Amino Acid Sequence of Ranibizumab/Bevacizumab Fab Heavy Chain

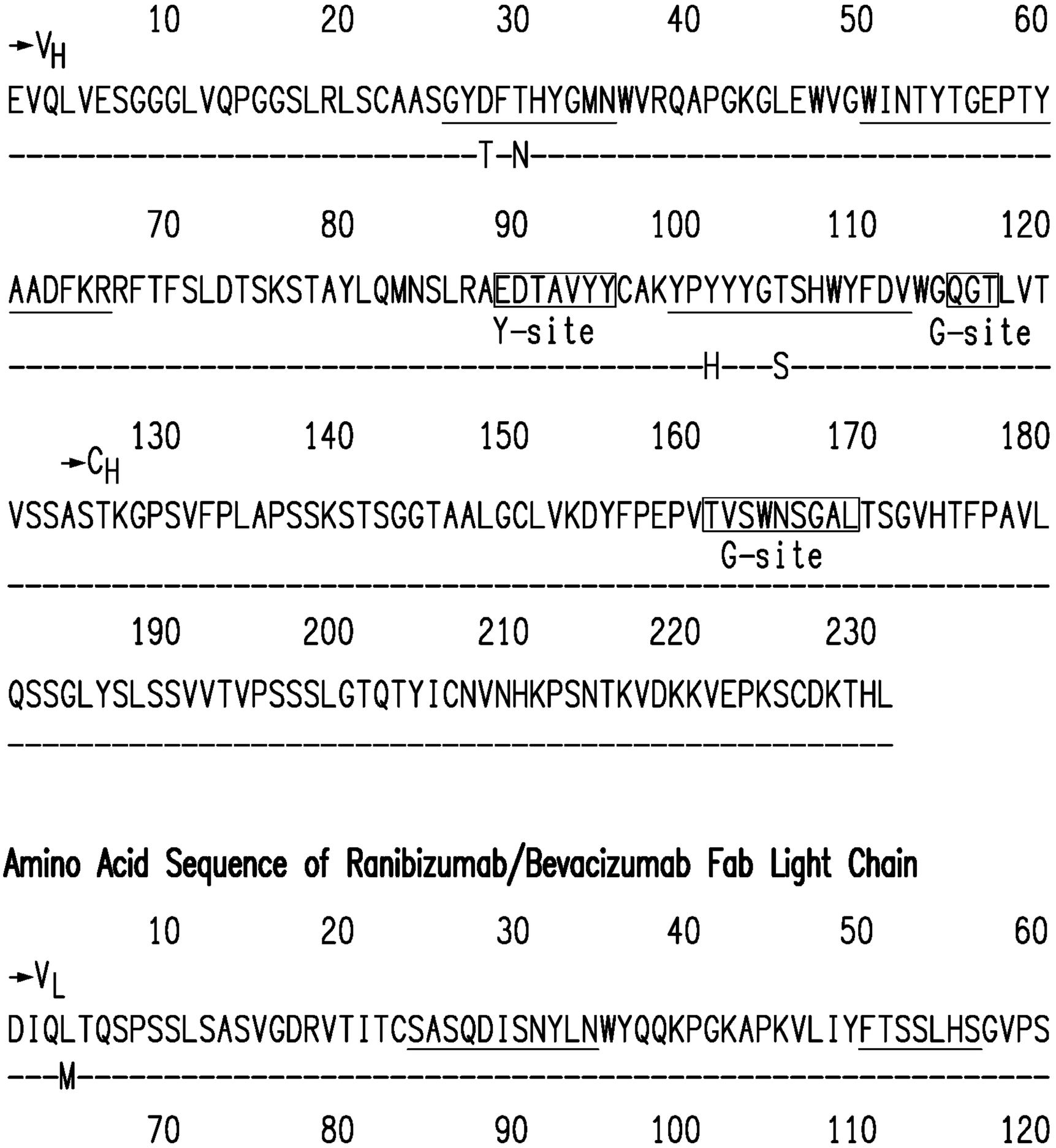


FIG. 1

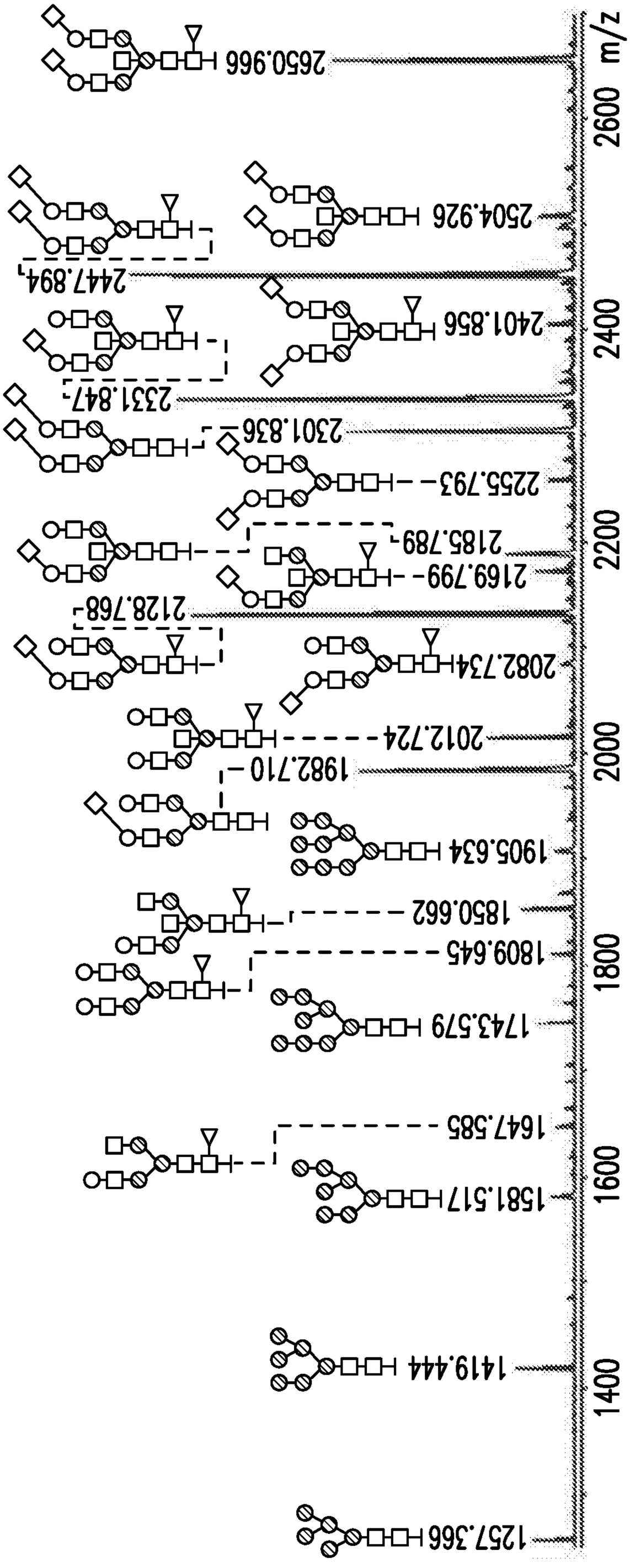

2650.966
2504.926
2447.894
2401.856
2331.847
2301.836
2255.793
2185.789
2169.799
2128.768
2082.734
2012.724
1982.710
1905.634
1850.662
1809.645
1743.579
1647.585
1581.517
1419.444
1257.366
2600 m/z
2400
2200
2000
1800
1600
1400
galactose
mannose
fucose
N-acetylglucosamine
α(2,3)-linked N-acetylneuraminic acid
α(2,6)-linked N-acetylneuraminic acid

FIG. 2

Amino Acid Sequence of Hyperglycosylated Ranibizumab/Bevacizumab Fab Heavy Chain

```
        10        20        30        40        50        60
→VH
EVQLVESGGLVQPGGSLRLSCAASGYDFTHYGMNWVRQAPGKGLEWVGWINTYTGEPTY
----------------------------T-N-------------------------------

        70        80        90        100       110       120
                                                        *
AADFKRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPYYYGTSHWYFDVWGQGTNVT
                            Y-site                  G-site
----------------------------------H---S-----------L--

        130       140       150       160       170       180
    →CH
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
                                      G-site
------------------------------------------------------------

        190       200       210       220       230
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHL
--------------------------------------------------
```

Amino Acid Sequence of Hyperglycoslated Ranibizumab/Bevacizumab Fab Light Chain

```
        10        20        30        40        50        60
→VL
DIQLTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPS
---M--------------------------------------------------------

        70        80        90        100       110       120
                                                →CL
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPP
                          Y-site          G-site
------------------------------------------------------------

        130       140       150       160       170       180
                                                *
                                                S
                                                *
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSNESVTEQDSKDSTYSLSSTLT
                                      G-site
----------------------------------------Q-------------------

        190       200       210
                *
LSKADYEKHKVYACNVTHQGLSSPVTKSFNRGEC
                          G-site
----------E-----------------------
```

FIG. 3

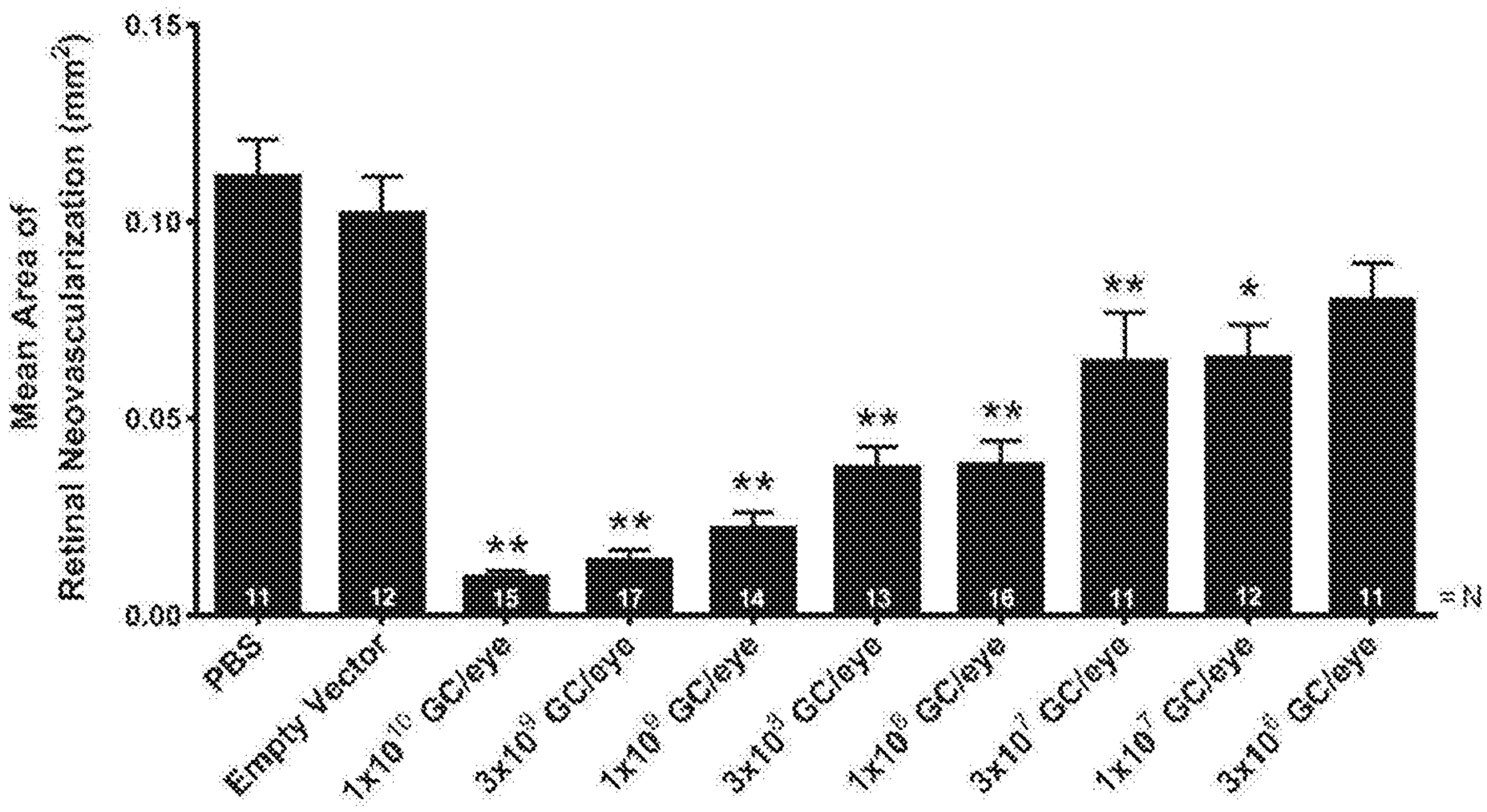

Mean Area of
Retinal Neovascularization (mm²)
0.15
0.10
0.05
0.00
11
12
15
17
14
15
16
11
12
11
n=12
**
*
PBS
Empty Vector
1x10¹⁰ GC/eye
3x10⁹ GC/eye
1x10⁹ GC/eye
3x10⁸ GC/eye
1x10⁸ GC/eye
3x10⁷ GC/eye
1x10⁷ GC/eye
3x10⁶ GC/eye

FIGURE 4

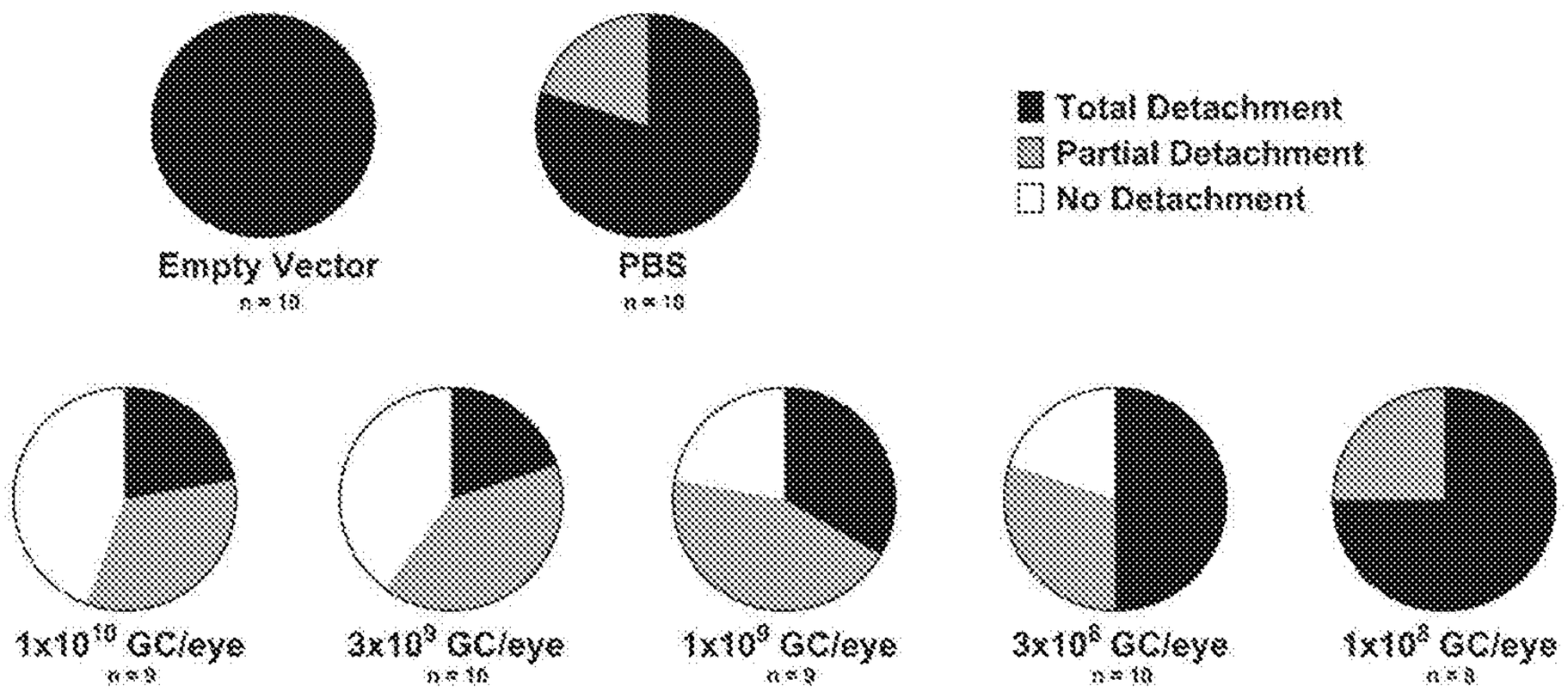

Empty Vector
n = 10
PBS
n = 10
Total Detachment
Partial Detachment
No Detachment
1x10^10 GC/eye
n = 9
3x10^9 GC/eye
n = 10
1x10^9 GC/eye
n = 9
3x10^8 GC/eye
n = 10
1x10^8 GC/eye
n = 9

