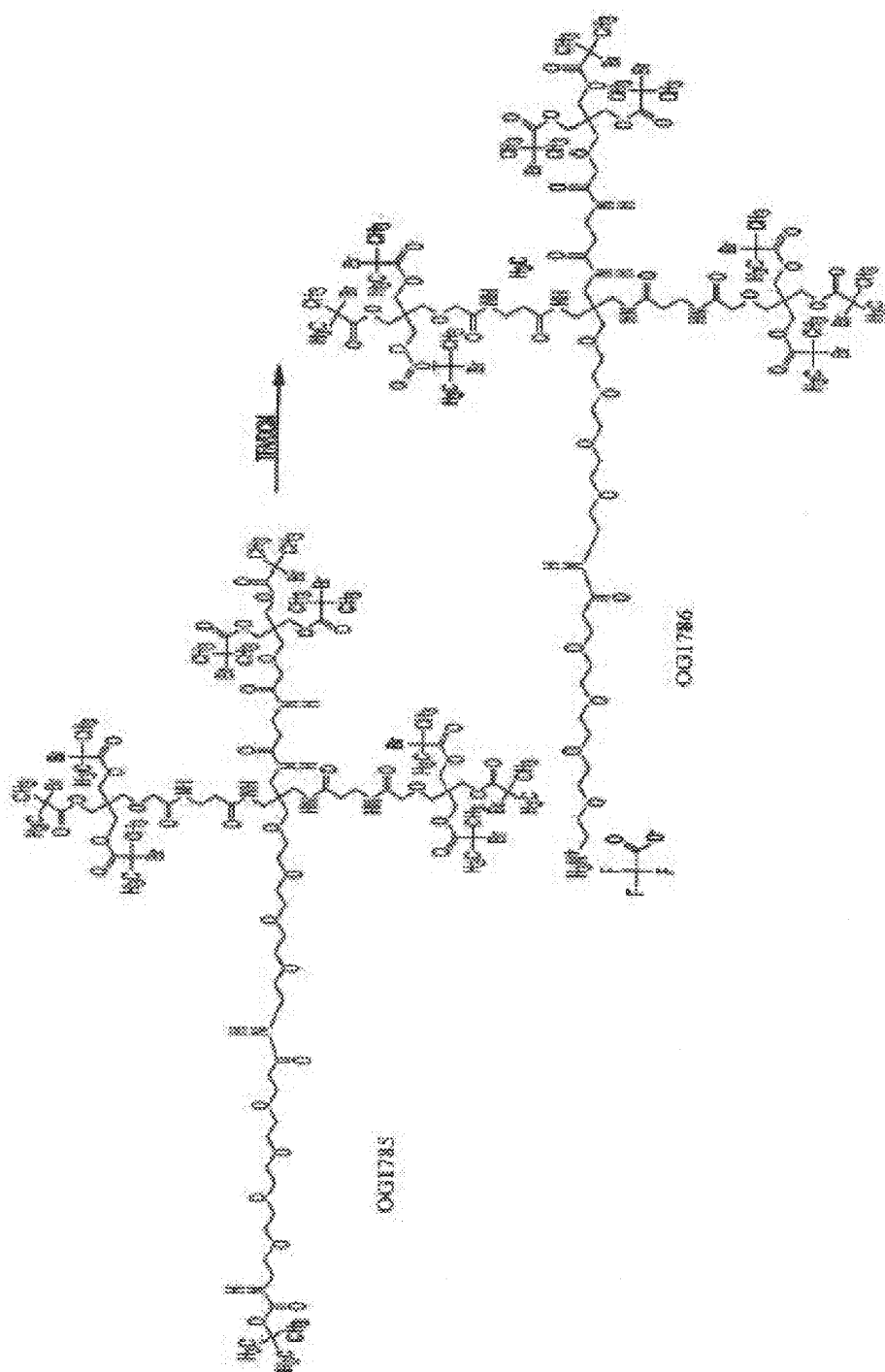
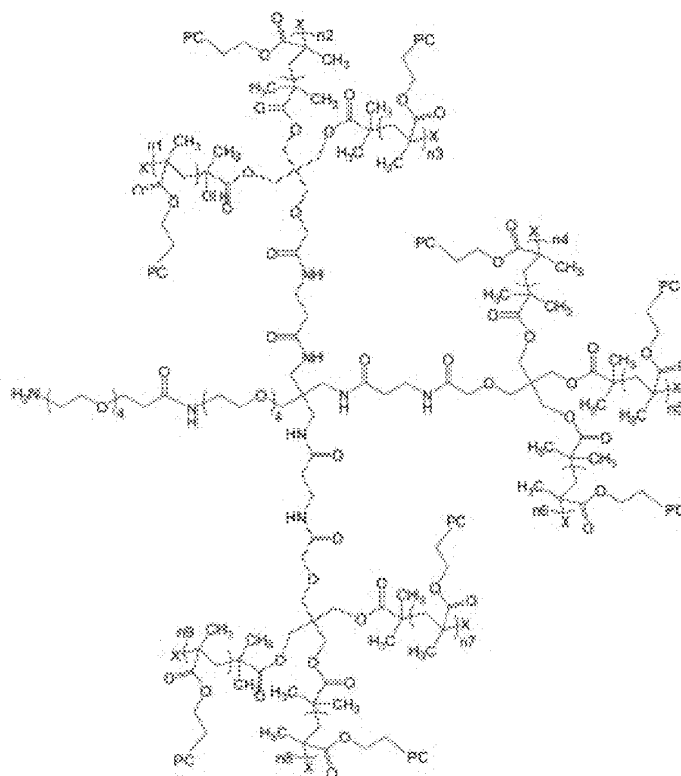


FIG. 21

11/135

OG1801



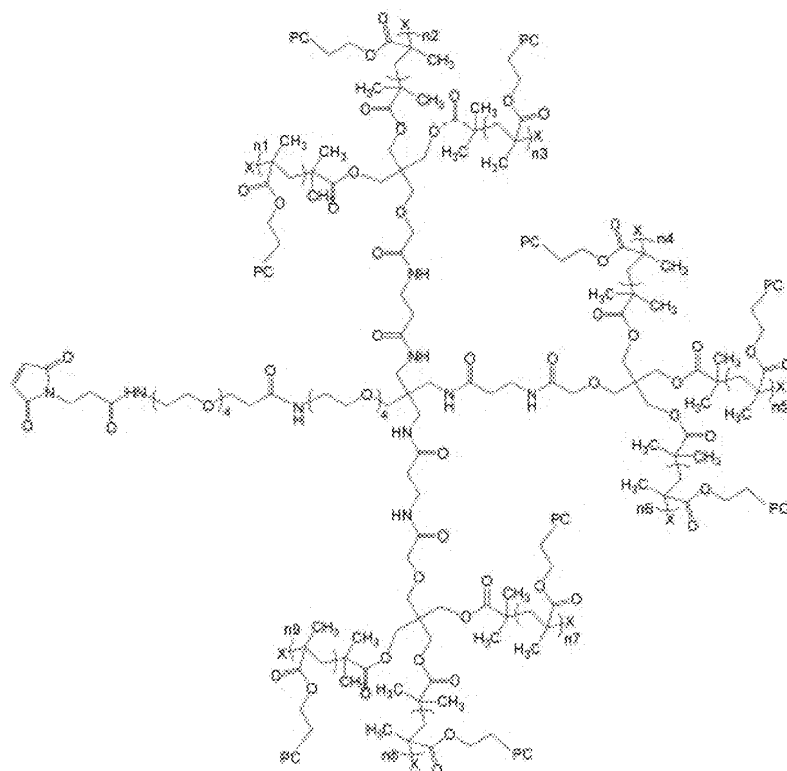
PC =



X=a) OR where R=H, methyl, ethyl, propyl, isopropyl, b) H, or c) any halide, including Br
 n1, n2, n3, n4, n5, n6, n7, n8 and n9 are the same or different such that the sum of n1, n2, n3, n4, n5, n6,
 n8, n7, n8 and n9 is 2500 plus or minus 15%.

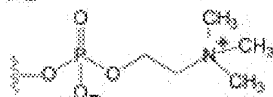
FIG. 2J

OG1802



Definitions:

PC =



X=a) OR where R=H, methyl, ethyl, propyl, isopropyl, b) H, or c) any halide, including Br

n1, n2, n3, n4, n5, n6, n7, n8 and n9 are the same or different such that the sum of n1, n2, n3, n4, n5, n6, n7, n8 and n9 is 2500 plus or minus 15%.

FIG. 2K

13/135

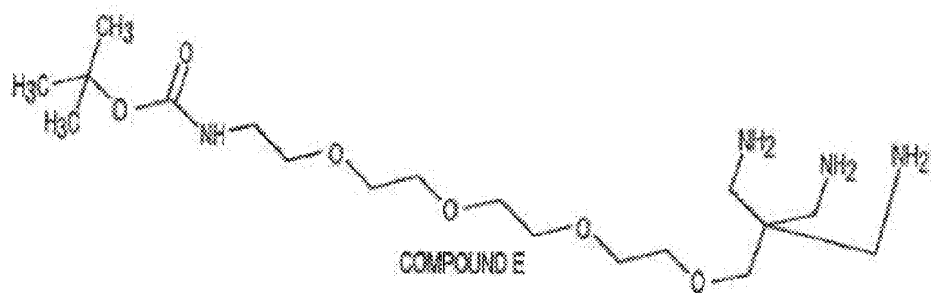


FIG. 2L

14/135

Generate library of randomized single-point mutations (except Met, Cys, and Asn) for putative CDR positions (total of 71).



Select single point mutations that display similar or improved k_{off} in comparison to the wild-type and introduce into mammalian system.



Validate IL-6 binding and antibody expression/stability.



Combine selected mutations into final construct.

FIG. 3

IL6/IL6R complex formation is inhibited by anti-IL6 mAb

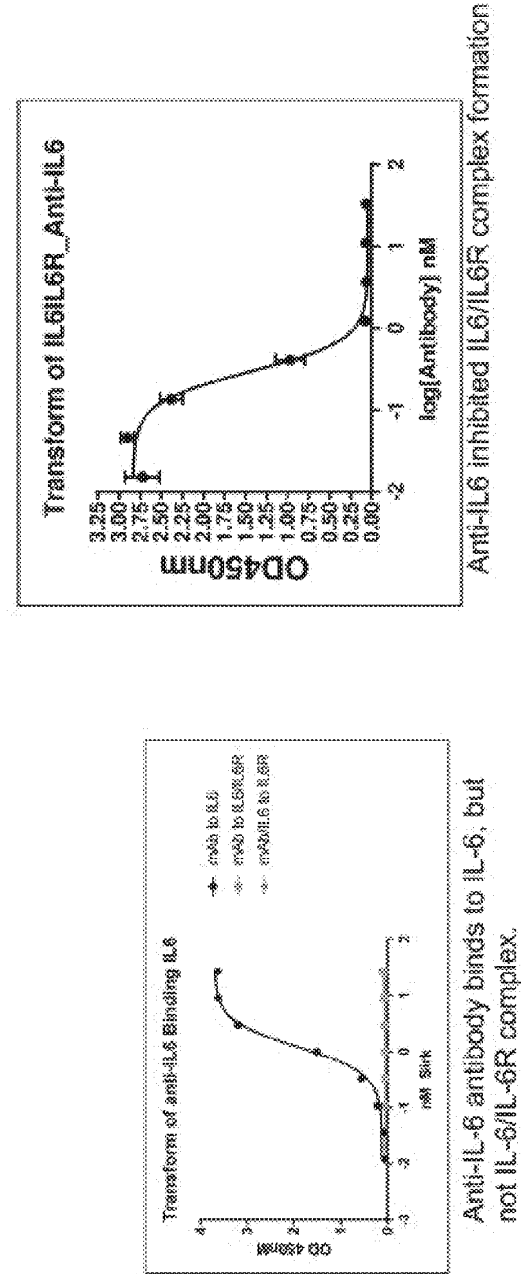


FIG. 4

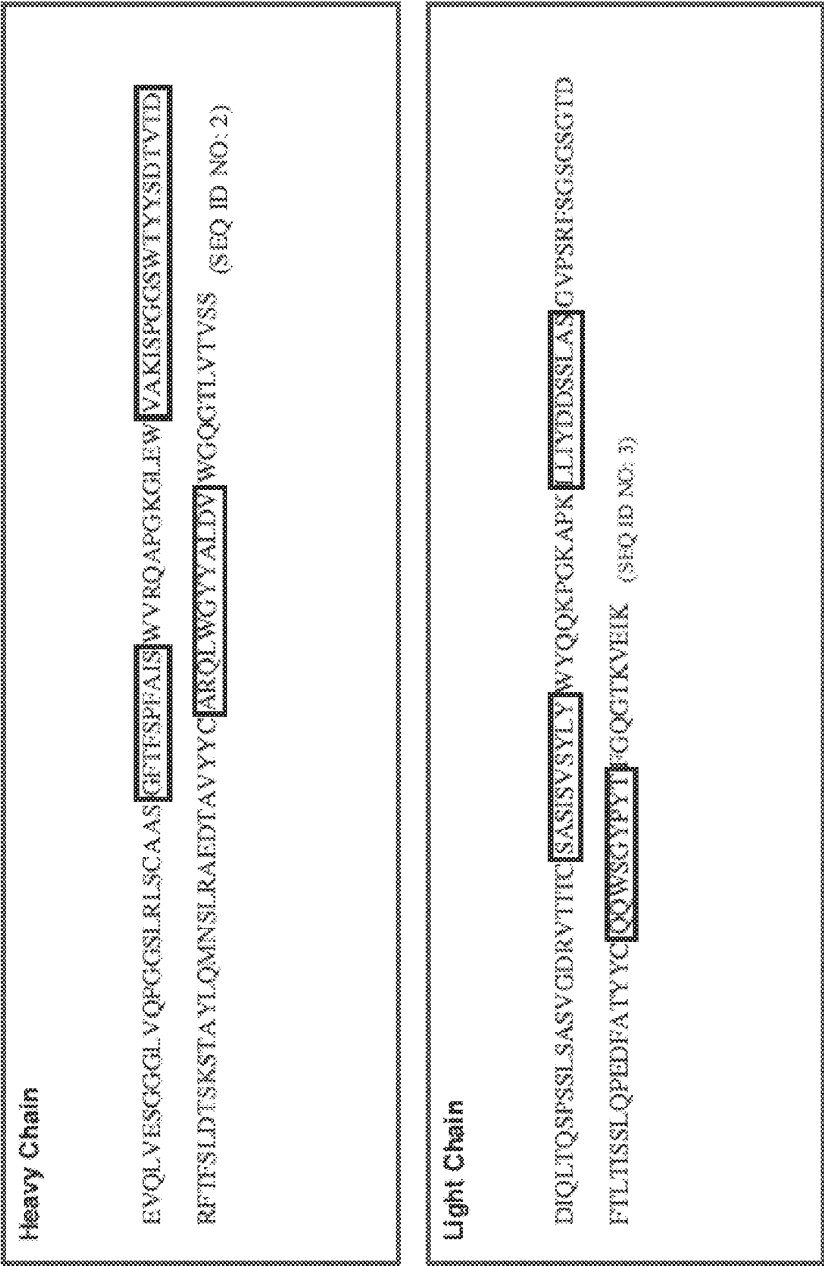


FIG. 5

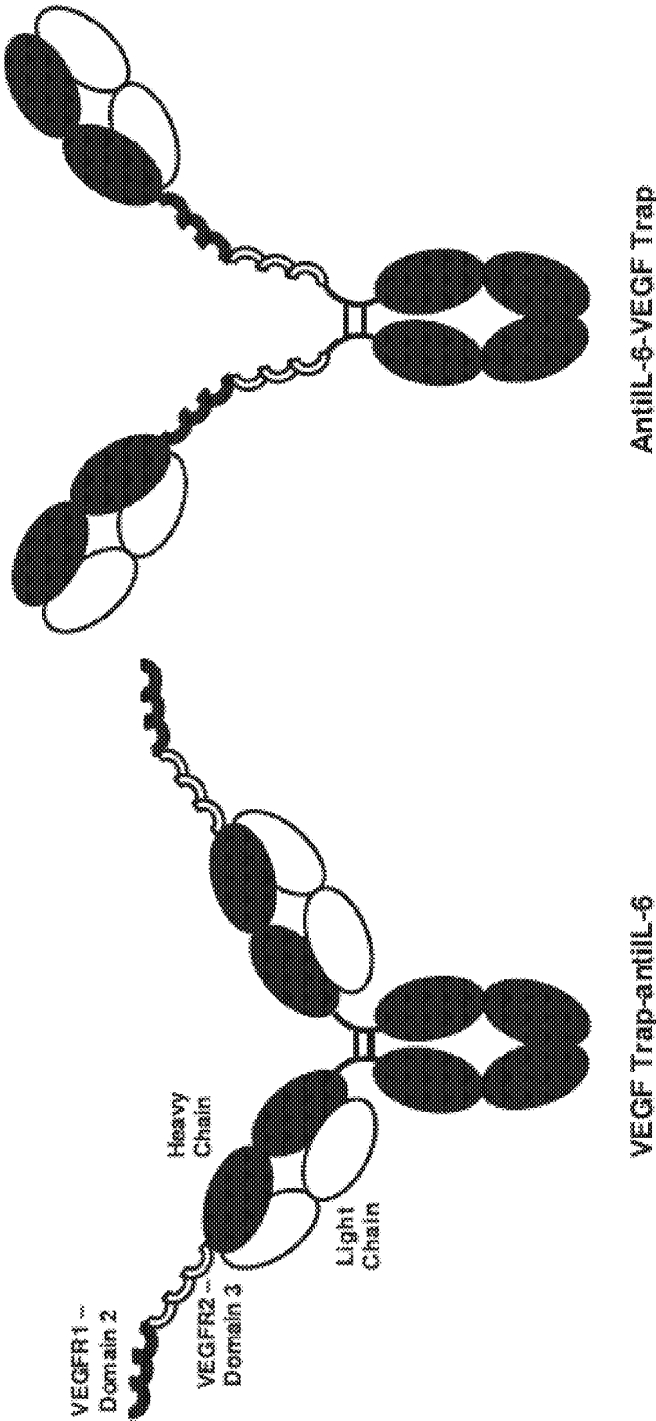


FIG. 6

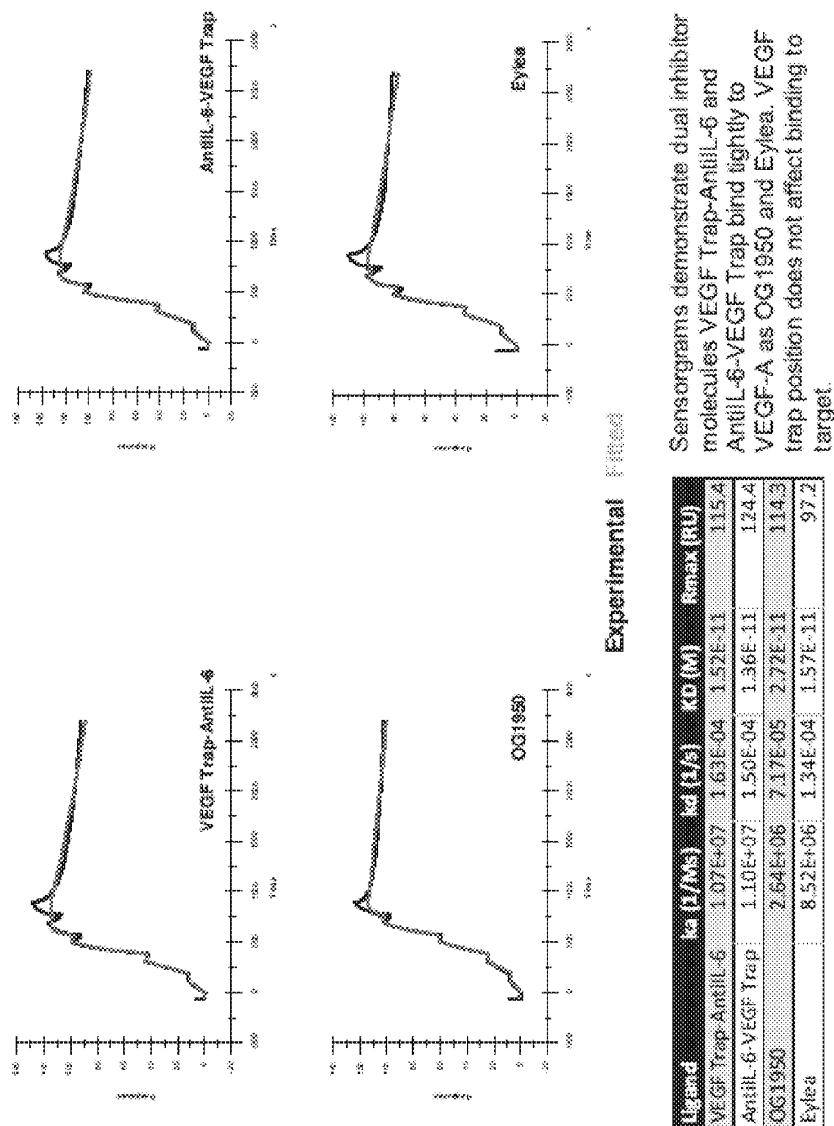


FIG. 7

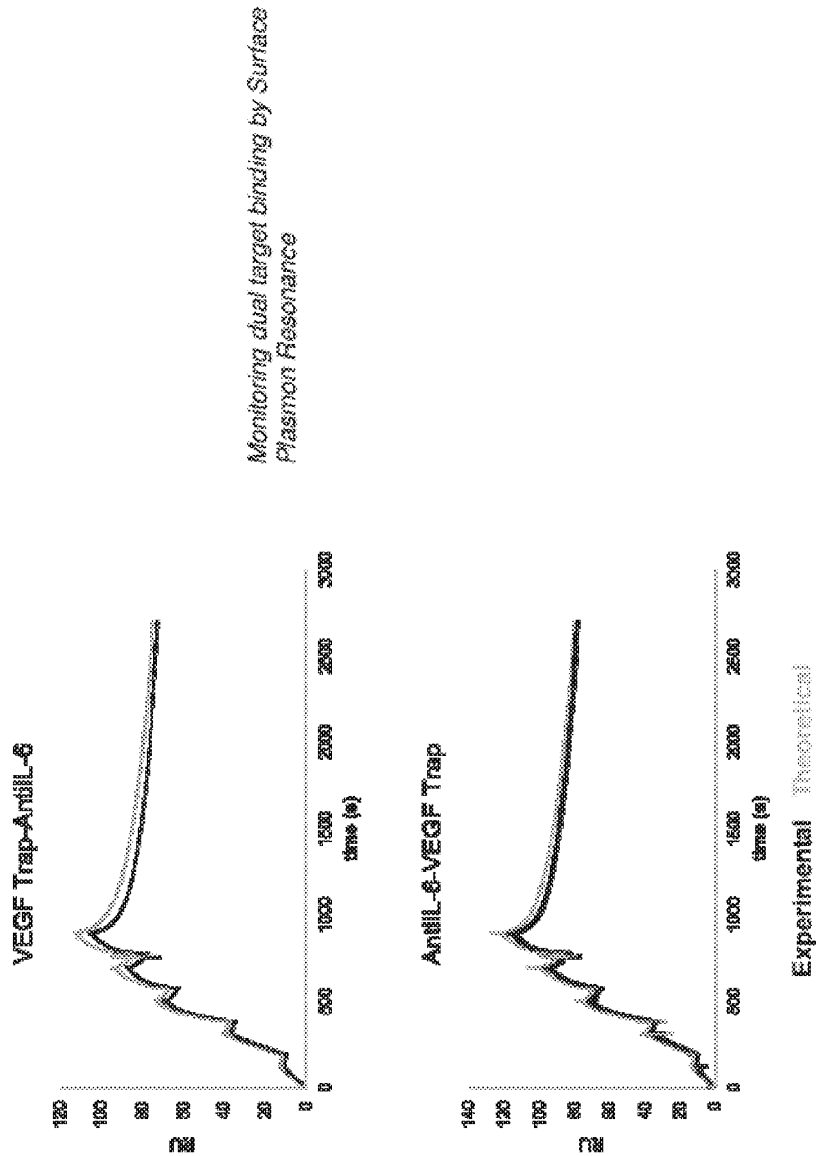


FIG. 8

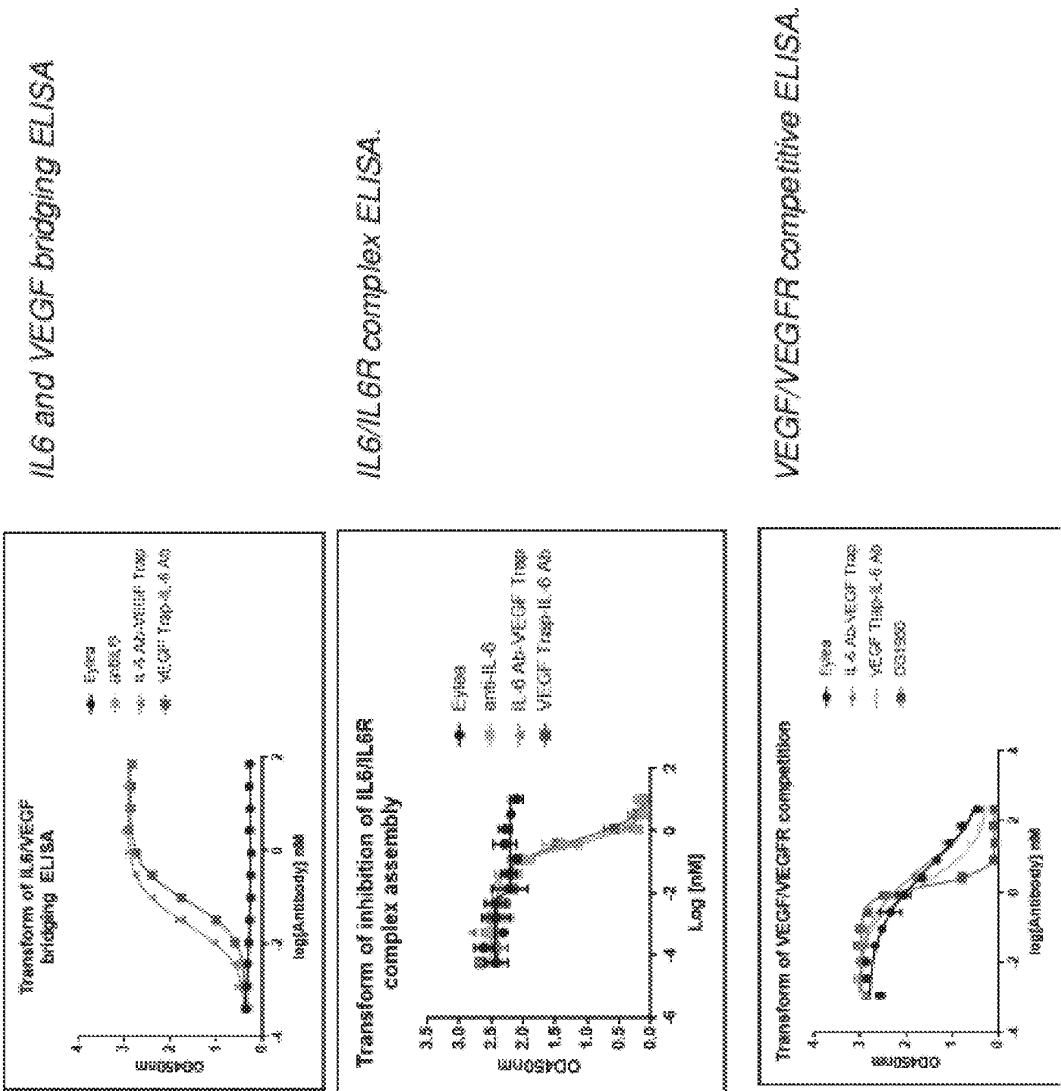


FIG. 9

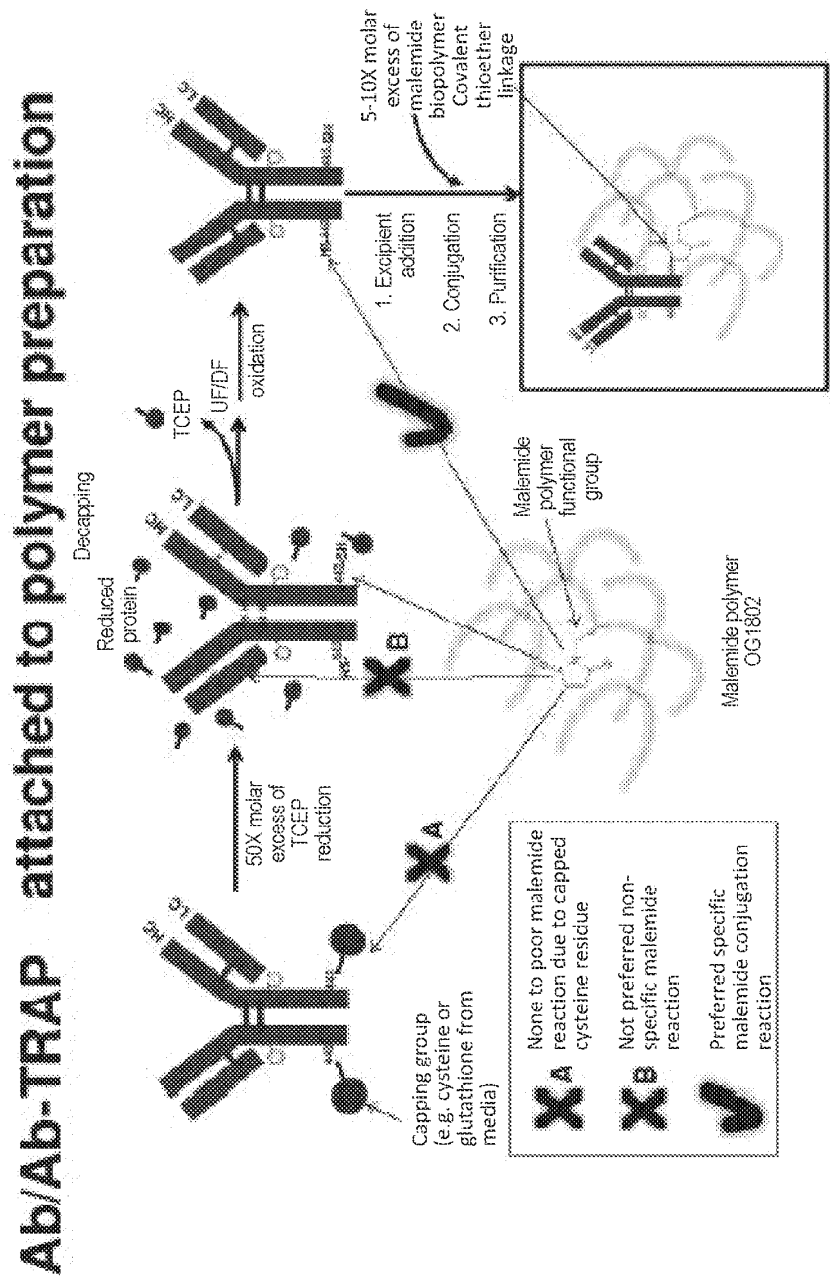


FIG. 10

22/135

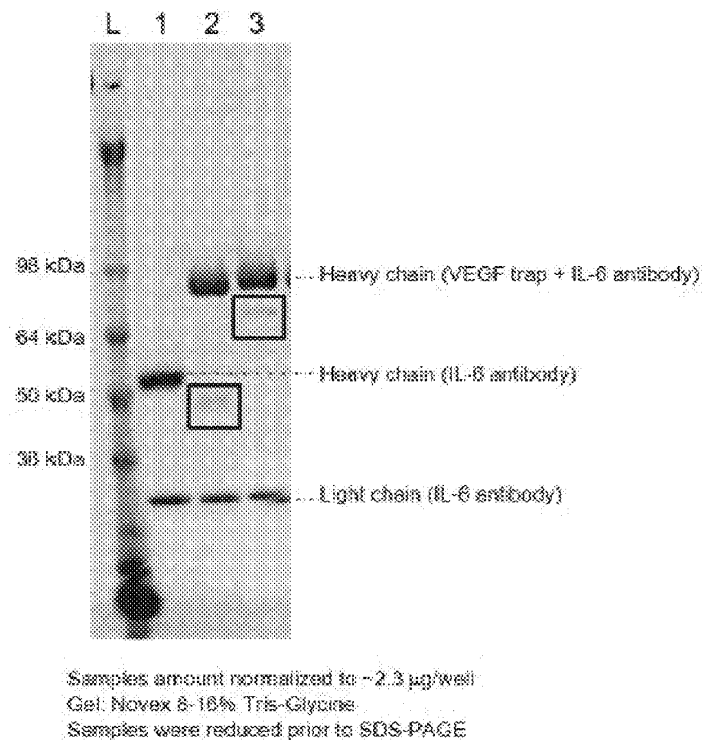


FIG. 11A

Lane #	Variant
L	SeeBlue®Plus2 standard
1	AntilL6
2	AntilL6-VEGFR
3	VEGFR-AntilL6

Protein-A purified VEGFR-AntilL6 and AntilL6-VEGFR products derived from ExpiCHO-S cells show the presence of unexpected bands (highlighted in the gel) with sizes dependent on construct orientations.

FIG. 11B



FIG. 11C

25/135

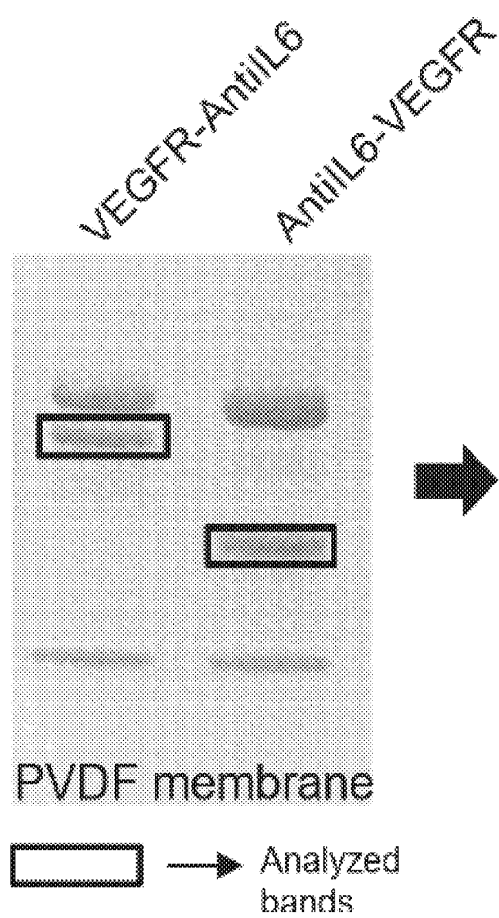


FIG. 12 (1 of 3)

N-terminal Edman Sequencing (6 residues)

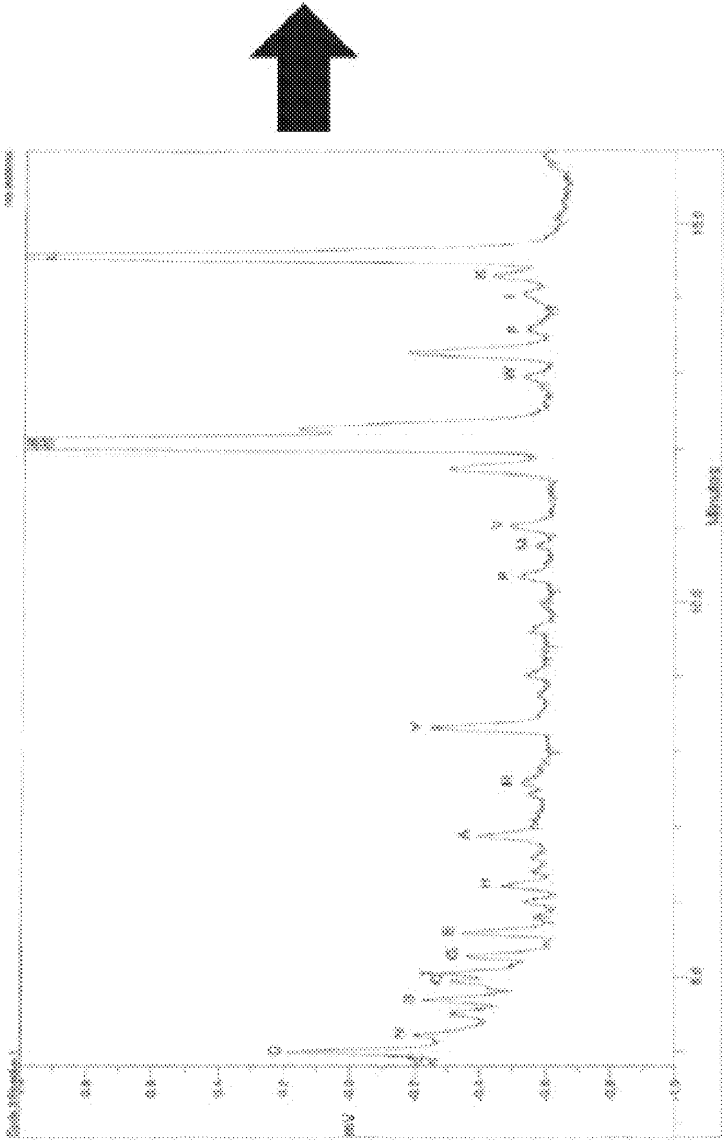
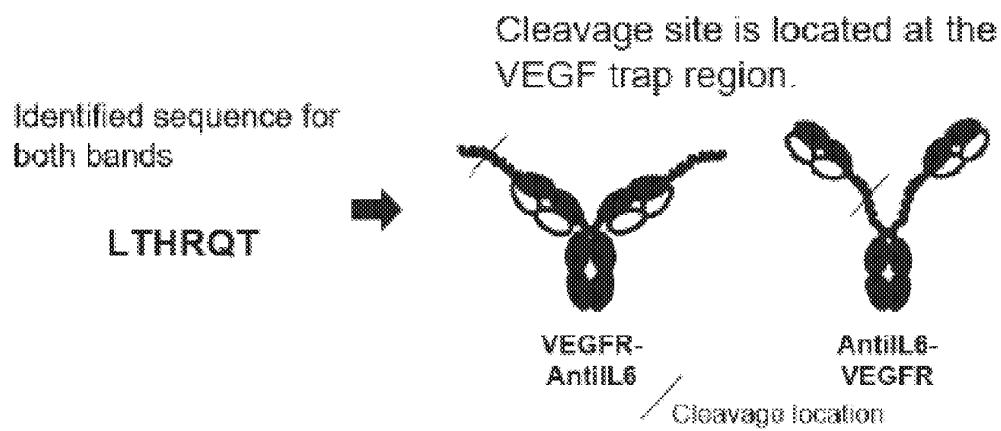


FIG. 12 (2 of 3)

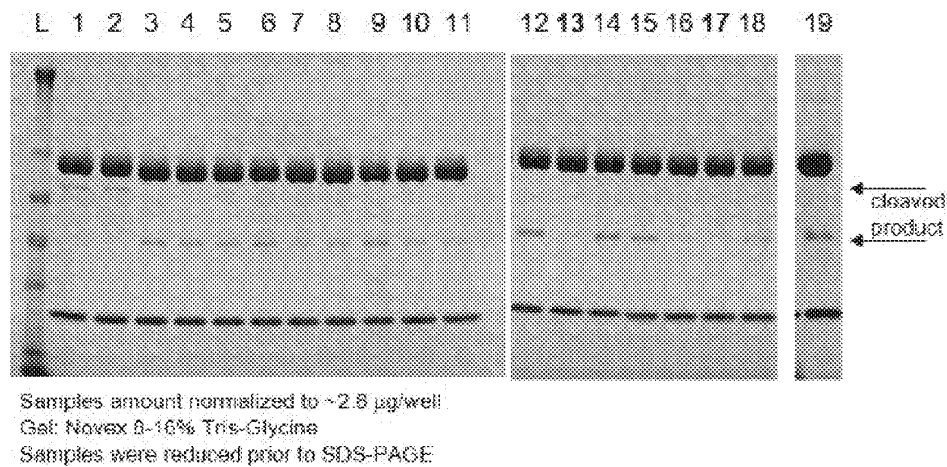
27/135



VEGFR-AntiIL6 and AntiIL6-VEGFR undergo cleavage at same site.
N-terminal Edman sequencing analysis show that both bands contain the same N-terminal sequence, LTHRQT, which is located at the VEGF trap region.

FIG. 12 (3 of 3)

28/135



Effect of single point mutations on VEGF trap cleavage.

SDS-PAGE of Antil6 VEGFR mutants demonstrates that modifications at the cleavage site tend to reduce the amount of cleaved product (arrows). Mutations T94I and H95I markedly reduced the VEGF trap cleavage.

FIG. 13A

Lane #	Variant
L	SeeBlue®Plus2 standard
1	VEGFR AntiIL6
2	VEGFR AntiIL6 choOptim ⁺
3	AntiIL6 VEGFR
4	AntiIL6 VEGFR K89Q
5	AntiIL6 VEGFR K89R
6	AntiIL6 VEGFR K89S
7	AntiIL6 VEGFR T90S
8	AntiIL6 VEGFR T90L
9	AntiIL6 VEGFR N91R
10	AntiIL6 VEGFR N91S
11	AntiIL6 VEGFR N91H
12	AntiIL6 VEGFR L93Y
13	AntiIL6 VEGFR T94I
14	AntiIL6 VEGFR T94L
15	AntiIL6 VEGFR H95Y
16	AntiIL6 VEGFR H95L
17	AntiIL6 VEGFR H95I
18	AntiIL6 VEGFR H95F
19	AntiIL6 VEGFR R96Q

(*) VEGFR variant has codon sequence optimized for expression in CHO cells

FIG. 13B

FIG. 13C

(SEQ ID NO: 4)

SDTGRFVEMVSEPEHMETGRELVFRCRVTPSNIVTLKKFLDYLTPDGKEIINDSKQFIISNATYKEIGLLTCEATVN
 GHLYKTYNTHRRQTNTHDVLSFSGHIELSVGEKLVNCTARTELNVGIDFNWEYTPSSKHQKKLVNRDLKTQSGSEM
 KKFLSTLTIDGVTRSDQGLYTCAAASSGLMTEKNSTFVRVHEK

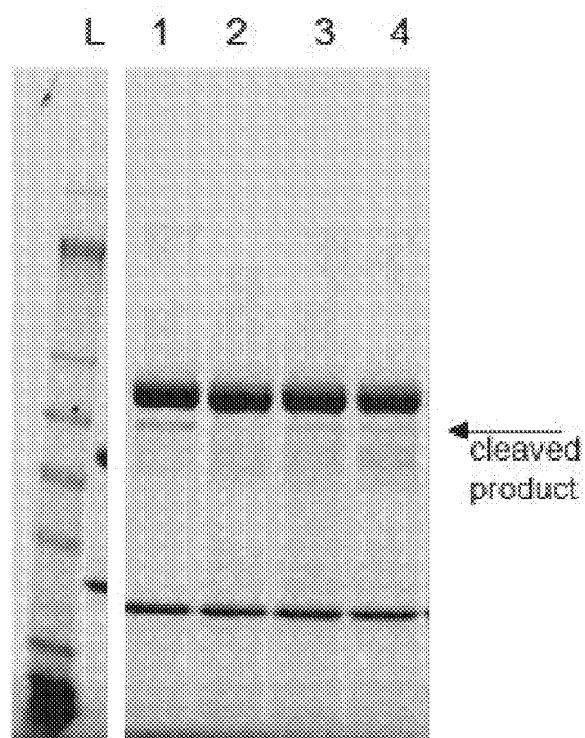
FIG. 13D

(SEQ ID NO: 5)

```
> VEGF_trap_Variant_3
```

(SEQ ID NO: 6)

31/135



Samples amount normalized to ~ 3.4 $\mu\text{g}/\text{well}$
Gel: Novex 8-16% Tris-Glycine
Samples were reduced prior to SDS-PAGE

FIG. 13F

Lane #	Variant
L	SeeBlue®Plus2 standard
1	VEGFR AntilL6
2	VEGFR variant 3 AntilL6, T94I/H95I
3	VEGFR variant 1 AntilL6, T94I
4	VEGFR variant 2 AntilL6, H95I

Effect of single point mutations on VEGF trap cleavage.

SDS-PAGE demonstrates mutations T94I and H95I reduced cleavage in VEGF trap for the dual inhibitor VEGFR-AntilL6 . The combination of both mutations reduced cleavage even further.

FIG. 13G

33/135

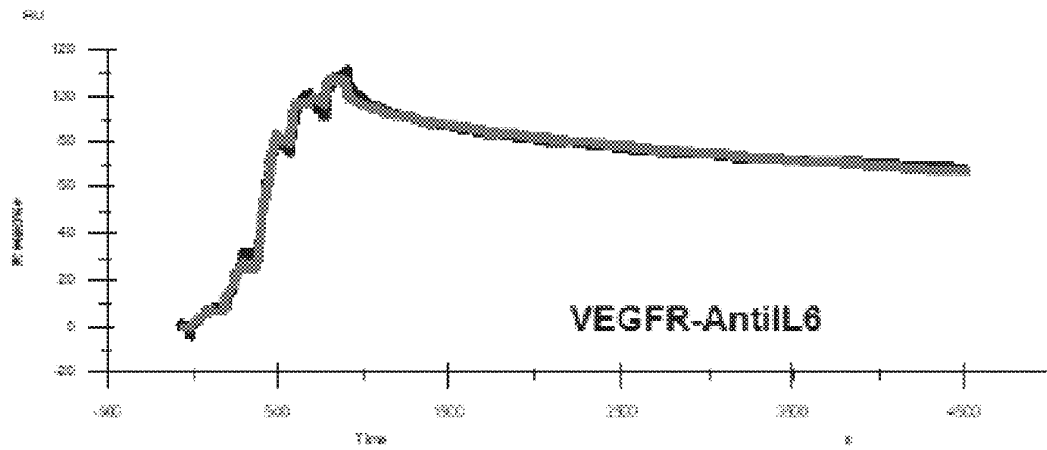


FIG. 14A

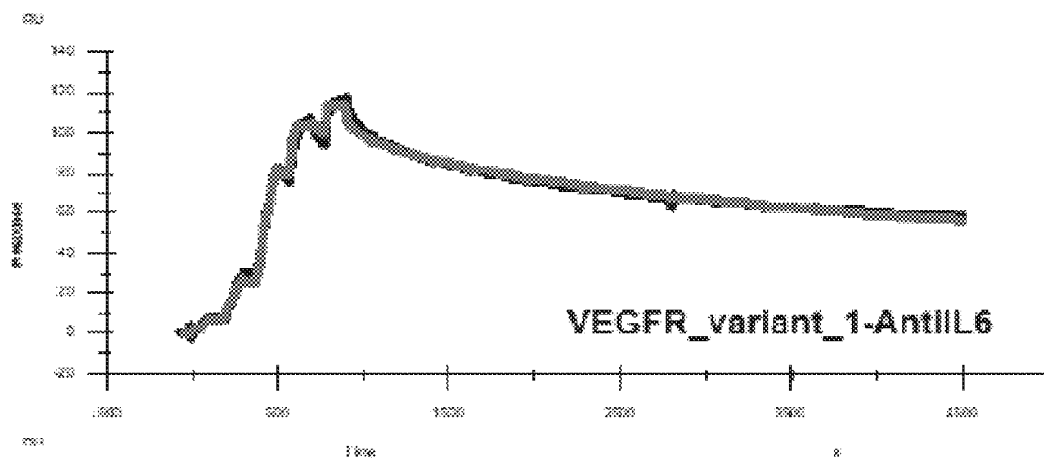


FIG. 14B

34/135

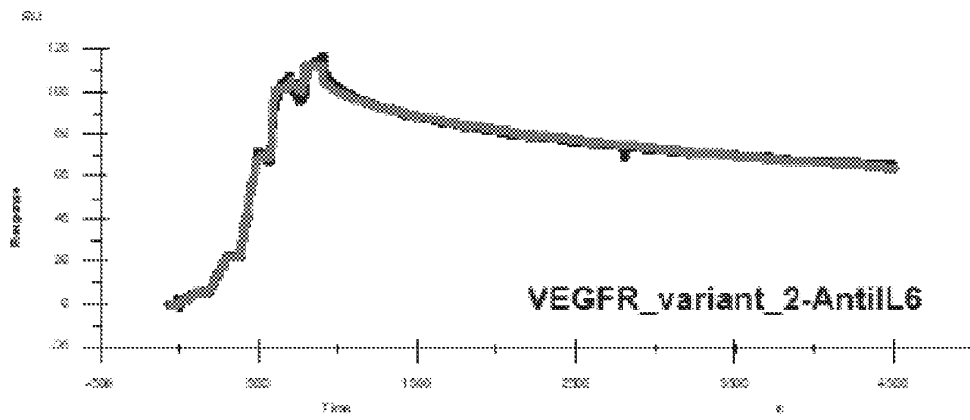


FIG. 14C

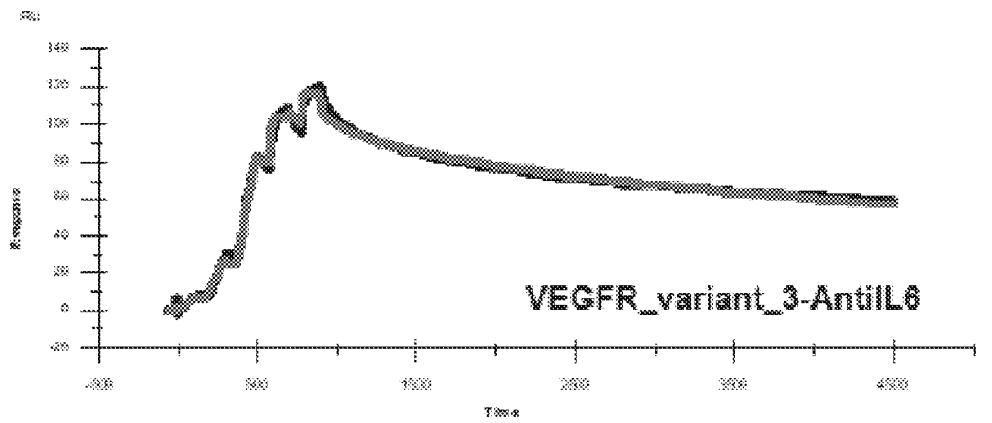


FIG. 14D

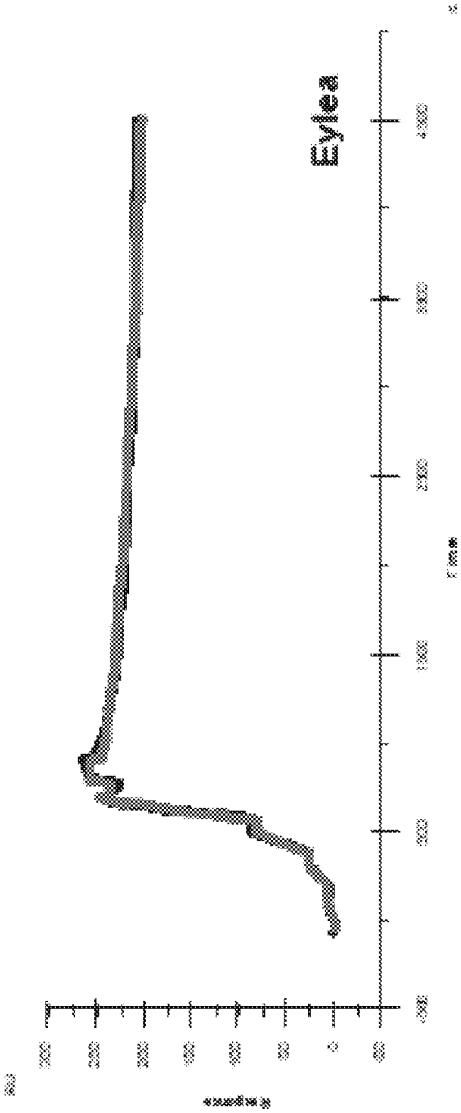


FIG. 14E

Ligand	ka(1/Ms)	kd(1/s)	KD(M)	Rmax(RU)
VEGFR-AntiIL6	7.55E+07	6.03E-04	7.98E-12	296.2
VEGFR_variant_1-AntiIL6	1.08E+08	1.99E-03	1.85E-11	345.6
VEGFR_variant_2-AntiIL6	1.15E+08	1.64E-03	1.43E-11	302.9
VEGFR_variant_3-AntiIL6	1.42E+08	2.66E-03	1.87E-11	317.2
Eylea	4.88E+07	2.61E-04	5.35E-12	477.4

FIG. 14F

36/135

Inhibition of VEGF mediated VEGFR activation

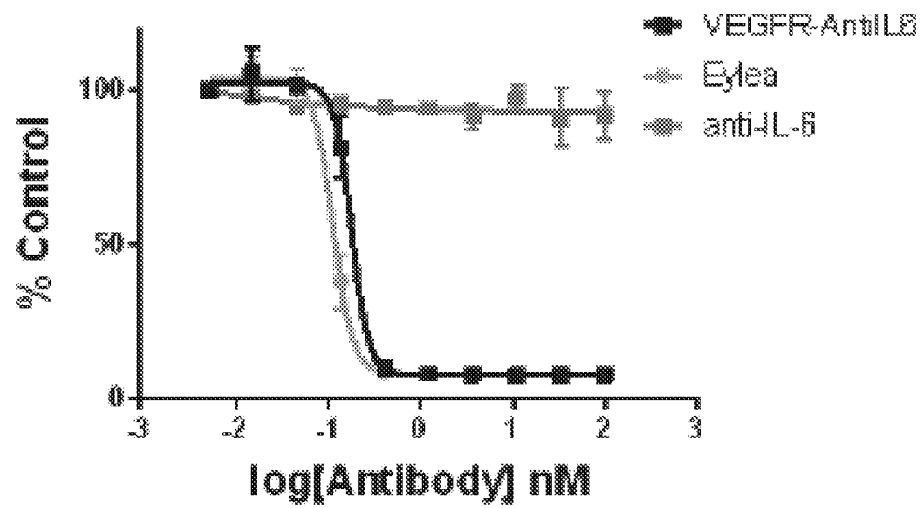


FIG. 15

Inhibition of VEGF/IL6 mediated HUVEC tubule formation

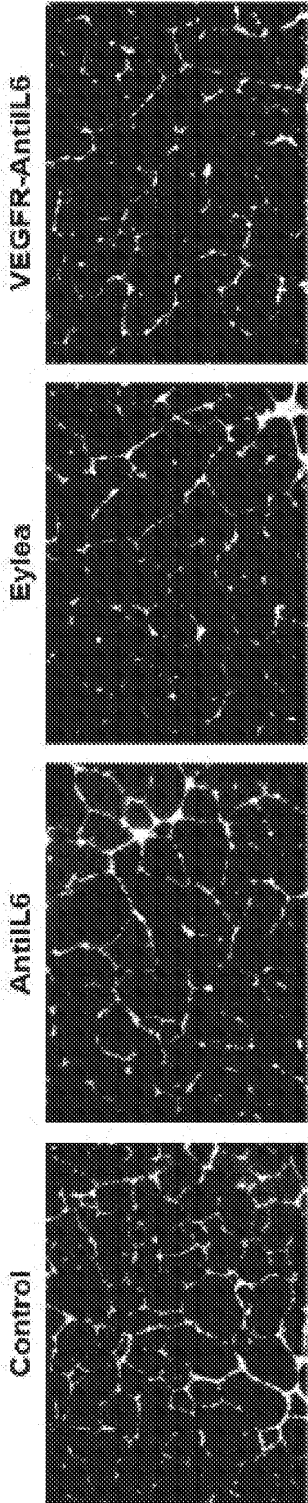
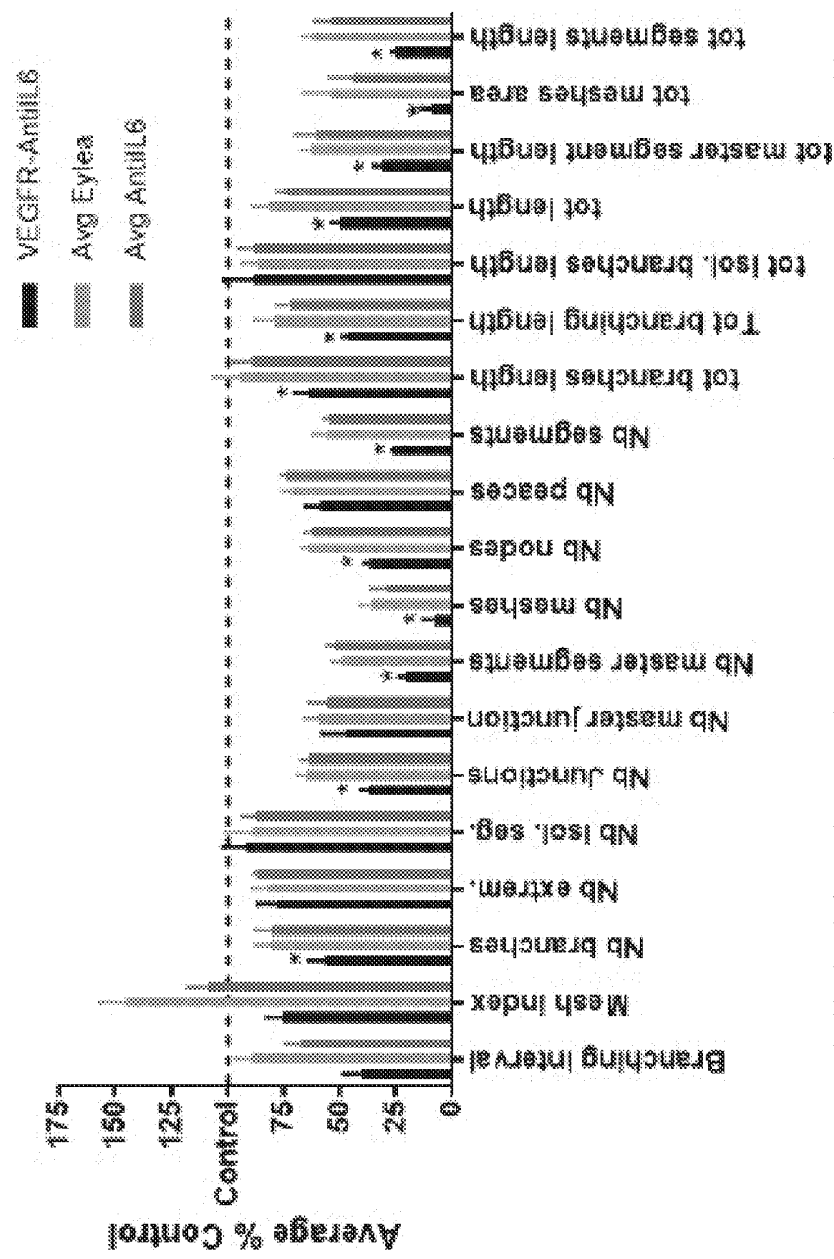


FIG. 16A



*VEGFR-AntiIL6 inhibited angiogenesis parameter better than both Eylea and AntiIL6; P<0.05

FIG. 16B

	VEGFR-AntiIL6 Sig.			
	ttest control	ttest eylee	ttest antiIL6	ttest control vs eylee
Branching interval	0.0004	0.0081	0.1337	0.3801
Mean Mesh Size	0.0003	0.0017	0.0235	0.1049
Mesh Index	0.3851	0.0537	0.3528	0.0929
Nb branches	0.0026	0.0151	0.0318	0.3175
Nb extrem.	0.0074	0.4043	0.1789	0.1249
Nb isol. seg.	0.8357	0.8243	0.9251	0.9400
Nb junctions	0.0012	0.0204	0.0259	0.0773
Nb master junction	0.0026	0.3645	0.4601	0.0271
Nb master segments	0.0009	0.0105	0.0021	0.0358
Nb meshes	0.0008	0.0076	0.0284	0.0140
Nb nodes	0.0015	0.0232	0.0231	0.0682
Nb peaces	0.0001	0.1038	0.0379	0.0047
Nb segments	0.0021	0.0334	0.0298	0.0682
tot branches length	0.0105	0.0066	0.0542	0.9644
Tot branching length	0.0009	0.0050	0.0356	0.2349
tot isol. branches length	0.9600	0.7893	0.8757	0.6795
tot length	0.0003	0.0013	0.0143	0.2020
tot master segments length	0.0006	0.0172	0.0150	0.0774
tot meshes area	0.0029	0.0057	0.0560	0.1282
tot segments length	0.0003	0.0081	0.0281	0.0757

*gray squares are statistically significant; P<0.05

FIG. 16C

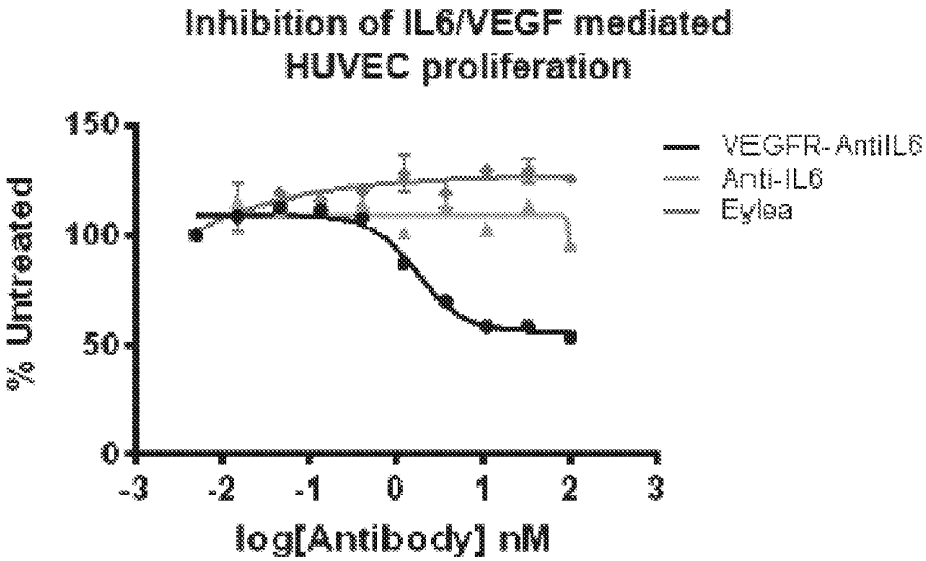


FIG. 17

ID	Sequence
VI	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAMHWVRQAPGKGLEWVAKISPGGSWYYSDIVTDRFTF SLDTSKSTAYLQMNSLRAEDTAVYYCARQAWGYYALDIWGQGILVTVSS
VII	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAMHWVRQAPGKGLEWVAKISPGGSWYYSDIVTDRFTF SLDTSKSTAYLQMNSLRAEDTAVYYCARQSWGYYALDIWGQGILVTVSS
VIII	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAMHWVRQAPGKGLEWVAKISPGGSWYYSDIVTDRFTF SLDTSKSTAYLQMNSLRAEDTAVYYCARQGWGYYALDIWGQGILVTVSS
IX	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAMHWVRQAPGKGLEWVAKISPGGSWYYSDIVTDRFTF SLDTSKSTAYLQMNSLRAEDTAVYYCARQITWGYIALDIWGQGILVTVSS
X	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAMHWVRQAPGKGLEWVAKISPGGSWYYSDIVTDRFTF SLDTSKSTAYLQMNSLRAEDTAVYYCARQVWGYIALDIWGQGILVTVSS
XI	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAMHWVRQAPGKGLEWVAKISPGGSWYYSDIVTDRFTF SLDTSKSTAYLQMNSLRAEDTAVYYCARQQWGYIALDIWGQGILVTVSS
XII	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAMHWVRQAPGKGLEWVAKISPGGSWYYSDIVTDRFTF SLDTSKSTAYLQMNSLRAEDTAVYYCARQKWGYYALDIWGQGILVTVSS

(SEQ ID NO: 7)

(SEQ ID NO: 8)

(SEQ ID NO: 9)

(SEQ ID NO: 10)

(SEQ ID NO: 11)

(SEQ ID NO: 12)

(SEQ ID NO: 13)

FIG. 18

ID	VEGF Trap Sequence	
1A	SDTGRPFVEMYSEIPEIHHMTEGRELVIPCRVTSPTNITVTLKKFPLDTLIPDGKRIWDSKKGFIHSNATYKEIGL LTCEATVNGHL YKTNYL IHRQTNIHDVVLSPSHGIELSVGEKLVNCTARTELNVGIDFNWEYPSKKHQH KKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDOGLYTCAASSGLMIKKNSTFVRVHEK	SEQ ID NO:14
1B	SDTGRPFVEMYSEIPEIHHMTEGRELVIPCRVTSPTNITVTLKKFPLDTLIPDGKRIWDSKKGFIHSNATYKEIGL LTCEATVNGHL YKTNYL IHRQTNIHDVVLSPSHGIELSVGEKLVNCTARTELNVGIDFNWEYPSKKHQH KKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDOGLYTCAASSGLMIKKNSTFVRVHEK	SEQ ID NO:15
1C	SDTGRPFVEMYSEIPEIHHMTEGRELVIPCRVTSPTNITVTLKKFPLDTLIPDGKRIWDSKKGFIHSNATYKEIGL LTCEATVNGHL YKTNYL IHRQTNIHDVVLSPSHGIELSVGEKLVNCTARTELNVGIDFNWEYPSKKHQH KKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDOGLYTCAASSGLMIKKNSTFVRVHEK	SEQ ID NO:16
1D	SDTGRPFVEMYSEIPEIHHMTEGRELVIPCRVTSPTNITVTLKKFPLDTLIPDGKRIWDSKKGFIHSNATYKEIGL LTCEATVNGHL YKTNYL IHRQTNIHDVVLSPSHGIELSVGEKLVNCTARTELNVGIDFNWEYPSKKHQH KKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDOGLYTCAASSGLMIKKNSTFVRVHEK	SEQ ID NO:17

FIG. 19

ID	Linker Sequence
2A	GGGSGGGG

(SEQ ID NO: 18)

FIG. 20

ID	Heavy chain Sequence	(SEQ ID NO: 19)	(SEQ ID NO: 20)	(SEQ ID NO: 21)	(SEQ ID NO: 22)	(SEQ ID NO: 23)	(SEQ ID NO: 24)	(SEQ ID NO: 25)	(SEQ ID NO: 26)	(SEQ ID NO: 27)
3A	EVQLVESGGGLVQPGGSLRLSCAASGFTFEFEEAMHWVRQAPGKGLEWYAKISPGGSWYYSDYIDTRFTF SLDTSKSTAYLQANSLRAEDTAVYVCARQWGGYALDIWQGGTLVTYSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTTTPAVLQSSGLYSLSVAVTPSSSLGTQTYICNVNHPKSNITK VDKKVEPKSCDKTHICPPCPAPEAAGAPSVFLPPKPKDILMSRTEFTCVVADVSHEDPEVKFNWYVDG VEVHNAKTRPEEQYNSTYRVVSVLTIVLHODWLNCKEYKCKVSNKALPAPEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPPVLDSDGSFELYSKLTVDKSRWQQGN VFSCSVMEHALHNHYTQKSLSCSPGK									
3B	EVQLVESGGGLVQPGGSLRLSCAASGFTFEFEEAMHWVRQAPGKGLEWYAKISPGGSWYYSDYIDTRFTF SLDTSKSTAYLQANSLRAEDTAVYVCARQWGGYALDIWQGGTLVTYSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTTTPAVLQSSGLYSLSVAVTPSSSLGTQTYICNVNHPKSNITK VDKKVEPKSCDKTHICPPCPAPEAAGAPSVFLPPKPKDILMSRTEFTCVVADVSHEDPEVKFNWYVDG VEVHNAKTRPEEQYNSTYRVVSVLTIVLHODWLNCKEYKCKVSNKALPAPEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPPVLDSDGSFELYSKLTVDKSRWQQGN VFSCSVMEHALHNHYTQKSLSCSPGK									
3C	EVQLVESGGGLVQPGGSLRLSCAASGFTFEFEEAMHWVRQAPGKGLEWYAKISPGGSWYYSDYIDTRFTF SLDTSKSTAYLQANSLRAEDTAVYVCARQWGGYALDIWQGGTLVTYSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTTTPAVLQSSGLYSLSVAVTPSSSLGTQTYICNVNHPKSNITK VDKKVEPKSCDKTHICPPCPAPEAAGAPSVFLPPKPKDILMSRTEFTCVVADVSHEDPEVKFNWYVDG VEVHNAKTRPEEQYNSTYRVVSVLTIVLHODWLNCKEYKCKVSNKALPAPEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPPVLDSDGSFELYSKLTVDKSRWQQGN VFSCSVMEHALHNHYTQKSLSCSPGK									
3D	EVQLVESGGGLVQPGGSLRLSCAASGFTFEFEEAMHWVRQAPGKGLEWYAKISPGGSWYYSDYIDTRFTF SLDTSKSTAYLQANSLRAEDTAVYVCARQWGGYALDIWQGGTLVTYSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTTTPAVLQSSGLYSLSVAVTPSSSLGTQTYICNVNHPKSNITK VDKKVEPKSCDKTHICPPCPAPEAAGAPSVFLPPKPKDILMSRTEFTCVVADVSHEDPEVKFNWYVDG VEVHNAKTRPEEQYNSTYRVVSVLTIVLHODWLNCKEYKCKVSNKALPAPEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPPVLDSDGSFELYSKLTVDKSRWQQGN VFSCSVMEHALHNHYTQKSLSCSPGK									
3E	EVQLVESGGGLVQPGGSLRLSCAASGFTFEFEEAMHWVRQAPGKGLEWYAKISPGGSWYYSDYIDTRFTF SLDTSKSTAYLQANSLRAEDTAVYVCARQWGGYALDIWQGGTLVTYSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTTTPAVLQSSGLYSLSVAVTPSSSLGTQTYICNVNHPKSNITK VDKKVEPKSCDKTHICPPCPAPEAAGAPSVFLPPKPKDILMSRTEFTCVVADVSHEDPEVKFNWYVDG VEVHNAKTRPEEQYNSTYRVVSVLTIVLHODWLNCKEYKCKVSNKALPAPEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPPVLDSDGSFELYSKLTVDKSRWQQGN VFSCSVMEHALHNHYTQKSLSCSPGK									
3F	EVQLVESGGGLVQPGGSLRLSCAASGFTFEFEEAMHWVRQAPGKGLEWYAKISPGGSWYYSDYIDTRFTF SLDTSKSTAYLQANSLRAEDTAVYVCARQWGGYALDIWQGGTLVTYSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTTTPAVLQSSGLYSLSVAVTPSSSLGTQTYICNVNHPKSNITK VDKKVEPKSCDKTHICPPCPAPEAAGAPSVFLPPKPKDILMSRTEFTCVVADVSHEDPEVKFNWYVDG VEVHNAKTRPEEQYNSTYRVVSVLTIVLHODWLNCKEYKCKVSNKALPAPEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPPVLDSDGSFELYSKLTVDKSRWQQGN VFSCSVMEHALHNHYTQKSLSCSPGK									
3G	EVQLVESGGGLVQPGGSLRLSCAASGFTFEFEEAMHWVRQAPGKGLEWYAKISPGGSWYYSDYIDTRFTF SLDTSKSTAYLQANSLRAEDTAVYVCARQWGGYALDIWQGGTLVTYSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTTTPAVLQSSGLYSLSVAVTPSSSLGTQTYICNVNHPKSNITK VDKKVEPKSCDKTHICPPCPAPEAAGAPSVFLPPKPKDILMSRTEFTCVVADVSHEDPEVKFNWYVDG VEVHNAKTRPEEQYNSTYRVVSVLTIVLHODWLNCKEYKCKVSNKALPAPEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPPVLDSDGSFELYSKLTVDKSRWQQGN VFSCSVMEHALHNHYTQKSLSCSPGK									
3H	EVQLVESGGGLVQPGGSLRLSCAASGFTFEFEEAMHWVRQAPGKGLEWYAKISPGGSWYYSDYIDTRFTF SLDTSKSTAYLQANSLRAEDTAVYVCARQWGGYALDIWQGGTLVTYSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTTTPAVLQSSGLYSLSVAVTPSSSLGTQTYICNVNHPKSNITK VDKKVEPKSCDKTHICPPCPAPEAAGAPSVFLPPKPKDILMSRTEFTCVVADVSHEDPEVKFNWYVDG VEVHNAKTRPEEQYNSTYRVVSVLTIVLHODWLNCKEYKCKVSNKALPAPEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPPVLDSDGSFELYSKLTVDKSRWQQGN VFSCSVMEHALHNHYTQKSLSCSPGK									
3I	EVQLVESGGGLVQPGGSLRLSCAASGFTFEFEEAMHWVRQAPGKGLEWYAKISPGGSWYYSDYIDTRFTF SLDTSKSTAYLQANSLRAEDTAVYVCARQWGGYALDIWQGGTLVTYSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTTTPAVLQSSGLYSLSVAVTPSSSLGTQTYICNVNHPKSNITK VDKKVEPKSCDKTHICPPCPAPEAAGAPSVFLPPKPKDILMSRTEFTCVVADVSHEDPEVKFNWYVDG VEVHNAKTRPEEQYNSTYRVVSVLTIVLHODWLNCKEYKCKVSNKALPAPEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPPVLDSDGSFELYSKLTVDKSRWQQGN VFSCSVMEHALHNHYTQKSLSCSPGK									

FIG. 21A

FIG. 21B

ID	Heavy chain Sequence
3A	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAMHWVRQAPGKGLEWYAKISPGGSWYYSDYSDTVTDRTF SLDTSKSTAYLQMNSLRAEDTA VYYCARQAWGYALDIWGQGTILVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLPPKPKDITLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLCSPGK (SEQ ID NO: 19)
3B	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAMHWVRQAPGKGLEWYAKISPGGSWYYSDYSDTVTDRTF SLDTSKSTAYLQMNSLRAEDTA VYYCARQSWGYALDIWGQGTILVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLPPKPKDITLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLCSPGK (SEQ ID NO: 20)
3C	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAMHWVRQAPGKGLEWYAKISPGGSWYYSDYSDTVTDRTF SLDTSKSTAYLQMNSLRAEDTA VYYCARQGWGYALDIWGQGTILVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLPPKPKDITLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLCSPGK (SEQ ID NO: 21)
3D	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAMHWVRQAPGKGLEWYAKISPGGSWYYSDYSDTVTDRTF SLDTSKSTAYLQMNSLRAEDTA VYYCARQTWGYALDIWGQGTILVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLPPKPKDITLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLCSPGK (SEQ ID NO: 22)
3E	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAMHWVRQAPGKGLEWYAKISPGGSWYYSDYSDTVTDRTF SLDTSKSTAYLQMNSLRAEDTA VYYCARQVWGYALDIWGQGTILVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLPPKPKDITLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLCSPGK (SEQ ID NO: 23)
3F	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAMHWVRQAPGKGLEWYAKISPGGSWYYSDYSDTVTDRTF SLDTSKSTAYLQMNSLRAEDTA VYYCARQWGYALDIWGQGTILVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK

	VDKKVEPKSCDKTHTCPPCPAPEAAAGAPSVFLFPPKPKDITLMISRTPETVCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 24)
3G	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAHWVRQAPGKGLEWVAKISPGGSWITYSDTVTDRTF SLDTSKSTAYLQMNSLRAEDTAVYYCAROKWGYALDIWGGQGLTVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAAGAPSVFLFPPKPKDITLMISRTPETVCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 25)
3H	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAISWVRQAPGKGLEWVAKISPGGSWITYSDTVTDRTFS LDTSKSTAYLQMNSLRAEDTAVYYCARQLWGYALDVWGGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAAGAPSVFLFPPKPKDITLMISRTPETVCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 26)
3I	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAWSWVRQAPGKGLEWVAKISPGGSWITYSDTVTDRTF SLDTSKSTAYLQMNSLRAEDTAVYYCARQLWGYALDVWGGQGLTVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPEAAAGAPSVFLFPPKPKDITLMISRTPETVCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 27)