FIGURE 5

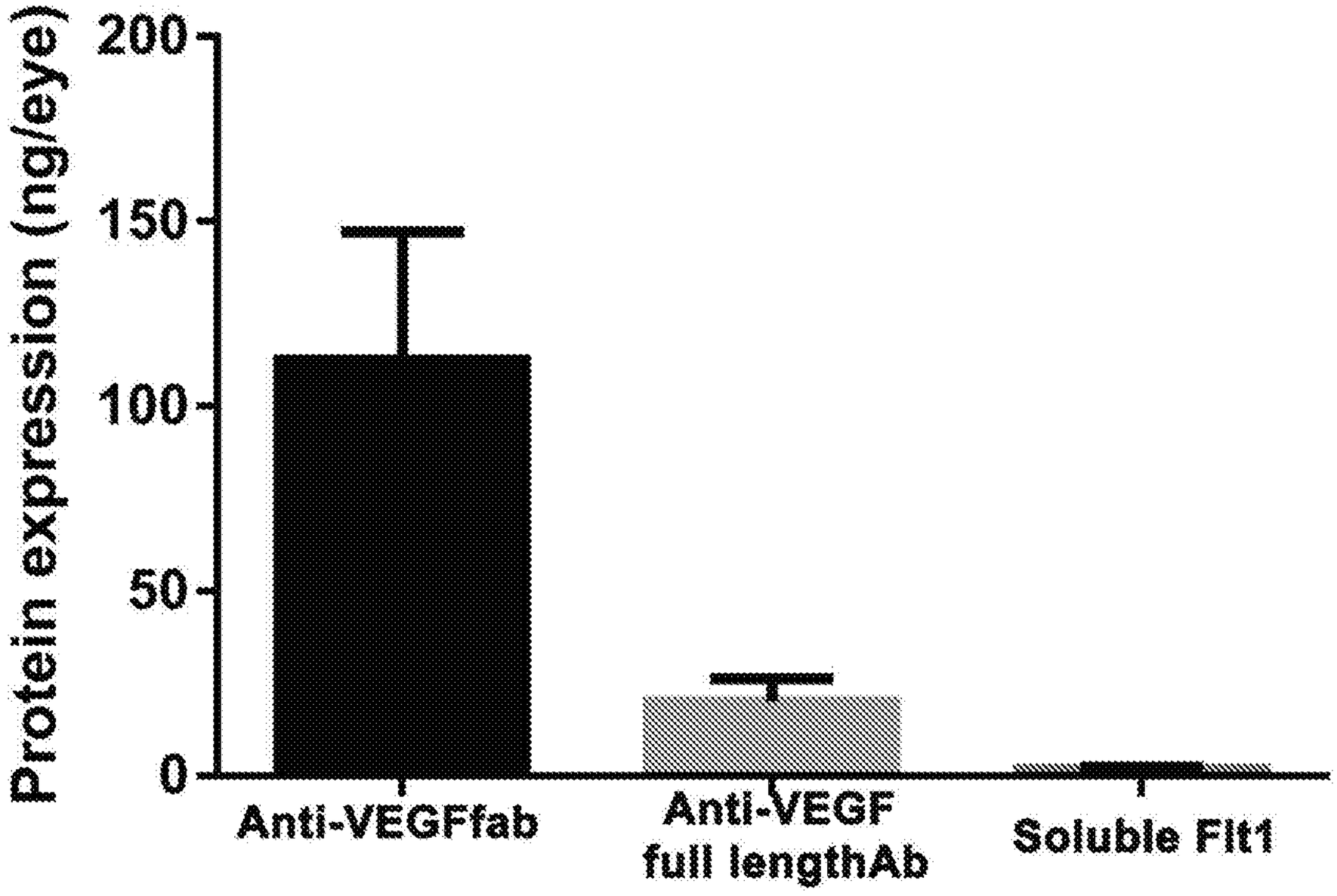

Protein expression (ng/eye)
200
150
100
50
0
Anti-VEGFfab
Anti-VEGF
full lengthAb
Soluble Flt1