FIG. 21B

ID	Light chain	
4A	DIQLTQSPSSLASVGDRAVITICSAISVSILYIYQOKPGKAPKLIHYDDSSLASGVPSEFSGSGGIDFILI SSLQPEDFATYYCQOWSGYPYTFGGTKVEIKRIVAAPSVEFPSPDEQLKSGTASVVCLLNINFPYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSIYSLSTILSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC	(SEQ ID NO: 28)
4B	DIQLTQSPSSLASVGDRAVITICSAISVSILYIYQOKPGKAPKLIHYDASSLASGVPSEFSGSGGIDFILI SSLQPEDFATYYCQOWSGYPYTFGGTKVEIKRIVAAPSVEFPSPDEQLKSGTASVVCLLNINFPYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSIYSLSTILSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC	(SEQ ID NO: 29)
4C	DIQLTQSPSSLASVGDRAVITICSAISVSILYIYQOKPGKAPKLIHYDDSNLASGVPSEFSGSGGIDFILI SSLQPEDFATYYCQOWSGYPYTFGGTKVEIKRIVAAPSVEFPSPDEQLKSGTASVVCLLNINFPYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSIYSLSTILSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC	(SEQ ID NO: 30)

FIG.
22A

FIG. 22B

ID	Light chain
4A	DIQLTQSPSSLASVGDRTTITCSASISVSYLEWYQQKPGKAPKLLIYDDSSLASGVPSRFSGSGTDFTLTI SSLQPEDFATYYCQQWSGYPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSITYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 28)
4B	DIQLTQSPSSLASVGDRTTITCSASISVSYLEWYQQKPGKAPKLLIYDASSLASGVPSRFSGSGTDFTLTI SSLQPEDFATYYCQQWSGYPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSITYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 29)
4C	DIQLTQSPSSLASVGDRTTITCSASISVSYLEWYQQKPGKAPKLLIYDDSNLASGVPSRFSGSGTDFTLTI SSLQPEDFATYYCQQWSGYPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSITYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 30)

ID	Heavy chain - Fab	Heavy chain - Fc	(SEQ ID NO: 31)	(SEQ ID NO: 32)	(SEQ ID NO: 33)	(SEQ ID NO: 34)	(SEQ ID NO: 35)	(SEQ ID NO: 36)	(SEQ ID NO: 37)	(SEQ ID NO: 38)	(SEQ ID NO: 39)																
5A	EVQLVESGGGLVQPGGSLRLSASGFTSPDAHWVR QAPGKGELEWASPGSNVTIDIVTFHPSFELDKS TATCAQNSLEEDTAVYCAQVAGVATLALDKGQTL LATYSSASTGSHFTAPPSKSTSGTALAGCLVNDYFP EPVTVSWNGALTSGLTHHPALQSGELSSNVATPSS SSGQTQTVNHNHSDNIKAKAEPPKSC	DKHTCPDPAELAGAPSVLTPPKKEDTLAERTPEVT CVAVDSHEDEVFNATVGGVEVNAKTRPEEQIN STTAVAVLTALQDNLNGEYKAKVNAKALPAPKPT IEAKGQRPQVTLTPPSEEMTNQVSLTCAKMGFTF SEAVENSGQENNTITPPLDSDQNTVSLTLYVE KRWVQGNVTSVAHAEALHNHTOKSLSCSPK	(SEQ ID NO: 40)	EVQLVESGGGLVQPGGSLRLSASGFTSPDAHWVR QAPGKGELEWASPGSNVTIDIVTFHPSFELDKS TATCAQNSLEEDTAVYCAQVAGVATLALDKGQTL LATYSSASTGSHFTAPPSKSTSGTALAGCLVNDYFP EPVTVSWNGALTSGLTHHPALQSGELSSNVATPSS SSGQTQTVNHNHSDNIKAKAEPPKSC	DKHTCPDPAELAGAPSVLTPPKKEDTLAERTPEVT CVAVDSHEDEVFNATVGGVEVNAKTRPEEQIN STTAVAVLTALQDNLNGEYKAKVNAKALPAPKPT IEAKGQRPQVTLTPPSEEMTNQVSLTCAKMGFTF SEAVENSGQENNTITPPLDSDQNTVSLTLYVE KRWVQGNVTSVAHAEALHNHTOKSLSCSPK	(SEQ ID NO: 41)	EVQLVESGGGLVQPGGSLRLSASGFTSPDAHWVR QAPGKGELEWASPGSNVTIDIVTFHPSFELDKS TATCAQNSLEEDTAVYCAQVAGVATLALDKGQTL LATYSSASTGSHFTAPPSKSTSGTALAGCLVNDYFP EPVTVSWNGALTSGLTHHPALQSGELSSNVATPSS SSGQTQTVNHNHSDNIKAKAEPPKSC	DKHTCPDPAELAGAPSVLTPPKKEDTLAERTPEVT CVAVDSHEDEVFNATVGGVEVNAKTRPEEQIN STTAVAVLTALQDNLNGEYKAKVNAKALPAPKPT IEAKGQRPQVTLTPPSEEMTNQVSLTCAKMGFTF SEAVENSGQENNTITPPLDSDQNTVSLTLYVE KRWVQGNVTSVAHAEALHNHTOKSLSCSPK	(SEQ ID NO: 42)	EVQLVESGGGLVQPGGSLRLSASGFTSPDAHWVR QAPGKGELEWASPGSNVTIDIVTFHPSFELDKS TATCAQNSLEEDTAVYCAQVAGVATLALDKGQTL LATYSSASTGSHFTAPPSKSTSGTALAGCLVNDYFP EPVTVSWNGALTSGLTHHPALQSGELSSNVATPSS SSGQTQTVNHNHSDNIKAKAEPPKSC	DKHTCPDPAELAGAPSVLTPPKKEDTLAERTPEVT CVAVDSHEDEVFNATVGGVEVNAKTRPEEQIN STTAVAVLTALQDNLNGEYKAKVNAKALPAPKPT IEAKGQRPQVTLTPPSEEMTNQVSLTCAKMGFTF SEAVENSGQENNTITPPLDSDQNTVSLTLYVE KRWVQGNVTSVAHAEALHNHTOKSLSCSPK	(SEQ ID NO: 43)	EVQLVESGGGLVQPGGSLRLSASGFTSPDAHWVR QAPGKGELEWASPGSNVTIDIVTFHPSFELDKS TATCAQNSLEEDTAVYCAQVAGVATLALDKGQTL LATYSSASTGSHFTAPPSKSTSGTALAGCLVNDYFP EPVTVSWNGALTSGLTHHPALQSGELSSNVATPSS SSGQTQTVNHNHSDNIKAKAEPPKSC	DKHTCPDPAELAGAPSVLTPPKKEDTLAERTPEVT CVAVDSHEDEVFNATVGGVEVNAKTRPEEQIN STTAVAVLTALQDNLNGEYKAKVNAKALPAPKPT IEAKGQRPQVTLTPPSEEMTNQVSLTCAKMGFTF SEAVENSGQENNTITPPLDSDQNTVSLTLYVE KRWVQGNVTSVAHAEALHNHTOKSLSCSPK	(SEQ ID NO: 44)	EVQLVESGGGLVQPGGSLRLSASGFTSPDAHWVR QAPGKGELEWASPGSNVTIDIVTFHPSFELDKS TATCAQNSLEEDTAVYCAQVAGVATLALDKGQTL LATYSSASTGSHFTAPPSKSTSGTALAGCLVNDYFP EPVTVSWNGALTSGLTHHPALQSGELSSNVATPSS SSGQTQTVNHNHSDNIKAKAEPPKSC	DKHTCPDPAELAGAPSVLTPPKKEDTLAERTPEVT CVAVDSHEDEVFNATVGGVEVNAKTRPEEQIN STTAVAVLTALQDNLNGEYKAKVNAKALPAPKPT IEAKGQRPQVTLTPPSEEMTNQVSLTCAKMGFTF SEAVENSGQENNTITPPLDSDQNTVSLTLYVE KRWVQGNVTSVAHAEALHNHTOKSLSCSPK	(SEQ ID NO: 45)	EVQLVESGGGLVQPGGSLRLSASGFTSPDAHWVR QAPGKGELEWASPGSNVTIDIVTFHPSFELDKS TATCAQNSLEEDTAVYCAQVAGVATLALDKGQTL LATYSSASTGSHFTAPPSKSTSGTALAGCLVNDYFP EPVTVSWNGALTSGLTHHPALQSGELSSNVATPSS SSGQTQTVNHNHSDNIKAKAEPPKSC	DKHTCPDPAELAGAPSVLTPPKKEDTLAERTPEVT CVAVDSHEDEVFNATVGGVEVNAKTRPEEQIN STTAVAVLTALQDNLNGEYKAKVNAKALPAPKPT IEAKGQRPQVTLTPPSEEMTNQVSLTCAKMGFTF SEAVENSGQENNTITPPLDSDQNTVSLTLYVE KRWVQGNVTSVAHAEALHNHTOKSLSCSPK	(SEQ ID NO: 46)	EVQLVESGGGLVQPGGSLRLSASGFTSPDAHWVR QAPGKGELEWASPGSNVTIDIVTFHPSFELDKS TATCAQNSLEEDTAVYCAQVAGVATLALDKGQTL LATYSSASTGSHFTAPPSKSTSGTALAGCLVNDYFP EPVTVSWNGALTSGLTHHPALQSGELSSNVATPSS SSGQTQTVNHNHSDNIKAKAEPPKSC	DKHTCPDPAELAGAPSVLTPPKKEDTLAERTPEVT CVAVDSHEDEVFNATVGGVEVNAKTRPEEQIN STTAVAVLTALQDNLNGEYKAKVNAKALPAPKPT IEAKGQRPQVTLTPPSEEMTNQVSLTCAKMGFTF SEAVENSGQENNTITPPLDSDQNTVSLTLYVE KRWVQGNVTSVAHAEALHNHTOKSLSCSPK	(SEQ ID NO: 47)	EVQLVESGGGLVQPGGSLRLSASGFTSPDAHWVR QAPGKGELEWASPGSNVTIDIVTFHPSFELDKS TATCAQNSLEEDTAVYCAQVAGVATLALDKGQTL LATYSSASTGSHFTAPPSKSTSGTALAGCLVNDYFP EPVTVSWNGALTSGLTHHPALQSGELSSNVATPSS SSGQTQTVNHNHSDNIKAKAEPPKSC	DKHTCPDPAELAGAPSVLTPPKKEDTLAERTPEVT CVAVDSHEDEVFNATVGGVEVNAKTRPEEQIN STTAVAVLTALQDNLNGEYKAKVNAKALPAPKPT IEAKGQRPQVTLTPPSEEMTNQVSLTCAKMGFTF SEAVENSGQENNTITPPLDSDQNTVSLTLYVE KRWVQGNVTSVAHAEALHNHTOKSLSCSPK	(SEQ ID NO: 48)

FIG. 23A

FIG. 23B

ID	Heavy chain - Fab	Heavy chain - Fc
5A	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAM HWVRQAPGKGLEWYAKISPGGSWYYSDIVTDR FTFSLDTSKSTAYLQMNSLRAEDTAVYYCARQA WGYALDIWGQGTLLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSC (SEQ ID NO: 31)	DKTHTCPPCPAPEAAGAPSVFLFPPKPKDITLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVHLQDWLNGKEYKC KVSNAKALPAPIEKTISKAKGQPREPQVYITLPPSRBE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KITPPVLDSDSGSFFLYSKLTVDKSRWQQGNVFSC SYMHEALHNHYTQKSLSLCSPGK (SEQ ID NO: 40)
	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAM HWVRQAPGKGLEWYAKISPGGSWYYSDIVTDR FTFSLDTSKSTAYLQMNSLRAEDTAVYYCARQSW GYALDIWGQGTLLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSC (SEQ ID NO: 32)	DKTHTCPPCPAPEAAGAPSVFLFPPKPKDITLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVHLQDWLNGKEYKC KVSNAKALPAPIEKTISKAKGQPREPQVYITLPPSRBE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KITPPVLDSDSGSFFLYSKLTVDKSRWQQGNVFSC SYMHEALHNHYTQKSLSLCSPGK (SEQ ID NO: 41)
5C	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAM HWVRQAPGKGLEWYAKISPGGSWYYSDIVTDR FTFSLDTSKSTAYLQMNSLRAEDTAVYYCARQG WGYALDIWGQGTLLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSC (SEQ ID NO: 33)	DKTHTCPPCPAPEAAGAPSVFLFPPKPKDITLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVHLQDWLNGKEYKC KVSNAKALPAPIEKTISKAKGQPREPQVYITLPPSRBE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KITPPVLDSDSGSFFLYSKLTVDKSRWQQGNVFSC SYMHEALHNHYTQKSLSLCSPGK (SEQ ID NO: 42)
	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAM HWVRQAPGKGLEWYAKISPGGSWYYSDIVTDR FTFSLDTSKSTAYLQMNSLRAEDTAVYYCARQTW GYALDIWGQGTLLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSC (SEQ ID NO: 34)	DKTHTCPPCPAPEAAGAPSVFLFPPKPKDITLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVHLQDWLNGKEYKC KVSNAKALPAPIEKTISKAKGQPREPQVYITLPPSRBE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KITPPVLDSDSGSFFLYSKLTVDKSRWQQGNVFSC SYMHEALHNHYTQKSLSLCSPGK (SEQ ID NO: 43)
5E	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAM HWVRQAPGKGLEWYAKISPGGSWYYSDIVTDR FTFSLDTSKSTAYLQMNSLRAEDTAVYYCARQV WGYALDIWGQGTLLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSC (SEQ ID NO: 35)	DKTHTCPPCPAPEAAGAPSVFLFPPKPKDITLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVHLQDWLNGKEYKC KVSNAKALPAPIEKTISKAKGQPREPQVYITLPPSRBE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KITPPVLDSDSGSFFLYSKLTVDKSRWQQGNVFSC SYMHEALHNHYTQKSLSLCSPGK (SEQ ID NO: 44)

5F	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAM HWVROAPGKGLEWVAKISPGGSWTYYSDIVTDR FTSLDTSKSTAYLQMNSLRAEDTAVYYCARQQ WGYALDIWGGQTLVTYSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSC (SEQ ID NO: 36)	DKTHTCPPCPAPEAAAGAPSVFLFPPKPKDITLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNAKLPAPIEKTIKAKGQPREPQVYITLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KITPPVLDSDSGSFLLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSGSPGK (SEQ ID NO: 45)
5G	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAM HWVROAPGKGLEWVAKISPGGSWTYYSDIVTDR FTSLDTSKSTAYLQMNSLRAEDTAVYYCARQK WGYALDIWGGQTLVTYSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSC (SEQ ID NO: 37)	DKTHTCPPCPAPEAAAGAPSVFLFPPKPKDITLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNAKLPAPIEKTIKAKGQPREPQVYITLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KITPPVLDSDSGSFLLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSGSPGK (SEQ ID NO: 46)
5H	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFALS WVROAPGKGLEWVAKISPGGSWTYYSDIVTDRF TFSLDTSKSTAYLQMNSLRAEDTAVYYCARQLW GYALDVGQGTLLVTYSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSC (SEQ ID NO: 38)	DKTHTCPPCPAPEAAAGAPSVFLFPPKPKDITLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNAKLPAPIEKTIKAKGQPREPQVYITLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KITPPVLDSDSGSFLLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSGSPGK (SEQ ID NO: 47)
5I	EVQLVESGGGLVQPGGSLRLSCAASGFTSPFAWS WVROAPGKGLEWVAKISPGGSWTYYSDIVTDRF TFSLDTSKSTAYLQMNSLRAEDTAVYYCARQLW GYALDVGQGTLLVTYSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSC (SEQ ID NO: 39)	DKTHTCPPCPAPEAAAGAPSVFLFPPKPKDITLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNAKLPAPIEKTIKAKGQPREPQVYITLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KITPPVLDSDSGSFLLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSGSPGK (SEQ ID NO: 48)

FIG. 23B

ID	(SEQ ID NO.) CDR1	(SEQ ID NO.) CDR2	(SEQ ID NO.) CDR3
3A / 5A	(49) GFISPFAMH	50VAKISPGGSWITYSDIVTD	51 ARQAWGYVALDI
3B / 5B	52 GFISPFAMH	53VAKISPGGSWITYSDIVTD	54 ARQSWGYVALDI
3C / 5C	55 GFISPFAMH	56VAKISPGGSWITYSDIVTD	57 ARQWGYVALDI
3D / 5D	58 GFISPFAMH	59VAKISPGGSWITYSDIVTD	60 ARQWGYVALDI
3E / 5E	61 GFISPFAMH	62VAKISPGGSWITYSDIVTD	63 ARQWGYVALDI
3F / 5F	64 GFISPFAMH	65VAKISPGGSWITYSDIVTD	66 ARQWGYVALDI
3G / 5G	67 GFISPFAMH	68VAKISPGGSWITYSDIVTD	69 ARQWGYVALDI
3H / 5H	70 GFISPFAMH	71VAKISPGGSWITYSDIVTD	72 ARQWGYVALDI
3I / 5I	73 GFISPFAMH	74VAKISPGGSWITYSDIVTD	75 ARQWGYVALDI

FIG. 24A

ID	(SEQ ID NO.) CDR1	(SEQ ID NO.) CDR2	(SEQ ID NO.) CDR3
4A	76 SASISVSPLY	77 LLYDSSSLAS	78 QQWSGYPTT
4B	79 SASISVSPLY	80 LLYDASSLAS	81 QQWSGYPTT
4C	82 SASISVSPLY	83 LLYDSSNLAS	84 QQWSGYPTT

FIG. 24B

ID	Sequence
4A	SDGRFTVEMVSEDEHRAEGREAVPCRVTSPTNVLAKPELDLPDCKHNDSEKGRNSATYKEGL LTCEATVNGHLVKTINVLTHQONTNDAVLSHGHLSYGEELVLMCTARTELNCGDNWVPSKHQHK KRLVNRDLKTQSGSEDAKFLSTLHIDGATRDQGLYTCASAGLMTKZSTFWVREKDKTHQCPAPEA AAGASTVLPFPKFDLAKERTPEVTCVVDYSHDEPFEKSNVYDQVEVNAKTRPEHQDSTATVYS SLVTLHQDLNCKETKCKVSNKALPAPERKTSKAGQGRPQVTLPPSEEMTKQVSLTCLVKGFTPS DIAVENEHQQENNVKTIPTPVLDSGGSEFLYSKLTVKSRWQQGVTSQVTSNHEALHNHTQKSLSCSP GK
4B	SDGRFTVEMVSEDEHRAEGREAVPCRVTSPTNVLAKPELDLPDCKHNDSEKGRNSATYKEGL LTCEATVNGHLVKTINVLTHQONTNDAVLSHGHLSYGEELVLMCTARTELNCGDNWVPSKHQHK KRLVNRDLKTQSGSEDAKFLSTLHIDGATRDQGLYTCASAGLMTKZSTFWVREKDKTHQCPAPEA AAGASTVLPFPKFDLAKERTPEVTCVVDYSHDEPFEKSNVYDQVEVNAKTRPEHQDSTATVYS SLVTLHQDLNCKETKCKVSNKALPAPERKTSKAGQGRPQVTLPPSEEMTKQVSLTCLVKGFTPS DIAVENEHQQENNVKTIPTPVLDSGGSEFLYSKLTVKSRWQQGVTSQVTSNHEALHNHTQKSLSCSP GK
4C	SDGRFTVEMVSEDEHRAEGREAVPCRVTSPTNVLAKPELDLPDCKHNDSEKGRNSATYKEGL LTCEATVNGHLVKTINVLTHQONTNDAVLSHGHLSYGEELVLMCTARTELNCGDNWVPSKHQHK KRLVNRDLKTQSGSEDAKFLSTLHIDGATRDQGLYTCASAGLMTKZSTFWVREKDKTHQCPAPEA AAGASTVLPFPKFDLAKERTPEVTCVVDYSHDEPFEKSNVYDQVEVNAKTRPEHQDSTATVYS SLVTLHQDLNCKETKCKVSNKALPAPERKTSKAGQGRPQVTLPPSEEMTKQVSLTCLVKGFTPS DIAVENEHQQENNVKTIPTPVLDSGGSEFLYSKLTVKSRWQQGVTSQVTSNHEALHNHTQKSLSCSP GK
4D	SDGRFTVEMVSEDEHRAEGREAVPCRVTSPTNVLAKPELDLPDCKHNDSEKGRNSATYKEGL LTCEATVNGHLVKTINVLTHQONTNDAVLSHGHLSYGEELVLMCTARTELNCGDNWVPSKHQHK KRLVNRDLKTQSGSEDAKFLSTLHIDGATRDQGLYTCASAGLMTKZSTFWVREKDKTHQCPAPEA AAGASTVLPFPKFDLAKERTPEVTCVVDYSHDEPFEKSNVYDQVEVNAKTRPEHQDSTATVYS SLVTLHQDLNCKETKCKVSNKALPAPERKTSKAGQGRPQVTLPPSEEMTKQVSLTCLVKGFTPS DIAVENEHQQENNVKTIPTPVLDSGGSEFLYSKLTVKSRWQQGVTSQVTSNHEALHNHTQKSLSCSP GK

FIG. 25

(SEQ ID NO: 85)

(SEQ ID NO: 86)

(SEQ ID NO: 87)

(SEQ ID NO: 88)

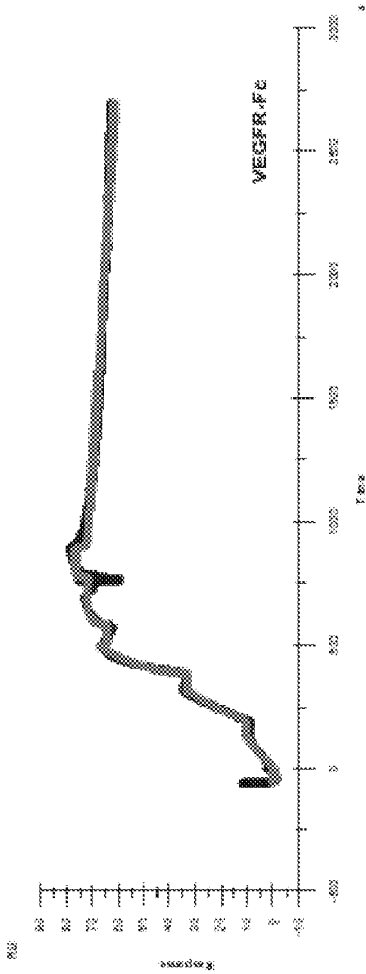


FIG. 26A

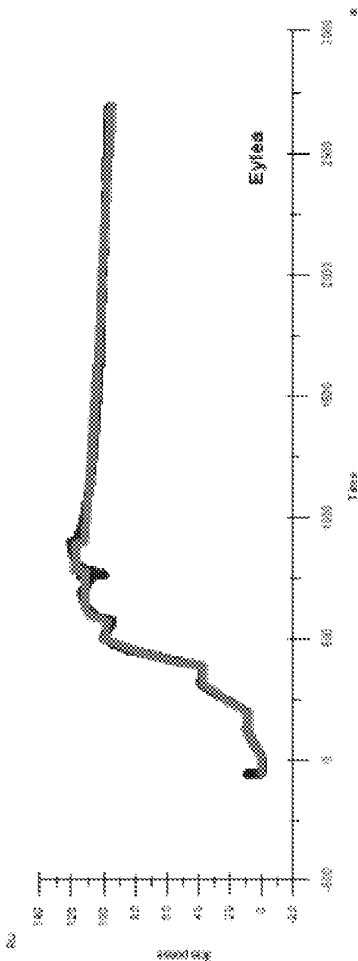


FIG. 26B

Legend	Int1/Mc	Int1/cj	Int1(M)	Int1(RU)
VEGFR-Fc	9.14E+05	9.29E+05	10.20E+12	11.9
Eylea	1.86E+07	1.16E+04	6.21E+12	11.8

FIG. 26C

55/135

Light Chain Sequence

DIQLTQSPSSLSASVGDRVITITCSASISVSYLWYQKPGKAPKLLIYDDSSLASGVPSRFSGSGSGT
DFTLTISLQPEDFATYYCQQWSGYPTFGQGKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN
FYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSP
VTKSFNRGEC (SEQ ID NO: 169)

VL

*CDR (Kabat Numbering)***Heavy Chain Sequence with Notations**

SDTGRPFVEMYSEIPIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYK
EIGLLTCEATVNGHLYKTNLYLTHRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELVGIDFNWEYPS
SKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSPEAMHWVRQAPGKGLEWVAKISPGGS
WYYSDDTVTDRTFSLDTSKSTAYLQMNSLRAEDTAVYYCARQAWGYALDIWGQGLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTP
SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMISRTP
EVTQVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSCSPGK (SEQ ID
NO: 170)

VEGFR

Linker

VH

CDR (Kabat Numbering)

FIG. 27

SDS-PAGE: VEGFR-AntiIL6 reduction (Cys – decapping) reaction products

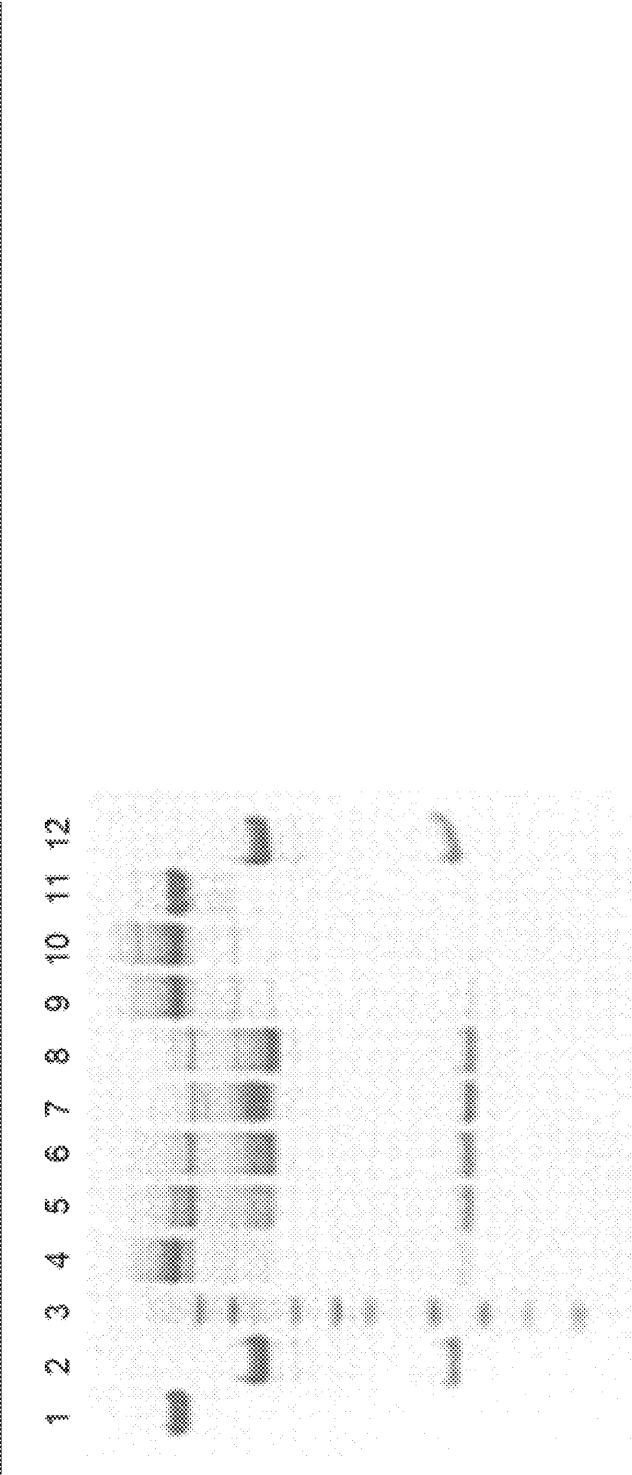


FIG. 28

SDS-PAGE: VEGFR-AntiIL6-OG1802 conjugate CEX chromatography

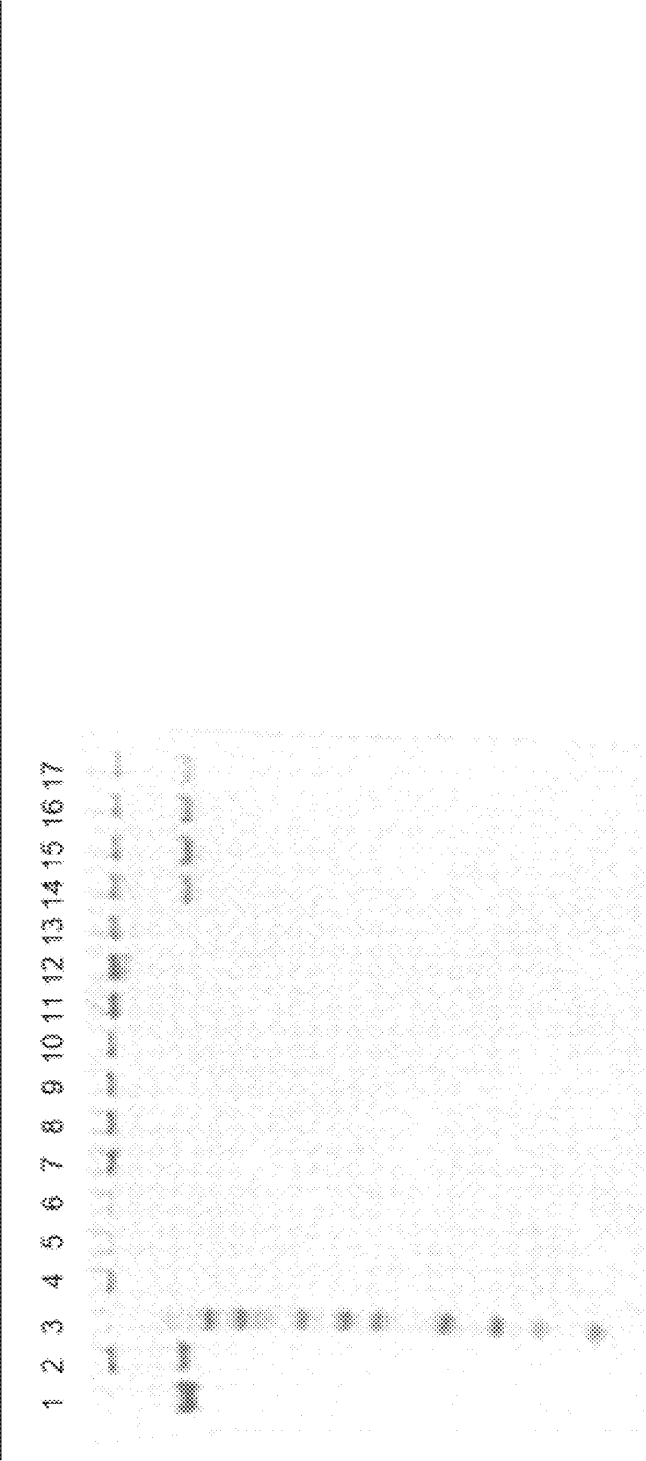


FIG. 29

SDS-PAGE: Protein-polymer conjugate vs non-conjugate protein material

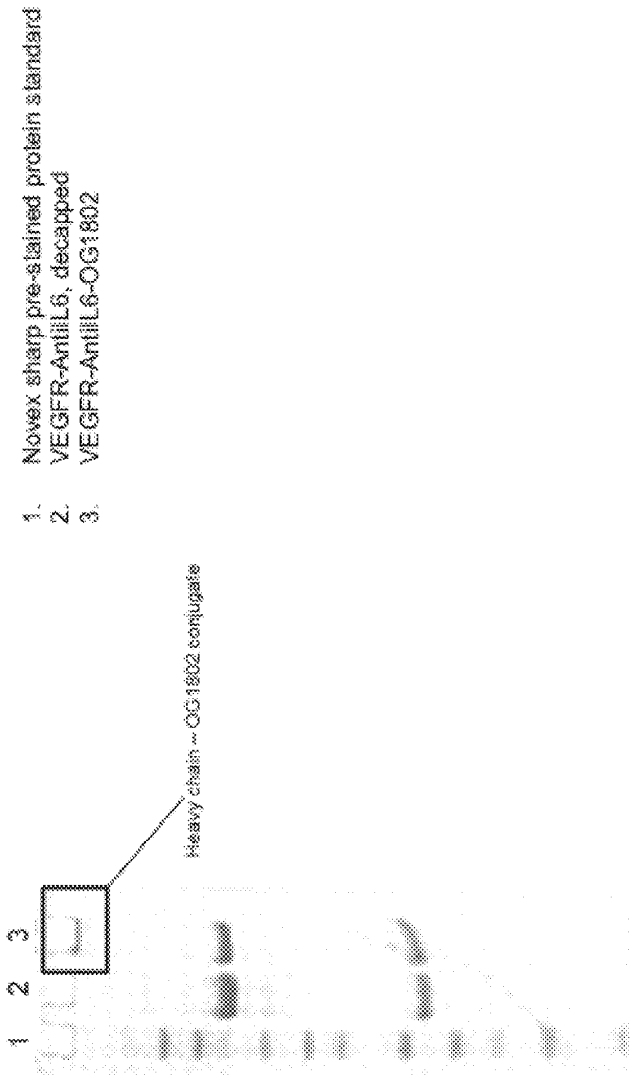


FIG. 30

SEC-MALS: VEGFR-AntiIL6-OG1802

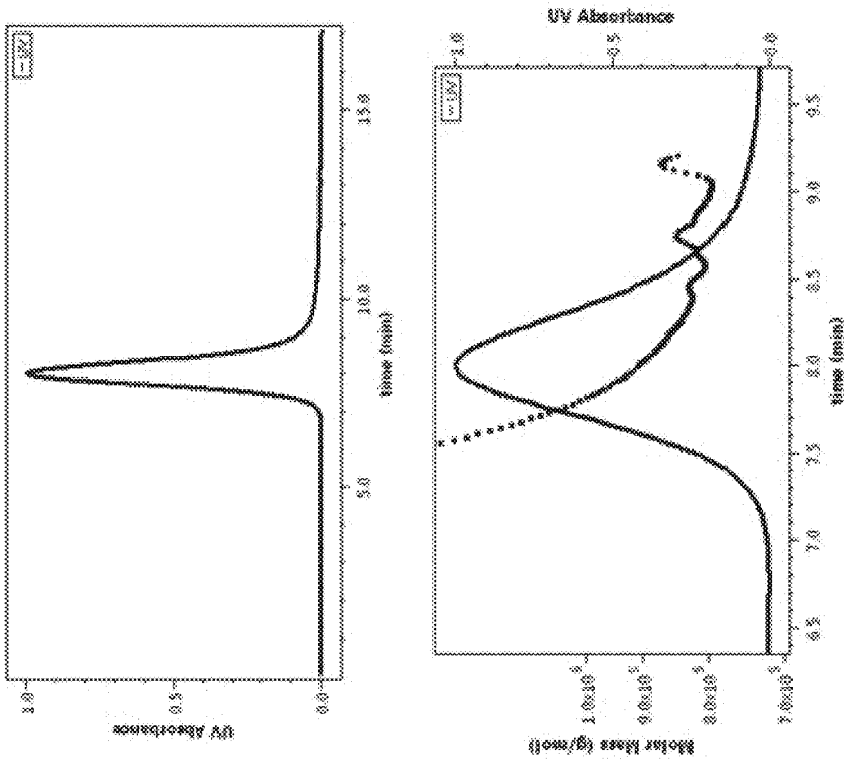


FIG. 31

VEGFR-AntiIL6 CEX chromatography

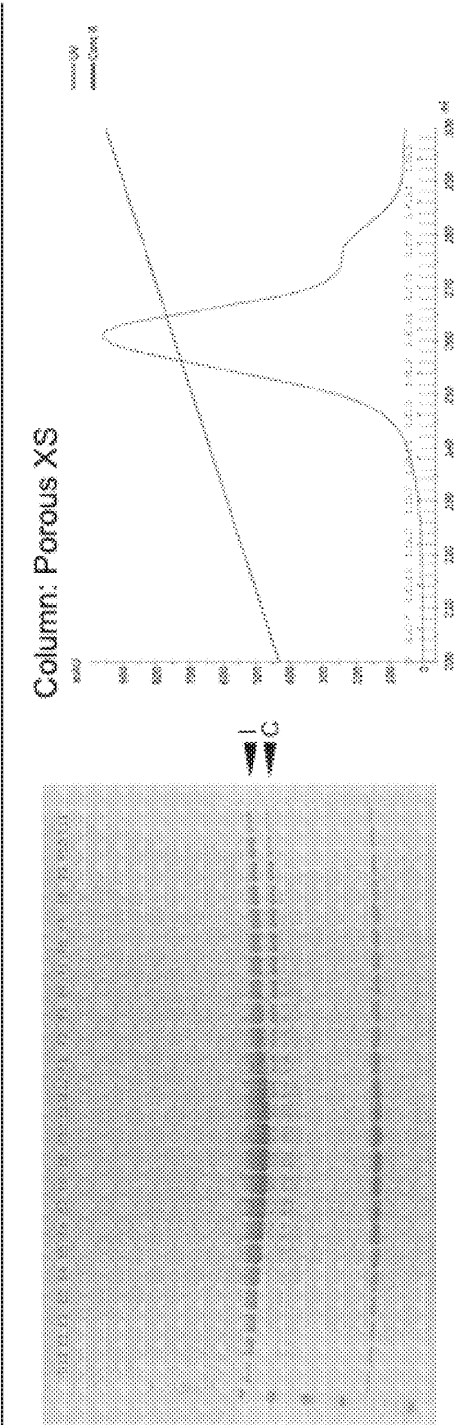


FIG. 32

VEGFR-AntiIL6 HIC chromatography

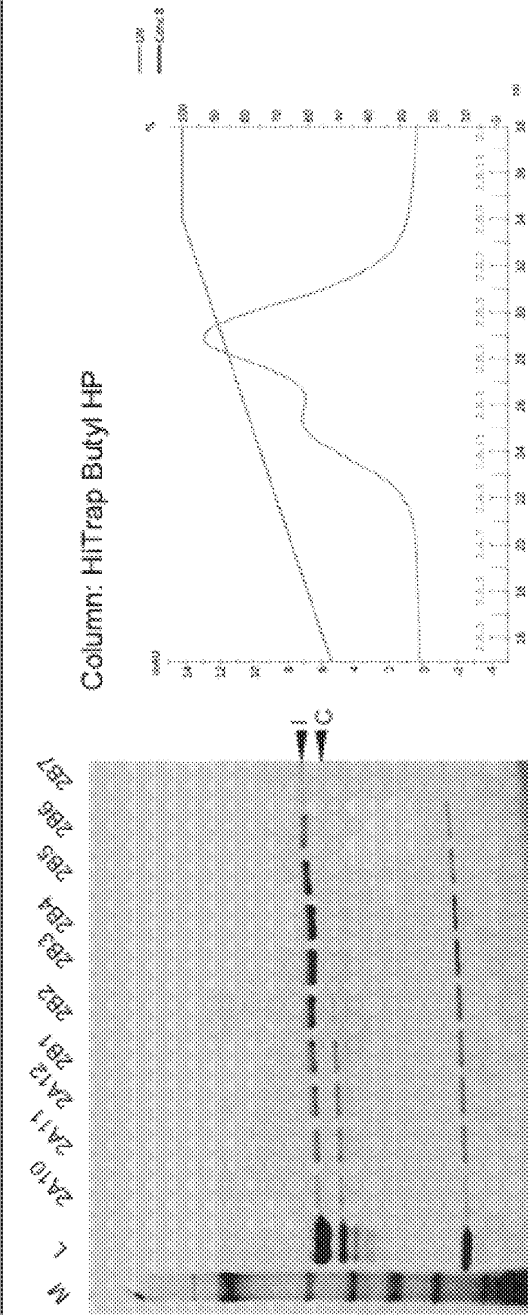


FIG. 33

VEGF/VEGFR competitive ELISA

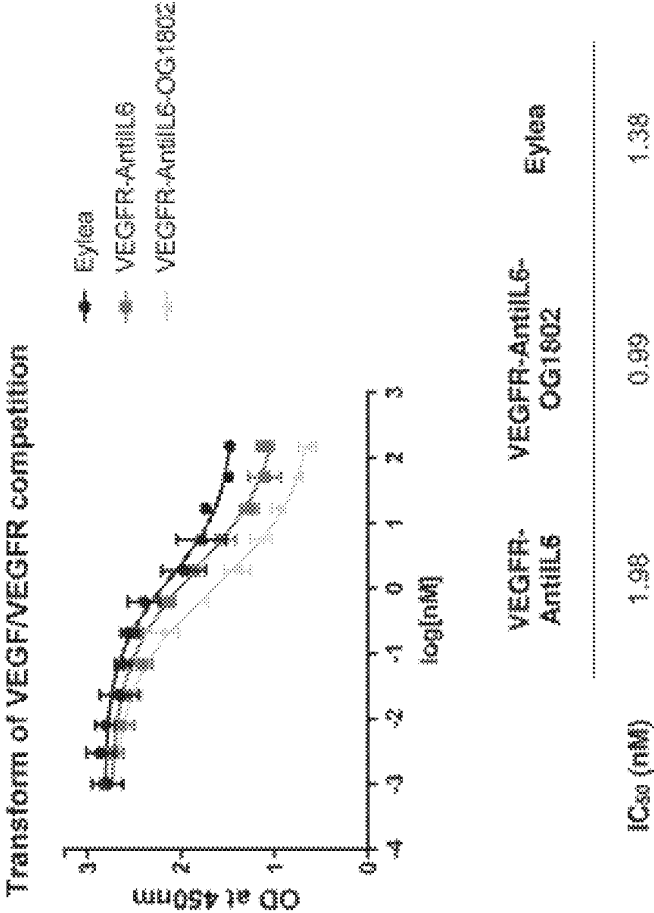


FIG. 34

IL6/IL6R complex ELISA

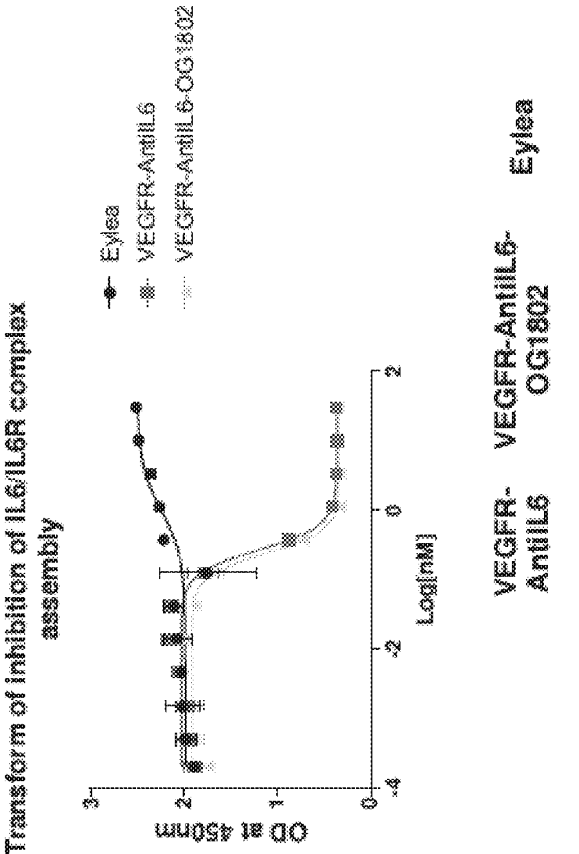
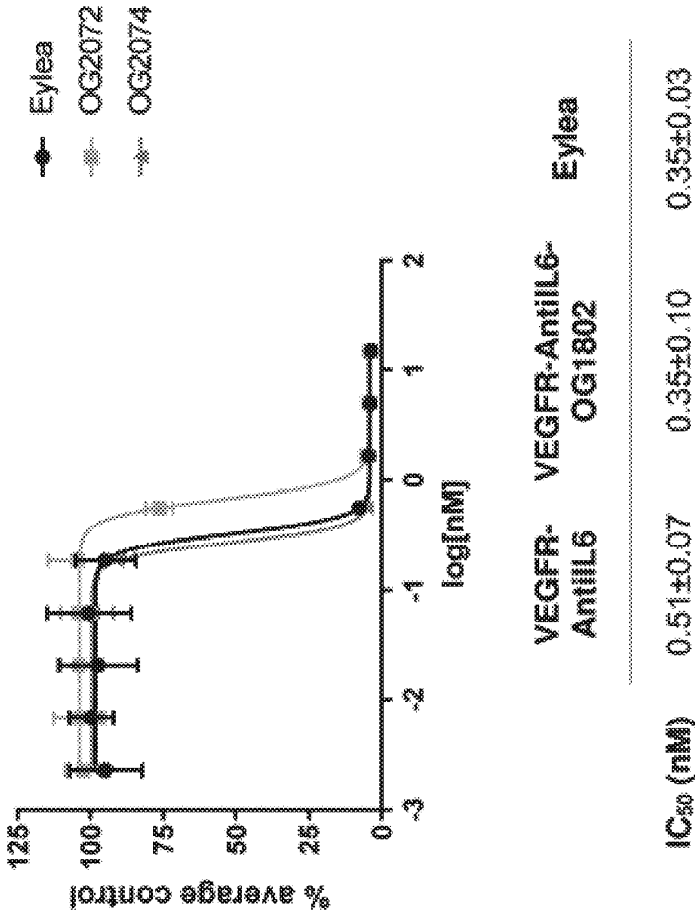


FIG. 35

Cell based VEGF stimulated VEGFR reporter assay



*average of 3 independent experiments

FIG. 36

Lipopolysaccharide stimulated tubule formation in HUVECs

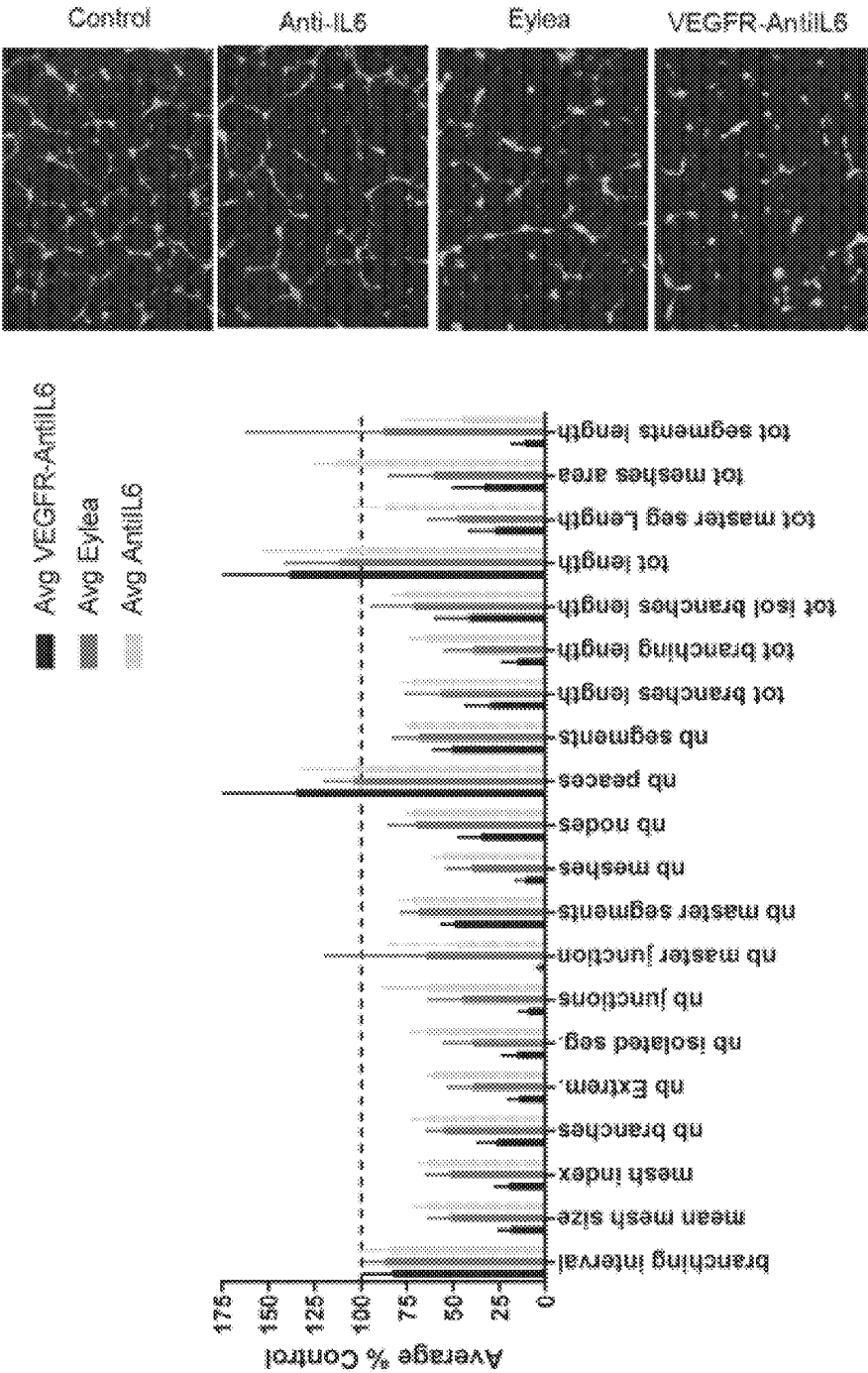


FIG. 37

Lipopolysaccharide stimulated tubule formation in HUVECs

	ttest control	ttest eylea	ttest sirik	ttest control vs eylea	ttest control vs antiIL6
Branching interval	0.1392	0.6240	0.9181	0.2131	0.1689
Mean Mesh Size	0.0025	0.0164	0.0724	0.0733	0.8074
Mesh index	0.0005	0.0245	0.0102	0.0447	0.9311
Nb branches	0.0048	0.0147	0.0082	0.0719	0.4840
Nb extrem.	0.0000	0.0599	0.0000	0.0041	0.9205
Nb isol. seg.	0.0001	0.1210	0.0003	0.0203	0.9159
Nb Junctions	0.0029	0.0306	0.0027	0.0701	0.2399
Nb master junction	0.0007	0.1723	0.0115	0.3979	0.2245
Nb master segments	0.0779	0.0376	0.6322	0.2705	0.1356
Nb meshes	0.0080	0.0383	0.1343	0.0792	0.0537
Nb nodes	0.0199	0.0243	0.1411	0.2684	0.1625
Nb peaces	0.2964	0.3322	0.0627	0.9589	0.0146
Nb segments	0.0639	0.1129	0.9692	0.2413	0.0952
tot branches length	0.0023	0.1139	0.0167	0.0754	0.4362
Tot branching length	0.0009	0.1307	0.0062	0.0215	0.1494
tot isol. branches length	0.0087	0.1475	0.0202	0.4444	0.9355
tot length	0.4559	0.5253	0.0843	0.8983	0.0904
tot master segments length	0.0074	0.2439	0.0943	0.0344	0.0469
tot meshes area	0.0654	0.2517	0.6446	0.2118	0.1869
tot segments length	0.0014	0.1900	0.0287	0.6551	0.0317
VEGFR-AntiIL6 Significance					

Statistical significance of HUVEC tubule inhibition shown in grey (p<0.05 by Student's t-test; n=3 independent experiments).

- First three columns are VEGFR-AntiIL6 compared to control, Eylea, or Anti-IL6.
- Next two columns are Eylea or Anti-IL6 compared to control

FIG. 38

Lipopolysaccharide stimulated tubule formation in HUVECs

VEGFR-AntiIL6 with and without biopolymer inhibit LPS mediated HUVEC tubule formation to similar degrees.

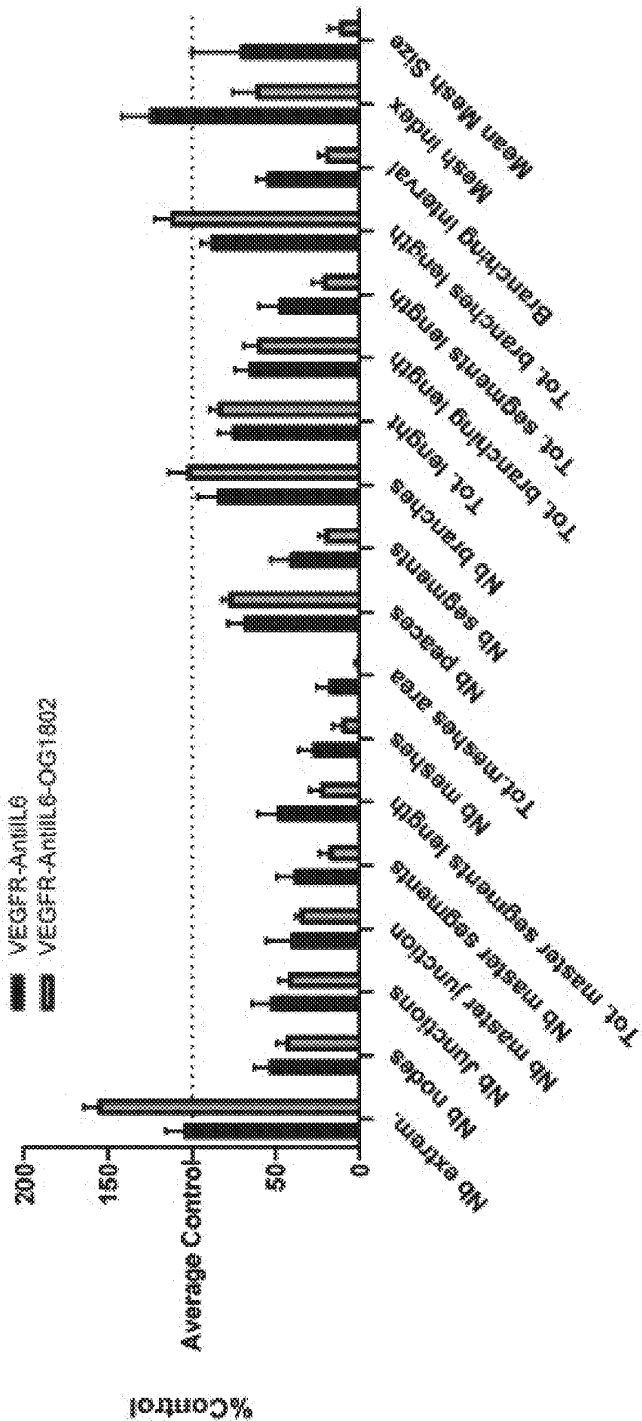


FIG. 39

HUVEC proliferation assay

FIG. 40A

Inhibit of VEGF/IL6 mediated proliferation of HUVECs

IL6/VEGF mediated HUVEC Proliferation

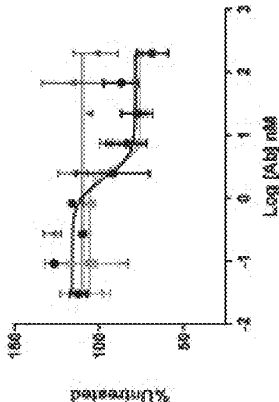
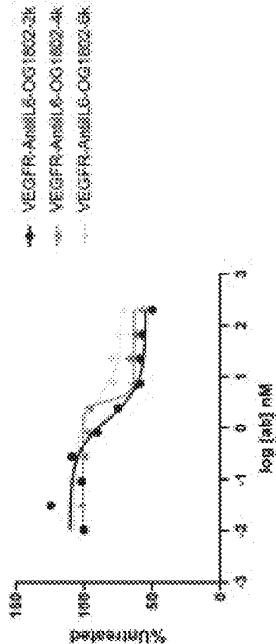


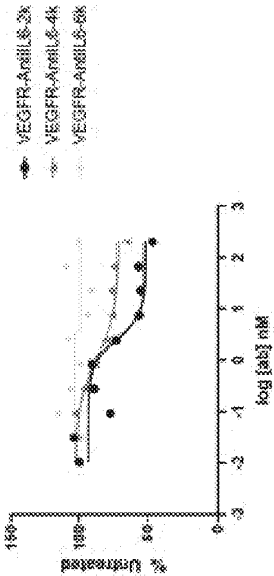
FIG. 40B

Inhibition of HUVEC proliferation with increasing number of cells per well

VEGFR-AntiIL6-OG1802



VEGFR-AntiIL6



Non-reducing SDS-PAGE gel (heated).

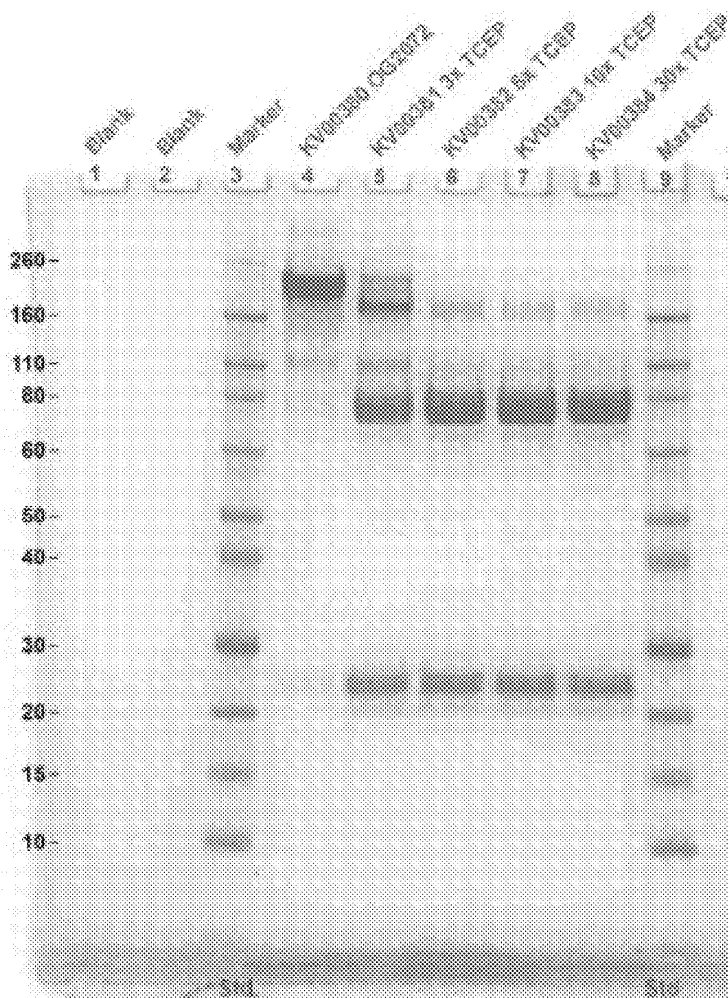


FIG. 41A

Non-reducing SDS-PAGE (left: heated, right: non-heated).

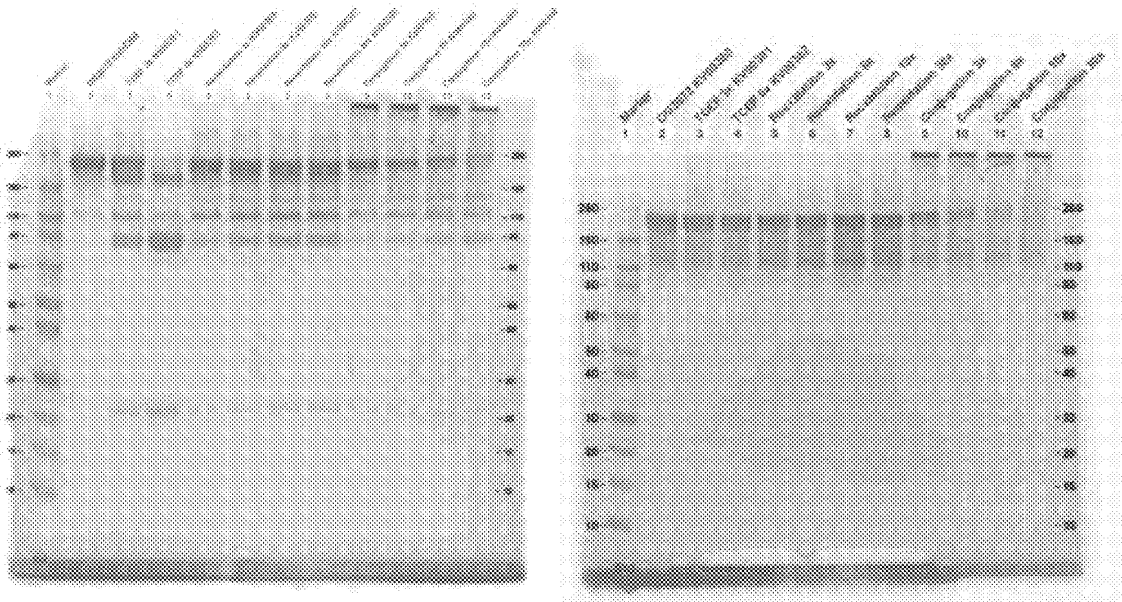


FIG. 41B

71/135

Native PAGE, left; IEF PAGE, right

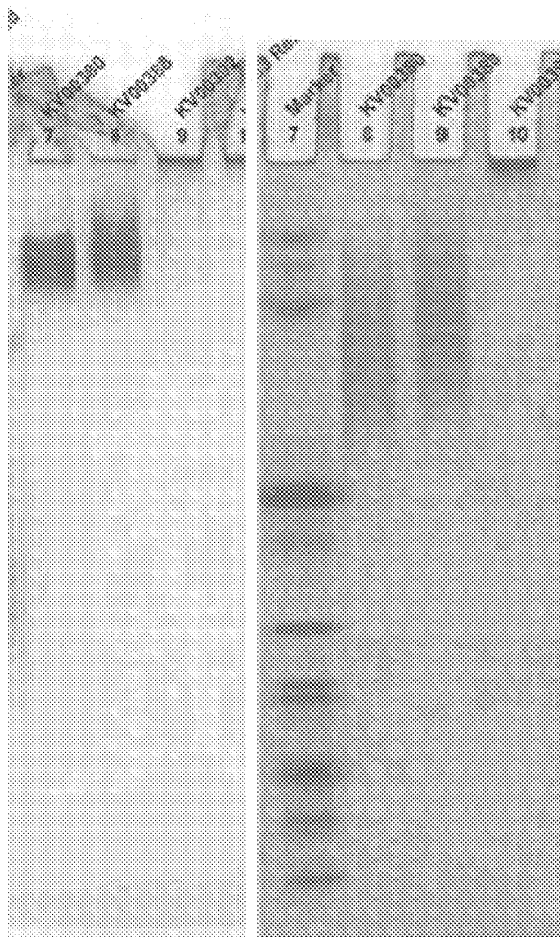


FIG. 41C

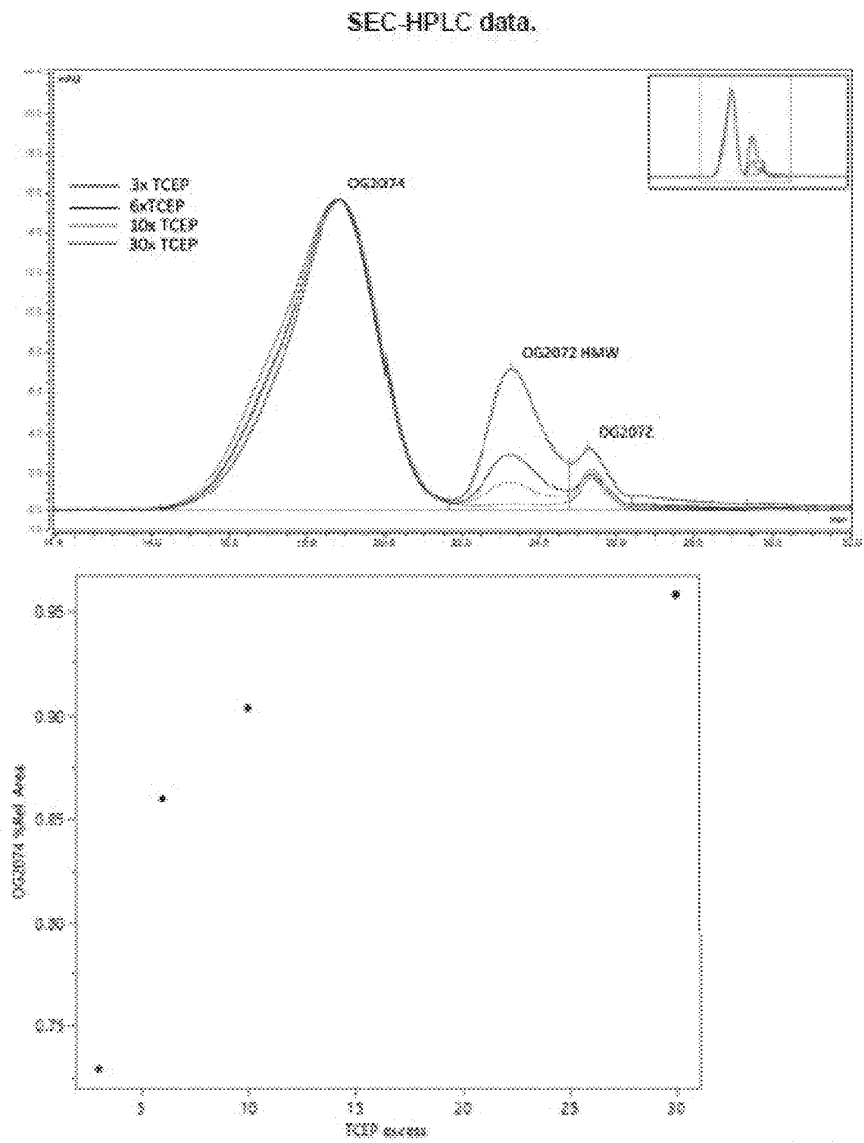


FIG. 42

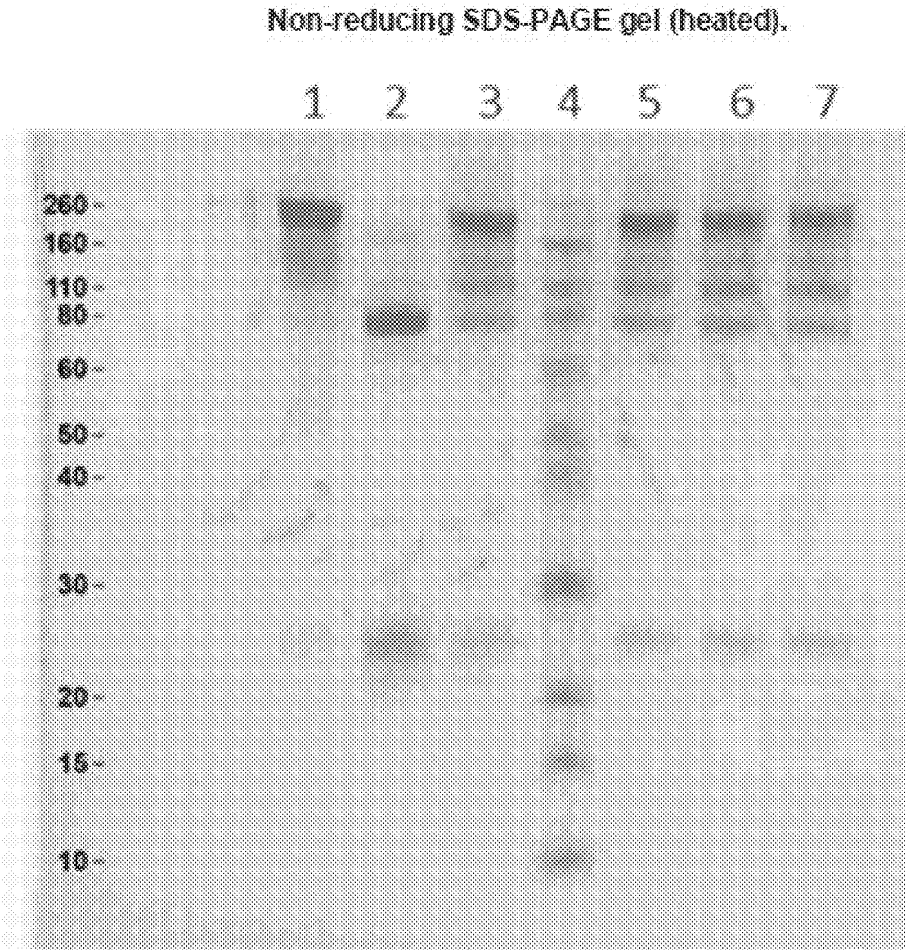


FIG. 43

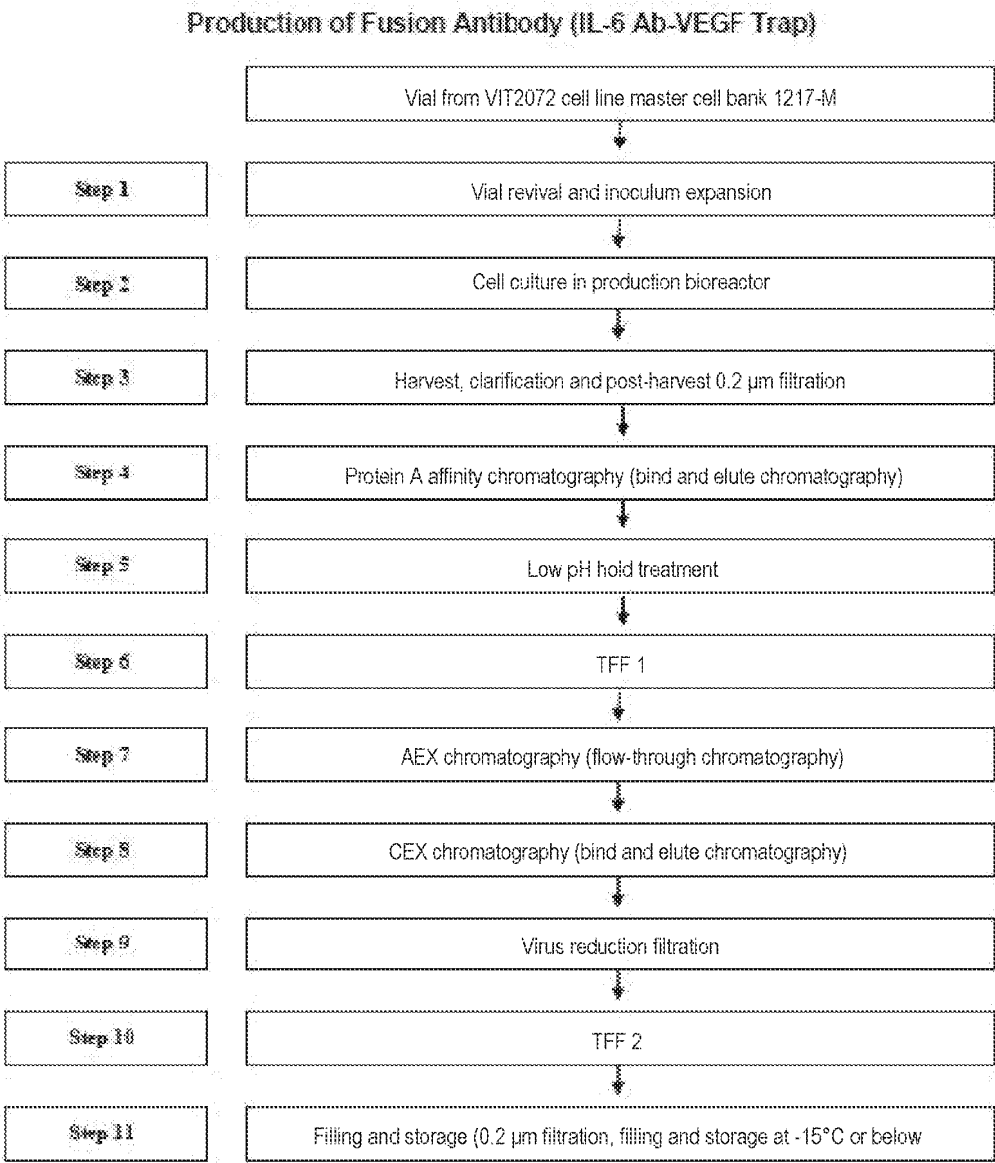


FIG. 44

Production of combined dual inhibitor molecule (VEGFR-AntiIL6-OG1802)

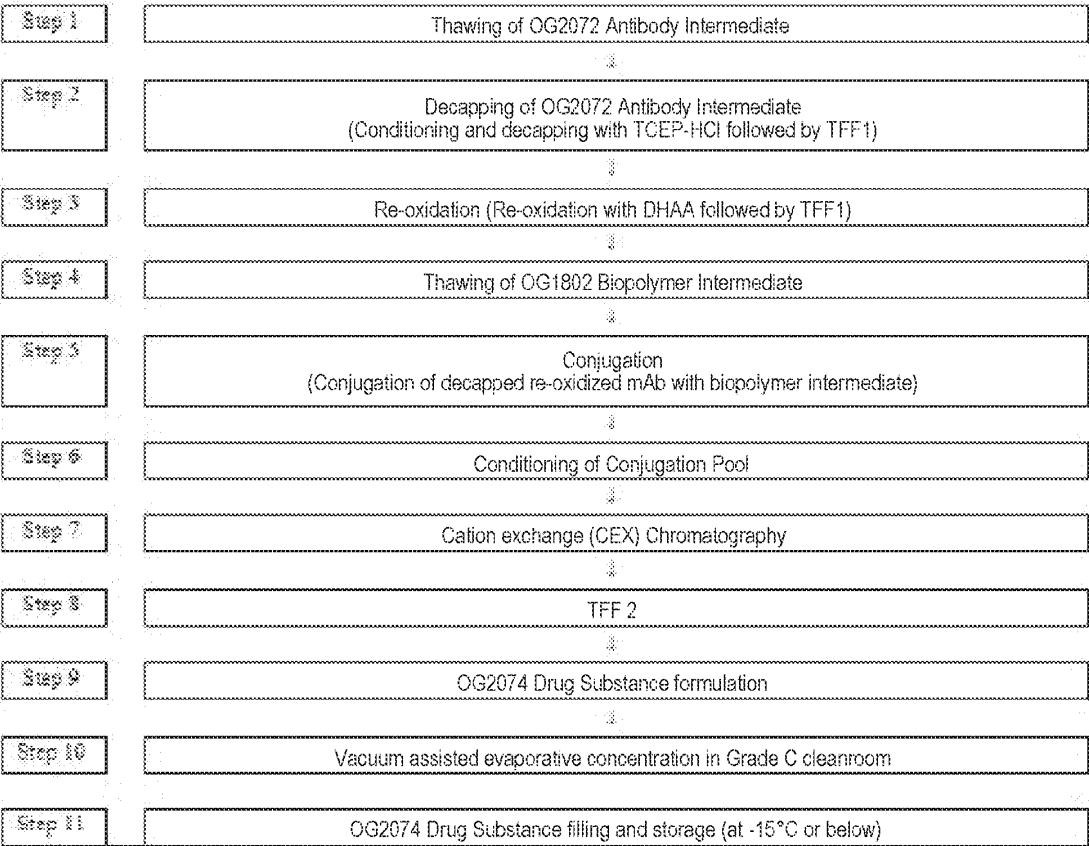


FIG. 45

Exp	OG2072 [g/L]	Buffering strength [mM]	pH	NaCl [mM]	Sucrose [%]
1	75	50	5.5	40	6
2	75	10	4.5	0	0
3	100	30	4.5	40	6
4	50	30	5.5	0	0
5	100	10	5	0	6
6	50	50	5	40	0
7	100	50	4.5	20	0
8	50	10	5.5	20	6
9	100	50	5.5	0	3
10	50	10	4.5	40	3
11	100	10	5.5	40	0
12	50	50	4.5	0	6
13	75	30	5	20	3
14	75	30	5	20	3