FIGURE 6

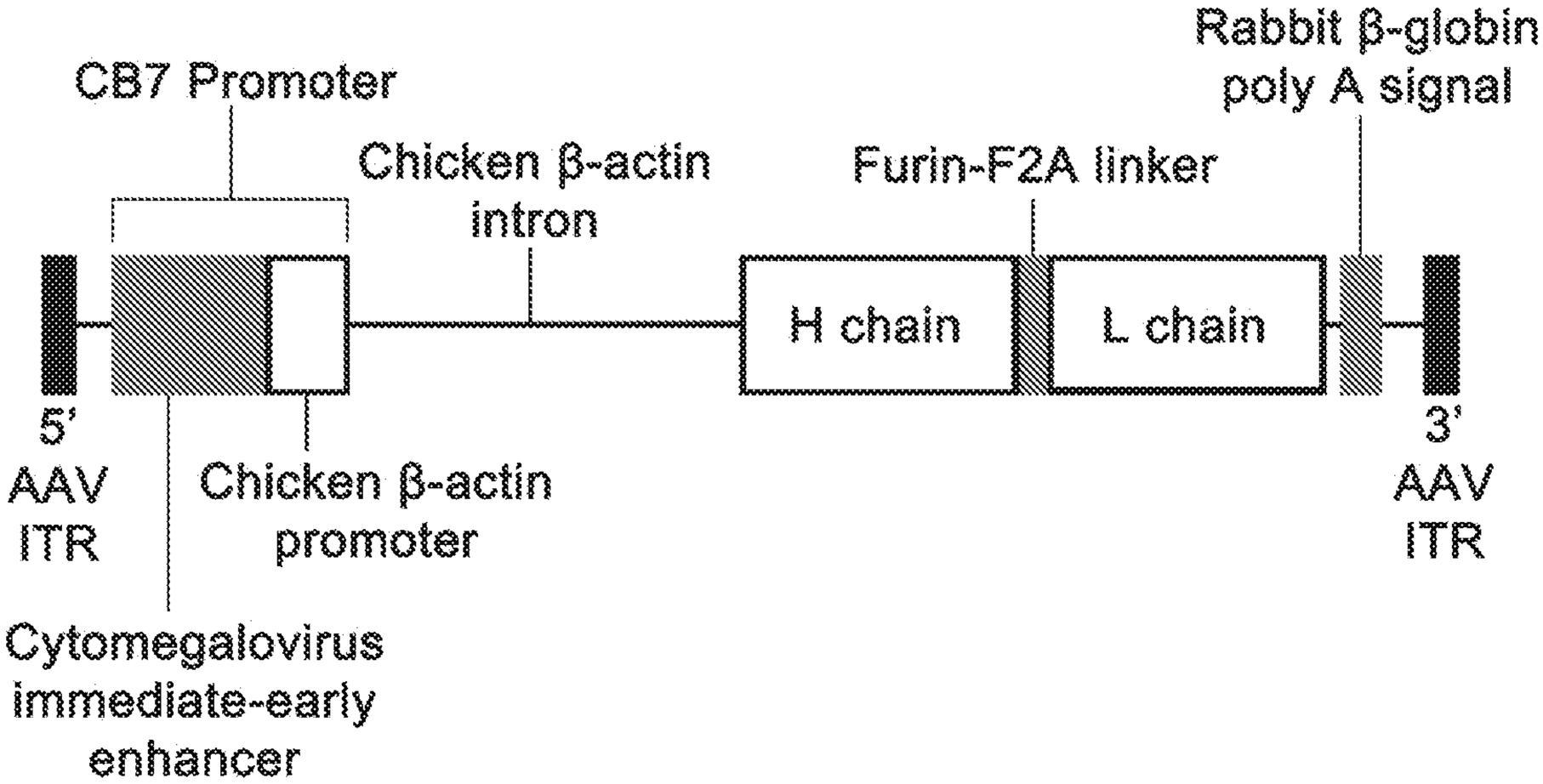


FIGURE 7A

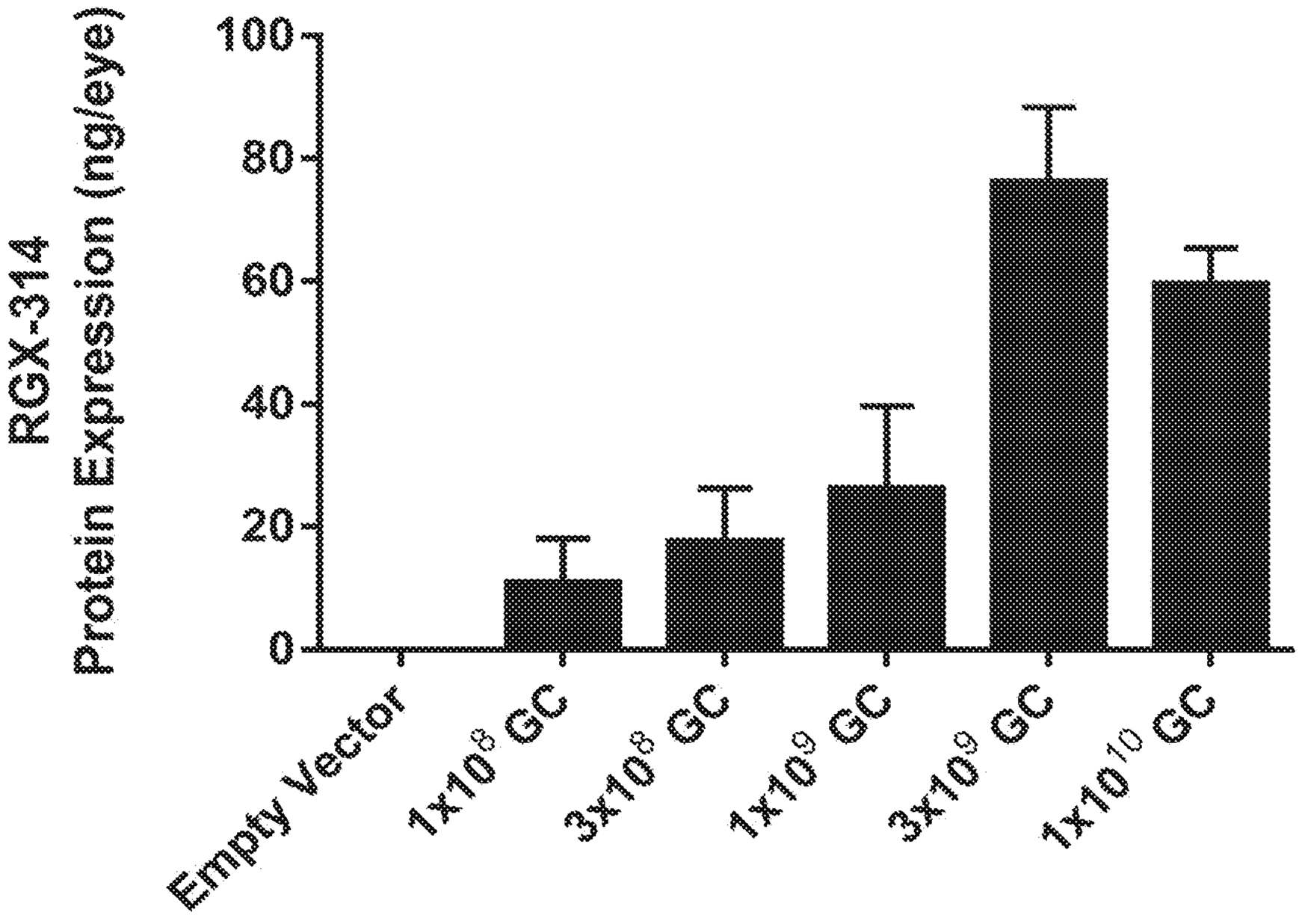


FIGURE 7B

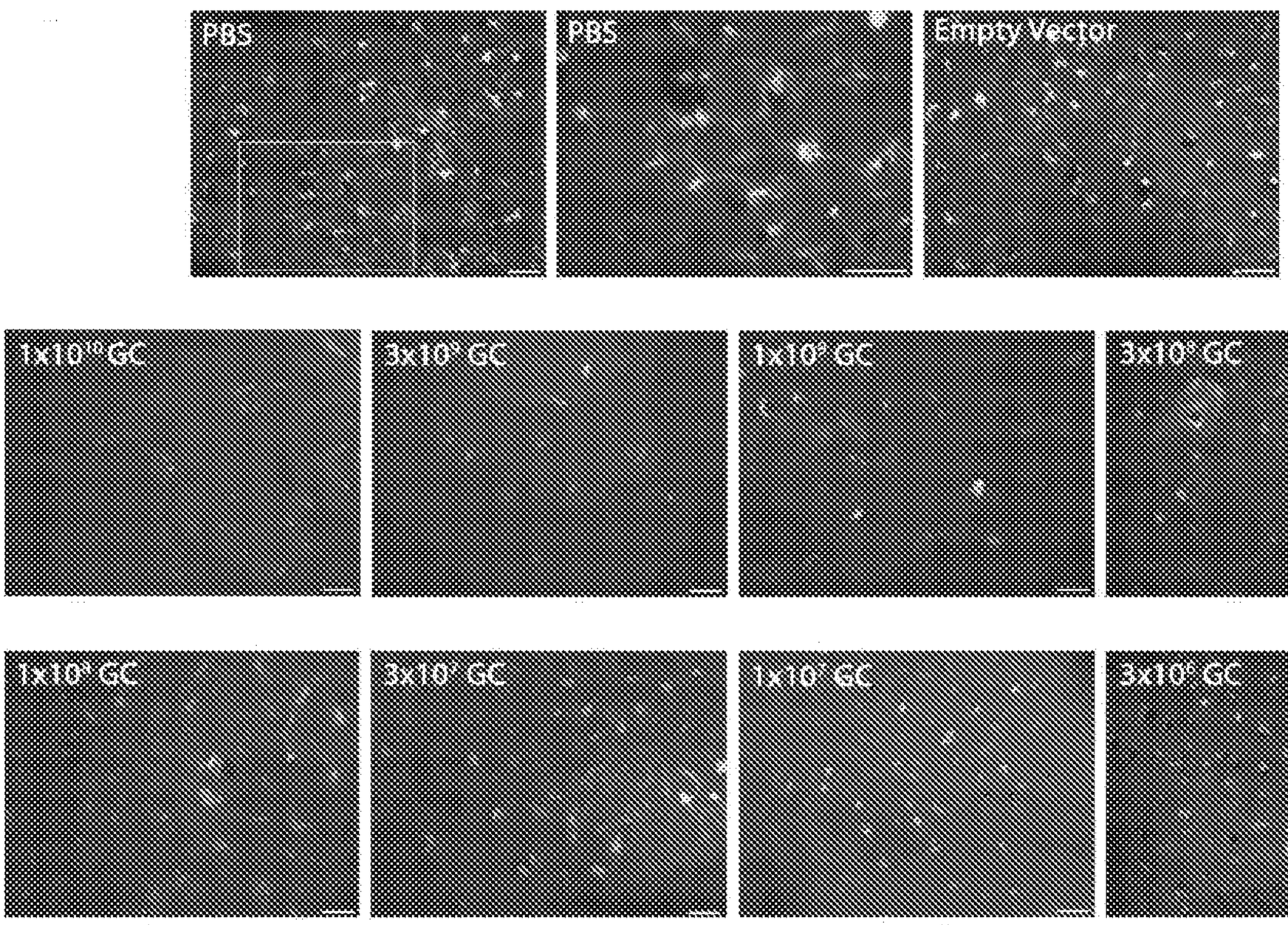


FIGURE 8A

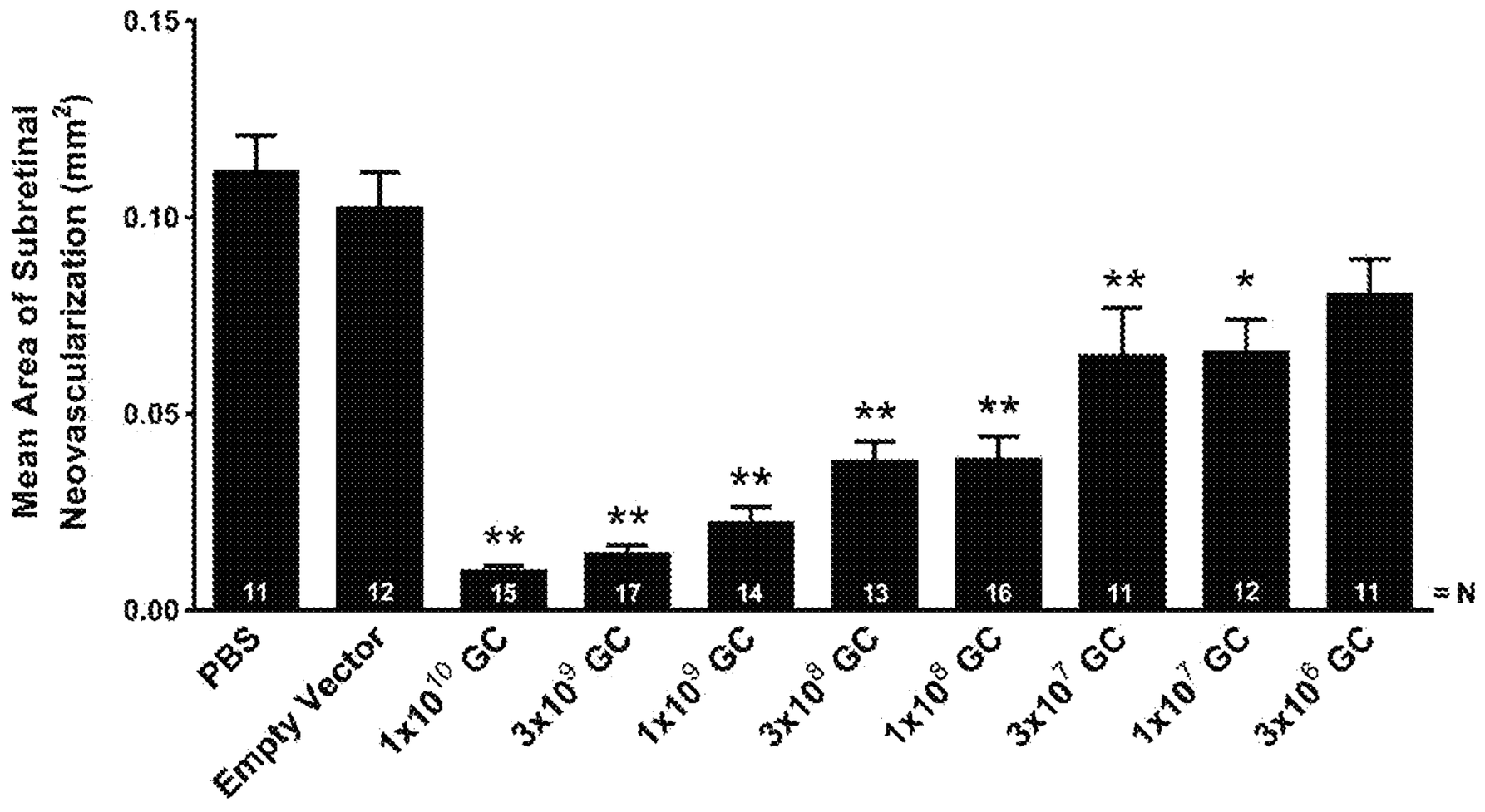


FIGURE 8B

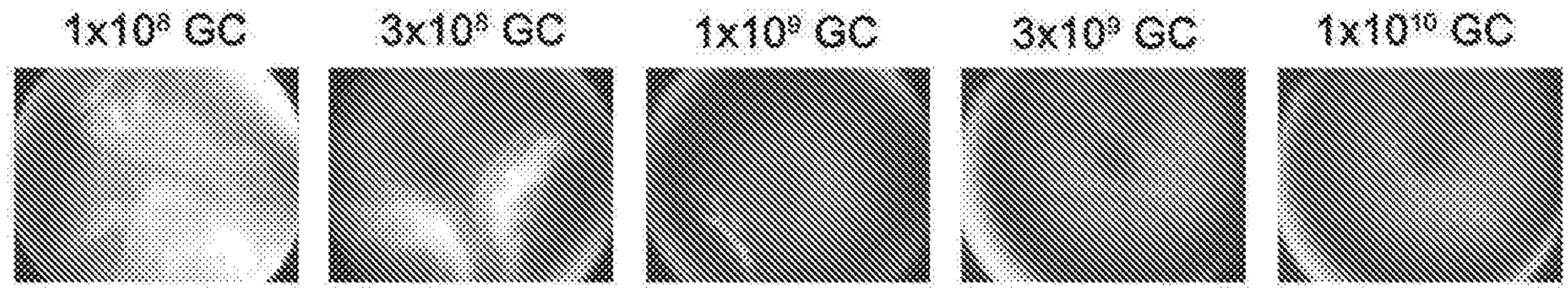


FIGURE 9A

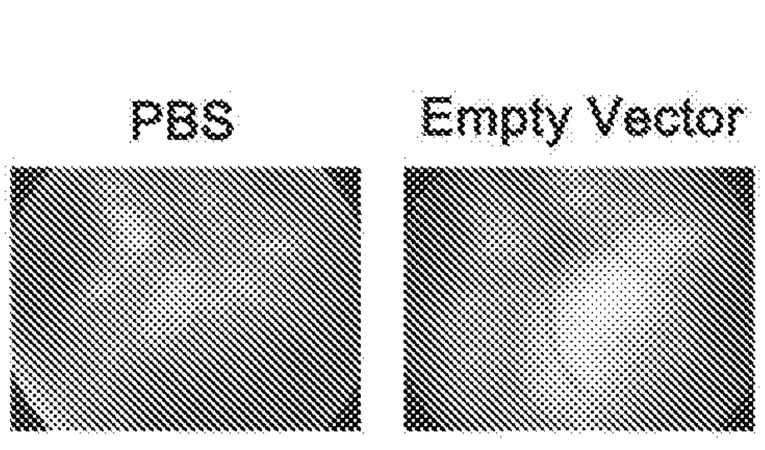


FIGURE 9B

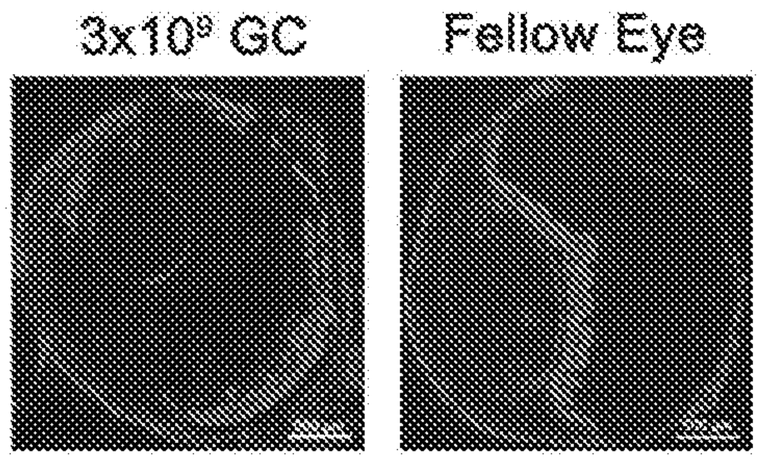


FIGURE 9C

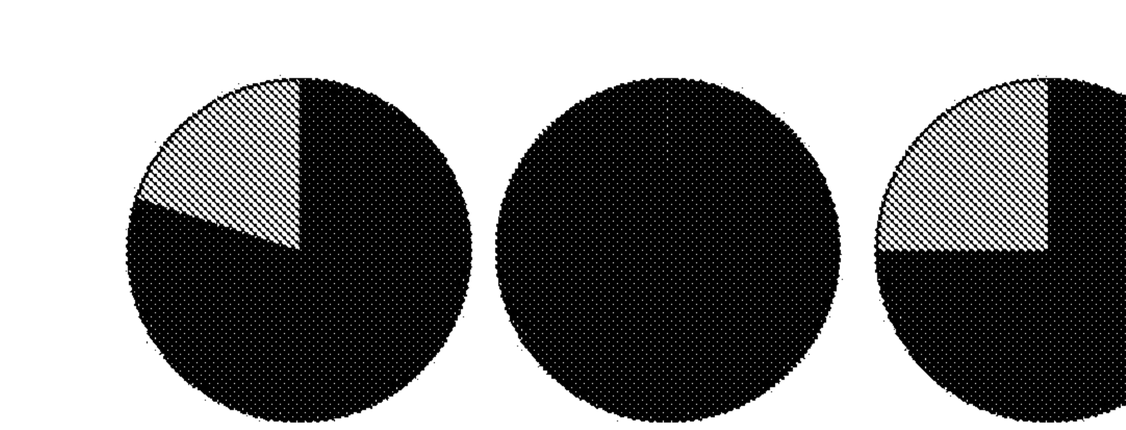


FIGURE 9D

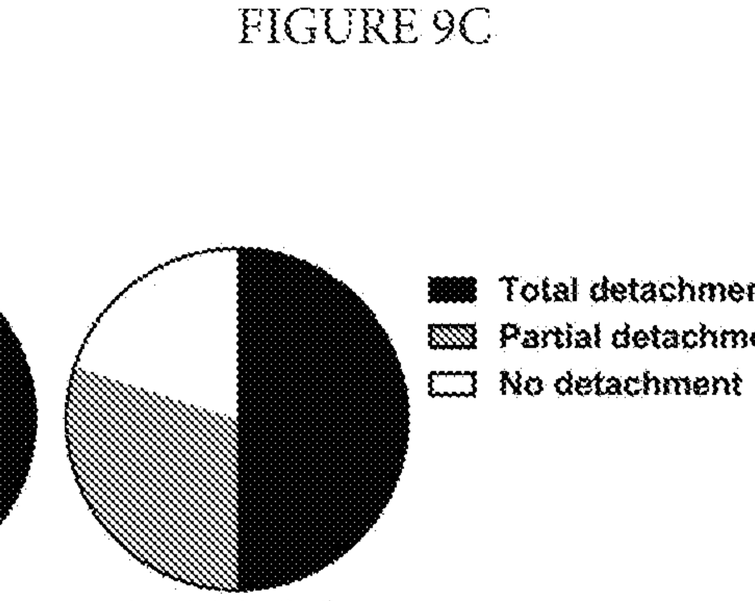


FIGURE 9E

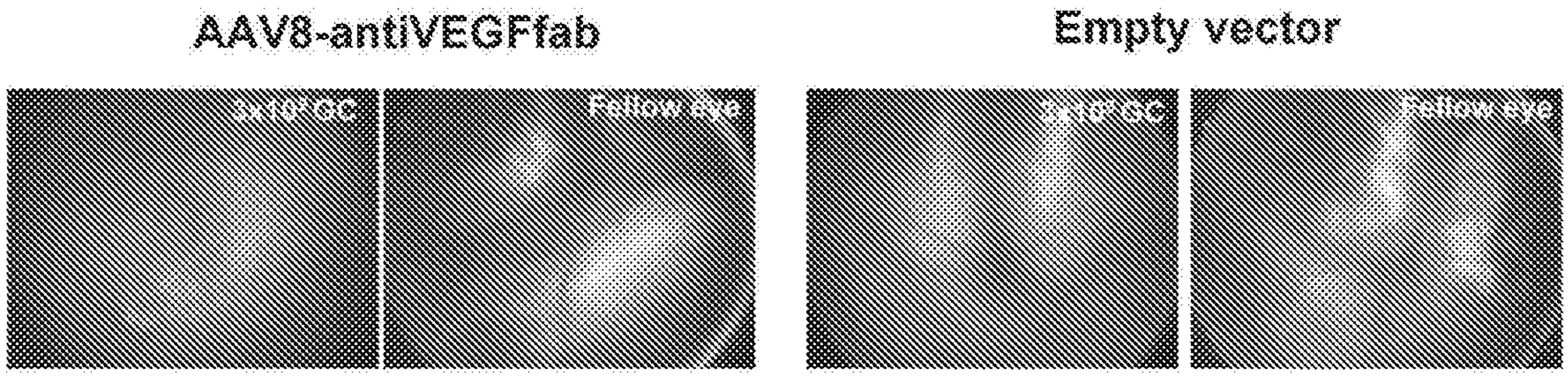


FIGURE 10A

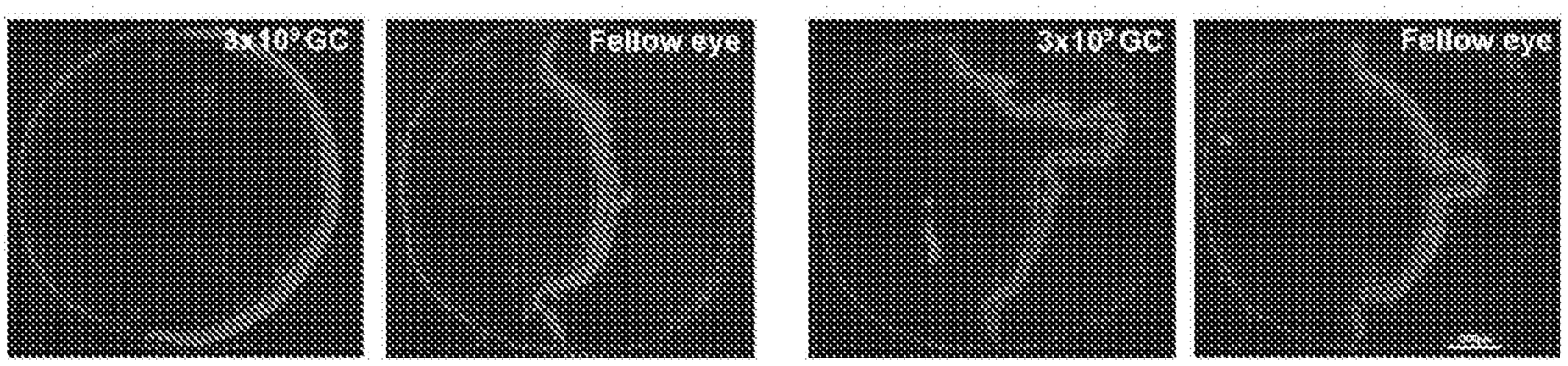


FIGURE 10B

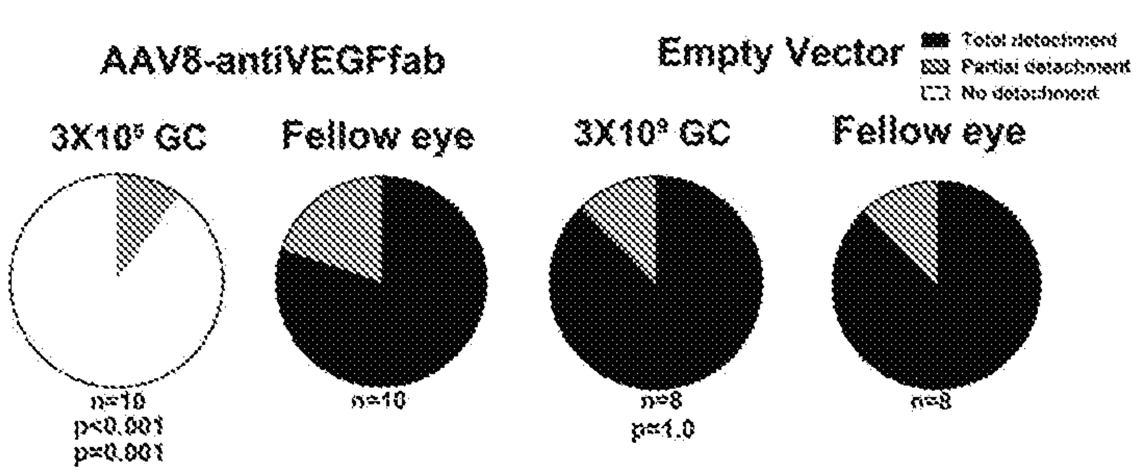


FIGURE 10C

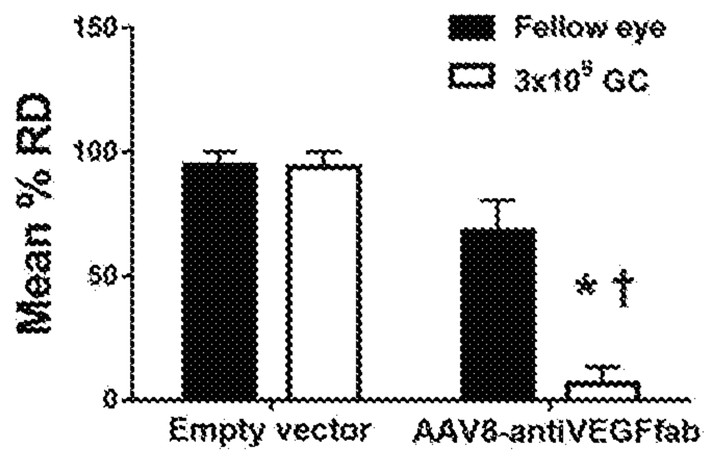


FIGURE 10D

LC

1 MDIQLTQSPS SLSASVGDRV TITCSASQDI SNYLNWYQQK PGKAPKVLIY FTSSLHSGVP SRFSGSGSGT DFTLTISSLQ
81 PEDFATYYCQ QYSTVPWTFG QGTKVEIKRT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK VDNALQSGNS
161 QESVTEQDSK DSTYSLSSTL TLSKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC (SEQ ID NO. 38)

HC

1 MEVQLVESGG GLVQPGGSLR LSCAASGYDF THYGMNWVRQ APGKGLEWVG WINTYTGEPT YAADFKRRFT FSLDTSKSTA
81 YLQMNSLRAE DTAVYYCAKY PYYYGTSHWY FDVWGQGTLV TVSSASTKGP SVFPLAPSSK STSGGTAALG CLVKDYFPEP
161 VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL GTQTYICNVN HKPSNTKVDK KVEPKSCDKT HLRKRR
(SEQ ID NO. 39)