FIG. 46

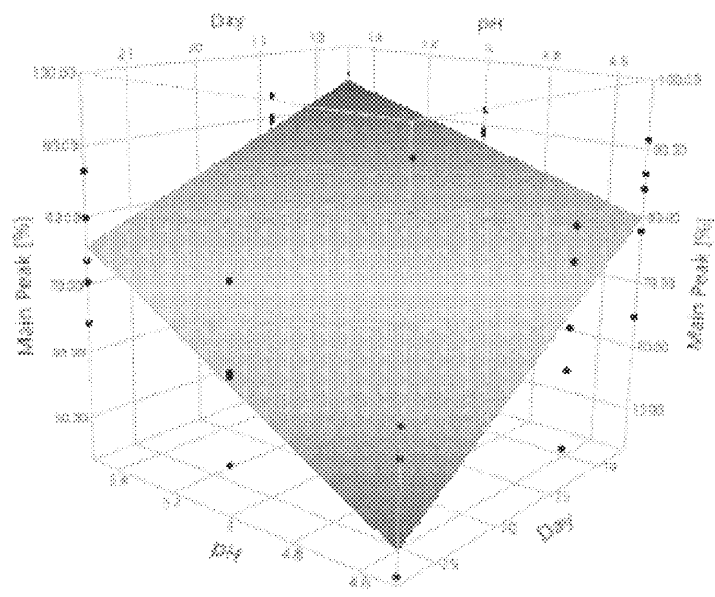


FIG. 47A

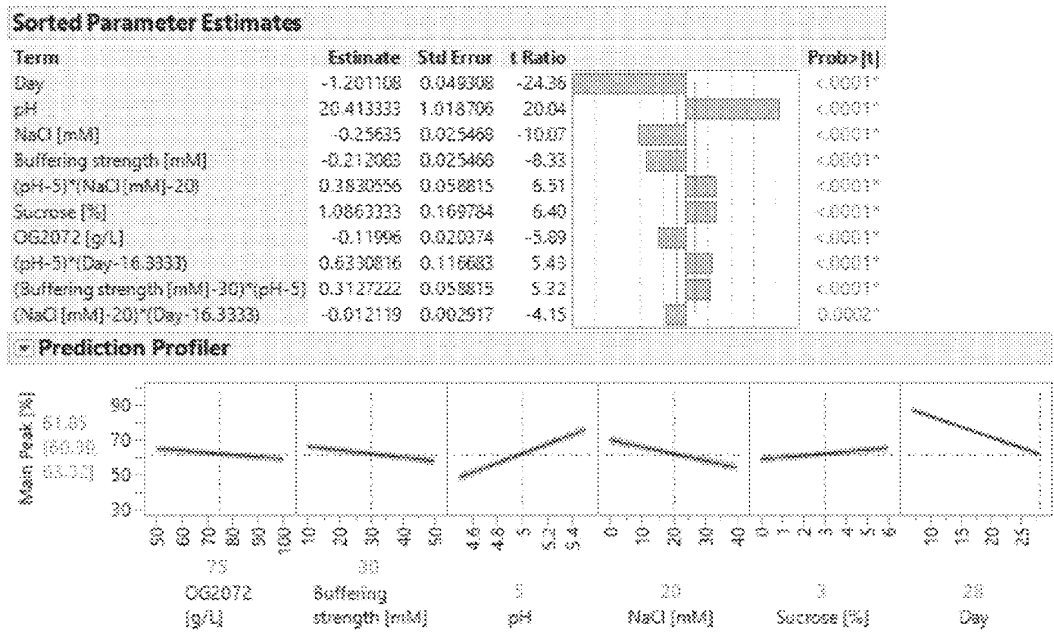


FIG. 47B

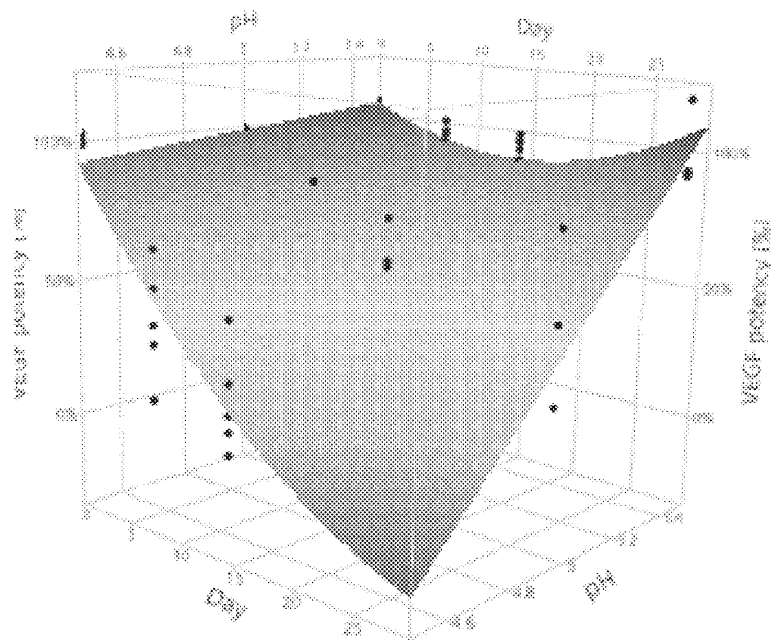


FIG. 48A

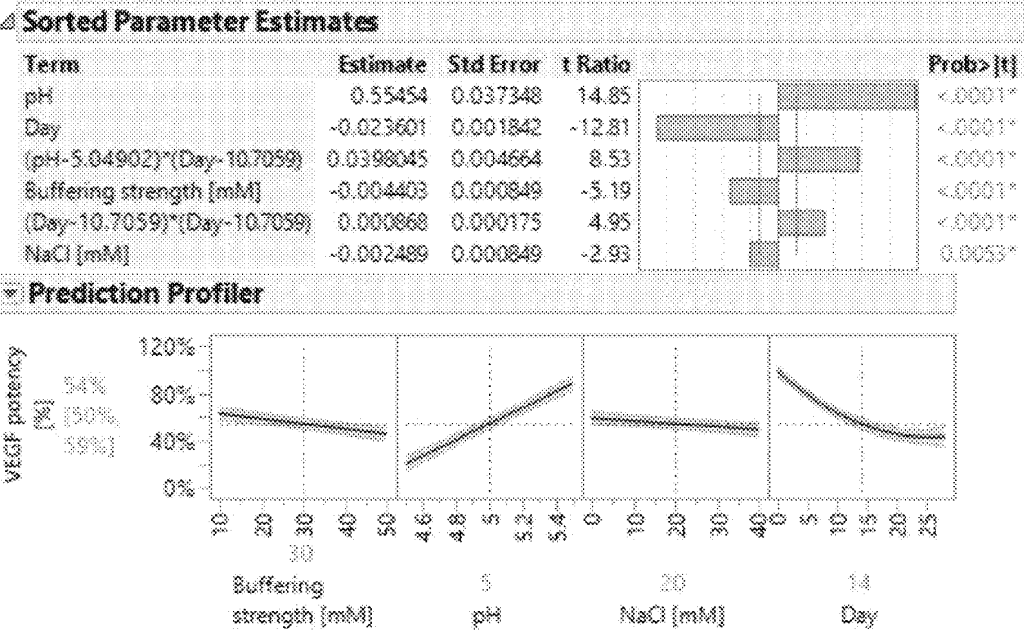


FIG. 48B

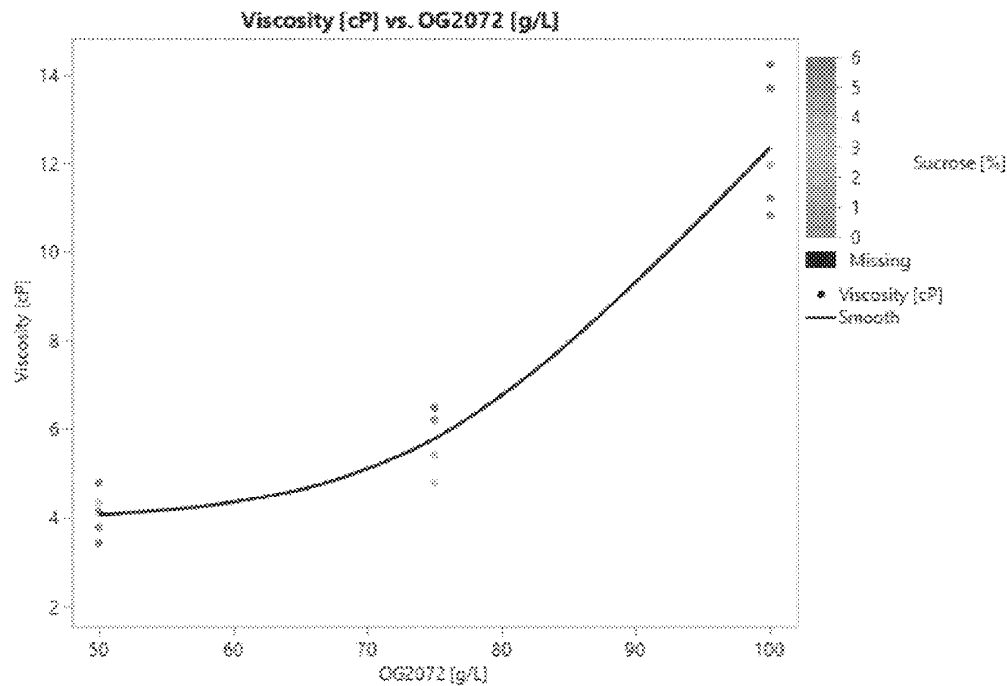


FIG. 49A

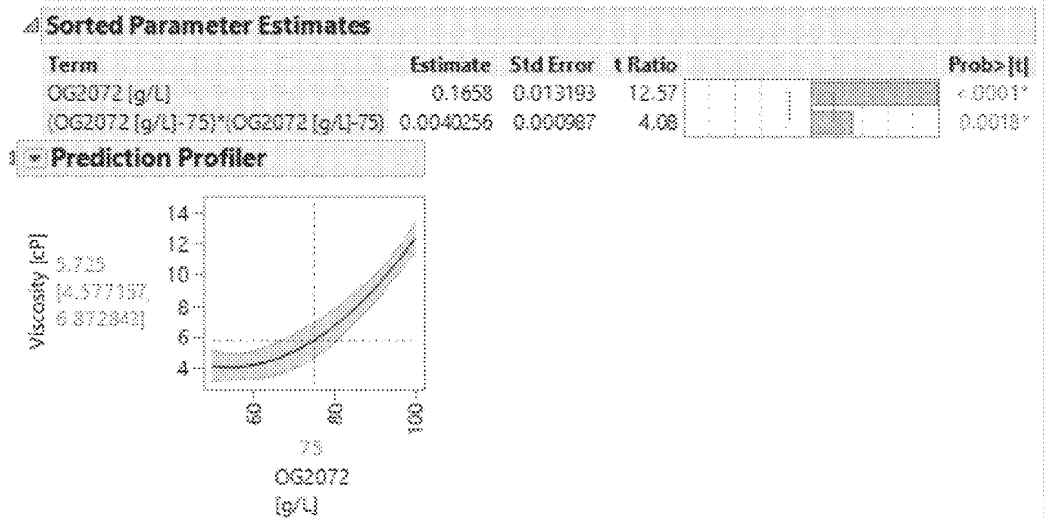


FIG. 49B

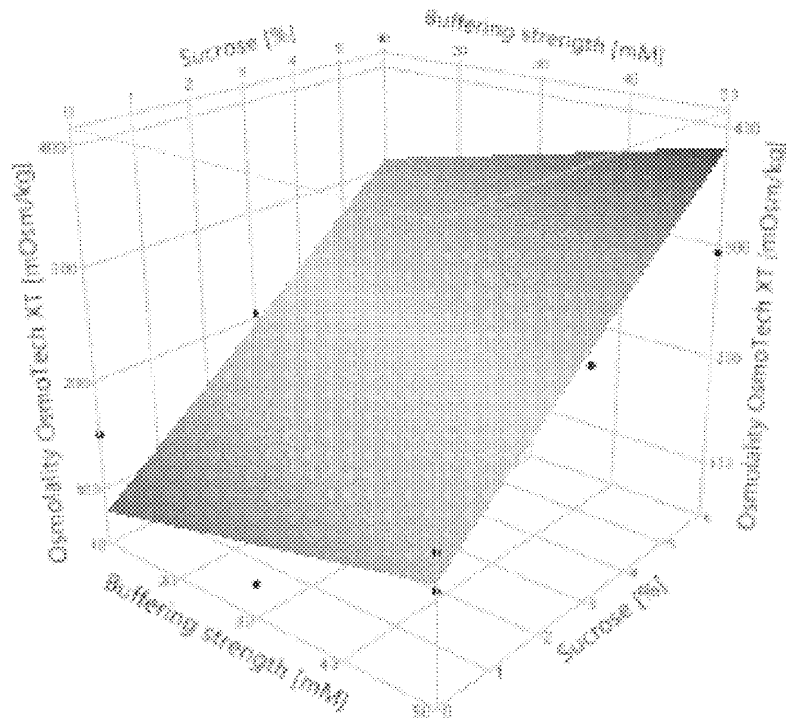


FIG. 50A

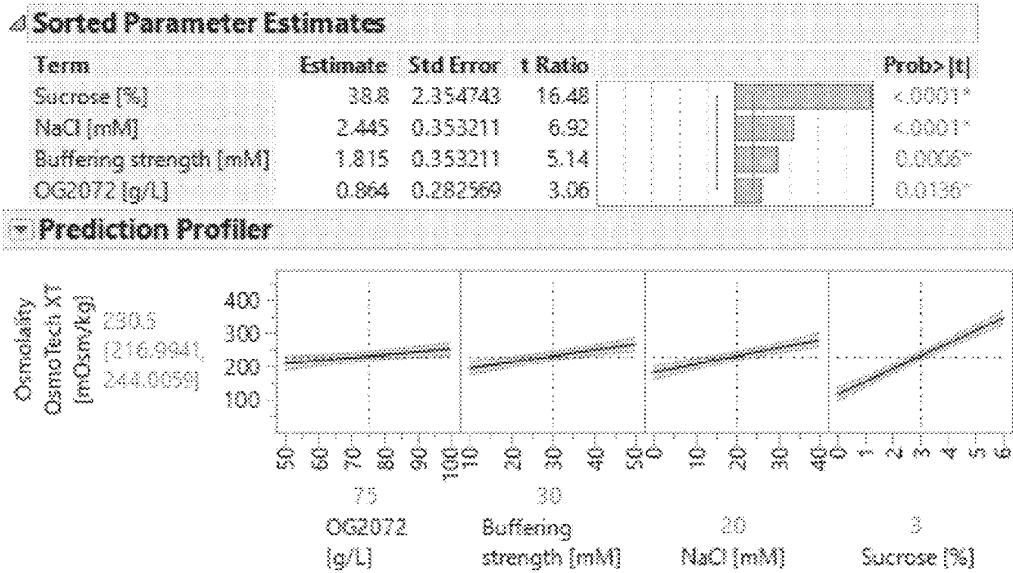


FIG. 50B

Parameter	SEC-HPLC	Potency	Viscosity	Osmolality
pH	+++	+++	0	0
OG2072 conc.	-	0	+++	+
NaCl	--	-	0	++
Buffering strength	-	-	0	++
Sucrose	+	0	0	+++

FIG. 51

	Current	Future
Unconjugated antibody	20 mM histidine 200 mM arginine pH 6.0 20 mg/ml protein concentration	15 mM sodium acetate 5.2% (w/v) sucrose 0.025% (w/w) polysorbate 20 pH 5.5 100 mg/ml protein concentration
Conjugated or partially conjugated antibody	15.2 mM sodium acetate 0.026% polysorbate 20 pH 5.0 52.5 mg/ml protein concentration 100% conjugated	50 mM sodium acetate 4% (w/v) sucrose 0.025% polysorbate 20 pH 5.0 50.0 mg/ml protein concentration 70% conjugated / 30% unconjugated or 25 mM histidine acetate 6% (w/v) sucrose 0.025% polysorbate 20 pH 5.5 50.0 mg/ml protein concentration 70% conjugated / 30% unconjugated

FIG. 52

Exp.	DS (68% OG2074, 32% OG2072)	sucrose
E5353	50.2 mg/ml, pH 4.97	-
E5366	50.0 mg/ml, pH 4.81	-
E5413	50.5 mg/ml, pH 4.83	-
E5456	52.5 mg/ml, pH 4.78	-
E5660	51.5 mg/ml, pH 4.87	+
E5682	51.1 mg/ml, pH 4.81	+

FIG. 53

Sample ID	Formulation buffer	Intended free antibody OG1950	Protein conc. (mg/ml)
#1	OG1950PUR 10%, OG1953 90% + 50mM histidine, 0.025% Tween20, pH 5.2	10.0%	53.4
#2	OG1950PUR 10%, OG1953 90% + 50mM sodium acetate, 0.025% Tween20, pH 5.0	10.0%	50.9
#3	OG1950PUR 15%, OG1953 85% + 50mM sodium acetate, 0.025% Tween20, pH 5.0	15.0%	50.5*
#4	OG1950PUR 20%, OG1953 80% + 50mM sodium acetate, 0.025% Tween20, pH 5.0	20.0%	49.8
#5	OG1950PUR 7.5%, OG1953 92.5% + 50mM histidine, 0.025% Tween20, pH 5.2	7.5%	51.9
#6	OG1950IAM 10%, OG1953 90% + 50mM histidine, 0.025% Tween20, pH 5.2	10.0%	52.6
#7	OG1950IAM 10%, OG1953 90% + 50mM sodium acetate, 0.025% Tween20, pH 5.0	10.0%	61.9
#8	OG1950IAM 15%, OG1953 85% + 50mM sodium acetate, 0.025% Tween20, pH 5.0	15.0%	53.5
#9	OG1950IAM 20%, OG1953 80% + 50mM sodium acetate, 0.025% Tween20, pH 5.0	20.0%	52.6
#10	7.5mg/ml OG1950PUR + 230mg/ml OG1801 polymer pH 5.2	100%	7.5

* Sample #3 contains 7.5mg/ml OG1950PUR as unconjugated form, 42.5mg/ml OG1950 in conjugated form with 225mg/ml polymer. Sample #10 is setup to evaluate the impact of polymer on 7.5mg/ml unconjugated protein.

FIG. 54

	Sample ID	Formulation buffer	IC50 (pM)	Percent relative potency (%RP)
Plate 1	OG1953 reference standard	5mM sodium phosphate, 0.01% Tween 20, pH 6.5	1507	100%
	#1	OG1950PUR_10%, OG1953_90% + 50mM histidine, 0.025% Tween20, pH 5.2	1598	94%
	#2	OG1950PUR_10%, OG1953_90% + 50mM sodium acetate, 0.025% Tween20, pH 5.0	1632	92%
	#3	OG1950PUR_15%, OG1953_85% + 50mM sodium acetate, 0.025% Tween20, pH 5.0	1669	90%
	#4	OG1950PUR_20%, OG1953_80% + 50mM sodium acetate, 0.025% Tween20, pH 5.0	1652	91%
Plate 2	OG1953 reference standard	5mM sodium phosphate, 0.01% Tween 20, pH 6.5	1505	100%
	#5	OG1950PUR_7.5%, OG1953_92.5% + 50mM histidine, 0.025% Tween20, pH 5.2	1561	96%
	#6	OG1950IAM_10%, OG1953_90% + 50mM histidine, 0.025% Tween20, pH 5.2	1622	93%
	#7	OG1950IAM_10%, OG1953_90% + 50mM sodium acetate, 0.025% Tween20, pH 5.0	1585	95%
	#8	OG1950IAM_15%, OG1953_85% + 50mM sodium acetate, 0.025% Tween20, pH 5.0	1565	96%
	#9	OG1950IAM_20%, OG1953_80% + 50mM sodium acetate, 0.025% Tween20, pH 5.0	1526	99%

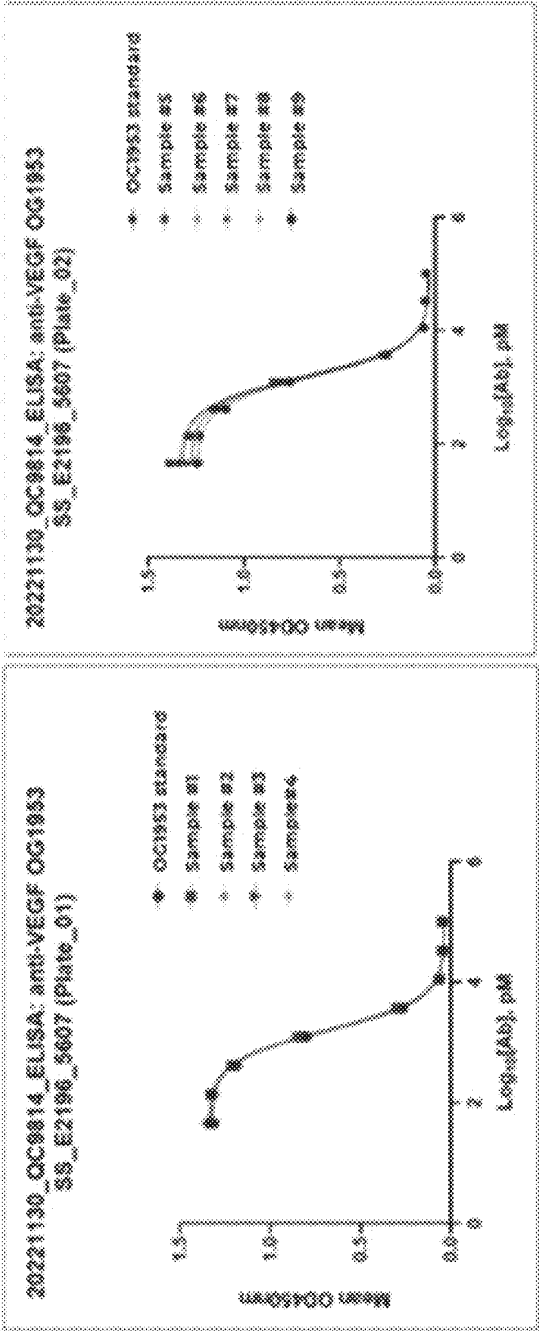


FIG. 55

85/135

Molecule of Interest	Sample/Sample ID	Sample Description	Time (Month)	Temp (C°)	Plate 1	%RP
					Plate 2	
RS 1	R9407A INT Scale DS	5mM Sodium phosphate pH 6.5, 0.01% T _w 20			1768	100%
RS 2	R9407A INT Scale DS	5mM Sodium phosphate pH 6.5, 0.01% T _w 20			1993	100%
E2196_5619#31	Sample #4	OG1950PUR 20%, OG1953 80% - 50mM Na-acetate, 0.025% Tween, pH 5.0	2	37	1882	94%
E2196_5619#40	Sample #4		2	25	1828	97%
E2196_5619#49	Sample #4		2	5	1776	100%
E2196_5619#36	Sample #9		2	37	2024	98%
E2196_5619#45	Sample #9	OG1950IAM 20%, OG1953 80% - 50mM Na-acetate, 0.025% Tween, pH 5.0	2	25	2058	97%
E2196_5619#54	Sample #9		2	5	2051	97%

FIG. 56

Legends	Time	Temp	Sample#	10.0%	10.0%	15.0%	20.0%	7.5%
A	0		T0_QC9772	53.45	50.94	50.48	49.81	51.86
B	1	5	T1M_5°C	52.59	50.10	50.02	49.31	51.02
C	1	25	T1M_25°C	52.49	50.12	49.74	49.18	51.14
D	1	37	T1M_37°C	52.42	49.89	49.49	48.98	50.74
E	2	5	T2M_5°C	53.17	49.82	49.96	49.29	50.65
F	2	25	T2M_25°C	52.48	49.98	49.61	49.27	51.08
G	2	37	T2M_37°C	52.28	49.67	49.59	48.96	51.17
H	6	5	T6M_5°C	53.30	50.35	49.70	48.74	50.69
I	6	25	T6M_25°C	52.83	50.29	49.77	49.39	51.92
J	6	37	T6M_37°C	51.17	51.18	50.05	49.93	52.10
			Mean	53.49	50.82	50.68	49.86	51.94
			%SD/mean	1.5%	2.7%	2.6%	2.6%	1.1%

Legends	Time	Temp	Sample#	10.0%	10.0%	15.0%	20.0%	100.0%
A	0		T0_QC9772	52.59	61.92	53.46	52.60	
B	1	5	T1M_5°C	53.29	61.37	52.72	52.20	
C	1	25	T1M_25°C	51.79	61.10	52.40	52.26	
D	1	37	T1M_37°C	51.61	60.66	51.85	52.07	
E	2	5	T2M_5°C	51.71	61.09	52.24	52.90	7.62
F	2	25	T2M_25°C	51.57	60.83	52.37	51.77	7.44
G	2	37	T2M_37°C	54.63	60.80	52.39	51.91	8.08
H	6	5	T6M_5°C	52.18	62.37	51.67	51.78	7.19
I	6	25	T6M_25°C	51.19	63.18	52.94	51.66	9.02
J	6	37	T6M_37°C	48.70	62.27	54.42	51.78	7.30
			Mean	52.46	62.46	53.52	52.65	8.32
			%SD/mean	3.4%	3.2%	2.7%	2.7%	8.9%

FIG. 57

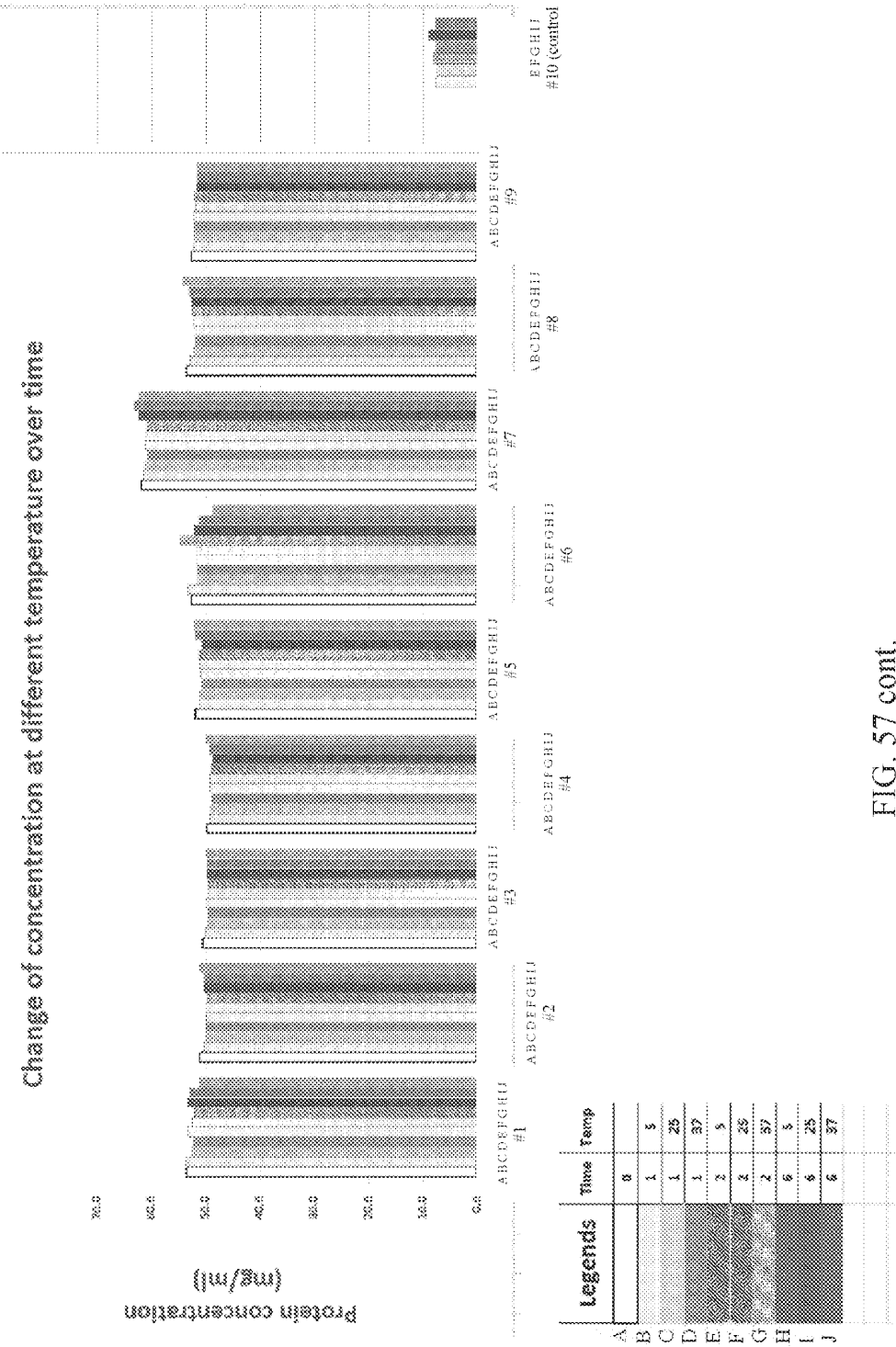


FIG. 57 cont.

88/135

		Time (Month)	5°C								
	Formulations		#1	#2	#3	#4	#5	#6	#7	#8	#9
Appearance	Color and clarity (Visual)	0	CCS ²	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
		1	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
		2	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
		3	Cloudy white	CCS	CCS	CCS	CCS	Cloudy white	CCS	CCS	CCS
		6	Cloudy white	CCS	CCS	CCS	CCS	Cloudy white	CCS	CCS	CCS
SeloVPE (Strength)	Protein concentration (mg/ml)	0	53.45	50.94	50.48	49.81	51.86	52.59	61.92	53.46	52.60
		1	53.59	50.20	50.02	49.31	51.02	53.29	61.57	52.72	52.20
		2	53.17	49.62	49.96	49.29	50.85	51.71	61.09	52.24	52.30
		3	56.57	53.45	53.28	52.60	55.59	55.48	66.26	56.13	55.49
		6	53.30	50.35	49.70	48.74	50.69	52.13	62.37	52.07	51.78
Tandem method analysis (Purity)	Bioconjugate main peak percent (LP1)		90.0%	90.0%	85.0%	80.0%	92.5%	90.0%	90.0%	85.0%	80.0%
		0			86.5%	81.3%					80.9%
		1			86.5%	81.4%					81.3%
		2			87.1%	82.0%					81.8%
		3			86.4%	81.1%					84.8%
		6			86.3%	80.3%					84.5%
			10.0%	10.0%	15.0%	20.0%	7.5%	10.0%	10.0%	15.0%	20.0%
	Free unconjugated protein monomer peak percent (monomer)	0			12.6%	17.8%					18.1%
		1			12.5%	17.6%					17.6%
		2			12.2%	17.1%					17.2%
		3			12.4%	17.4%					17.9%
		6			12.2%	17.6%					16.9%
	All other peak percent	0			0.9%	0.9%					1.0%
		1			0.9%	1.0%					1.1%
		2			0.7%	0.9%					0.9%
		3			1.2%	1.4%					-2.7%
		6			1.5%	2.1%					-1.4%
SEC-HPIC (Purity)	Bioconjugate specific aggregate	0	All below 5%								
		1									
		2									
		3									
		6									
SEC/MALS (Purity and Identity)	weighted averaged molecular weight (M _w) kDa	0	1007.0	997.3	998.0	976.2	988.1	974.0	982.3	976.3	981.1
		6	1001.0	987.2	977.8	973.4	980.8	972.5	977.2	968.4	969.1
	Polydispersity Index (PDI)	0	1.063	1.059	1.054	1.056	1.064	1.047	1.051	1.052	1.047
		1	1.084	1.079	1.076	1.073	1.080	1.073	1.073	1.076	1.072
		2	1.085	1.057	1.092	1.091	1.056	1.051	1.047	1.052	1.048
		3	1.057	1.059	1.054	1.054	1.061	1.051	1.058	1.055	1.057
		6	1.053	1.056	1.053	1.049	1.058	1.049	1.054	1.051	1.050
Competitive ELISA (Potency)	Percent activity relative to Reference standard	0	94	92	90	91	96	93	95	96	99
		1									
		2					160				97
		3					162				
		6					92				

¹There is assay measurement issue that result in arbitrarily higher values.²CCS is a clear and colorless solution; Cloudy white is the solution appears visually cloudy and/or no longer colorless.

FIG. 58

89/135

		Time (Month)	25°C								
	Formulations		#1	#2	#3	#4	#5	#6	#7	#8	#9
Appearance	Color and clarity (Visual)	0	CCS ²	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
		1	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
		2	Cloudy white	CCS	CCS	CCS	CCS	Cloudy white	CCS	CCS	CCS
		3	Cloudy white	CCS	CCS	CCS	CCS	Cloudy white	CCS	CCS	CCS
		6	Cloudy white	CCS	CCS	CCS	CCS	Cloudy white	CCS	CCS	CCS
SolVPE (Strength)	Protein concentration (mg/ml)	0	53.45	50.94	50.48	49.81	51.86	52.59	61.92	53.46	52.60
		1	52.49	50.12	49.74	49.19	51.14	51.73	61.20	52.40	51.28
		2	52.48	49.98	49.61	49.27	51.08	51.57	60.83	52.37	51.77
		3	56.18	53.95	52.48	52.80	55.19	54.85	66.73	56.25	55.94
		6	52.83	50.29	49.77	49.39	51.92	51.29	63.14	52.94	51.66
Tandem method analysis (Purity)	Bioconjugate main peak percent (LP1)	0	90.0%	90.0%	85.0%	80.0%	92.5%	90.0%	90.0%	85.0%	80.0%
		1			86.5%	81.3%					80.9%
		2			85.8%	80.6%					80.3%
		3			86.1%	81.1%					80.8%
		6			84.6%	79.3%					81.0%
		6			83.7%	77.5%					78.4%
	Free unconjugated protein monomer peak percent (monomer)	0	10.0%	10.0%	15.0%	20.0%	7.5%	10.0%	10.0%	15.0%	20.0%
		1			12.6%	17.8%					18.1%
		2			12.7%	18.0%					18.1%
		3			12.2%	17.4%					17.5%
		6			13.2%	18.2%					17.5%
		6			13.1%	18.5%					17.8%
	All other peak percent	0			0.9%	0.9%					1.0%
		1			1.4%	1.4%					1.6%
		2			1.7%	1.6%					1.7%
		3			2.2%	2.4%					1.4%
		6			3.2%	3.6%					3.8%
SEC-HPLC (Purity)	Bioconjugate specific aggregate	0	All below 5%								
		1									
		2									
		3									
		6									
SEC/MALS (Purity and Identity)	weighted averaged molecular weight (M _w) kDa	0	1007.0	997.8	988.0	976.2	988.1	974.0	982.3	978.9	981.1
		6	997.2	998.1	973.5	970.9	993.0	975.3	993.5	971.1	988.3
	Polydispersity Index (PDI)	0	1.063	1.059	1.054	1.056	1.054	1.047	1.051	1.052	1.047
		1	1.082	1.080	1.075	1.069	1.079	1.068	1.075	1.076	1.078
		2	1.054	1.055	1.054	1.049	1.059	1.054	1.064	1.053	1.054
		3	1.068	1.061	1.047	1.061	1.059	1.051	1.060	1.053	1.049
		6	1.062	1.055	1.053	1.052	1.060	1.053	1.059	1.054	1.049
		6	1.062	1.055	1.053	1.052	1.060	1.053	1.059	1.054	1.049
Competitive ELISA (Potency)	Percent activity relative to Reference standard	0	93	92	90	91	96	93	95	96	93
		1									
		2				92					92
		3				97					
		6				96					

FIG. 58 cont.

90/135

		Time (Month)	37°C								
	Formulations		#1	#2	#3	#4	#5	#6	#7	#8	#9
Appearance	Color and clarity (Visual)	0	CCS ²	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
		1	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
		2	Cloudy white	CCS	CCS	CCS	CCS	Cloudy white	CCS	CCS	CCS
		3									
		6	Cloudy white	CCS	CCS	CCS	CCS	Cloudy white	CCS	CCS	CCS
SolVPE (Strength)	Protein concentration (mg/ml)	0	53.45	50.94	50.48	49.81	51.66	52.59	61.92	53.46	52.60
		1	52.42	49.89	49.49	48.95	50.74	51.61	60.66	51.85	52.07
		2	52.23	49.67	49.58	48.96	51.17	54.63	60.80	52.39	51.91
		3									
		6	51.17	51.18	50.05	49.93	52.10	48.70	62.37	54.42	52.76
Tandem method analysis (Purity)	Bioconjugate main peak percent (LP1)		90.0%	90.0%	85.0%	80.0%	92.5%	90.0%	90.0%	85.0%	80.0%
		0			86.5%	81.3%					80.9%
		1			83.7%	78.9%					78.6%
		2			81.8%	77.5%					77.6%
		3									
		6			77.1%	71.7%					71.8%
	Free unconjugated protein monomer peak percent (monomer)		10.0%	10.0%	15.0%	20.0%	7.5%	10.0%	10.0%	15.0%	20.0%
		0			12.6%	17.8%					18.1%
		1			13.7%	18.6%					18.9%
		2			14.2%	18.8%					19.1%
		3									
		6			15.2%	20.1%					20.1%
	All other peak percent	0			0.9%	0.9%					1.0%
		1			2.6%	2.5%					2.5%
		2			4.0%	3.7%					3.3%
		3									
		6			7.7%	8.3%					8.1%
SEC-HPLC (Purity)	Bioconjugate specific aggregate	0									
		1									
		2									
		3									
		6									
SEC/MALS (Purity and Identity)	weighted averaged molecular weight (M _w) kDa	0	1007.0	997.8	998.0	976.2	968.1	974.0	981.3	978.9	981.1
		6	1143.6	1034.2	987.5	970.7	1024.2	1077.2	1007.4	976.9	966.1
	Polydispersity Index (PDI)	0	1.063	1.059	1.054	1.056	1.054	1.047	1.061	1.052	1.047
		1	1.084	1.083	1.075	1.073	1.052	1.070	1.081	1.071	1.074
		2	1.058	1.062	1.052	1.050	1.063	1.052	1.055	1.051	1.046
		3									
		6	1.087	1.068	1.063	1.050	1.069	1.072	1.085	1.057	1.054
		0	94	92	90	91	96	93	95	96	99
Competitive ELISA (Potency)	Percent activity relative to Reference standard	1									
		2				94					98
		3									
		6				87					

FIG. 58 cont.

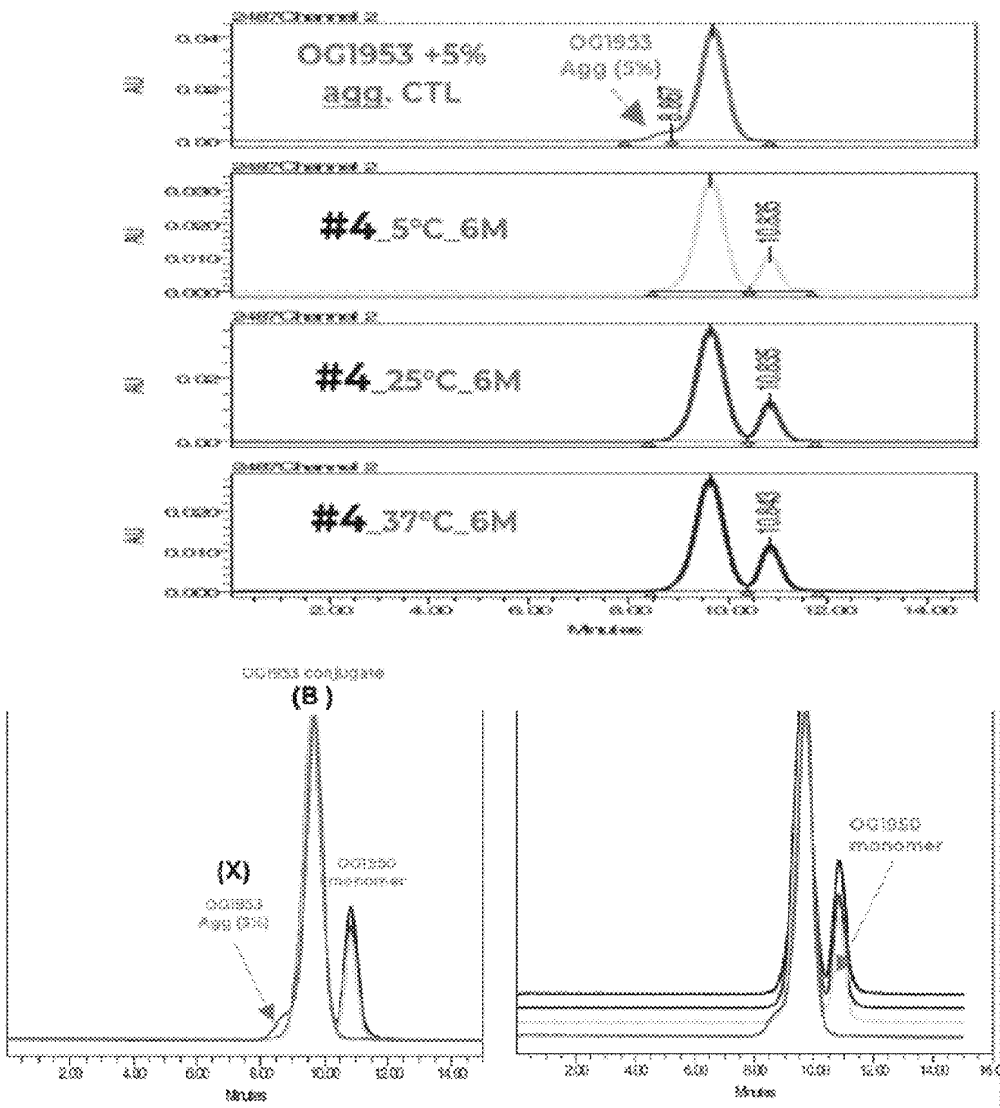


FIG. 59A

	#1	#2	#3	#4	#5	#6	#7	#8	#9
T0									
T1M_5°C	93.6%	93.6%	82.1%	82.8%	94.2%	91.5%	92.1%	87.5%	82.6%
T1M_25°C	92.3%	92.6%	87.5%	82.4%	93.7%	91.1%	91.6%	87.0%	82.6%
T1M_37°C	89.4%	90.7%	85.5%	81.4%	93.5%	88.5%	90.6%	85.8%	81.4%
T2M_5°C	93.2%	93.3%	90.4%	84.0%	94.9%	92.6%	93.0%	88.9%	84.0%
T2M_25°C	92.3%	91.4%	88.3%	83.4%	94.6%	92.4%	92.6%	87.8%	83.8%
T2M_37°C	89.7%	91.1%	86.4%	81.6%	93.4%	89.5%	90.7%	87.1%	84.8%
T3M_5°C	93.5%	93.7%	89.5%	85.0%	94.9%	92.4%	93.1%	89.2%	84.8%
T3M_25°C	87.6%	92.5%	88.6%	83.5%	94.4%	92.0%	92.2%	88.0%	83.6%
T6M_5°C	92.2%	92.4%	87.7%	82.3%	94.8%	91.9%	92.1%	88.1%	82.0%
T6M_25°C	91.5%	90.6%	86.6%	80.9%	93.8%	92.5%	91.2%	86.8%	80.7%
T6M_37°C	91.5%	87.0%	82.4%	77.4%	91.2%	91.9%	88.1%	81.9%	78.0%
Change vs Time T0_5°C	-0.7%	-4.1%	4.2%	-3.1%	-1.0%	0.7%	-1.8%	-2.1%	-2.8%

Change of peak percent over time and temperature (OG1953)

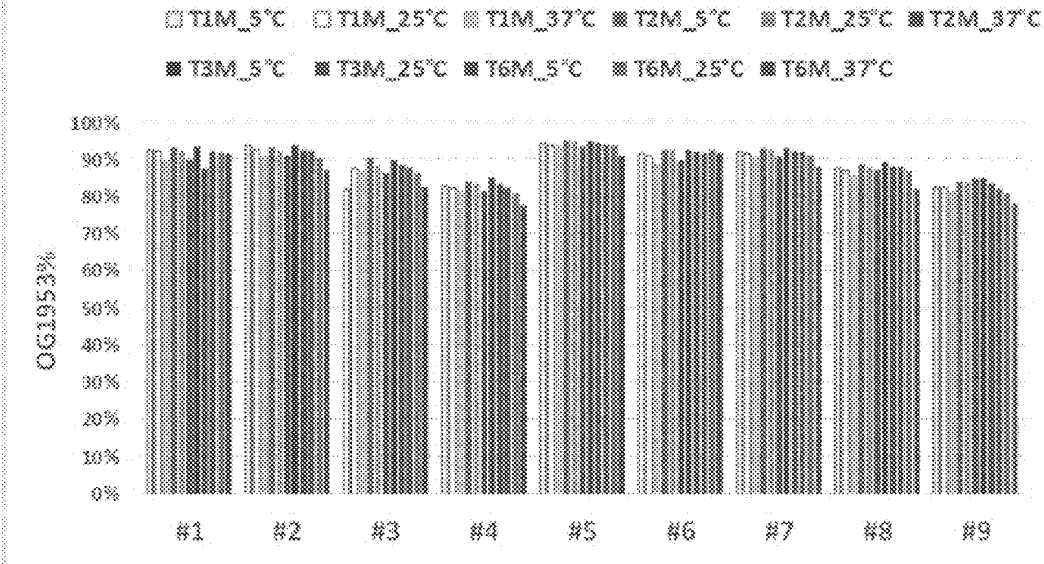


FIG. 59B

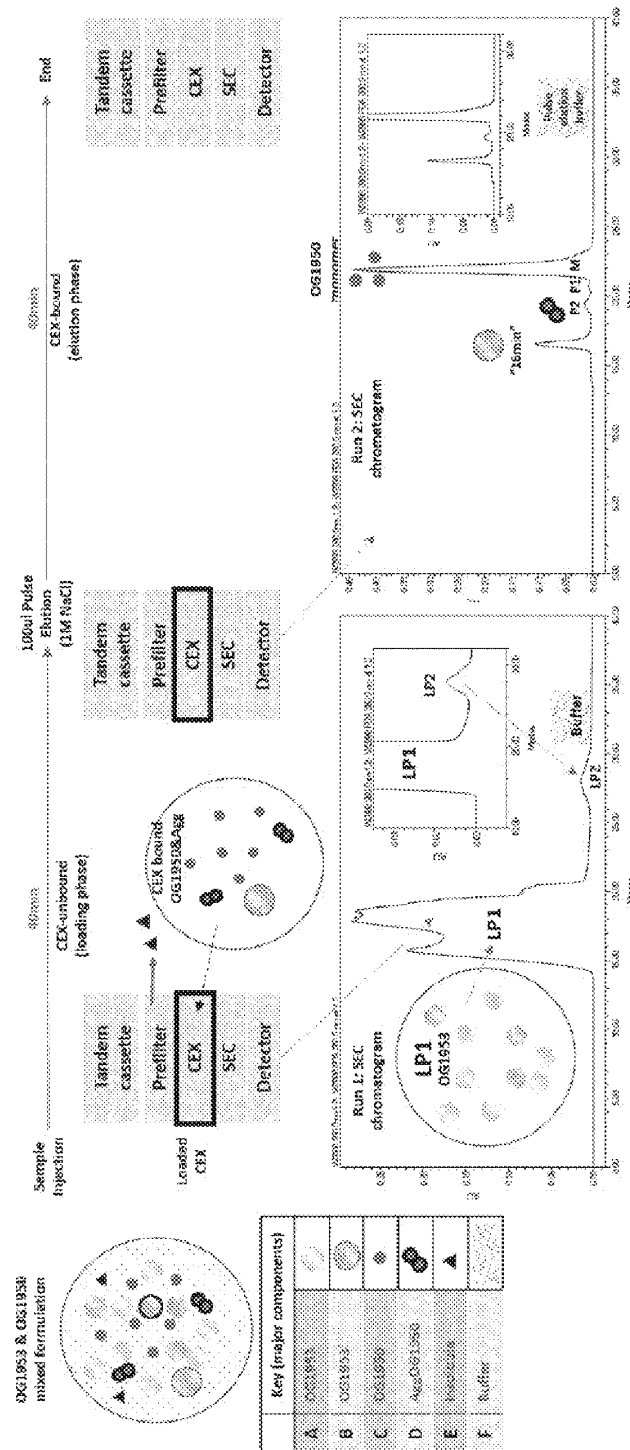


FIG. 60A

Total OC1950 free protein (monomer + P1+P2)/Total protein percent change over time and temperature										
Target%	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
Y0	10.0%	10.0%	10.0%	10.0%	7.5%	10.0%	10.0%	10.0%	20.0%	100.0%
T1M_5°C	7.58%	8.21%	12.55%	18.12%	5.98%	8.69%	8.95%	13.69%	16.36%	81.0%
T1M_25°C	7.66%	7.99%	12.78%	17.97%	6.72%	8.41%	8.53%	13.25%	18.00%	80.18%
T1M_37°C	7.73%	8.34%	13.06%	18.45%	6.59%	8.66%	8.59%	13.56%	18.56%	80.66%
T2M_5°C	9.45%	9.48%	14.38%	19.24%	7.07%	9.84%	9.48%	14.69%	19.56%	80.39%
T2M_25°C	6.91%	7.43%	12.37%	17.32%	6.37%	8.02%	8.04%	12.91%	17.41%	79.63%
T2M_37°C	7.48%	7.92%	12.37%	17.69%	5.98%	7.78%	8.31%	13.20%	17.66%	79.98%
T3M_5°C	9.88%	9.84%	14.55%	19.53%	7.05%	10.19%	9.77%	14.66%	19.77%	79.29%
T3M_25°C	7.43%	7.83%	12.69%	17.84%	6.70%	8.39%	8.74%	13.34%	18.47%	81.42%
T3M_37°C	8.13%	8.76%	13.58%	18.78%	6.42%	8.10%	8.86%	13.84%	17.98%	81.84%
Start sampled										
T5M_5°C			17.46%	18.08%					17.36%	
T5M_25°C			13.43%	19.47%					18.41%	
T5M_37°C			16.31%	21.84%					21.71%	

FIG. 60B

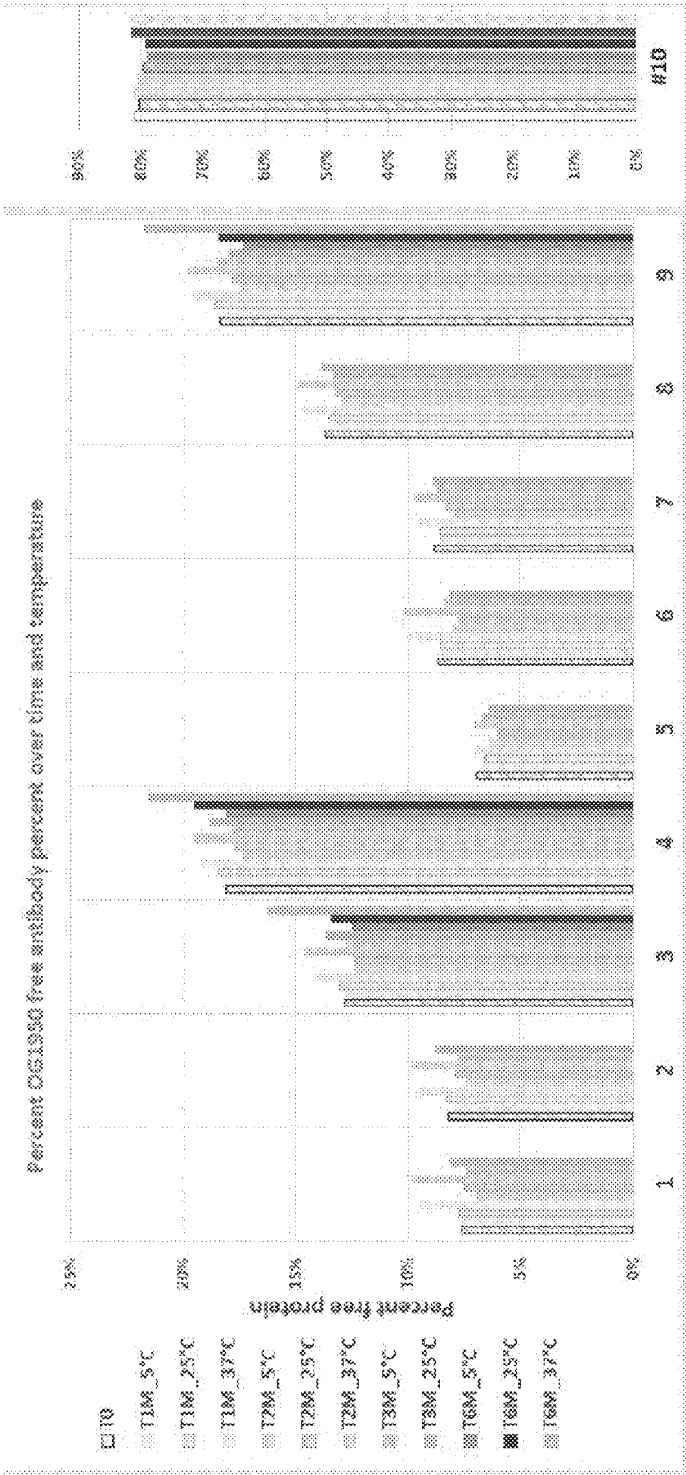
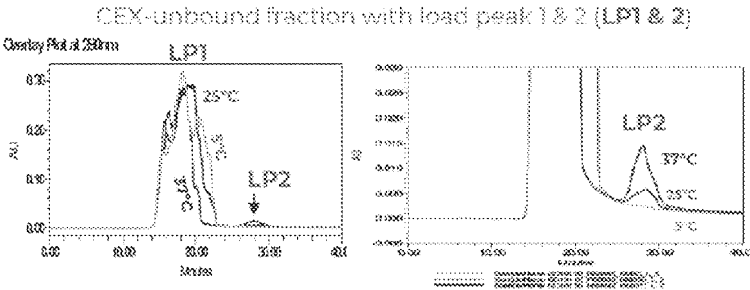


FIG. 60B cont.

Sample #4 280nm chromatograms



CEX-bound fraction elution run profile

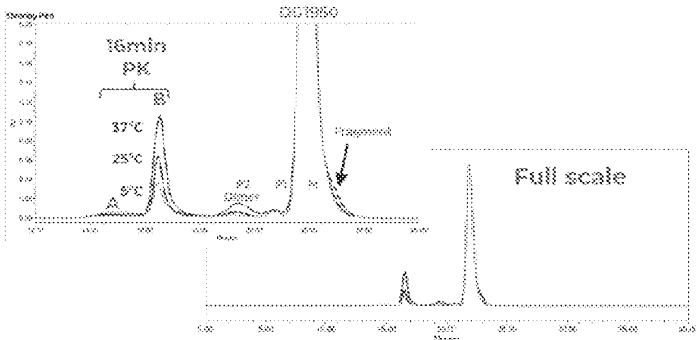


FIG. 60C

Temp	Time	OG1953	Impurities				Monomer	All impurities	Recovery
°C	Month	LP1 (main)	LP2 (side)	16min	P2	P1	M	LP2+16min+P2+P1	Mean actual
5°C	0	81.3%	0.00%	0.61%	0.12%	0.17%	17.8%	0.9%	97.6%
	1	81.4%	0.00%	0.62%	0.16%	0.21%	17.6%	1.0%	100.3%
	2	82.0%	0.00%	0.66%	0.07%	0.16%	17.1%	0.9%	105.8%
	3	81.1%	0.00%	1.05%	0.18%	0.22%	17.4%	1.4%	99.5%
	6	80.3%	0.00%	1.64%	0.22%	0.22%	17.6%	2.1%	108.3%
25°C	0	81.3%	0.00%	0.61%	0.12%	0.17%	17.8%	0.9%	97.6%
	1	80.6%	0.08%	0.88%	0.20%	0.22%	18.0%	1.4%	98.8%
	2	81.1%	0.18%	1.10%	0.12%	0.16%	17.4%	1.6%	107.0%
	3	79.3%	0.25%	1.69%	0.29%	0.23%	18.2%	2.4%	98.8%
	6	77.5%	0.61%	2.39%	0.36%	0.24%	18.9%	3.6%	94.2%
37°C	0	81.3%	0.00%	0.61%	0.12%	0.17%	17.8%	0.9%	97.6%
	1	78.9%	0.37%	1.52%	0.36%	0.23%	18.6%	2.5%	97.5%
	2	77.5%	0.74%	2.35%	0.36%	0.21%	18.8%	3.7%	97.3%
	6	71.7%	2.14%	4.65%	1.08%	0.40%	20.1%	8.3%	97.5%

* Sum of all degradants percent includes only LP2, 16min, P2, and P1. The retro reaction derived monomeric form OG1950 is excluded from this calculation.

FIG. 60D

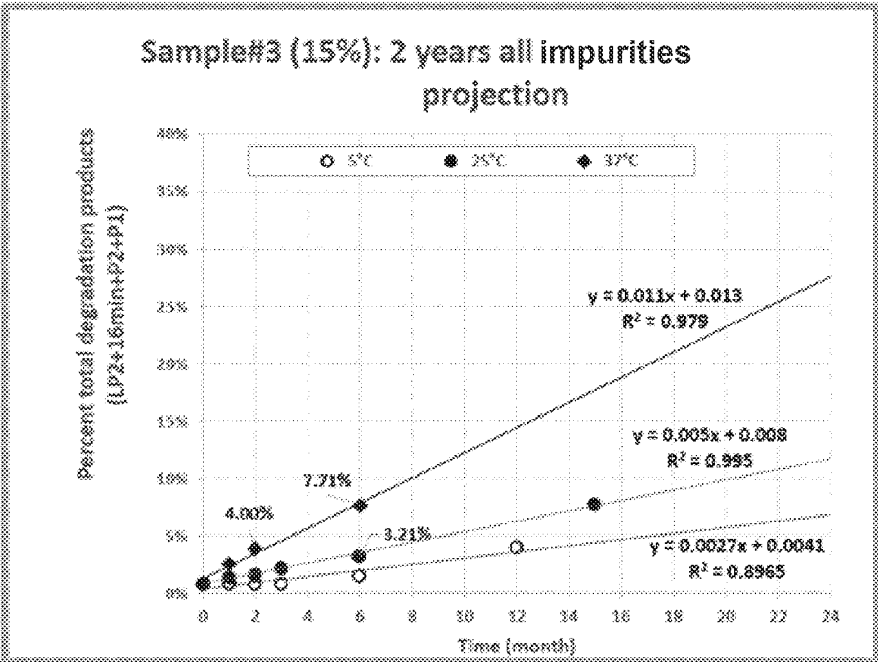


FIG. 61A

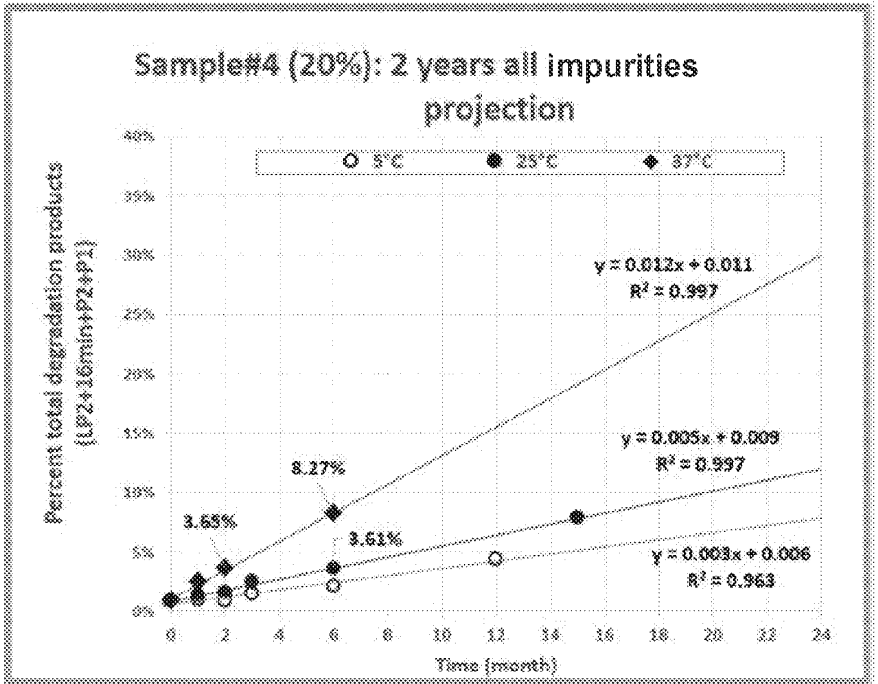


FIG. 61B

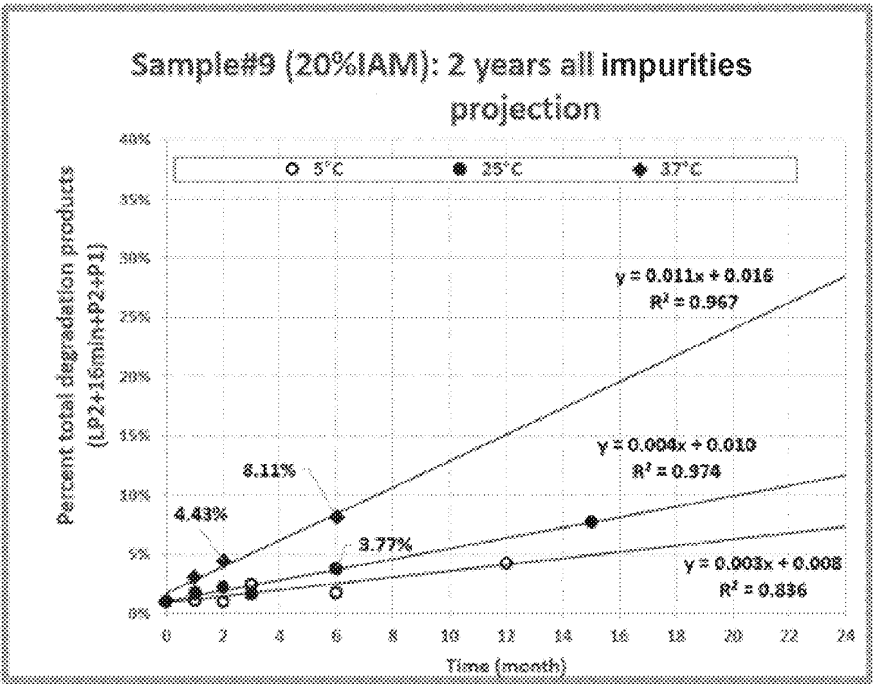


FIG. 61C

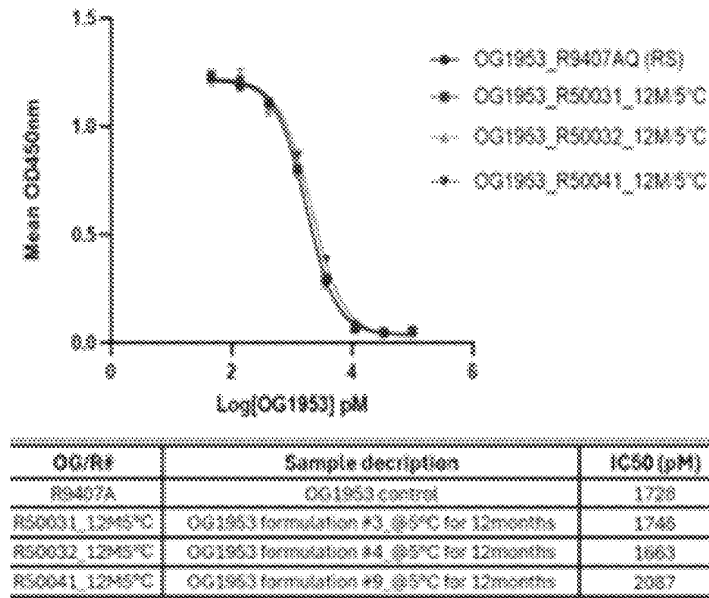


FIG. 62A

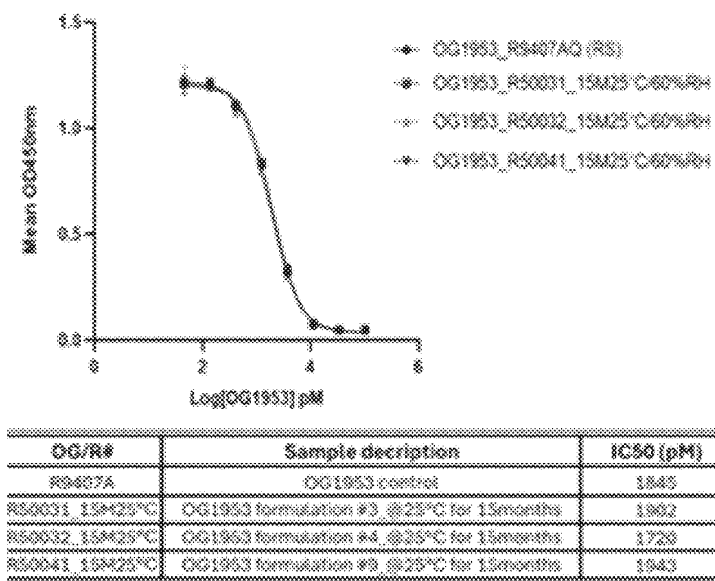


FIG. 62B

Anti-VEGF antibody (e.g., OG1950)
Anti-VEGF antibody conjugate (e.g., OG1953)
Sodium Acetate
Polysorbate 20
~pH4.5-5.5 (e.g., ~pH5)

FIG. 63A

Anti-IL-6 antibody fused to VEGF trap (e.g., OG2072)
Anti-IL-6 antibody fused to VEGF trap conjugate (e.g., OG2074)
Sodium Acetate
Polysorbate 20
Sucrose (optional)
~pH4.8-5 (e.g., ~pH5)

FIG. 63B

Anti-IL-6 antibody fused to VEGF trap (e.g., OG2072)
Anti-IL-6 antibody fused to VEGF trap conjugate (e.g., OG2074)
Histidine Acetate
Polysorbate 20
Sucrose (optional)
~pH5.2-6.2 (e.g., ~pH5.7)

FIG. 63C

KSI-501 Drug Substance Batch Number:		KSI-501DS_102	KSI-501DS_103	KSI-501DS_104
Test	Method	Results		
Colour	Visual	= Y5 Slightly yellow	= Y5 Slightly yellow	≤ Y5 Slightly yellow
Clarity	Instrumental	2.70 NTU = Ref. 1 clear	2.63 NTU = Ref. 1 clear	2.40 NTU < Ref. 1 clear
pH	Potentiometry	4.8	4.7	4.8
Protein Concentration (mg/mL)	UV A _{280nm} Solo VPE	51.5	50.4	50.4
OG2074 Molecular Weight (kDa)	SEC-MALS	1118	1075	1126
OG2074 Polydispersity		1.074	1.074	1.070
OG2074 Bioconjugate (% area)	CEX-HPLC	69.1	65.2	70.1
OG2072 Unconjugated Antibody (% area)		30.9	34.8	29.9
OG1802 Unreacted Polymer (mg/mL)		≤ 5	≤ 5	≤ 5
OG2074 Bioconjugate Main Peak (% area)	SEC-HPLC	72.0	68.9	72.5
OG2074 HMW Forms (% area)		0.0	0.0	0.0
OG2074 LMW Form (including OG2072 Antibody) (% area)		28.0	31.1	27.5
OG2074 Bioconjugate (% area)	Tandem-HPLC	65.4	61.5	66.1
OG2072 Antibody (% area)		29.4	32.2	29.3
Impurities (% area)		5.2	6.3	4.6
Potency (αVEGF) (% relative to reference standard)	Cell Based Assay (HEK293)	100	105	91
Potency (αIL-6) (% relative to reference standard)	ELISA	87	76	80

FIG. 64

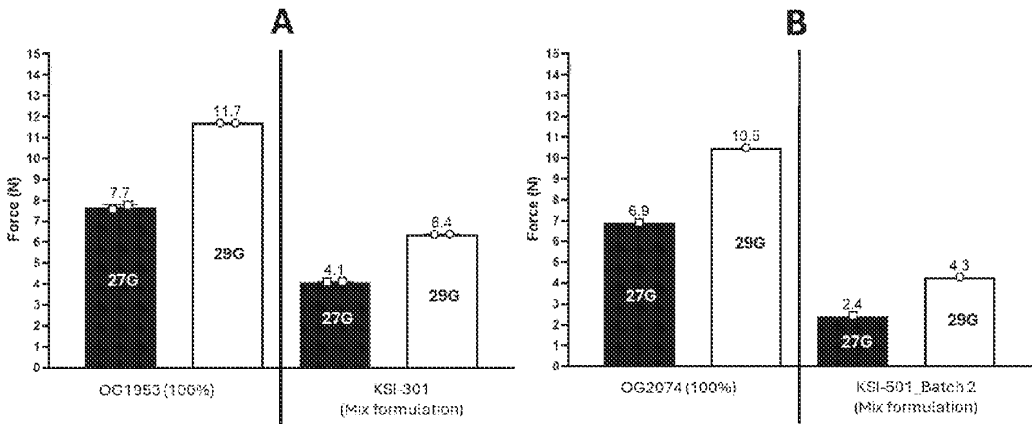


FIG. 65

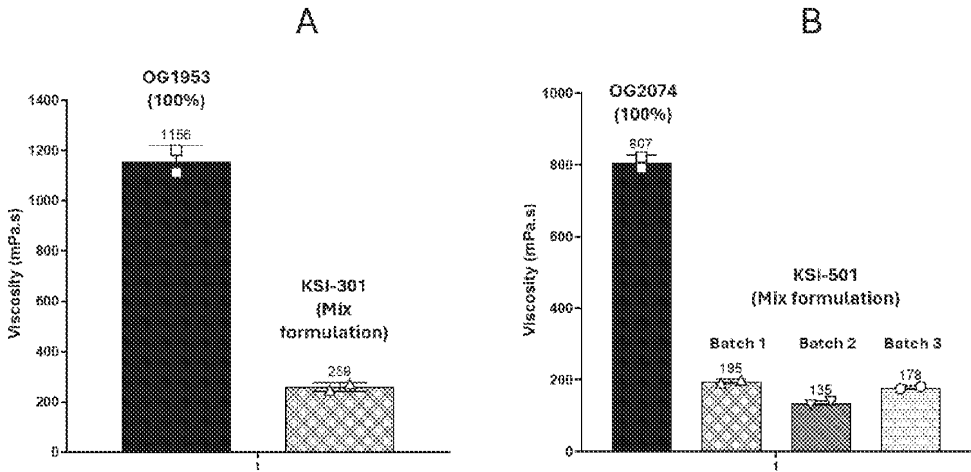


FIG. 66

Tandem method run with PDA
(200-800nm but showing only 200-350nm)

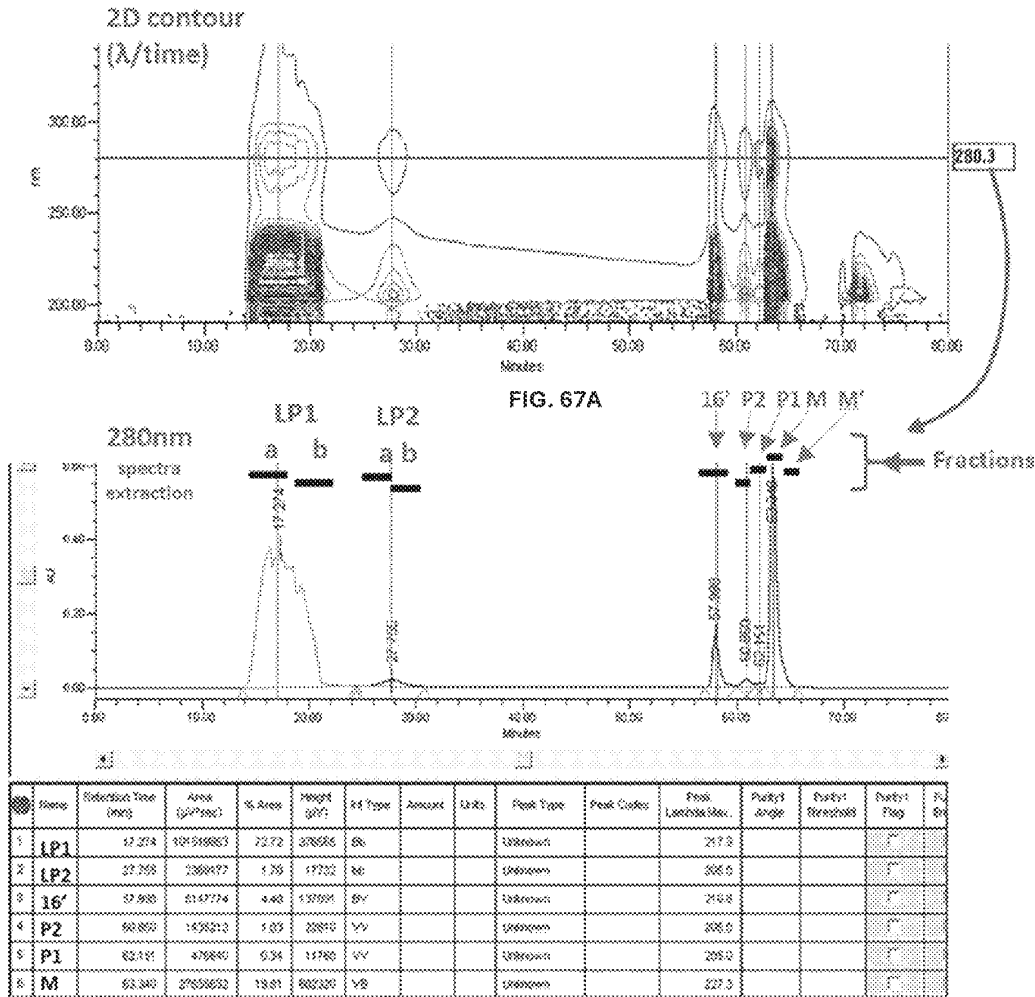


FIG. 67B

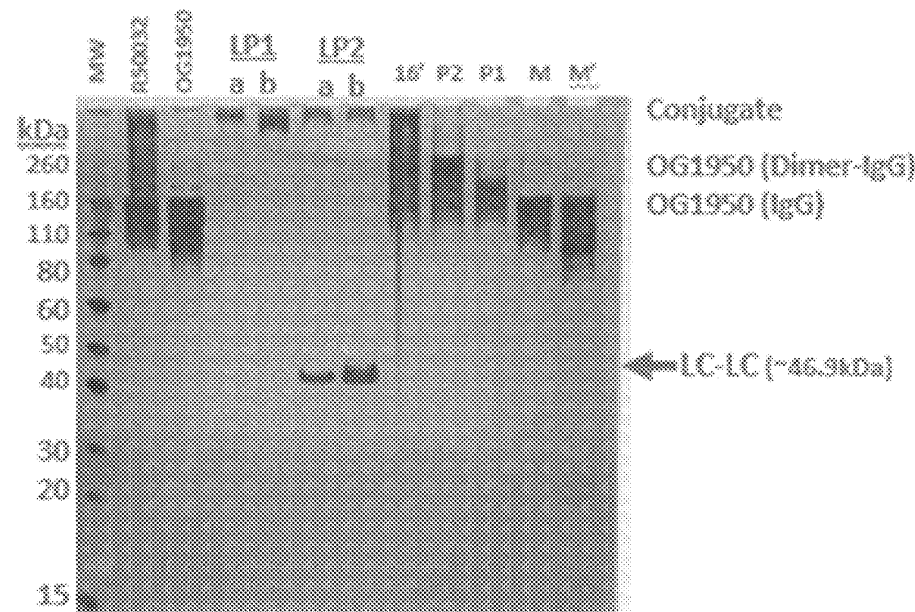


FIG. 67C

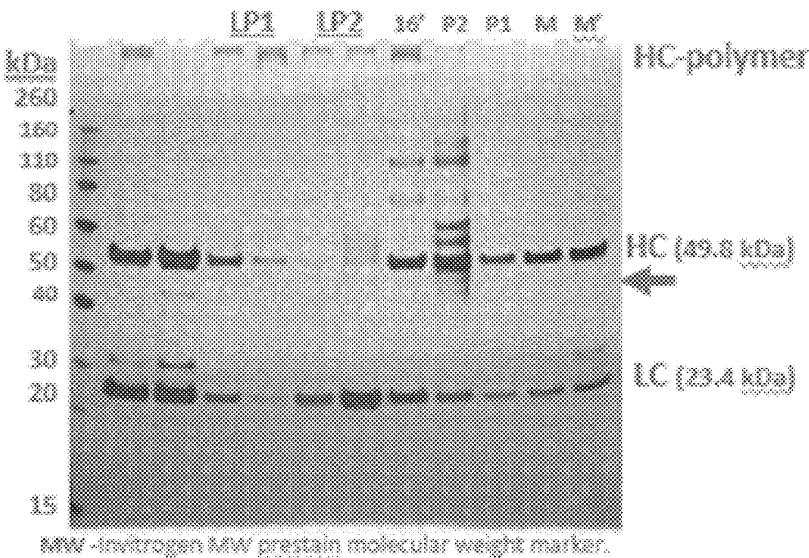


FIG. 67D

104/135

EVQLVESGGGLVQPGGSLRLSCAASGYDFTHYGMNWVRQAPGKGLEWVGWINTYTGEPTYAADFKRRFTTSLDTSKS
TAYLQMNSLRAEDTAVYYCAKYPYYGTSHWYFDVWGQGTIVTVSSASTKGPSVFELAPSSKSTSGGTAALGCLVKD
YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
CPPCPAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV
EWESNGCPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCVMHEALHNHYTQKSLSCSPGK