FIGURE 11

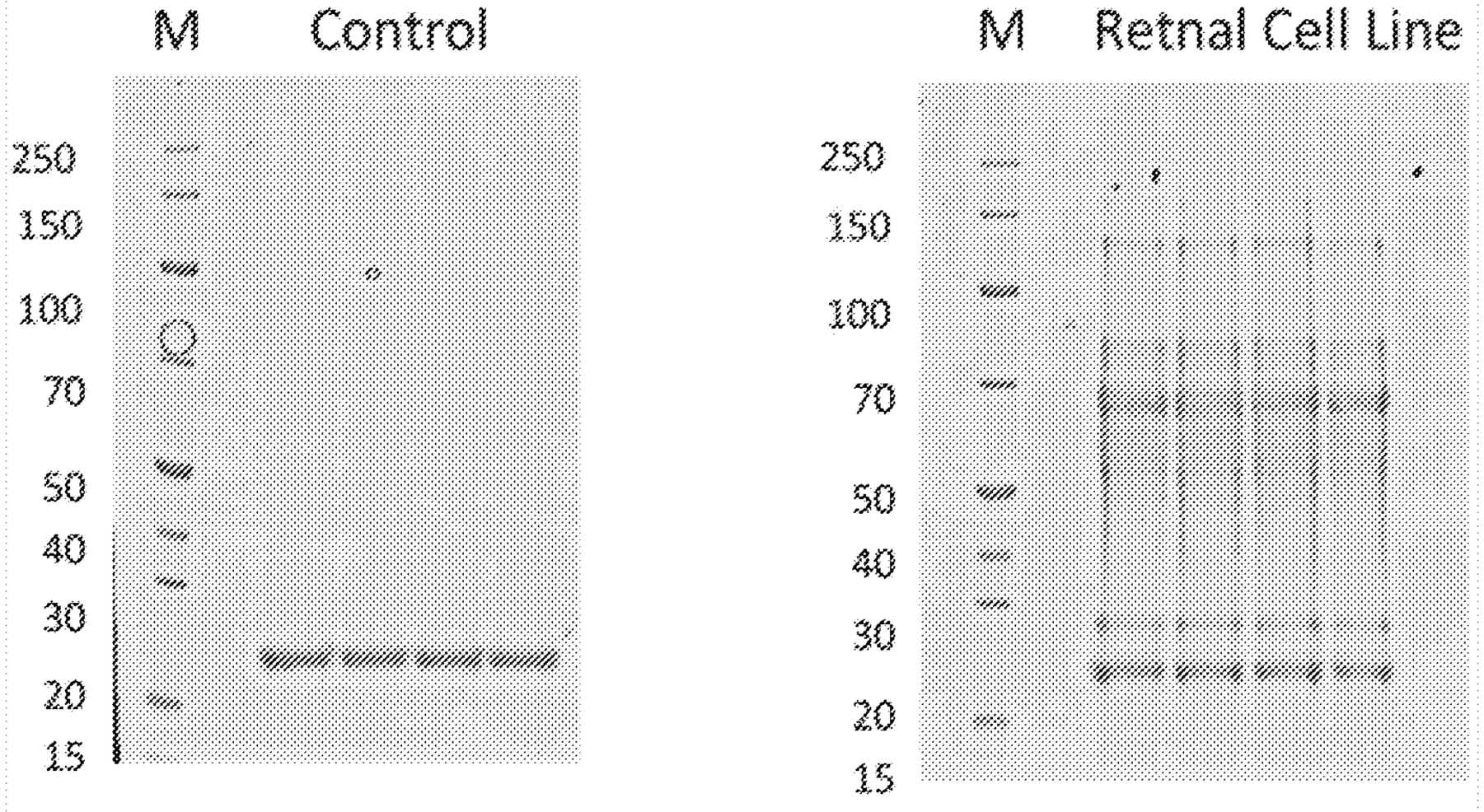


FIGURE 12

```
MDIQLTQSPS  SLSASVGDRV  TITCSASQDI  SNYLNWYQQK  PGKAPKVLIY
FTSSLHSGVP  SRFSGSGSGT  DFTLTISSLQ  PEDFATYYCQ  QYSTVPWTFG
QGTKVEIKRT  VAAPSVFIFP  PSDEQLKSGT  ASVVCLLNNF  YPREAKVQWK
VDNALQSGNS  QESVTEQDSK  DSTYSLSSTL  TLSKADYEKH  KVYACEVTHQ
GLSSPVTKSF  NRGEC  (SEQ ID NO. 38)
```

```
MEVQLVESGG  GLVQPGGSLR  LSCAASGYDF  THYGMNWVRQ  APGKGLEWVG
WINTYTGEPT  YAADFKRRFT  FSLDTSKSTA  YLQMNSLRAE  DTAVYYCAKY
PYYYGTSHWY  FDVWGQGTLV  TVSSASTKGP  SVFPLAPSSK  STSGGTAALG
CLVKDYFPEP  VTVSWNSGAL  TSGVHTFPAV  LQSSGLYSLS  SVVTVPSSSL
GTQTYICNVN  HKPSNTKVDK  KVEPKSCDKT  HL  (SEQ ID NO. 40)
```

FIGURE 13

MDIQLTQSPS SLSASVGDRV TITCSASQDI SNYLNWYQQK PGKAPKVLIY
FTSSLHSGVP SRFSGSGSGT DFTLTISSLQ PEDFATYYCQ QYSTVPWTFG
QGTKVEIKRT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK
VDNALQSGNS QESVTEQDSK DSTYSLSSTL TLSKADYEKH KVYACEVTHQ
GLSSPVTKSF NRGEC (SEQ ID NO. 38)

MEVQLVESGG GLVQPGGSLR LSCAASGYDF THYGMNWVRQ APGKGLEWVG
WINTYTGEPT YAADFKRRFT FSLDTSKSTA YLQMNSLRAE DTAVYYCAKY
PYYYGTSHWY FDVWGQGTLV TVSSASTKGP SVFPLAPSSK STSGGTAALG
CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL
GTQTYICNVN HKPSNTKVDK KVEPKSCDKT HL (SEQ ID NO. 40)

FIGURE 14

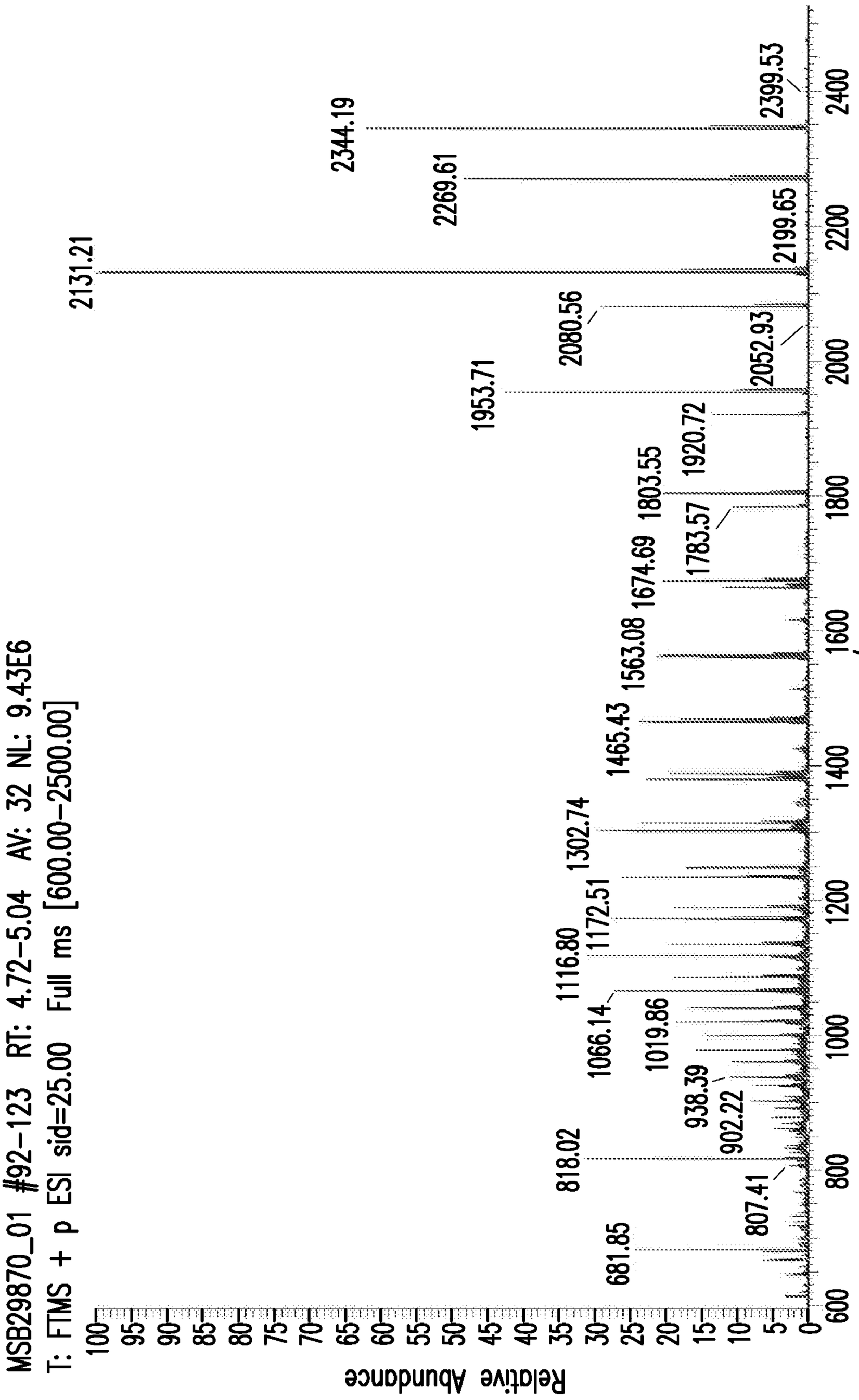
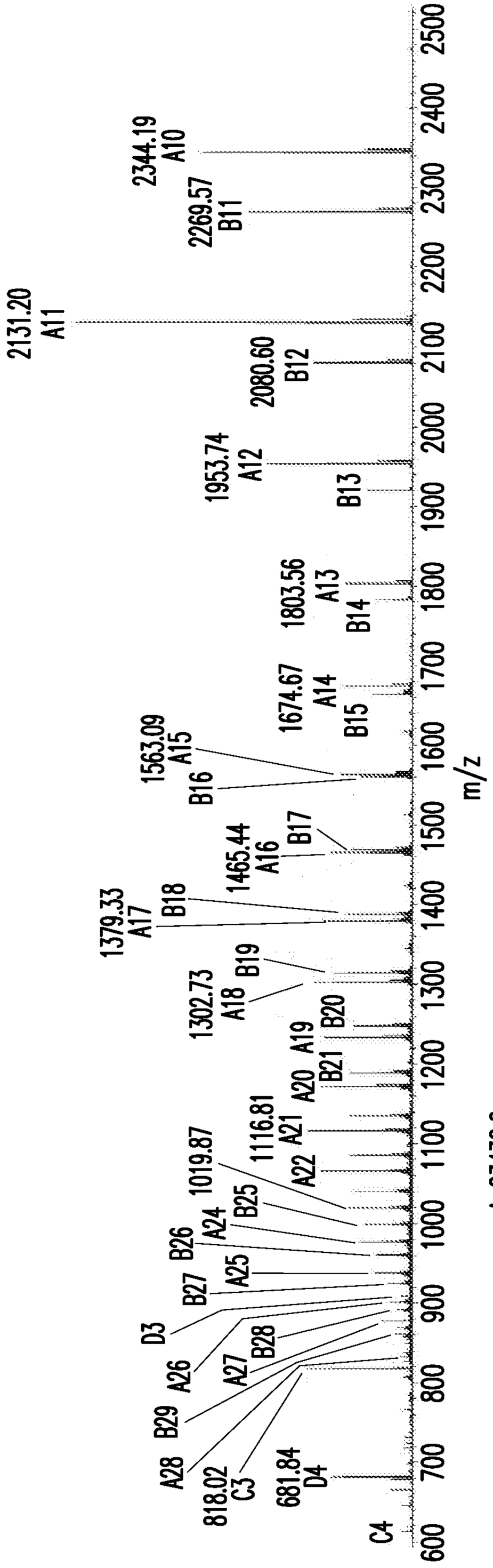

MSB29870_01 #92-123 RT: 4.72-5.04 AV: 32 NL: 9.43E6
T: FTMS + p ESI sid=25.00 Full ms [600.00-2500.00]
Relative Abundance
m/z
2131.21
2344.19
2399.53
2269.61
1953.71
2080.56
2052.93
2199.65
1920.72
1803.55
1783.57
1674.69
1563.08
1465.43
1302.74
1172.51
1116.80
1066.14
1019.86
938.39
902.22
818.02
807.41
681.85

FIG. 15A



	Error		
		LC	HC
Theoretical Mass*	43ppm	23,433.0	24,957.0
Measured Mass	40ppm	23,432.0	24,956.0

* Assuming no N-terminal Met

FIG. 15B

```
MDIQLTQSPS  SLSASVGDRV  TITCSASQDI  SNYLNWYQQK  PGKAPKVLIY
FTSSLHSGVP  SRFSGSGSGT  DFTLTISSLQ  PEDFATYYCQ  QYSTVPWTFG
QGTKVEIKRT  VAAPSVFIFP  PSDEQLKSGT  ASVVCLLNNF  YPREAKVQWK
VDNALQSGNS  QESVTEQDSK  DSTYSLSSTL  TLSKADYEKH  KVYACEVTHQ
GLSSPVTKSF  NRGEC (SEQ ID NO. 38)

MEVQLVESGG  GLVQPGGSLR  LSCAASGYDF  THYGMNWVRQ  APGKGLEWVG
WINTYTGEPT  YAADFKRRFT  FSLDTSKSTA  YLQMNSLRAE  DTAVYYCAKY
PYYYGTSHWY  FDVWGQGTLV  TVSSASTKGP  SVFPLAPSSK  STSGGTAALG
CLVKDYFPEP  VTVSWNSGAL  TSGVHTFPAV  LQSSGLYSLS  SVVTVPSSSL
GTQTYICNVN  HKPSNTKVDK  KVEPKSCDKT  HLRKRR (SEQ ID NO. 39)
```