(SEQ ID NO: 270)

FIG. 68

DIQLTQSPSSLSASVGDRTITCSASQDISNYLNWYQQKPGKAPKVLIIYFTSSLHSGVPSRFSGSGSGTDFTLTISS
LQPEDEATYYCQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL
QSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

(SEQ ID NO: 271)

FIG. 69

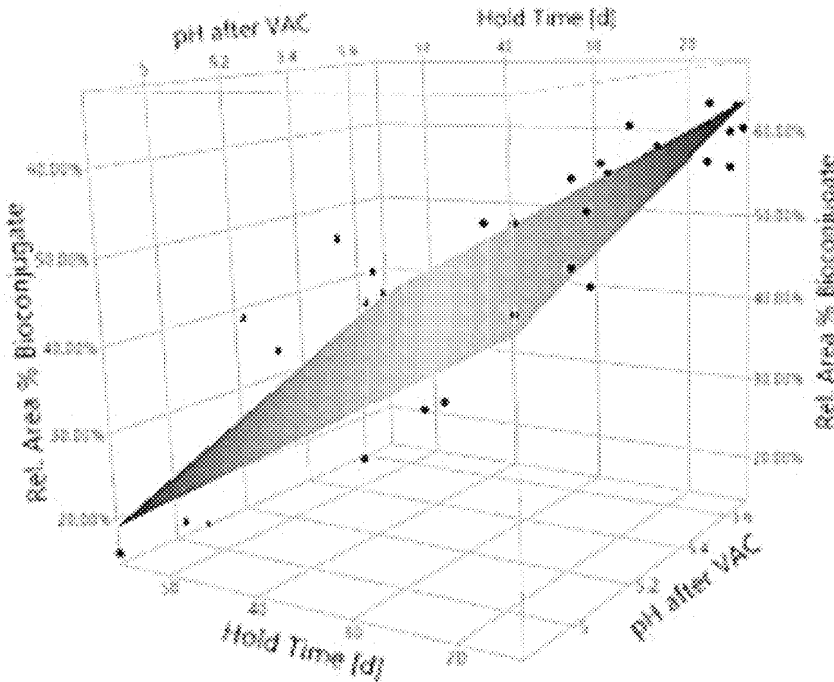


FIG. 70A

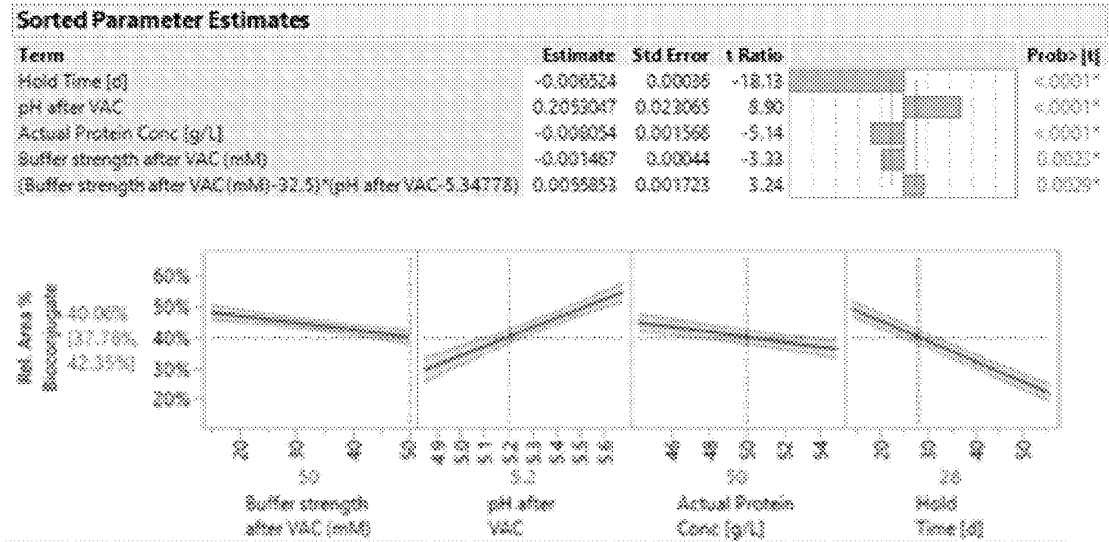


FIG. 70B

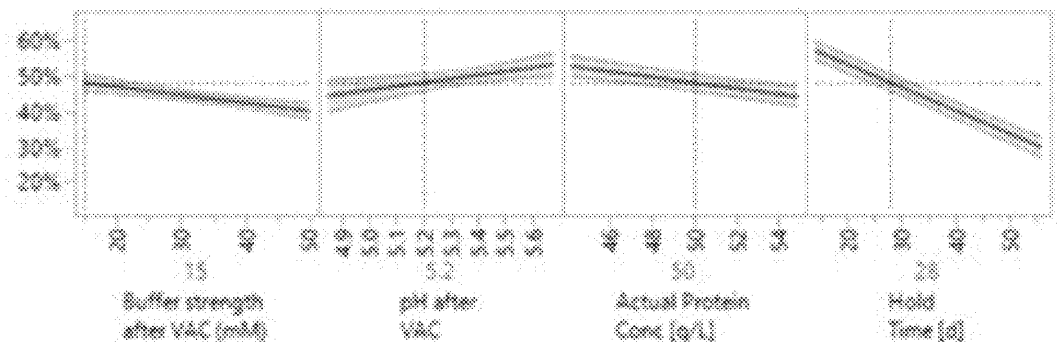


FIG. 70B (Cont.)

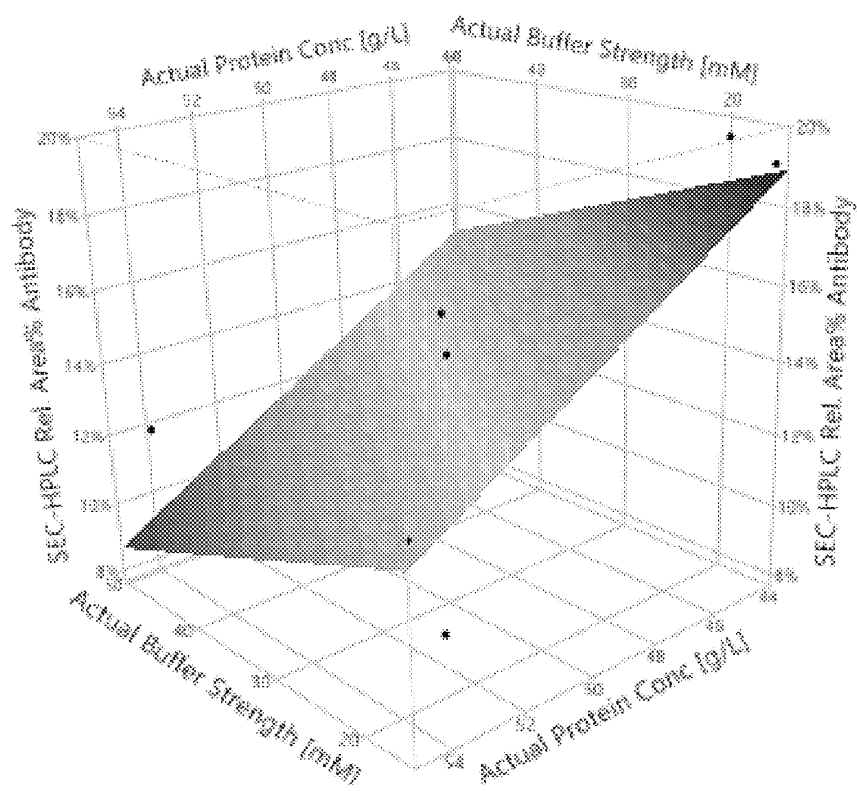


FIG. 71A

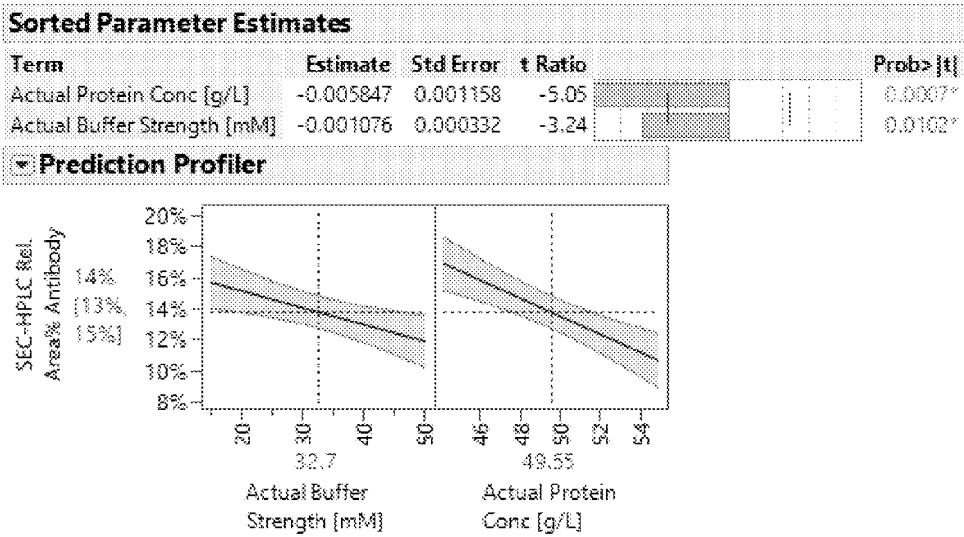


FIG. 71B

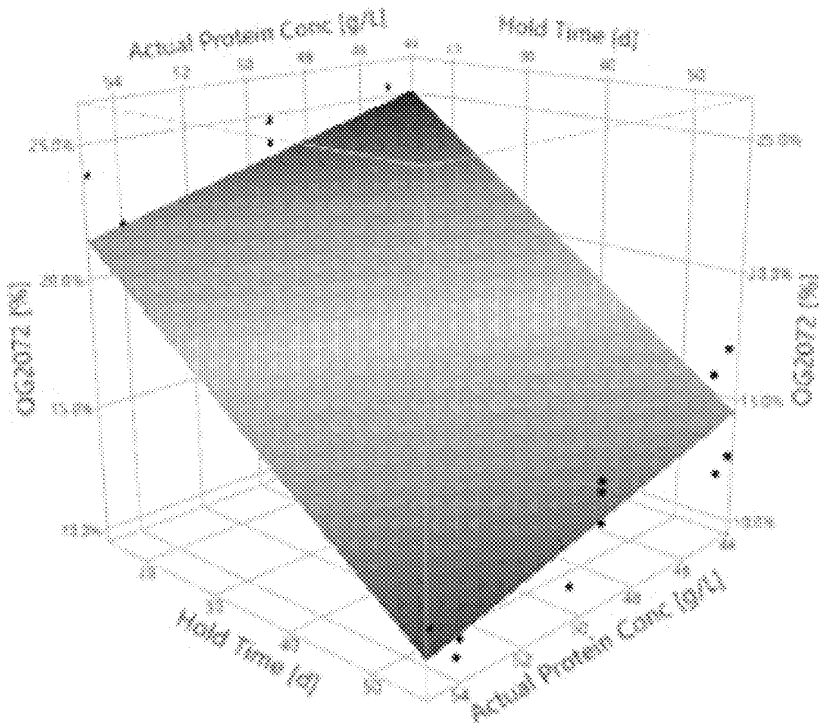


FIG. 72A

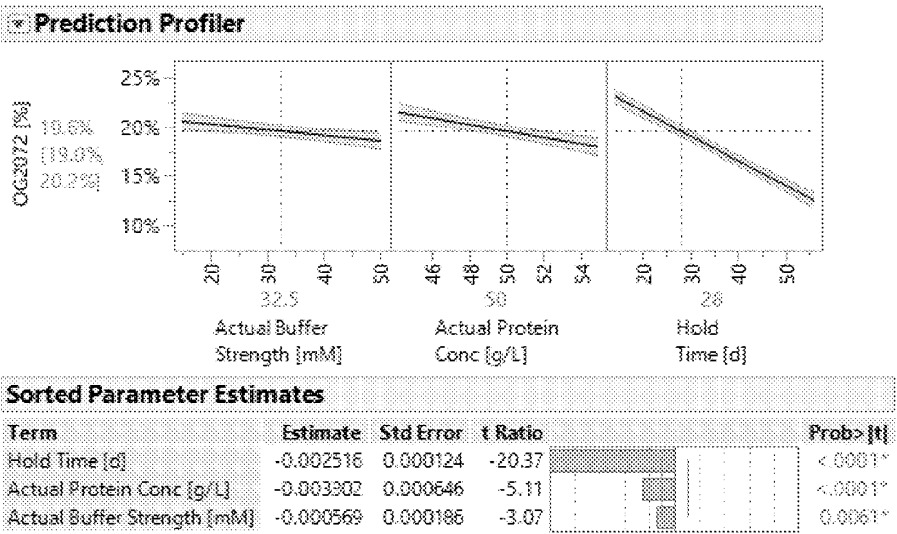


FIG. 72B

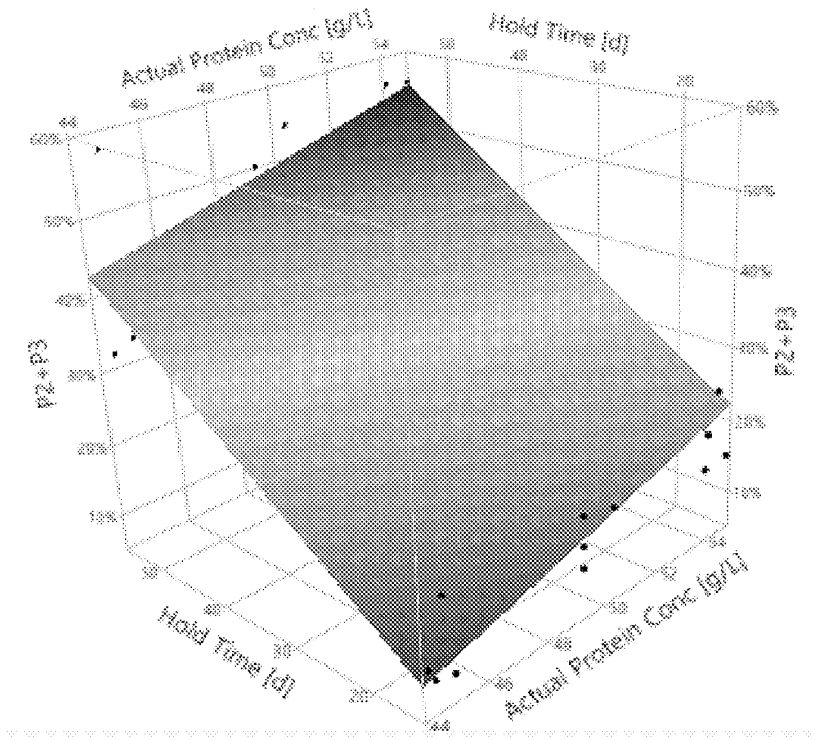


FIG. 73A

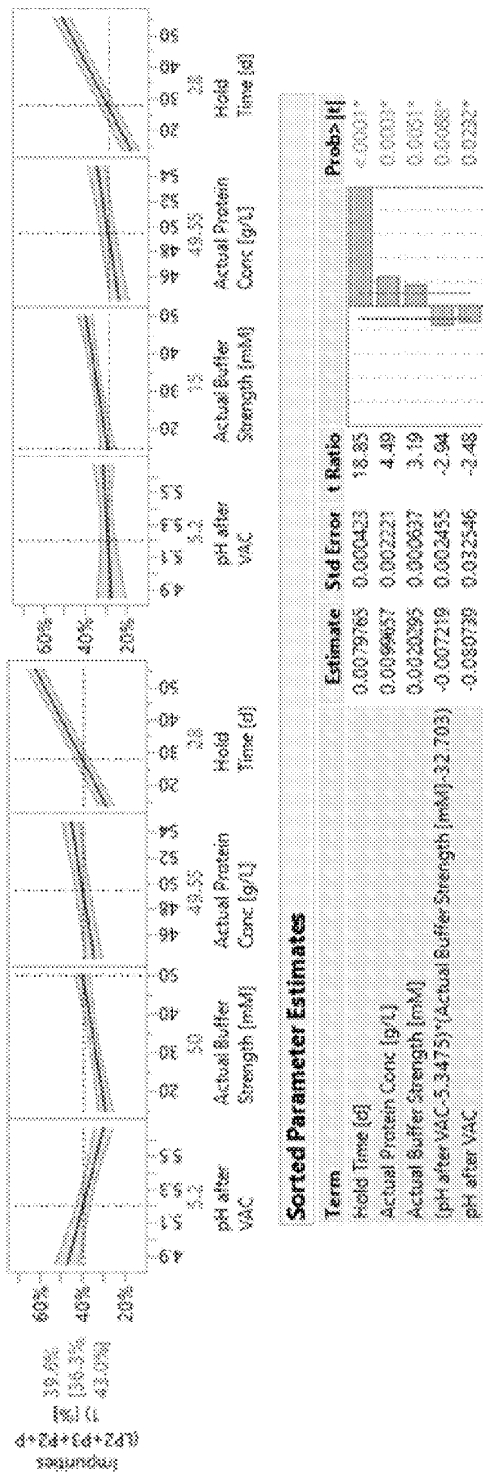


FIG. 73B

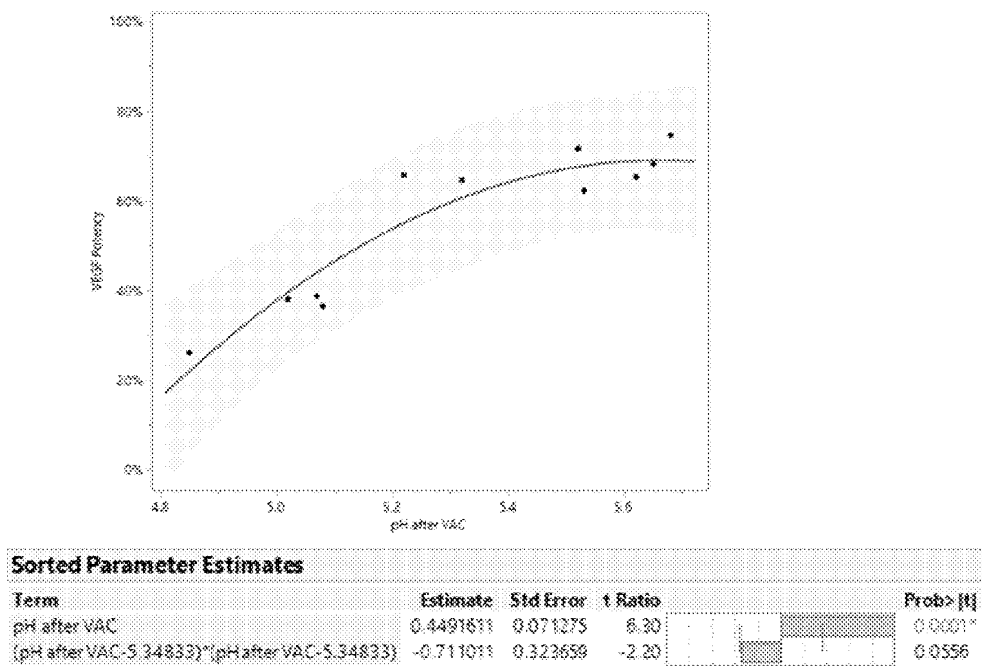


FIG. 74A

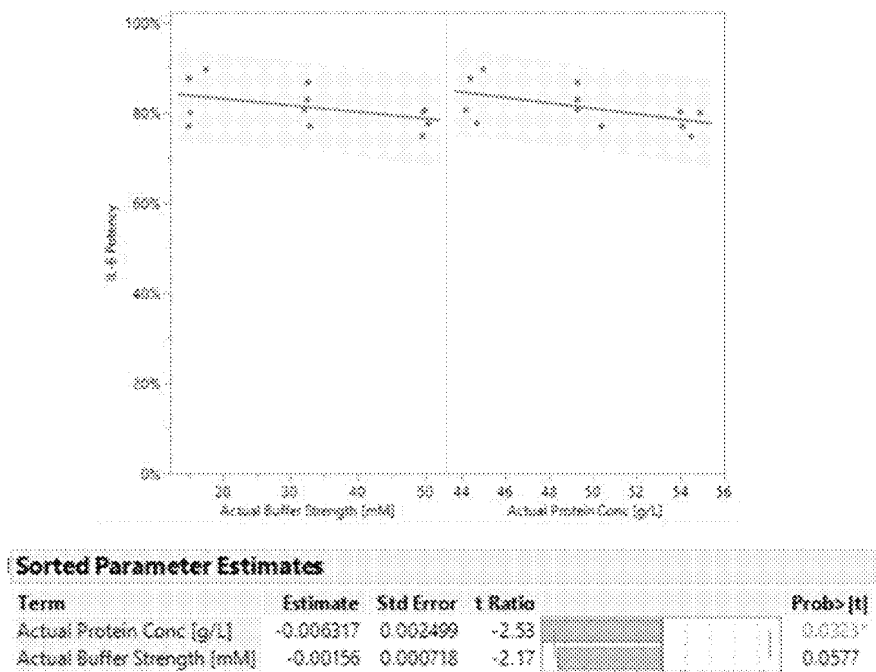


FIG. 74B

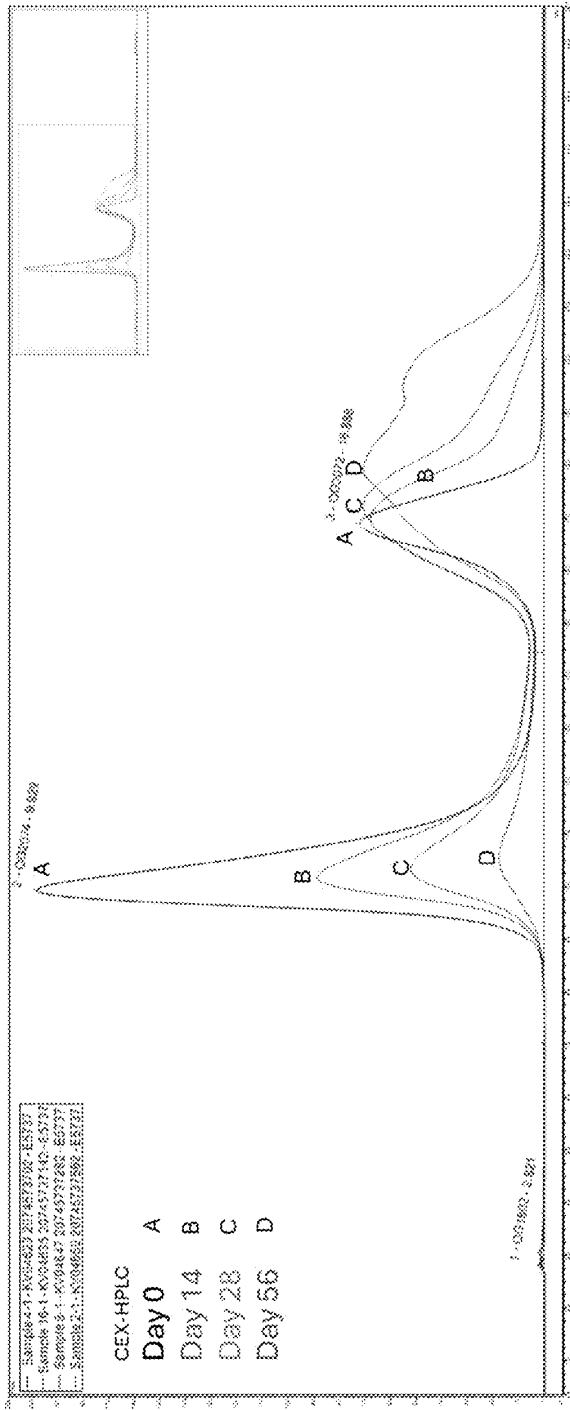


FIG. 75A

113/135

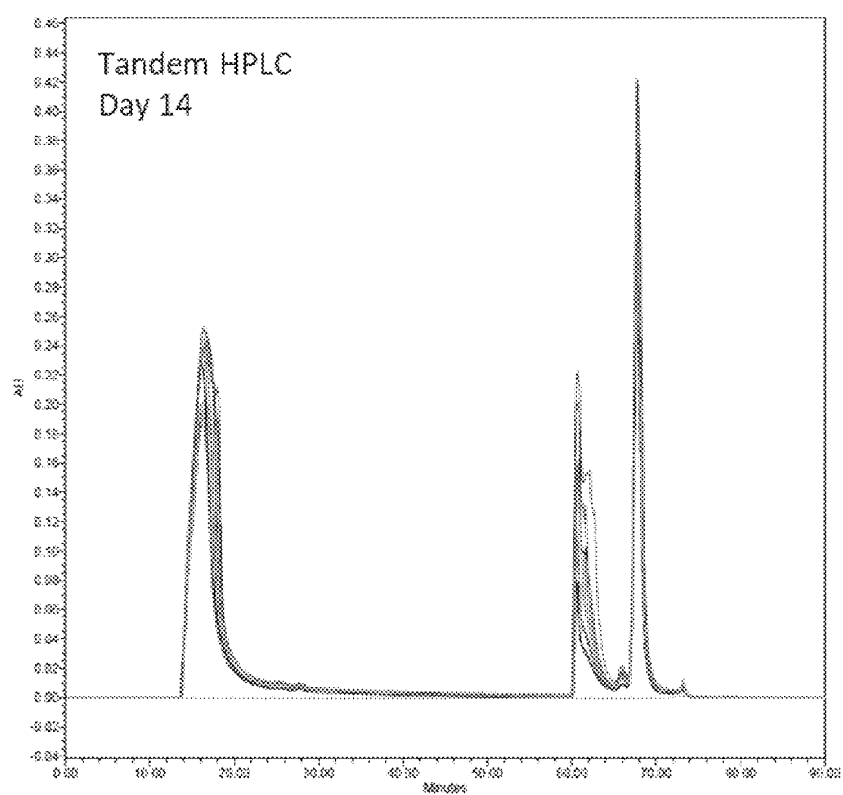


FIG. 76

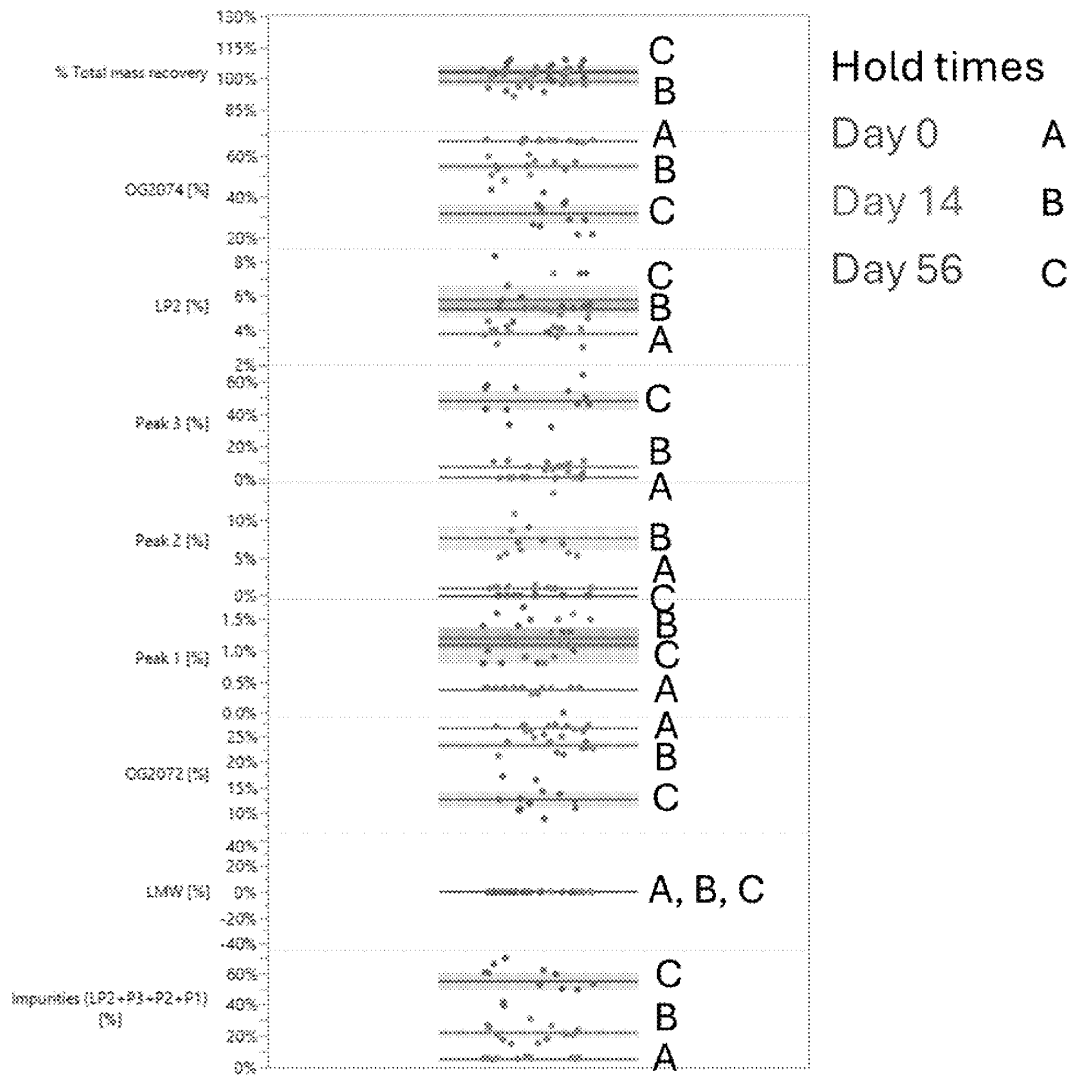


FIG. 77A

Quality Attribute	Estimates			p-values			Model analysis		
	Protein conc. [g/L]	Buffering strength [mM]	pH	Protein conc. [g/L]	Buffering strength [mM]	pH	p-value	R ²	adjR ²
Total mass recovery [%]	n/a	n/a	0.146	n/a	n/a	0.0054	0.0054	0.559	0.511
OG2074 [%]	n/a	n/a	0.146	n/a	n/a	0.0526	0.0526	0.326	0.258
LP2 [%]	-0.00159	n/a	-0.0309	0.0074	n/a	0.0013	0.0011	0.78	0.731
Peak 3 [%]	0.0149	n/a	n/a	0.0269	n/a	n/a	0.0269	0.402	0.342
Peak 2 [%]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Peak 1 [%]	n/a	n/a	0.0108	n/a	n/a	0.0182	0.0182	0.443	0.387
OG2072 [%]	-0.00439	-0.000838	n/a	0.00078	0.00935	n/a	0.0009	0.79	0.744
Impurities [%]	0.0129	n/a	n/a	0.0479	n/a	n/a	0.0479	0.337	0.270

FIG. 77B

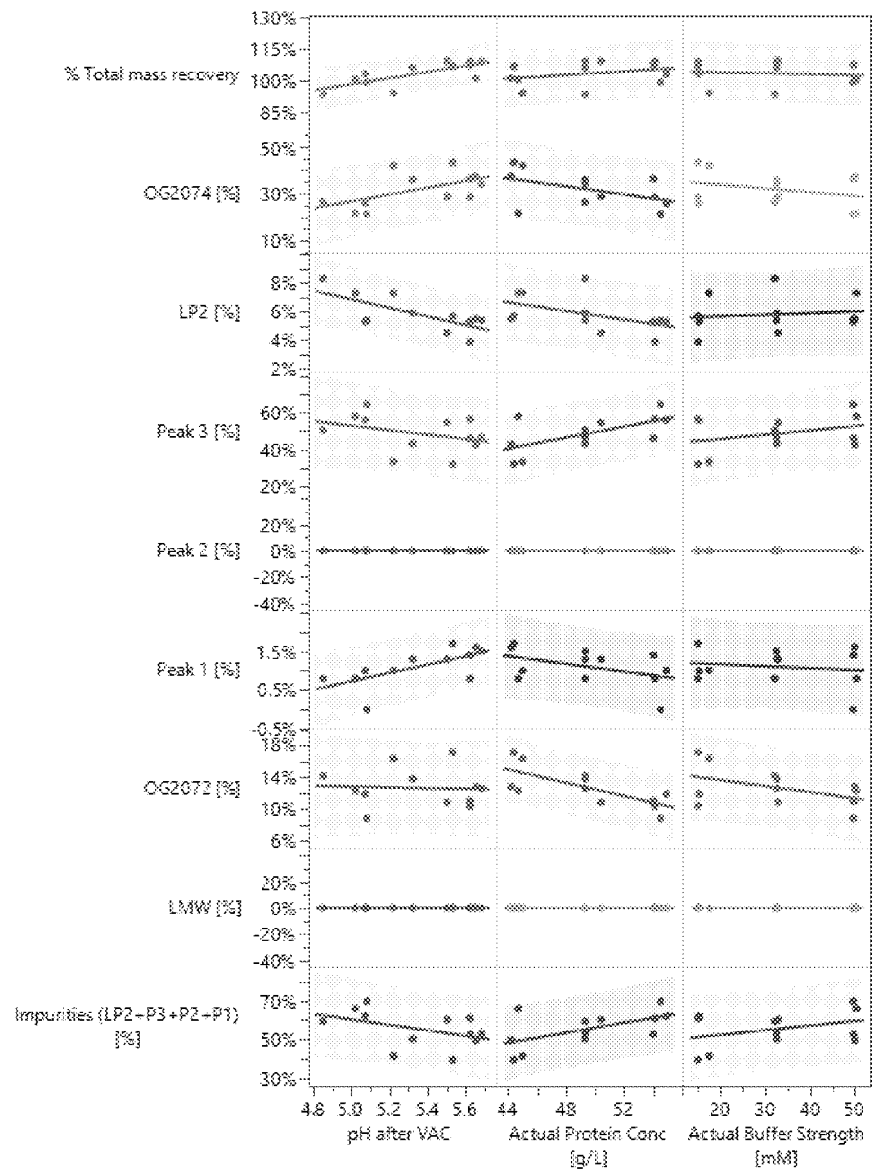


FIG. 77C

Buffer strength [mM]	Buffer system	pH	Carbohydrate [%]	Carbohydrate type	Excipient	CEX-HPLC Bioconjugate [%area] Day 56	VEGF Potency [%] Day 28	IL-6 Potency [%] Day 56	Tandem HPLC Impurities [%area] Day 56
50	Na-ac	5.09	4	sucrose	PS20	10.4	161	59.8	-
50	Na-ac	5.09	0	n/a	PS20	15.1	19.4	74.1	-
25	His-ac	5.58	4	sucrose	PS20	54.2	63.2	97.6	36.0
25	His-ac	5.61	4	trehalose	PS20	55.8	65.2	97.3	-
25	His-ac	5.54	0	n/a	PS20	48.8	56.9	95.9	43.2
25	His-ac	5.57	0	n/a	PS80	61.9	57.1	104.5	-
25	His-ac	5.55	0	n/a	PX88	52.4	63.0	108.0	-
75	His-ac	6.15	0	n/a	PS20	66.7	74.5	110.8	35.5

FIG. 78

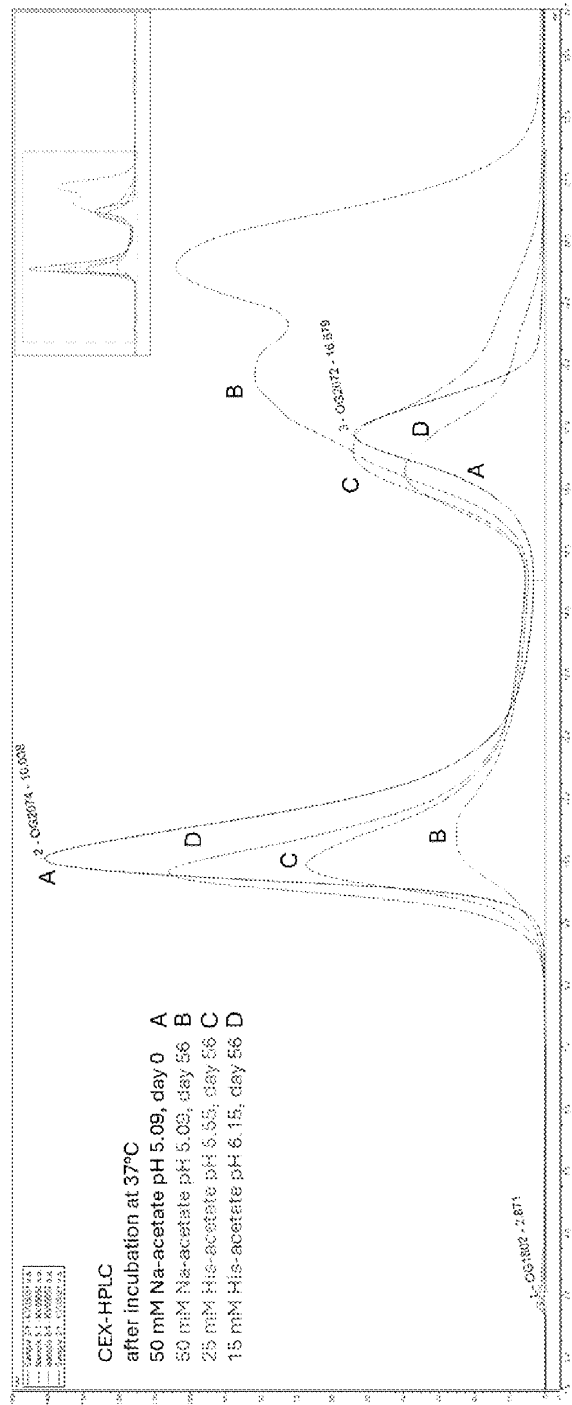


FIG. 79A

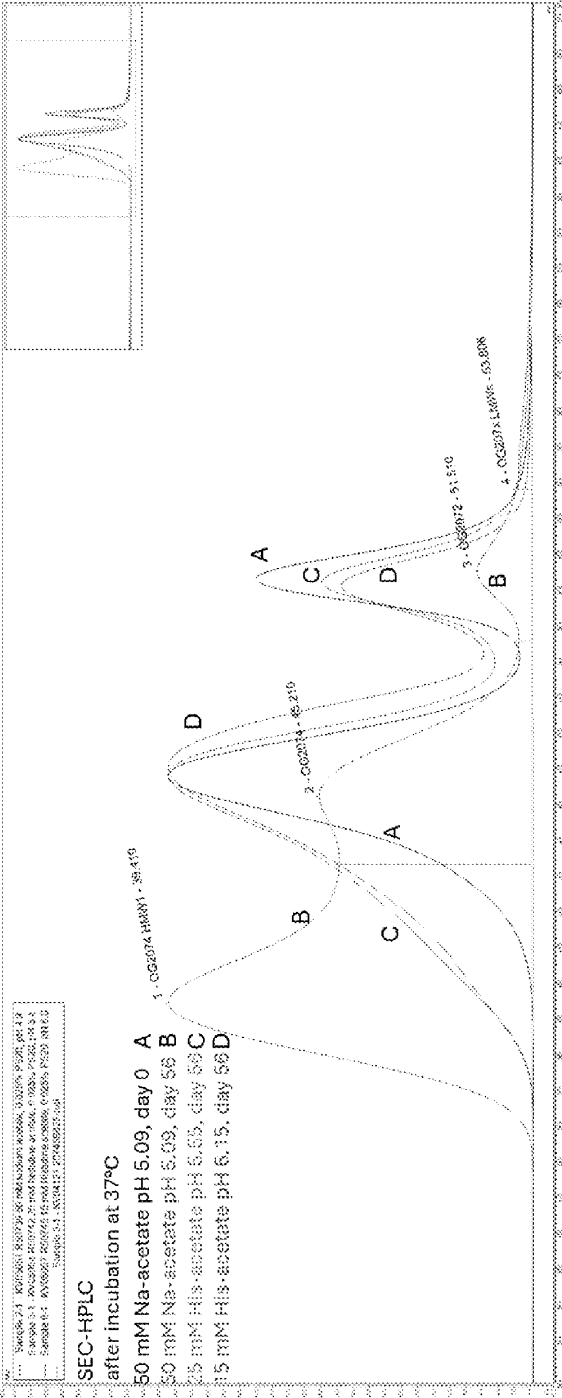


FIG. 79B

Target pH	Sucrose [%]	Diafiltration buffer pH	pH after VAC
5.9	0.0	5.62	5.96
5.9	3.6	5.62	5.89
6.2	0.0	5.92	6.23
6.2	3.6	5.92	6.23
6.5	0.0	6.21	6.46
6.5	3.6	6.21	6.45

FIG. 80A

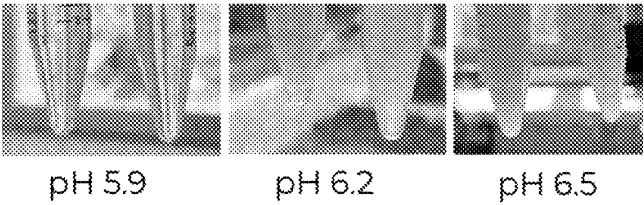


FIG. 80B

Batch number		101			103		
Formulation		25 mM sodium acetate buffer pH 5.2, 52.4 g/L (100% OG2074)			50 mM sodium acetate, 4% sucrose pH 4.8, 50.4 g/L (70% OG2074, 30% OG2072)		
Storage condition		-20°C	+5°C	+25°C	-20°C	+5°C	+25°C
Method	Test	3M	3M	3M	3M	3M	3M
CEX-HPLC	OG2074 Bioconjugate [% area]	98.3	98.0	92.6	67.3	66.7	54.6
	Impurities [% area]	1.7	2.0	7.4	32.7	33.3	45.4
	OG1802 Unreacted Polymer [mg/ml]	≤5	≤5	≤5	≤5	≤5	≤5
SEC-HPLC	OG2074 Bioconjugate Main Peak [% area]	100.0	100.0	100.0	69.5	69.8	78.8
	OG2074 HMW Forms [% area]	0.0	0.0	0.0	0.0	0.0	0.0
	OG2074 LMW Forms (including OG2072 Antibody) [% area]	0.0	0.0	0.0	30.5	30.2	23.2
Tandem-HPLC	OG2074 Bioconjugate Main Peak [% area]	n/a	n/a	n/a	62.5	62.3	44.4
	OG2072 Antibody [% area]	n/a	n/a	n/a	31.3	30.6	26.3
	Impurities [% area]	n/a	n/a	n/a	6.3	7.1	29.3
Cell-based Assay	Potency VEGF [%]	86	92	81	99	98	<50
ELISA	Potency IL-6 [%]	104	105	104	104	101	92

FIG. 81

Component	Mean concentration	Unit	charge	mM charge
Sodium	18.78	mM	+	18.78
Acetate	50	mM	+	50
Polysorbate 20	0.20	mM	none	0
Sucrose	105	mM	none	0
Antibody	50,000 0.26	mg/L mM	172+ / 154-	86
Biopolymer	146,000 0.18	mg/L mM	2,250+ / 2,250-	810
Density	1.070	g/mL	n/a	n/a
Water content	815	%	n/a	n/a
Osmolality	260 to 284	mOsm/kg	n/a	n/a
Overall				867

FIG. 82A

Component	Mean concentration	Unit	charge	mM charge
Histidine	7.46	mM	2+/-	22.38
Acetate	7.39	mM	+	7.39
Polysorbate 20	0.20	mM	none	0
Sucrose	0	mM	none	0
Antibody	50,000 0.26	mg/L mM	172+ / 154-	88
Biopolymer	146,000 0.18	mg/L mM	2,250+ / 2,250-	810
Density	-	g/mL	n/a	n/a
Water content	-	%	n/a	n/a
Osmolality	-	mOsm/kg	n/a	n/a
Overall				928

FIG. 82B

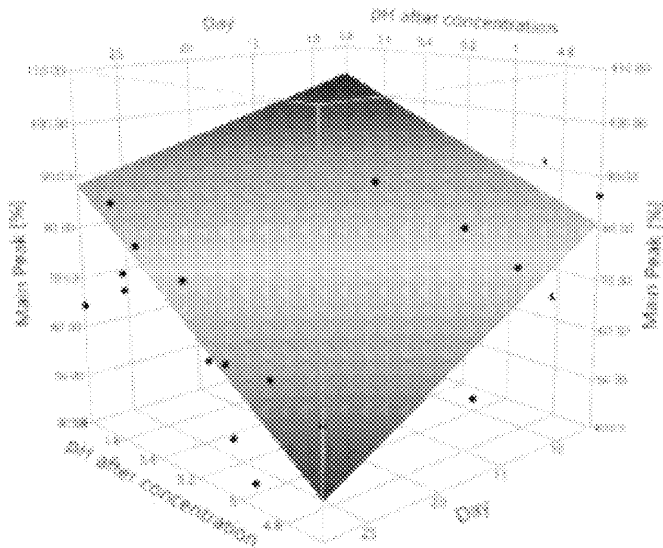


FIG. 83A

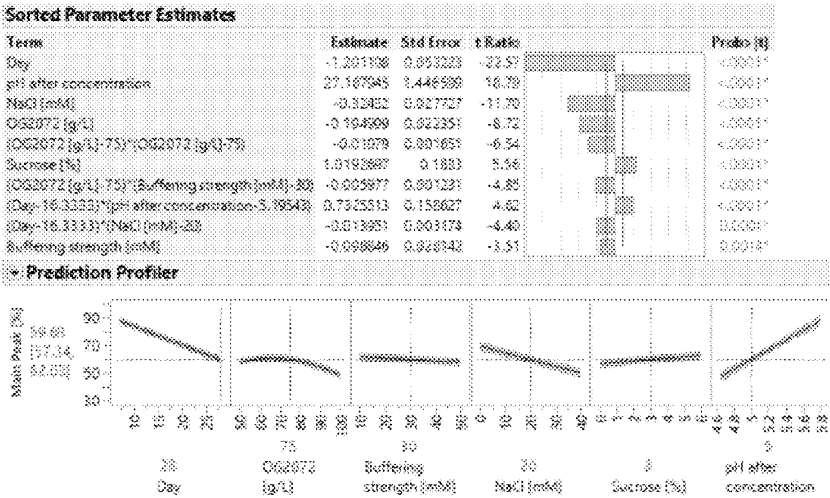


FIG. 83B

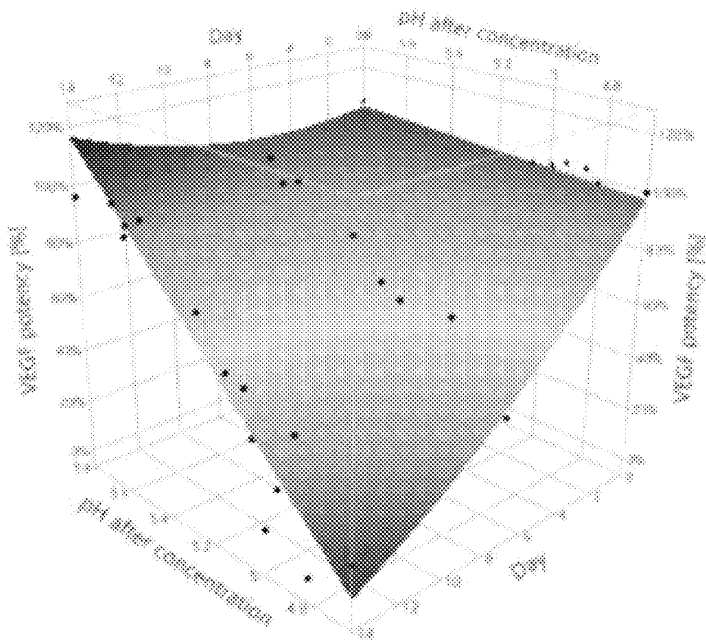


FIG. 84A

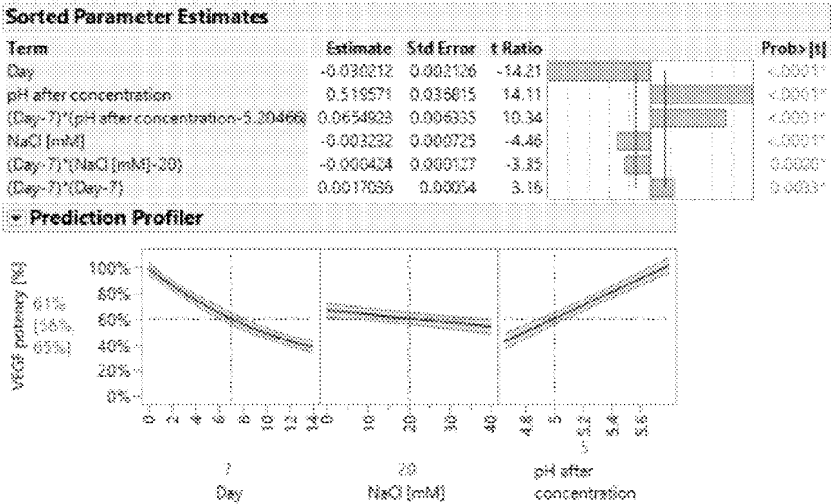


FIG. 84B

Parameter	SEC-HPLC	Potency	Viscosity	Osmolality	current setpoint
pH	+++	+++	0	0	5.5
OG2072 conc. [g/L]	-	0	+++	+	100
NaCl [mM]	-	-	0	++	0
Buffering strength [mM]	-	0	0	++	15
Sucrose [%]	+	0	0	+++	5.2

FIG. 85

Exp	OG2072 [g/L]	Buffering strength [mM]	pH	Sucrose [%]
1	100	30	6.0	3
2	110	50	6.5	0
3	110	10	5.5	0
4	100	30	6.0	3
5	75	50	5.5	0
6	75	10	6.5	0
7	110	10	6.5	0
8	120	30	6.0	3
9	75	10	5.5	0
10	75	50	6.5	0
11	110	50	5.5	0
12	60	30	6.0	3
13	75	50	6.5	6
14	75	10	5.5	6
15	110	50	5.5	6
16	100	30	6.8	3
17	100	30	5.2	3
18	110	10	6.5	6
19	75	50	5.5	6
20	100	30	6.0	3
21	110	50	6.5	6
22	110	10	5.5	6
23	75	10	6.5	6
24	100	30	5.2	3

FIG. 86

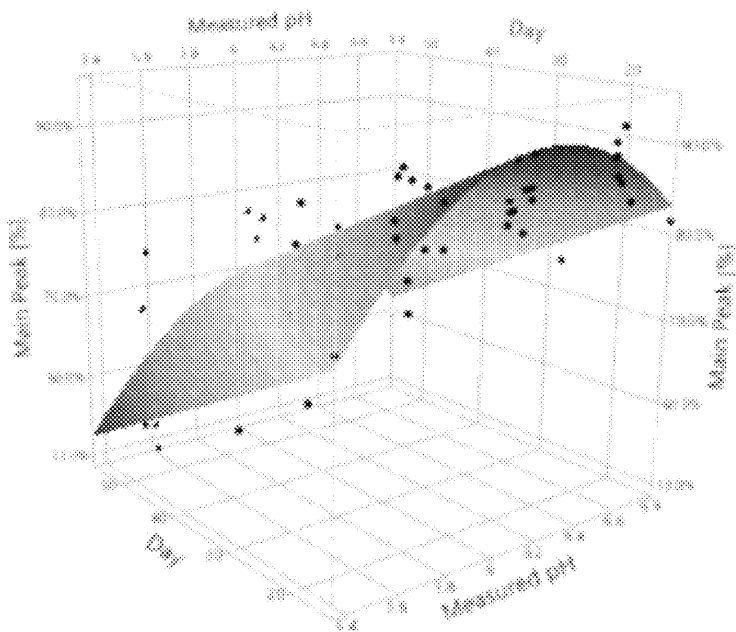


FIG. 87A

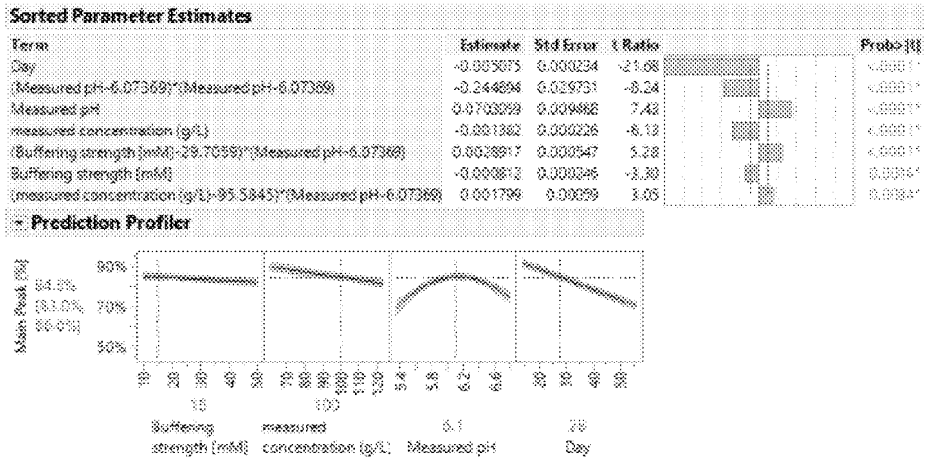


FIG. 87B

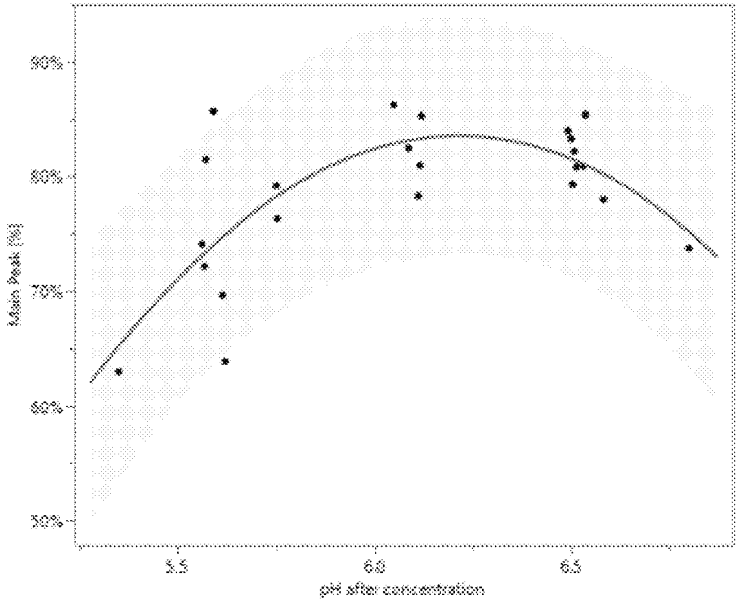


FIG. 87C

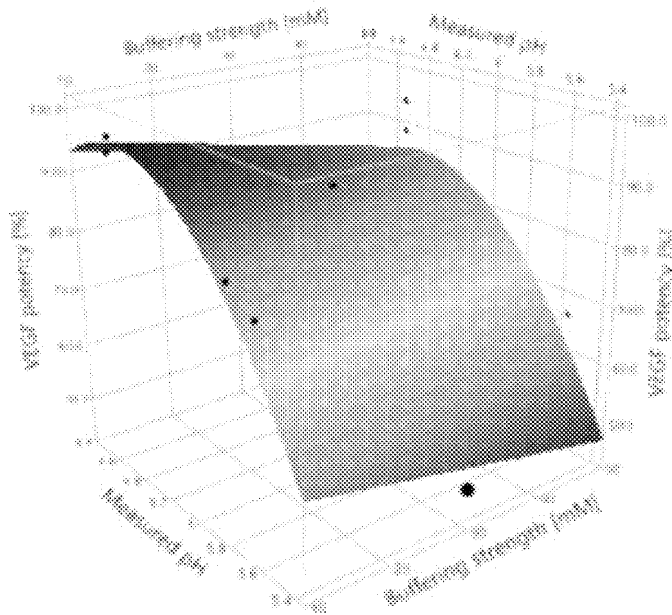


FIG. 88A

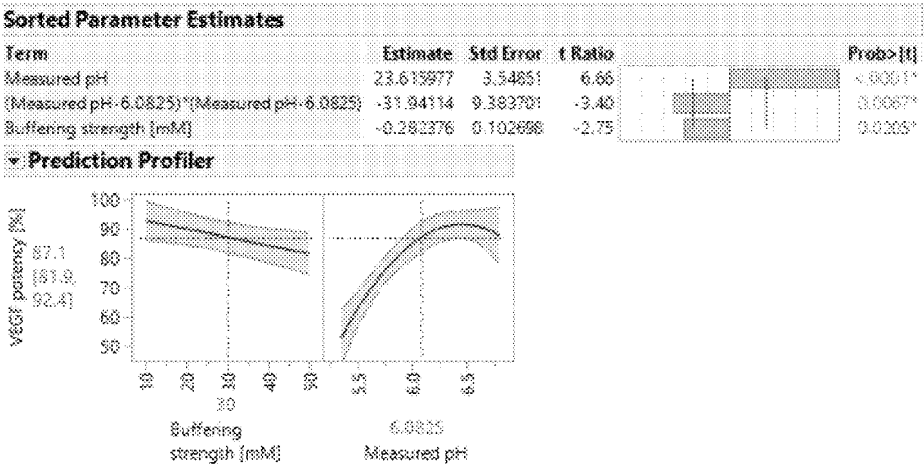


FIG. 88B

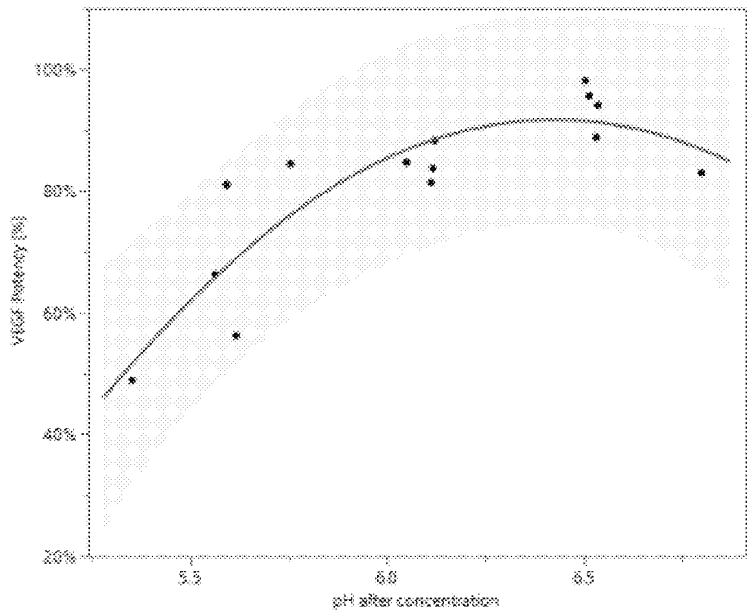


FIG. 88C

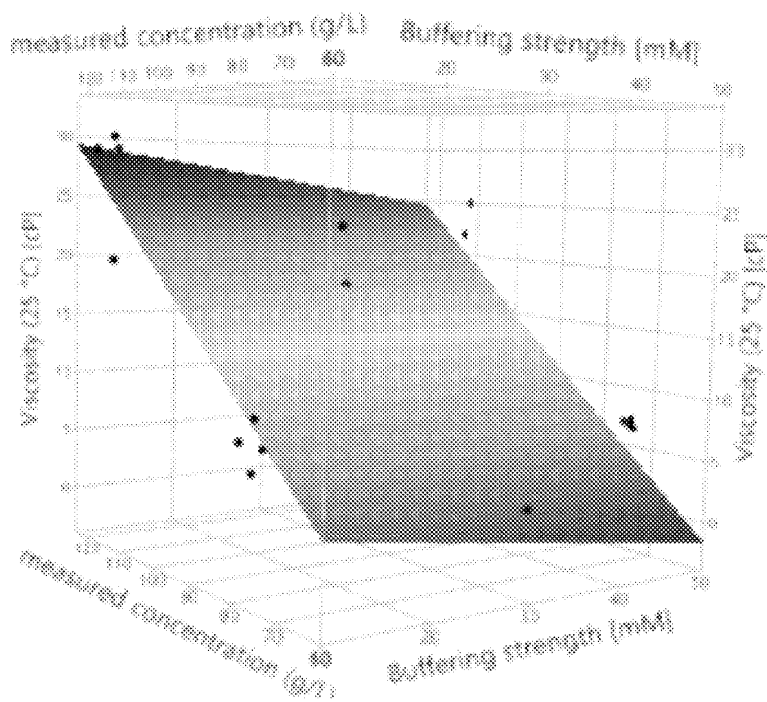


FIG. 89

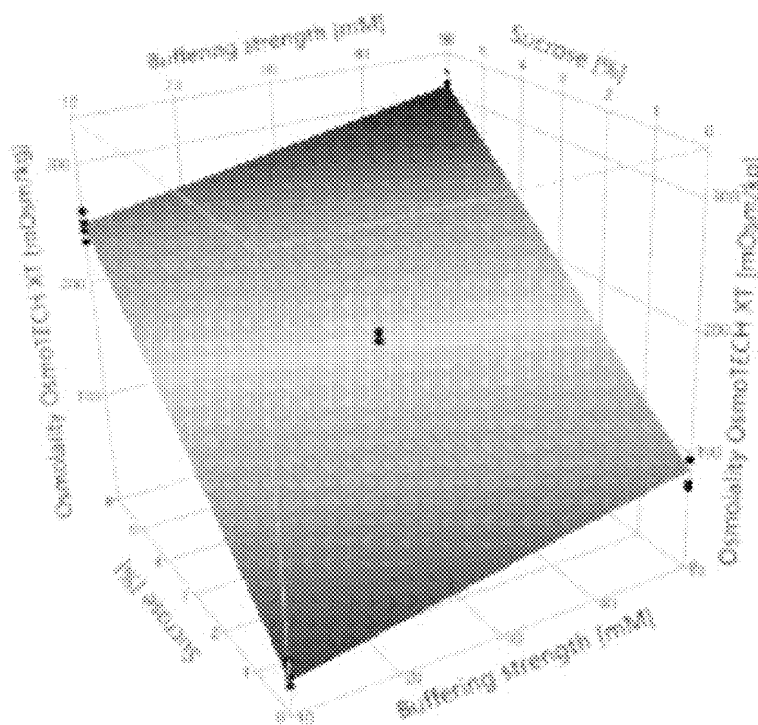


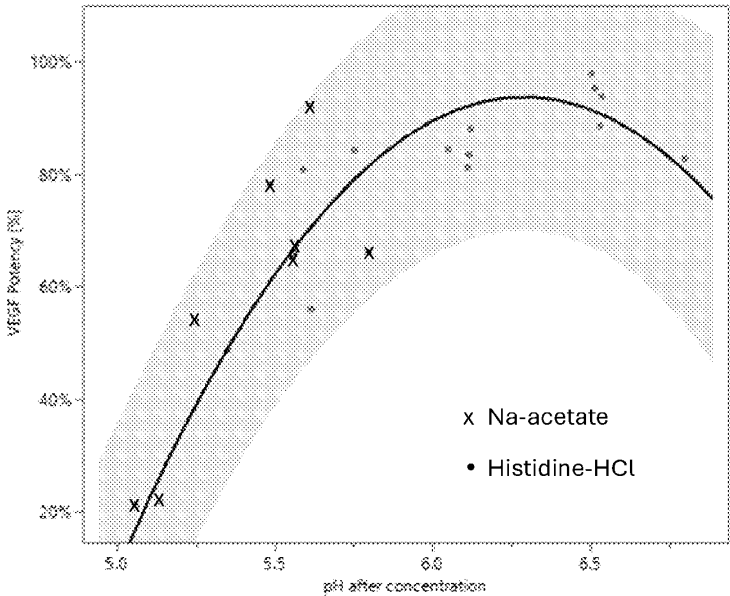
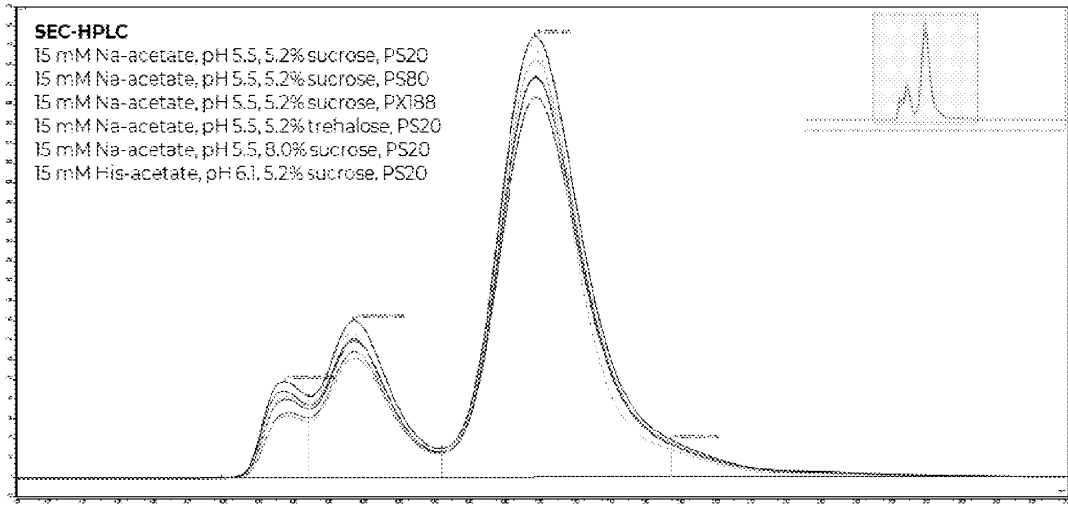
FIG.90

Parameter	SEC-HPLC	Potency	Viscosity	Osmolality
pH	+++	+++	0	0
OG2072 conc. [g/L]	-	0	+++	0
Buffering strength [mM]	-	-	-	+
Sucrose [%]	0	0	+	+++

FIG. 91

Run	pH	Buffer system	sugar	sugar %	Excipient
1	5.5	Na-ac	sucrose	5.2	PS20
2	5.5	Na-ac	sucrose	5.2	PS80
3	5.5	Na-ac	sucrose	5.2	PX188
4	5.5	Na-ac	trehalose	5.2	PS20
5	5.5	Na-ac	sucrose	8.0	PS20
6	6.1	His-Ac	sucrose	5.2	PS20

FIG. 92A



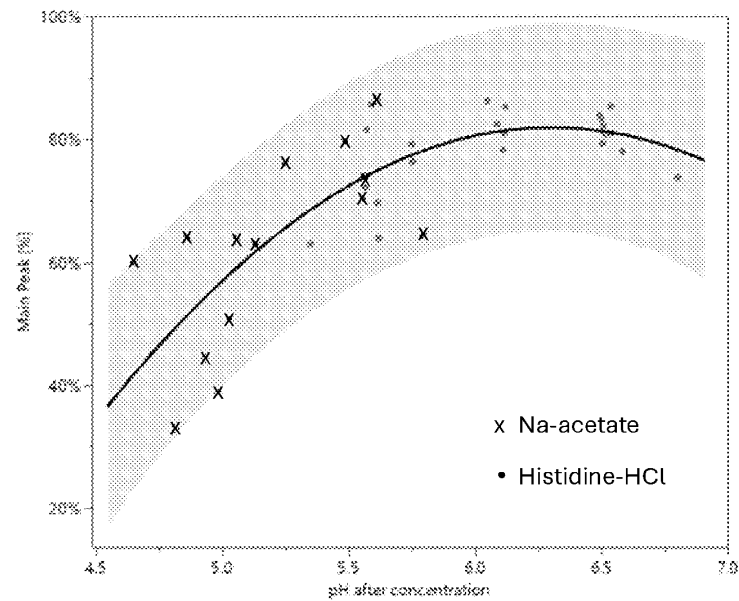


FIG. 93B

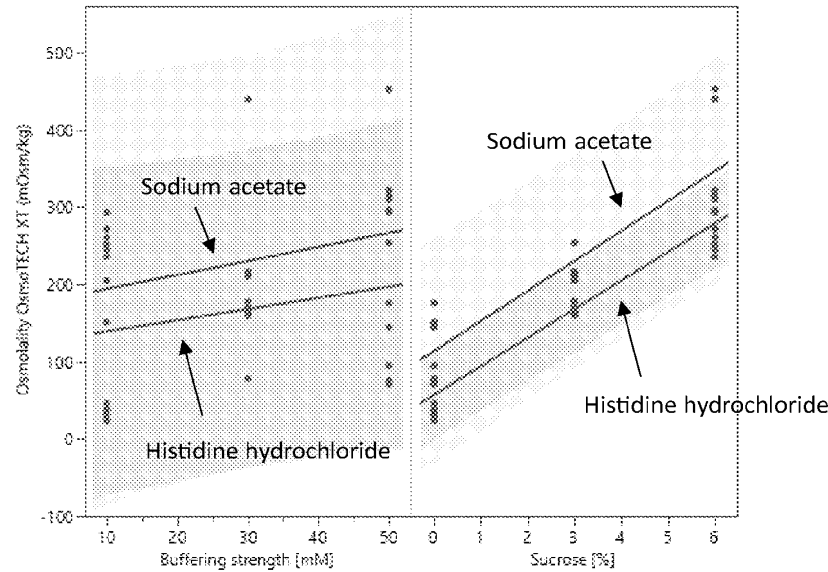


FIG. 94A

134/135

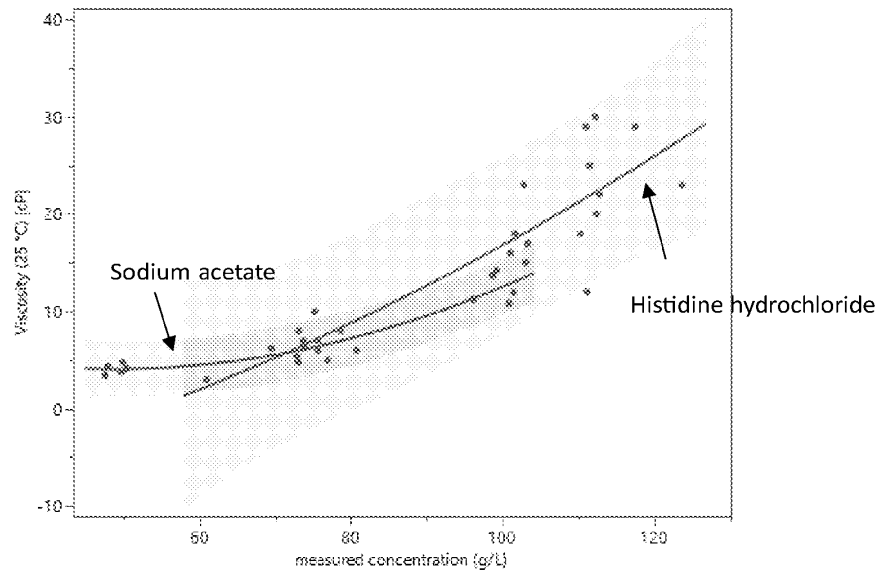
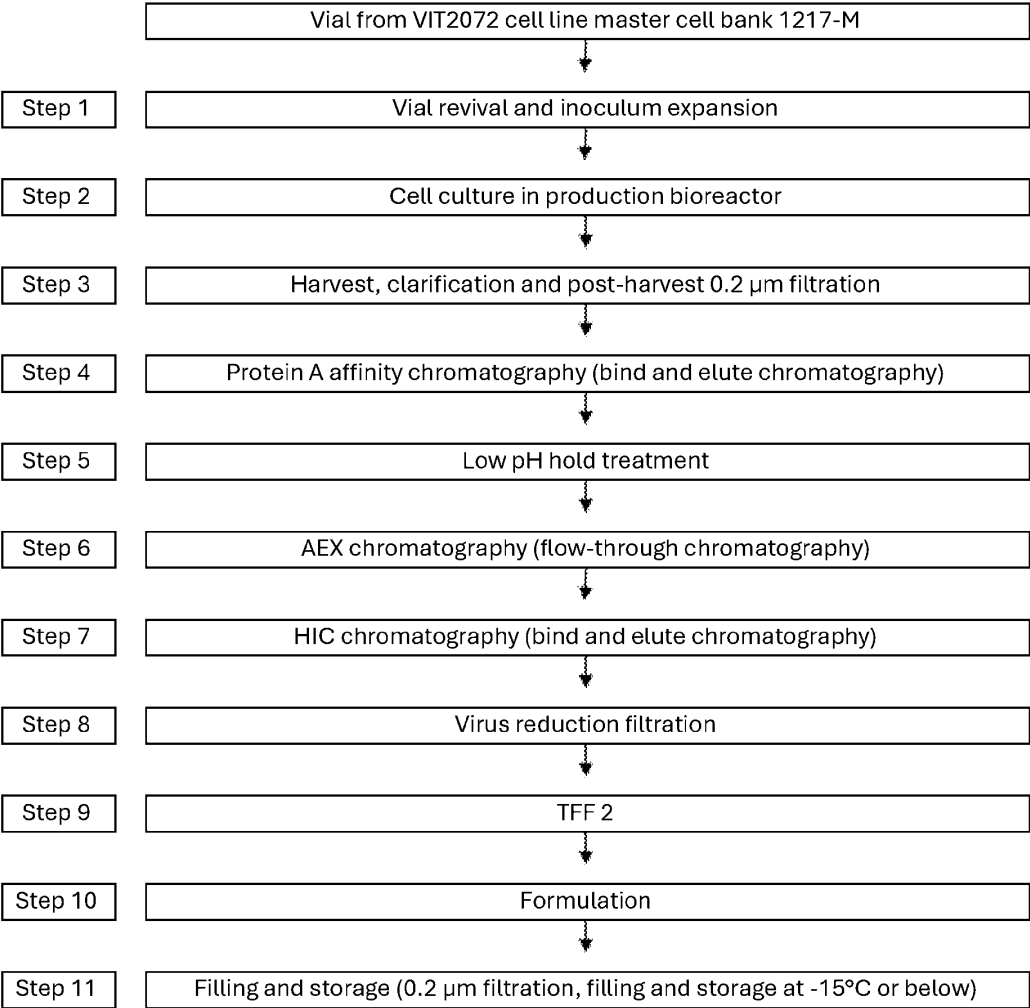


Fig. 94B



Abbreviation(s): TFF = tangential flow filtration; AEX = anion exchange; HIC = hydrophobic interaction exchange; µm = micrometer; °C = degree Celsius.

FIG. 95