FIGURE 16

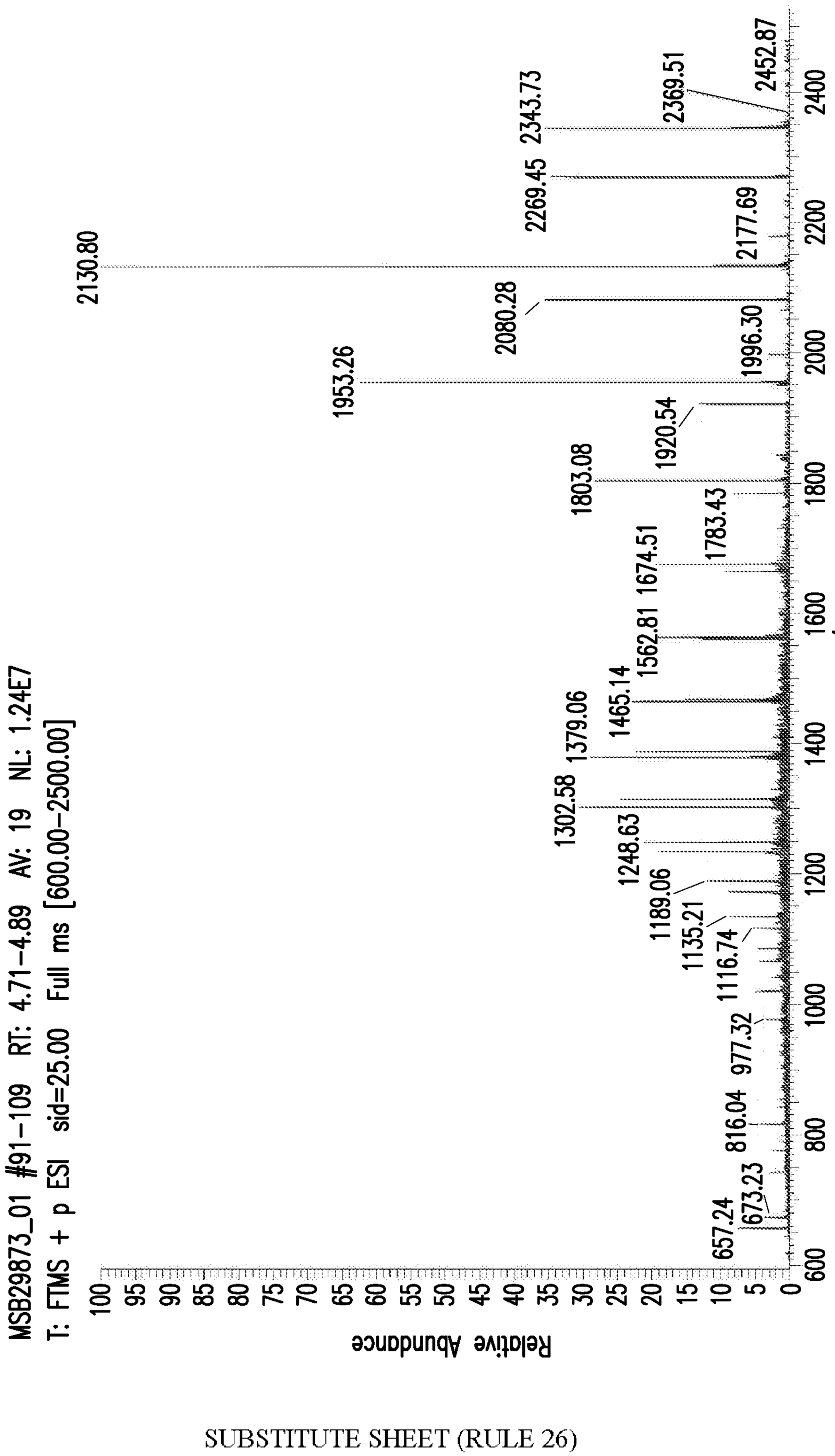
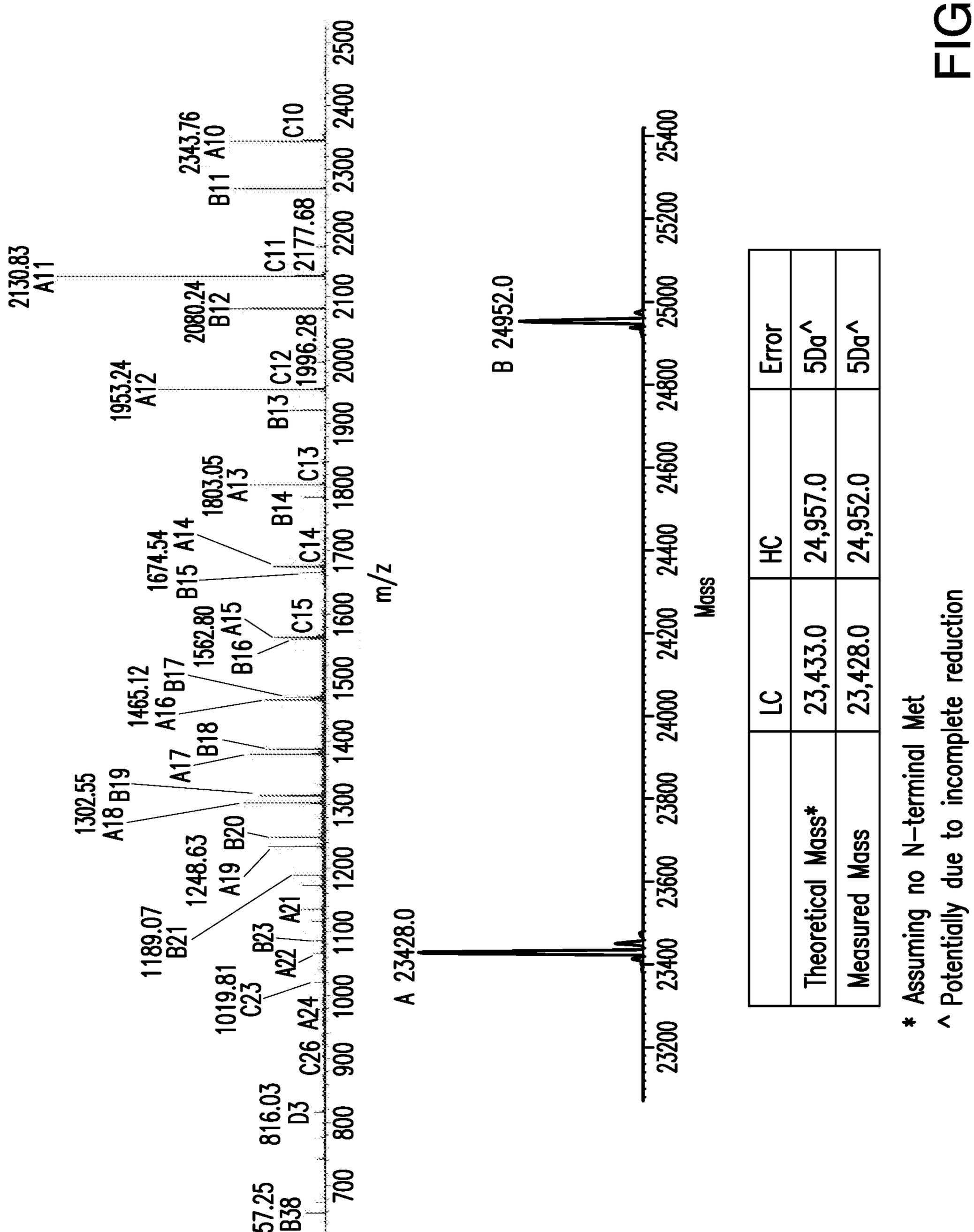

MSB29873_01 #91–109 RT: 4.71–4.89 AV: 19 NL: 1.24E7
T: FTMS + p ESI sid=25.00 Full ms [600.00–2500.00]
Relative Abundance
m/z
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
600
800
1000
1200
1400
1600
1800
2000
2200
2400
657.24
673.23
816.04
977.32
1116.74
1135.21
1189.06
1248.63
1302.58
1379.06
1465.14
1562.81
1674.51
1783.43
1803.08
1920.54
1953.26
1996.30
2080.28
2130.80
2177.69
2269.45
2343.73
2369.51
2452.87

FIG. 17A



	LC	HC	Error
Theoretical Mass*	23,433.0	24,957.0	5Da^
Measured Mass	23,428.0	24,952.0	5Da^

* Assuming no N-terminal Met
^ Potentially due to incomplete reduction

FIG. 17B

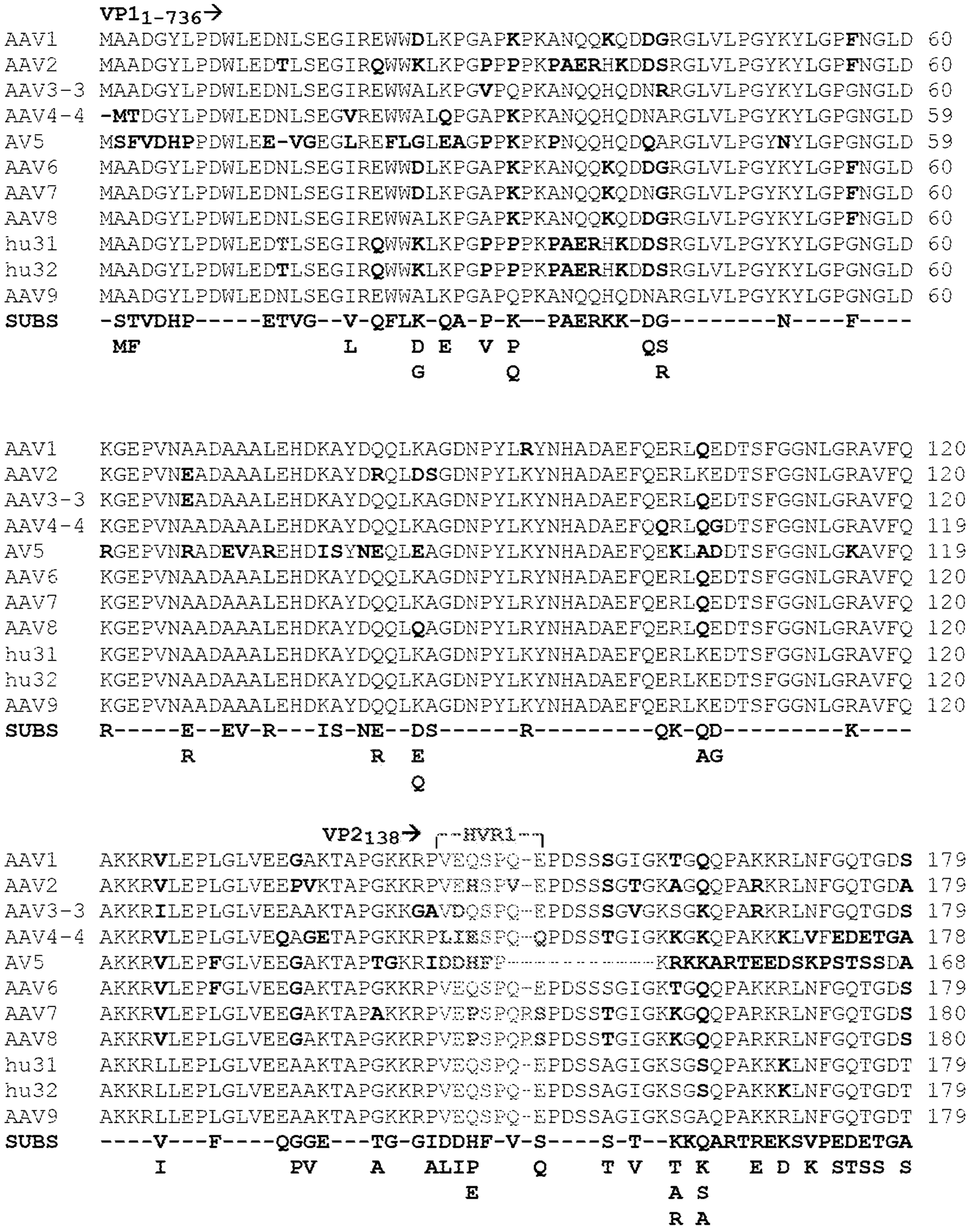

VP1 1-736→
AAV1 MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
AAV2 MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPFNGLD 60
AAV3-3 MAADGYLPDWLEDNLSEGIREWWALKPGVPQPKANQQHQDNRRGLVLPGYKYLGPGNGLD 60
AAV4-4 -MTDGYLPDWLEDNLSEGVREWWALQPGAPKPKANQQHQDNARGLVLPGYKYLGPGNGLD 59
AV5 MSFVDHPPDWLEE-VGEGLREFLGLEAGPPKPKPNQQHQDQARGLVLPGYNYLGPGNGLD 59
AAV6 MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
AAV7 MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDNGRGLVLPGYKYLGPFNGLD 60
AAV8 MAADGYLPDWLEDNLSEGIREWWALKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
hu31 MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPGNGLD 60
hu32 MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPGNGLD 60
AAV9 MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGLD 60
SUBS -STVDHP-----ETVG--V-QFLK-QA-P-K--PAERKK-DG--------N----F----
MF L D E V P QS
G Q R
AAV1 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
AAV2 KGEPVNEADAAALEHDKAYDRQLDSGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ 120
AAV3-3 KGEPVNEADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
AAV4-4 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQQRLQGDTSFGGNLGRAVFQ 119
AV5 RGEPVNRADEVAREHDISYNEQLEAGDNPYLKYNHADAEFQEKLADDTSFGGNLGKAVFQ 119
AAV6 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
AAV7 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
AAV8 KGEPVNAADAAALEHDKAYDQQLQAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
hu31 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ 120
hu32 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ 120
AAV9 KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ 120
SUBS R-----E--EV-R---IS-NE--DS------R---------QK-QD---------K----
R R E AG
Q
VP2 138→ ┌--HVR1--┐
AAV1 AKKRVLEPLGLVEEGAKTAPGKKRPVEQSPQ-EPDSSSGIGKTGQQPAKKRLNFGQTGDS 179
AAV2 AKKRVLEPLGLVEEPVKTAPGKKRPVEHSPV-EPDSSSGTGKAGQQPARKRLNFGQTGDA 179
AAV3-3 AKKRILEPLGLVEEAAKTAPGKKGAVDQSPQ-EPDSSSGVGKSGKQPARKRLNFGQTGDS 179
AAV4-4 AKKRVLEPLGLVEQAGETAPGKKRPLIESPQ-QPDSSTGIGKKGKQPAKKKLVFEDETGA 178
AV5 AKKRVLEPFGLVEEGAKTAPTGKRIDDHFP----------KRKKARTEEDSKPSTSSDA 168
AAV6 AKKRVLEPFGLVEEGAKTAPGKKRPVEQSPQ-EPDSSSGIGKTGQQPAKKRLNFGQTGDS 179
AAV7 AKKRVLEPLGLVEEGAKTAPAKKRPVEPSPQRSPDSSTGIGKKGQQPARKRLNFGQTGDS 180
AAV8 AKKRVLEPLGLVEEGAKTAPGKKRPVEPSPQRSPDSSTGIGKKGQQPARKRLNFGQTGDS 180
hu31 AKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQ-EPDSSAGIGKSGSQPAKKKLNFGQTGDT 179
hu32 AKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQ-EPDSSAGIGKSGSQPAKKKLNFGQTGDT 179
AAV9 AKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQ-EPDSSAGIGKSGAQPAKKRLNFGQTGDT 179
SUBS ----V---F----QGGE---TG-GIDDHF-V-S----S-T--KKQARTREKSVPEDETGA
I PV A ALIP Q T V T K E D K STSS S
E A S
R A

FIGURE 18

```
                  ┌HVR2┐                    VP3203→
AAV1    ESVPD-PQPLGEPPATPAAVGPTTMASGGGAPMADNNEGADGVGNASGNWHCDSTWLGDR 238
AAV2    DSVPD-PQPLGQPPAAPSGLGTNTMATGSGAPMADNNEGADGVGNSSGNWHCDSTWMGDR 238
AAV3-3  ESVPD-PQPLGEPPAAPTSLGSNTMASGGGAPMADNNEGADGVGNSSGNWHCDSQWLGDR 238
AAV4-4  GDGP------PEGSTSGAMS--DDSEMRAAAGGAAVEGGQGADGVGNASGDWHCDSTWSEGH 232
AV5     EAGPSGSQQLQIPAQPASSLGADTMSAGGGGPLGDNNQGADGVGNASGDWHCDSTWMGDR 228
AAV6    ESVPD-PQPLGEPPATPAAVGPTTMASGGGAPMADNNEGADGVGNASGNWHCDSTWLGDR 238
AAV7    ESVPD-PQPLGEPPAAPSSVGSGTVAAGGGAPMADNNEGADGVGNASGNWHCDSTWLGDR 239
AAV8    ESVPD-PQPLGEPPAAPSGVGPNTMAAGGGAPMADNNEGADGVGSSSGNWHCDSTWLGDR 239
hu31    ESVPD-PQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDR 238
hu32    ESVPD-PQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDR 238
AAV9    ESVPD-PQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDR 238
SUBS    GDG-S-S-QLQQTSGTMASLDPNEVRAAA-GAMGEGGQ------NA--D-----T-MEGH
        DA       E S AQPATA  AG  ST S   LV                    S
                   I      -- DT        A
                             TD
                              S

                                    ┌HVR3┐
AAV1    VITTSTRTWALPTYNNHLYKQIS-SASTGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDW 297
AAV2    VITTSTRTWALPTYNNHLYKQIS--SQSGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDW 296
AAV3-3  VITTSTRTWALPTYNNHLYKQIS--SQSGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDW 296
AAV4-4  VTTTSTRTWVLPTYNNHLYKRLG-----ESLQSNTYNGFSTPWGYFDFNRFHCHFSPRDW 287
AV5     VVTKSTRTWVLPSYNNHQYREIKS-GSVDGSNANAYFGYSTPWGYFDFNRFHSHWSPRDW 287
AAV6    VITTSTRTWALPTYNNHLYKQISSASST-GASNDNHYFGYSTPWGYFDFNRFHCHFSPRDW 297
AAV7    VITTSTRTWALPTYNNHLYKQISS-ETAGSTNDNTYFGYSTPWGYFDFNRFHCHFSPRDW 298
AAV8    VITTSTRTWALPTYNNHLYKQISNGTSGGATNDNTYFGYSTPWGYFDFNRFHCHFSPRDW 299
hu31    VITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDW 298
hu32    VITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDW 298
AAV9    VITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDW 298
SUBS    -T-K-----V--S----Q-RRLGSGSQSDATQA-T----------------S-W-----
         V                    E K AATTEGL S H
                                G V
                                E A

AAV1    QRLINNNWGFRPKRLNFKLFNIQVKEVTTNDGVTTIANNLTSTVQVFSDSEYQLPYVLGS 357
AAV2    QRLINNNWGFRPKRLNFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
AAV3-3  QRLINNNWGFRPKKLSFKLFNIQVRGVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
AAV4-4  QRLINNNWGMRPKAMRVKIFNIQVKEVTTSNGETTVANNLTSTVQIFADSSYELPYVMDA 347
AV5     QRLINNYWGFRPRSLRVKIFNIQVKEVTVQDSTTTIANNLTSTVQVFTDDDYQLPYVVGN 347
AAV6    QRLINNNWGFRPKRLNFKLFNIQVKEVTTNDGVTTIANNLTSTVQVFSDSEYQLPYVLGS 357
AAV7    QRLINNNWGFRPKKLRFKLFNIQVKEVTTNDGVTTIANNLTSTIQVFSDSEYQLPYVLGS 358
AAV8    QRLINNNWGFRPKRLSFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGS 359
hu31    QRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGS 358
hu32    QRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGS 358
AAV9    QRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGS 358
SUBS    ---------M--RAMRV-I---------VQDSTT---------I-I-S-DE-E----MDA
        K S                 QSE E                   A   S
        S
```

FIGURE 18 (CON'T)

```
                                        HVR4
AAV1    AHQGCLPPFPADVFMIPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFTFSY 414
AAV2    AHQGCLPPFPADVFMVPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFTFSY 413
AAV3-3  AHQGCLPPFPADVFMVPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFQFSY 413
AAV4-4  GQEGSLPPFPNDVFMVPQYGYCGLVTGNTSQQQTDRNAFYCLEYFPSQMLRTGNNFEITY 407
AV5     GTEGCLPAFPPQVFTLPQYGYATLNRD-NTENPTERSSFFCLEYFPSKMLRTGNNFEFTY 406
AAV6    AHQGCLPPFPADVFMIPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFTFSY 414
AAV7    AHQGCLPPFPADVFMIPQYGYLTLNNG---SQSVGRSSFYCLEYFPSQMLRTGNNFEFSY 415
AAV8    AHQGCLPPFPADVFMIPQYGYLTLNNG---SQAVGRSSFYCLEYFPSQMLRTGNNFQFTY 416
hu31    AHEGCLPPFPADVFMIPQYGYLTLNDG---GQAVGRSSFYCLEYFPSQMLRTGNNFQFSY 415
hu32    AHEGCLPPFPADVFMIPQYGYLTLNDG---SQAVGRSSFYCLEYFPSQMLRTGNNFQFSY 415
AAV9    AHEGCLPPFPADVFMIPQYGYLTLNDG---SQAVGRSSFYCLEYFPSQMLRTGNNFQFSY 415
SUBS    GQQ-S--A--PQ--TL-----CG-VND---GNPTD-NA-F----------------EIT-
         T        N    V     A   T    Q Q E                      T
                                  R    E S

                                                  ----------HVR5----------
AAV1    TFEEVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQ-NQSGSAQNKDLLFSRGSPAGMSV 473
AAV2    TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTN-TPSGTTTQSRLQFSQAGASDIRD 472
AAV3-3  TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQGTTSGTTNQSRLLFSQAGPQSMSL 473
AAV4-4  SFEKVPFHSMYAHSQSLDRLMNPLIDQYLWGLQSTTTGTTLNAGTATTNFTKLRPTNFSN 467
AV5     NFEEVPFHSSFAPSQNLFKLANPLVDQYLYRFVSTN----------NTGGVQFNKNLAGRYAN 459
AAV6    TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQ-NQSGSAQNKDLLFSRGSPAGMSV 473
AAV7    SFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLARTQSNPGGTAGNRELQFYQGGPSTMAE 475
AAV8    TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQT-TGGTANTQTLGFSQGGPNTMAN 475
hu31    EFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGSG--QNQQTLKFSVAGPSNMAV 473
hu32    EFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGSG--QNQQTLKFSVAGPSNMAV 473
AAV9    EFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGSG--QNQQTLKFSVAGPSNMAV 473
SUBS    T--D-----MF---------A---V----WGFNR-QTNTS--AGTKRTQ-TQGSAATFSN
        S  E                      QS NSTPT   TQNSDVN NKNL QGYRD
        N  K                      V  TG Q     T AE L YRLR TRI L
                                  A               RG G      GS  E
                                                            ND

        ┌┐                  ┌HVR6┐        ┌HVR7┐          ┌--HVR8--┐
AAV1    QPKNWLPGPCYRQQRVSKTKTDN-----NNSNFTWTGASKYNLNGRESIINPGTAMASHK 528
AAV2    QSRNWLPGPCYRQQRVSKTSADN-----NNSEYSWTGATKYHLNGRDSLVNPGPAMASHK 527
AAV3-3  QARNWLPGPCYRQQRLSKTANDN-----NNSNFPWTAASKYHLNGRDSLVNPGPAMASHK 528
AAV4-4  FKKNWLPGPSIKQQGFSKTANQNYKIPATGSDSLIKYETHSTLDGRWSALTPGPPMATAG 527
AV5     TYKNWFPGPMGRTQGWNLGSGVN-----RASVSAFATTNRMELEGASYQVPPQPNGMTNN 514
AAV6    QPKNWLPGPCYRQQRVSKTKTDN-----NNSNFTWTGASKYNLNGRESIINPGTAMASHK 528
AAV7    QAKNWLPGPCFRQQRVSKTLDQN-----NNSNFAWTGATKYHLNGRNSLVNPGVAMATHK 530
AAV8    QAKNWLPGPCYRQQRVSTTTGQN-----NNSNFAWTAGTKYHLNGRNSLANPGIAMATHK 530
hu31    QGRNYIPGPSYRQQRVSTTVTQN-----NNSEFAWPGASSWALNGRNSLMNPGPAMASHK 528
hu32    QGRNYIPGPSYRQQRVSTTVTQN-----NNSEFAWPGASSWALNGRNSLMNPGPAMASHK 528
AAV9    QGRNYIPGPSYRQQRVSTTVTQN-----NNSEFAWPGASSWALNGRNSLMNPGPAMASHK 528
SUBS    FAK-WL---CIKT-GWNLGSGV------TG-DSLIKYETHST-D-ASYQVP-QTPGMTAG
        TP    F    MG     F K AND       RA NYTFATTNRME E   D ALT   VN    NN
         K        F     L    KA            V P TAG KYN     W II    I
         Y                   LD               S         H    E  A
         S                   T
```

FIGURE 18 (CON'T)

```
                  ┌----------HVR9----------┐                                  ┌--┐
AAV1    DDEDKFFPMSGVMIFGKESA--GASNTALD-NVMITDEEEIKATNPVATERFGTVAVNFQ 585
AAV2    DDEEKFFPQSGVLIFGKQGS--EKTNVDIE-KVMITDEEEIRTTNPVATEQYGSVSTNLQ 584
AAV3-3  DDEEKFFPMHGNLIFGKEGT--TASNAELD-NVMITDEEEIRTTNPVATEQYGTVANNLQ 585
AAV4-4  PADSKFS-NSQLIFAGPKQN--GNTATVPG-TLIFTSEEELAATNATDTDMWGNLPGGDQ 583
AV5     LQGSNTYALENTMIFNSQPANPGTTATYLEGNMLITSESETQPVNRVAYNVGGQMATNNQ 574
AAV6    DDKDKFFPMSGVMIFGKESA--GASNTALD-NVMITDEEEIKATNPVATERFGTVAVNLQ 585
AAV7    DDEDRFFPSSGVLIFGKTGA--TN-KTTLE-NVLMTNEEEIRPTNPVATEEYGIVSSNLQ 586
AAV8    DDEERFFPSNGILIFGKQNA--ARDNADYS-DVMLTSEEEIKTTNPVATEEYGIVADNLQ 587
hu31    EGEDRFFPLSGSLIFGKQGT--GRDNVDAD-KVMITNEEEIKTTNPVATESYGQVATNHQ 585
hu32    EGEDRFFPLSGSLIFGKQGT--GRDNVDAD-KVMITNEEEIKTTNPVATESYGQVATNHQ 585
AAV9    EGEDRFFPLSGSLIFGKQGT--GRDNVDAD-KVMITNEEEIKTTNPVATESYGQVATNHQ 585
SUBS    LQGSNTYAMENTMFANPKQN--TNTATVPG-TLIF-S-S-TQPV-ATDYDMW-NLPGGD-
        PADEK S QHQLI   SESA  EASKAALE-NMLM D    RA  R   NVF TMSN L
        DDK    NN V     TPS  AK  KTY     L      A        QG I  V N
               S  I      N        EI                      E  S  S F
                  N                Y                      R     D

        ┌--HVR10---┐
AAV1    SSSTDPATGDVHAMGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKNPPP 645
AAV2    RGNRQAATADVNTQGVLPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPPP 644
AAV3-3  SSNTAPTTGTVNHQGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPPP 645
AAV4-4  SNSNLPTVDRLTALGAVPGMVWQNRDIYYQGPIWAKIPHTDGHFHPSPLIGGFGLKHPPP 643
AV5     SSTTAPATGTYNLQEIVPGSVWMERDVYLQGPIWAKIPETGAHFHPSPAMGGFGLKHPPP 634
AAV6    SSSTDPATGDVHVMGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPPP 645
AAV7    AANTAAQTQVVNNQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPP 646
AAV8    QQNTAPQIGTVNSQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPP 647
hu31    SAQAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPP 645
hu32    SAQAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPP 645
AAV9    SAQAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPP 645
SUBS    RNSNLPTVDRLTALEAV--S--ME--I----------E-GAH-----AI----L-N---
        ASNTA AIADYHTM V       N
        QGTRD   QT NH
         Q       V  L
                    V
                    S

                    ┌---HVR11--┐
AAV1    QILIKNTPVPANPPAEFSATKFASFITQYSTGQVSVEIEWELQKENSKRWNPEVQYTSNY 705
AAV2    QILIKNTPVPANPSTTFSAAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 704
AAV3-3  QIMIKNTPVPANPPTTFSPAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
AAV4-4  QIFIKNTPVPANPATTFSSTFVNSFITQYSTGQVSVQIDWEIQKERSKRWNPEVQFTSNY 703
AV5     MMLIKNTPVPGNI-TSFSDVPVSSFITQYSTGQVTVEMEWELKKENSKRWNPEIQYTNNY 693
AAV6    QILIKNTPVPANPPAEFSATKFASFITQYSTGQVSVEIEWELQKENSKRWNPEVQYTSNY 705
AAV7    QILIKNTPVPANPPEVFTPAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNF 706
AAV8    QILIKNTPVPADPPTTFNQSKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 707
hu31    QILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
hu32    QILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
AAV9    QILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
SUBS    MMM-------G-IAAE-SDVPVS-------------QMD--IK--R-------V------
          F           SET TAA FA
                        S  PT
                        V  QS
                           S
```

FIGURE 18 (CON'T)

```
          ┌-----HVR12-----┐
AAV1      AKSANVDFTVDNNGLYTEPRPIGTRYLTRPL 736   (SEQ ID NO. 41)
AAV2      NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL 735   (SEQ ID NO. 42)
AAV3-3    NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL 736   (SEQ ID NO. 43)
AAV4-4    GQQNSLLWAPDAAGKYTEPRAIGTRYLTHHL 734   (SEQ ID NO. 44)
AV5       NDPQFVDFAPDSTGEYRTTRPIGTRYLTRPL 724   (SEQ ID NO. 45)
AAV6      AKSANVDFTVDNNGLYTEPRPIGTRYLTRPL 736   (SEQ ID NO. 46)
AAV7      EKQTGVDFAVDSQGVYSEPRPIGTRYLTRNL 737   (SEQ ID NO. 47)
AAV8      YKSTSVDFAVNTEGVYSEPRPIGTRYLTRNL 738   (SEQ ID NO. 48)
hu31      YKSNNVEFAVSTEGVYSEPRPIGTRYLTRNL 736   (SEQ ID NO. 49)
hu32      YKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL 736   (SEQ ID NO. 50)
AAV9      YKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL 736   (SEQ ID NO. 51)
SUBS      GQQVSLLWTPDAA-K-RTT-A-------HP-
          NDPQF D   SSN E T            H
          A  TG      NQ L
          E  A        T
```

FIGURE 18 (CONT)

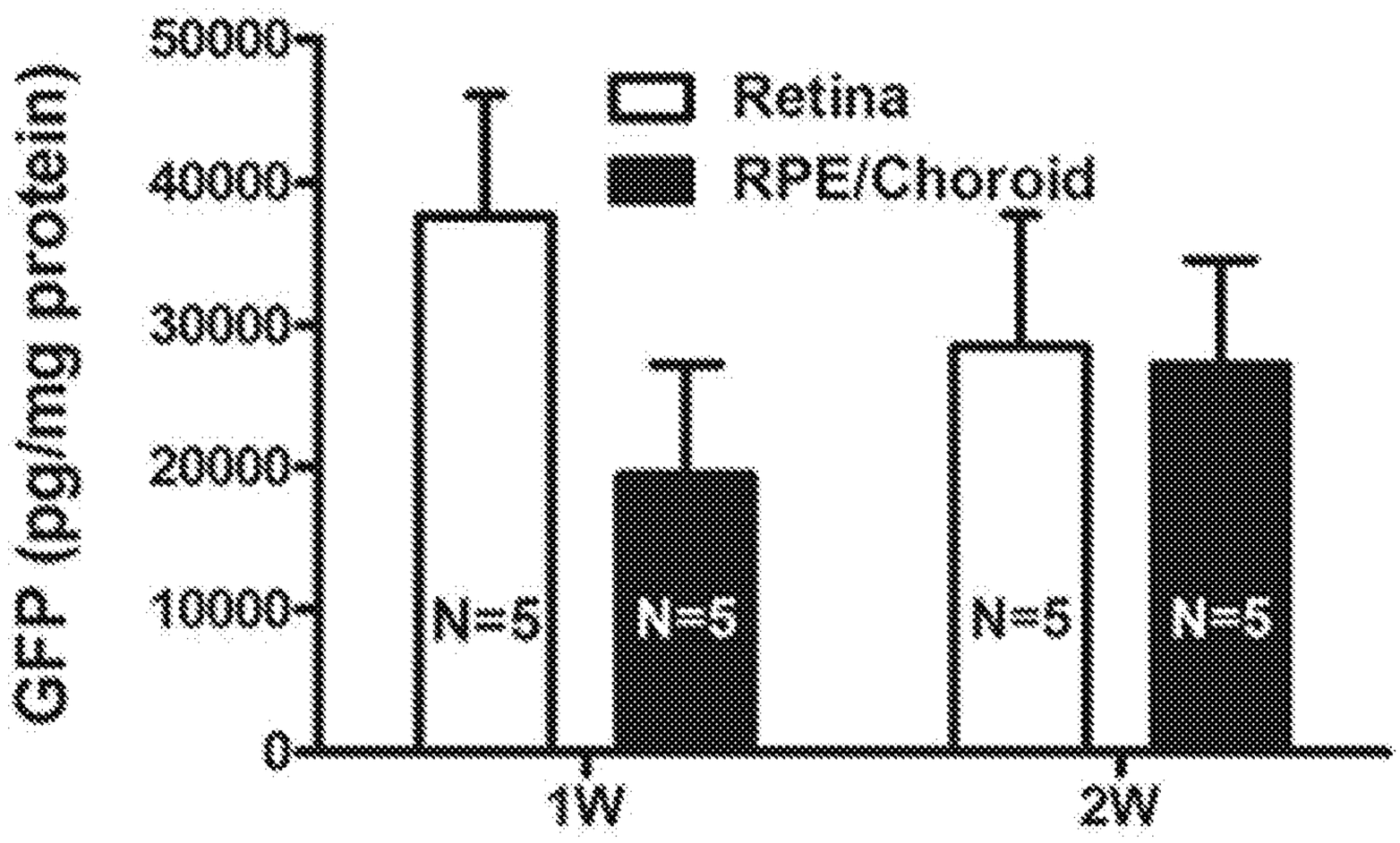

GFP (pg/mg protein)
50000
40000
30000
20000
10000
0
Retina
RPE/Choroid
N=5
N=5
N=5
N=5
1W
2W

FIGURE 19

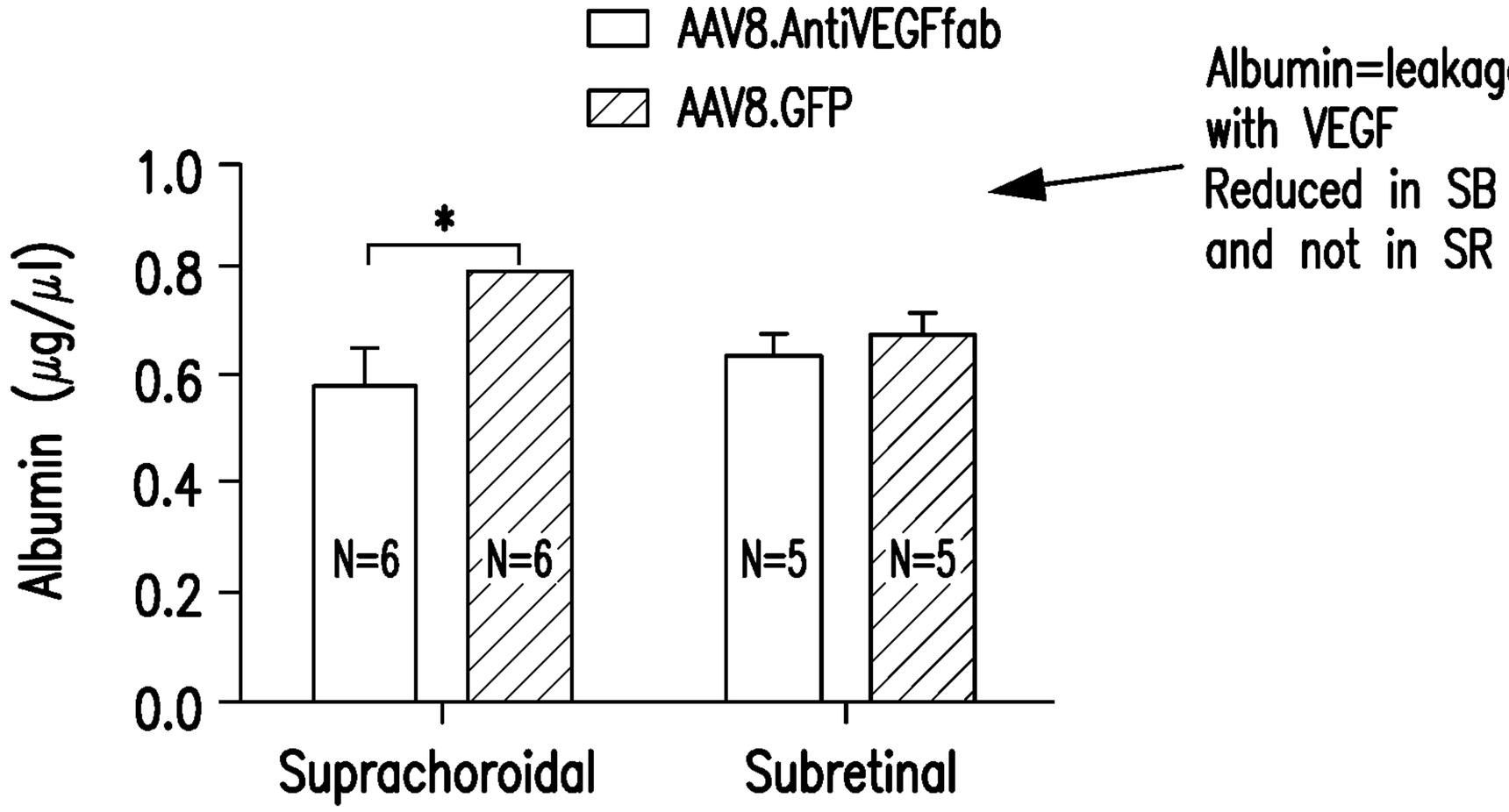


FIG. 20A

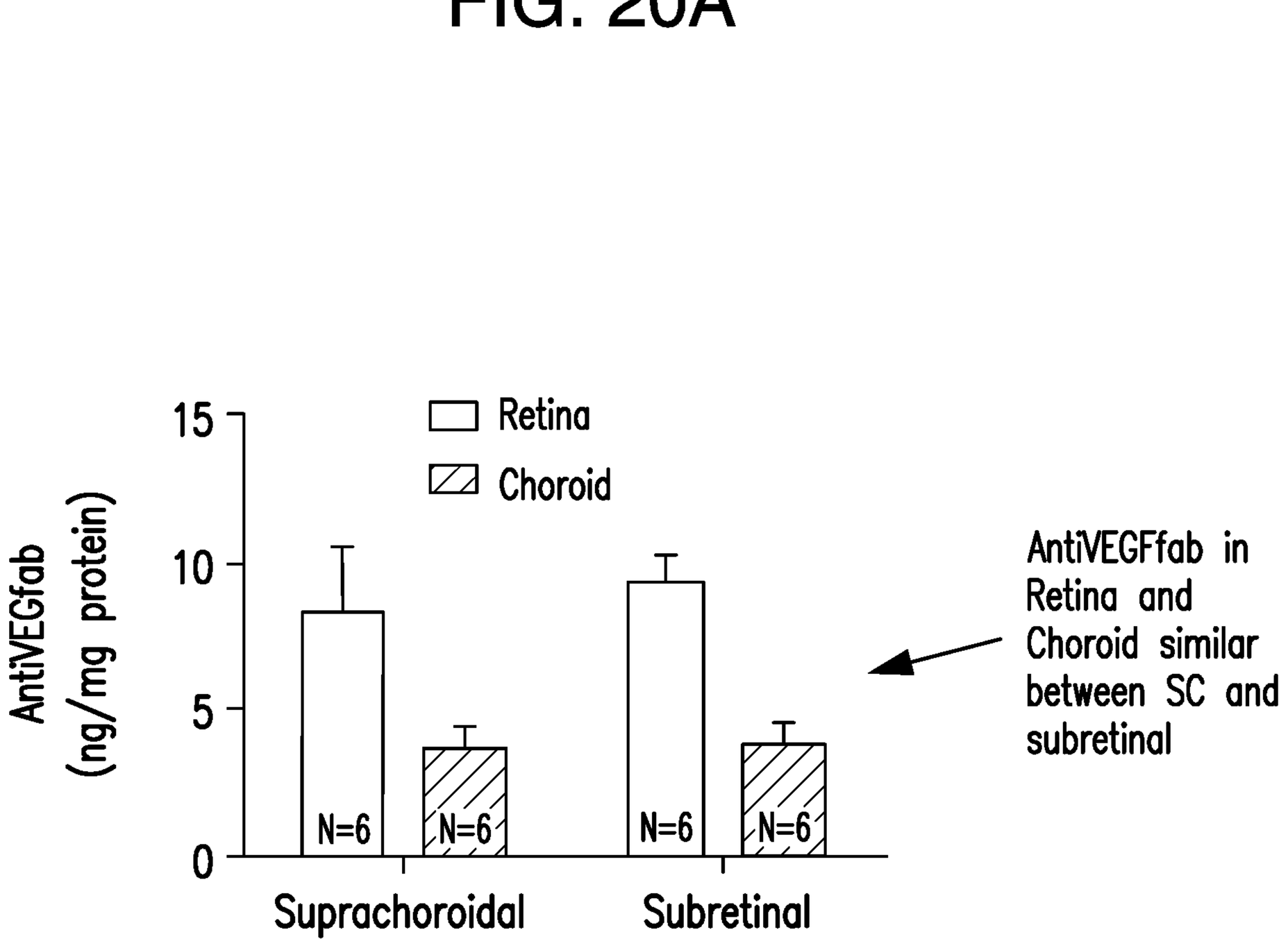


FIG. 20B

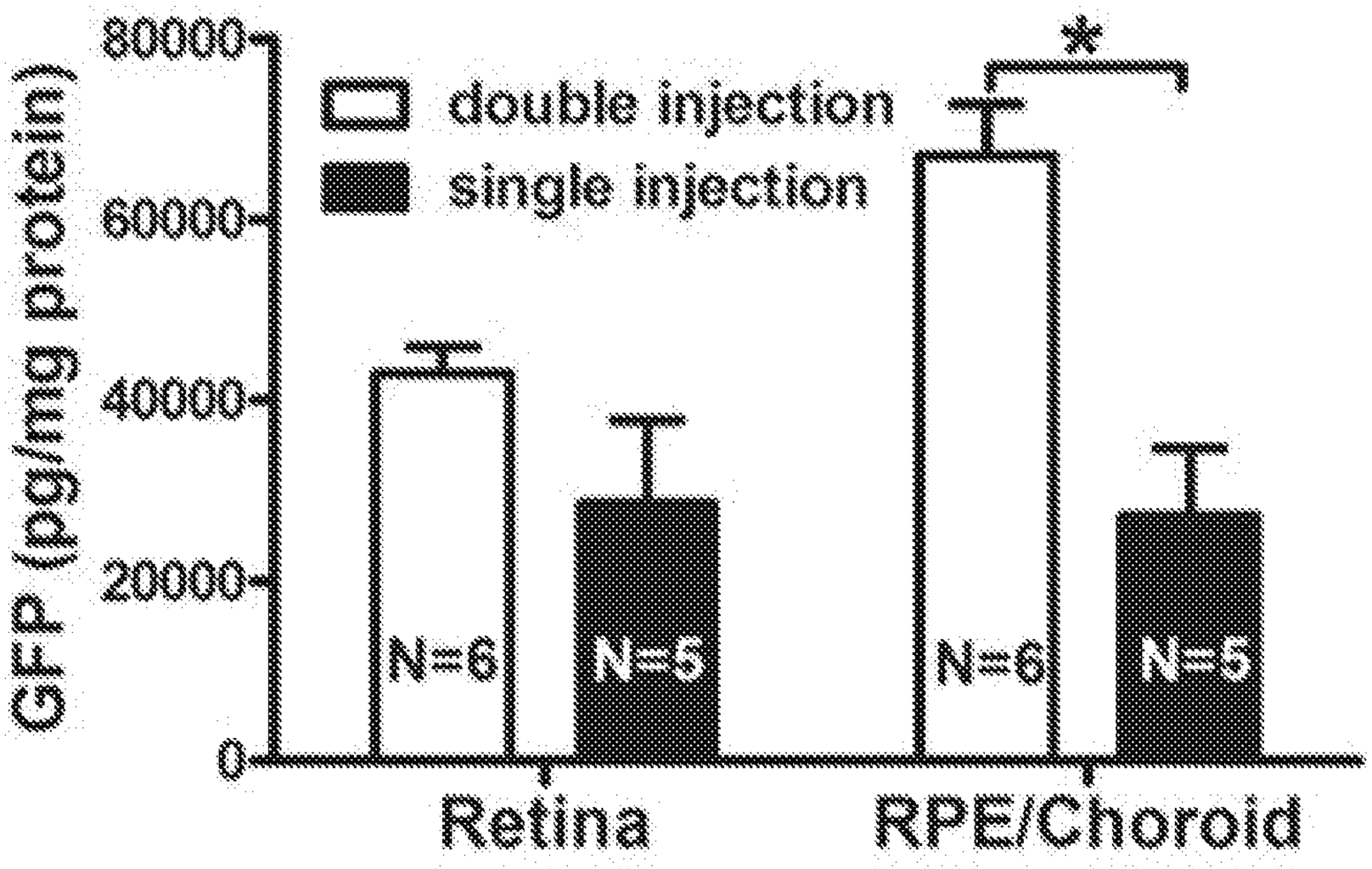

GFP (pg/mg protein)
80000
60000
40000
20000
0
double injection
single injection
*
N=6
N=5
N=6
N=5
Retina
RPE/Choroid

FIGURE 21

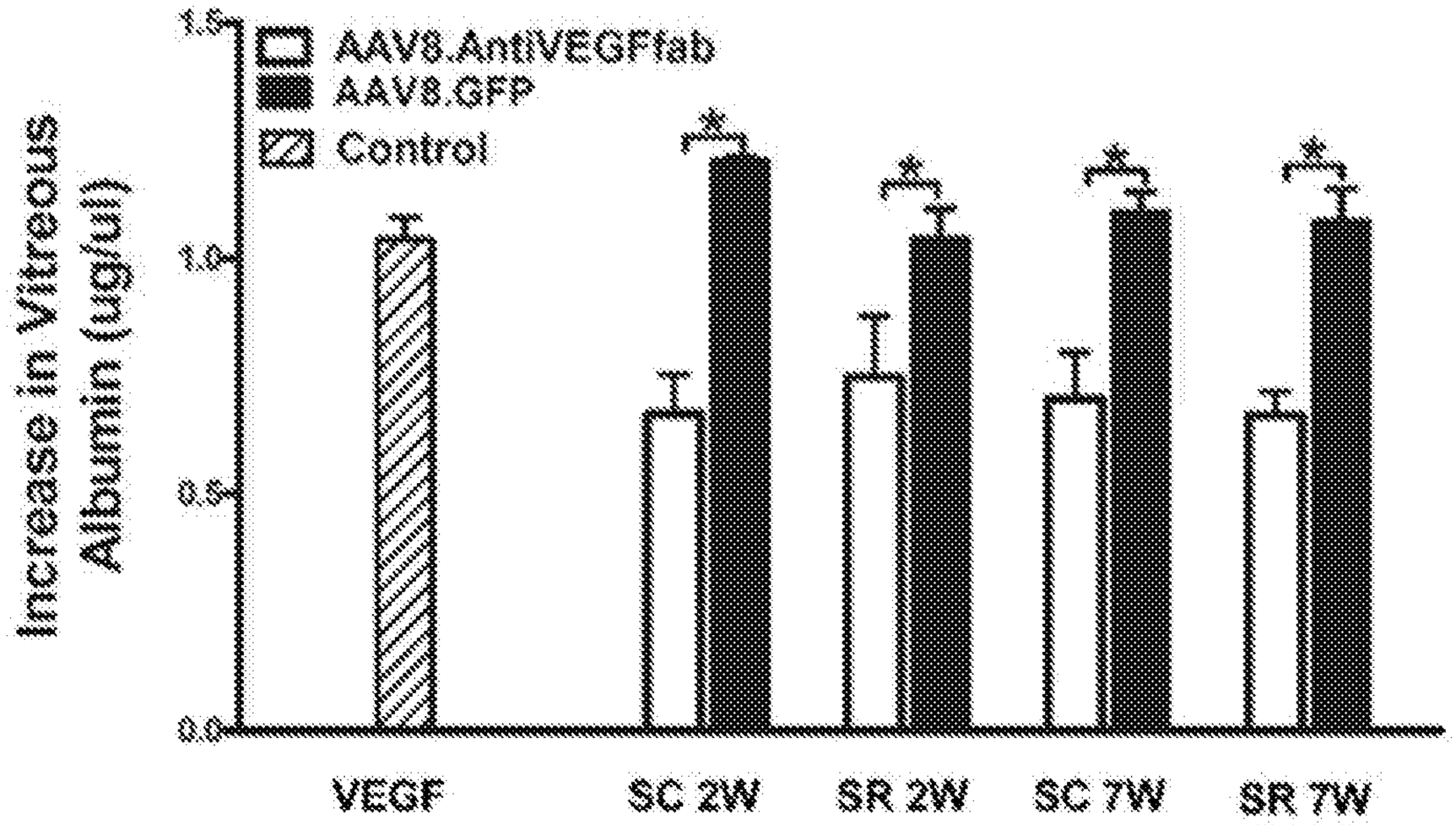

AAV8.AntiVEGFfab
AAV8.GFP
Control
Increase in Vitreous Albumin (ug/ul)
1.5
1.0
0.5
0.0
VEGF
SC 2W
SR 2W
SC 7W
SR 7W

FIGURE 22

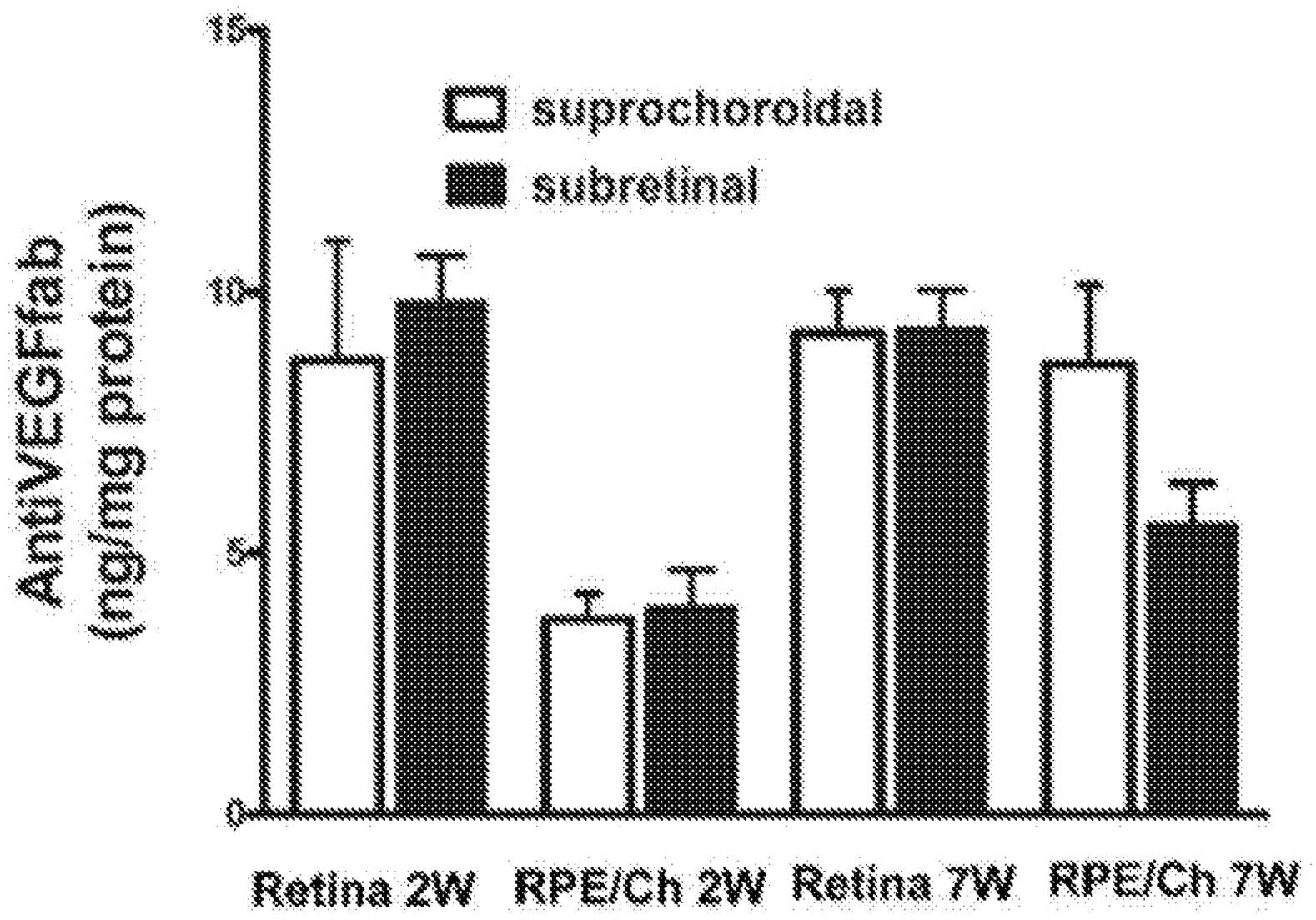

suprochoroidal
subretinal
AntiVEGFfab
(ng/mg protein)
15
10
5
0
Retina 2W
RPE/Ch 2W
Retina 7W
RPE/Ch 7W

FIGURE 23

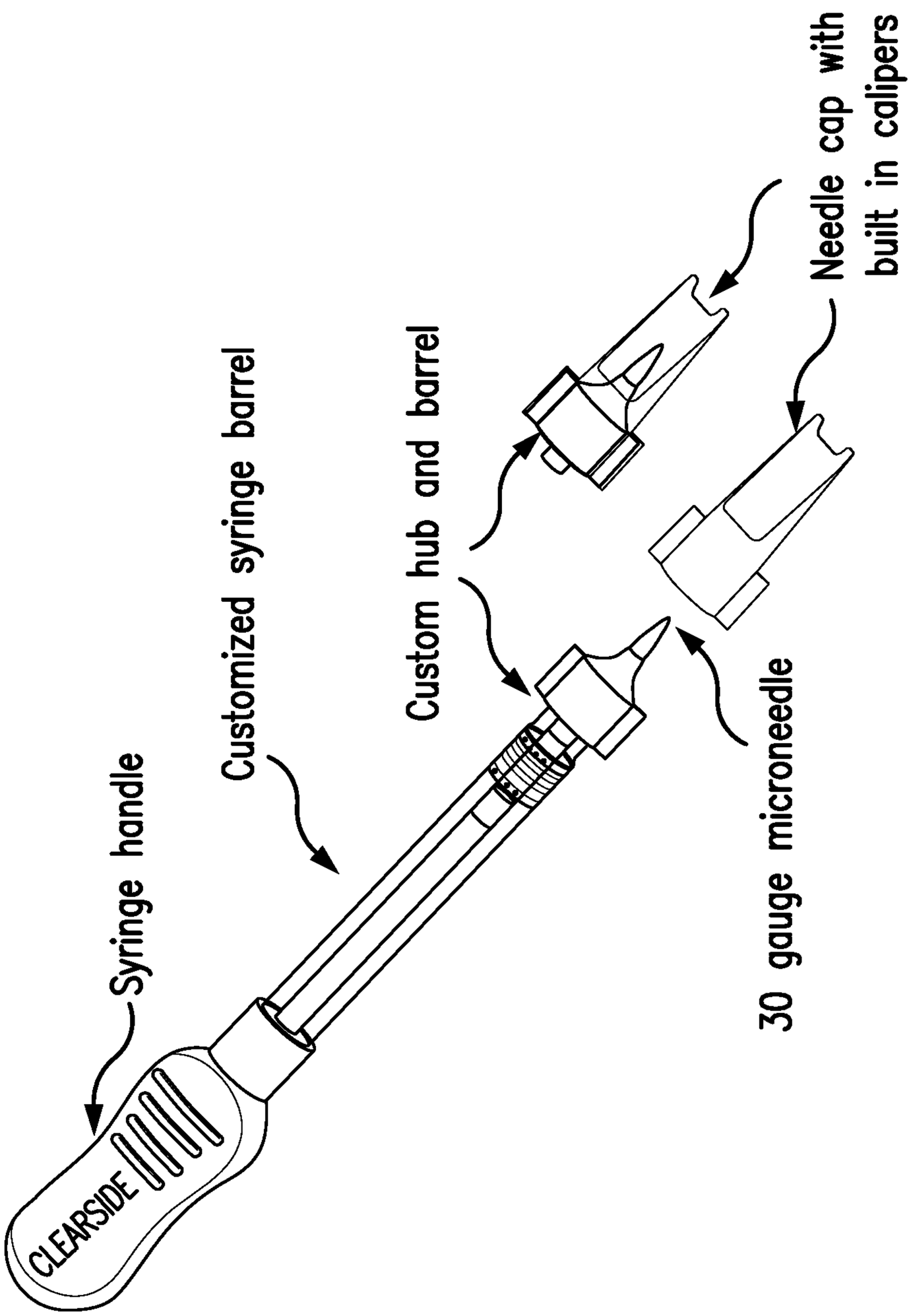

Syringe handle
Customized syringe barrel
Custom hub and barrel
Needle cap with built in calipers
CLEARSIDE
30 gauge microneedle

FIG. 24

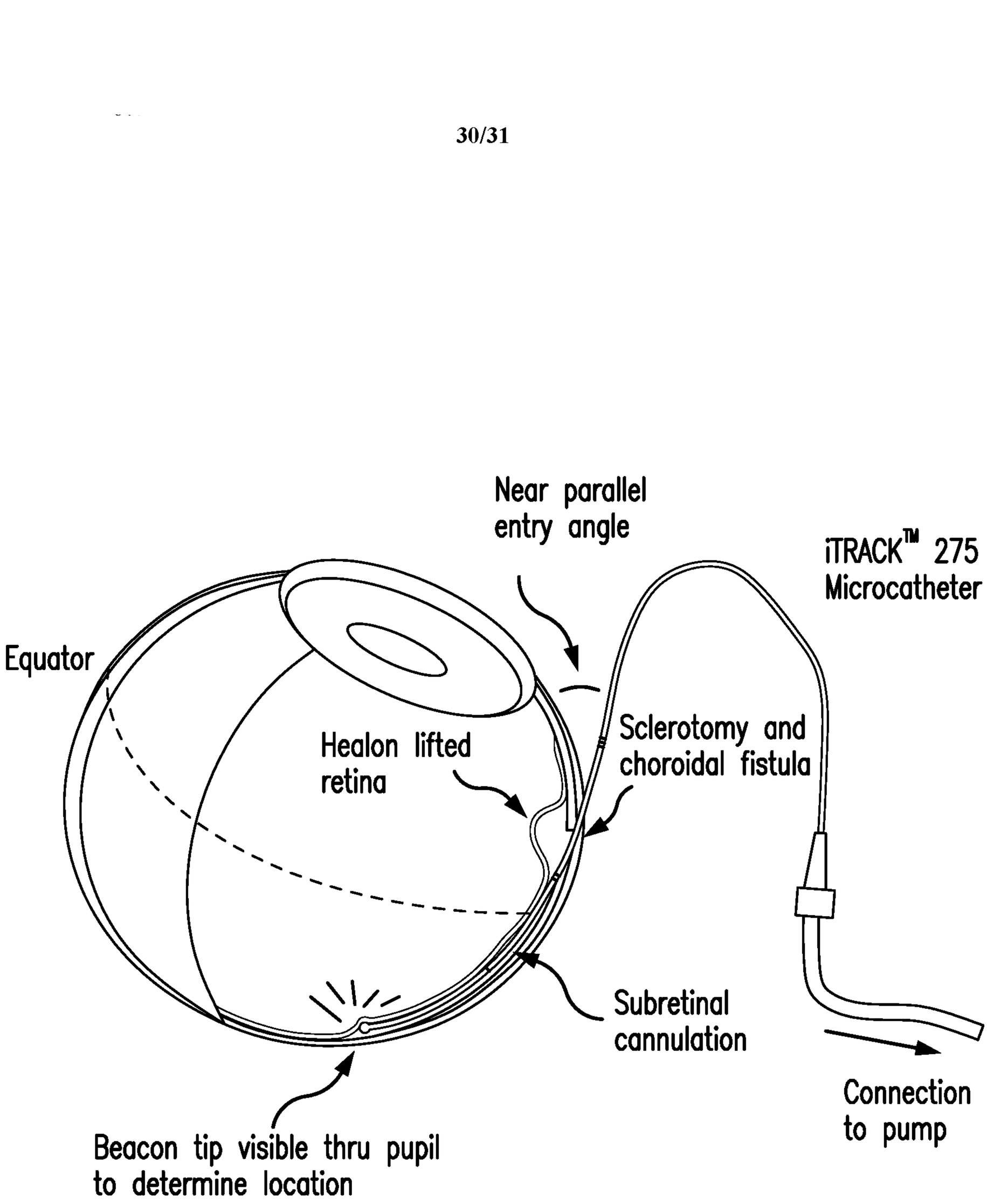

Near parallel
entry angle
iTRACK™ 275
Microcatheter
Equator
Healon lifted
retina
Sclerotomy and
choroidal fistula
Subretinal
cannulation
Connection
to pump
Beacon tip visible thru pupil
to determine location

FIG. 25

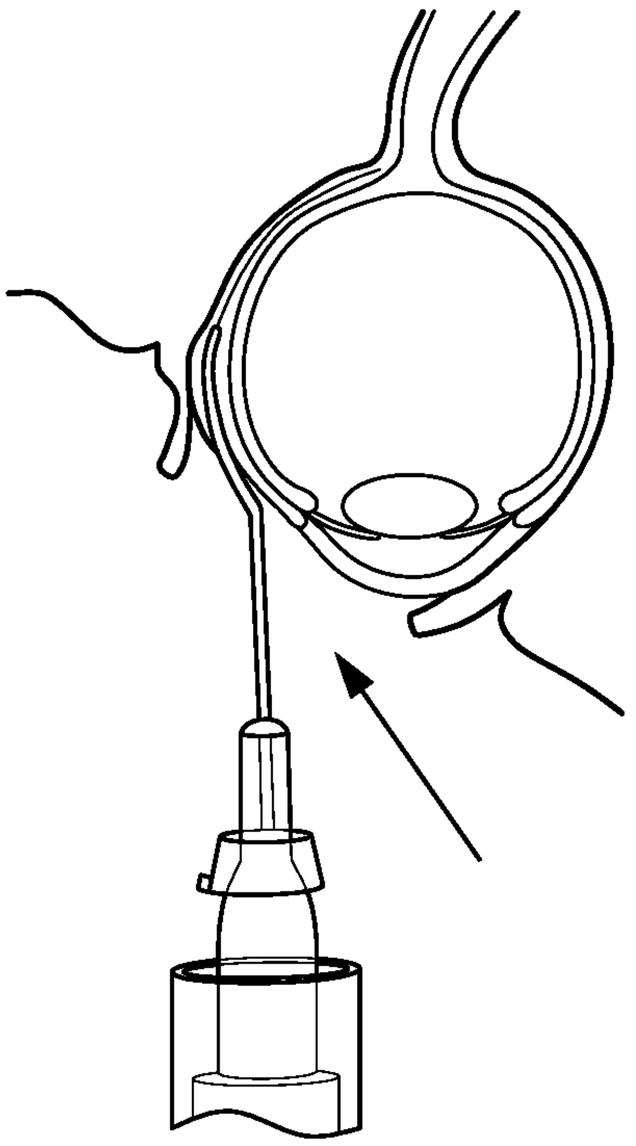


FIG. 26B

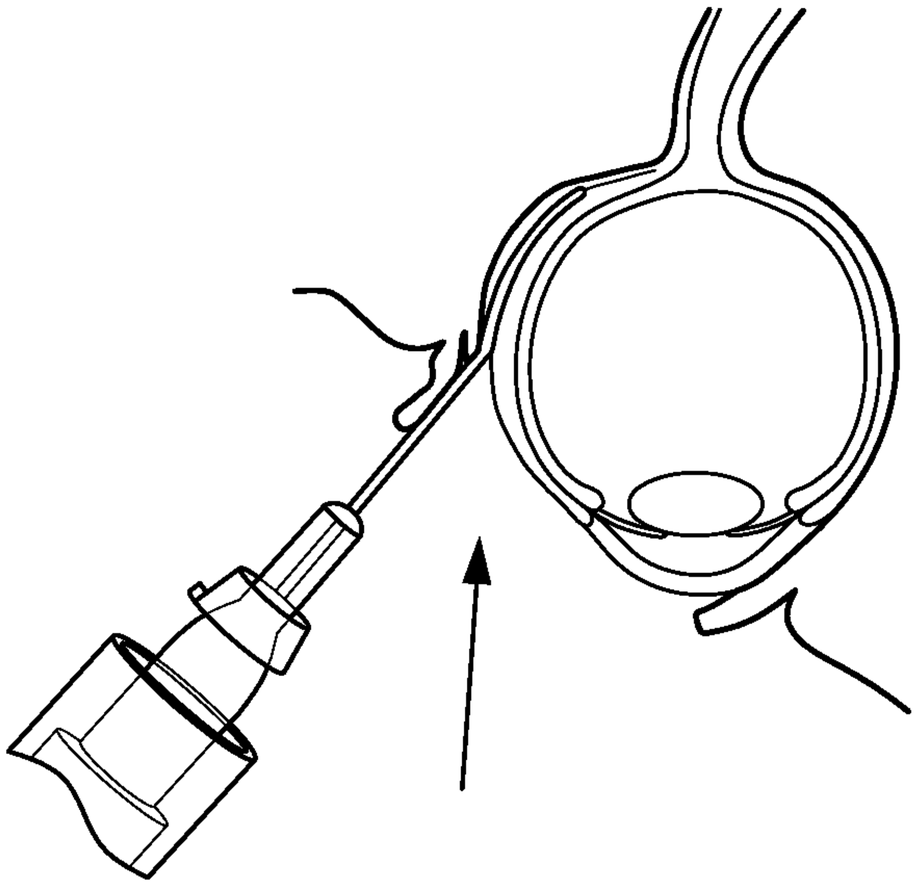


FIG. 26D

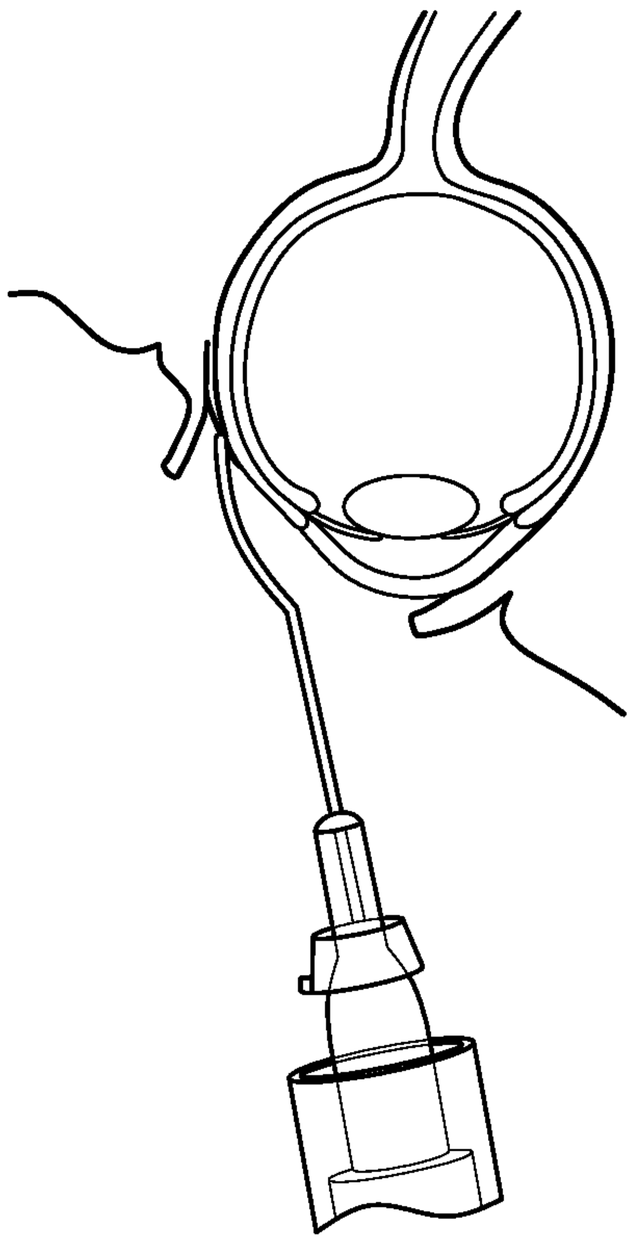


FIG. 26A

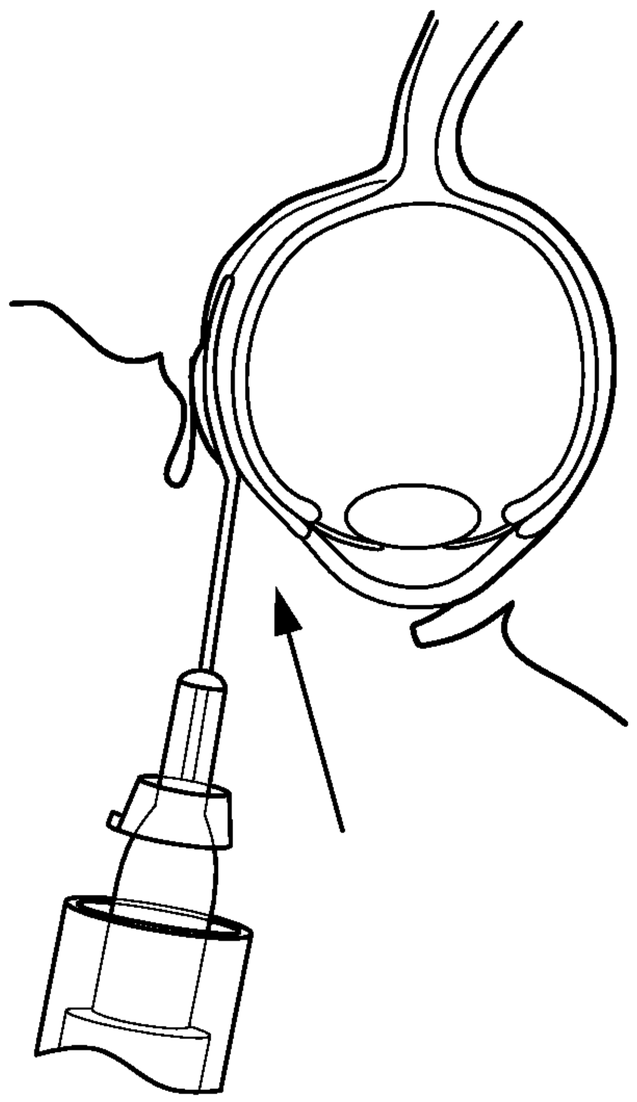


FIG. 26C