Amino Acid Sequence of Ranibizumab/Bevacizumab Fab Heavy Chain

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

          70        80        90        100       110       120
AADFKRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPYYYGTSHWYFDVWGQGTLVT
                                Y-site                  G-site
---------------------------------------H---S---------------

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

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

Amino Acid Sequence of 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
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
                                    G-site
------------------------------------------------------------

          190       200       210
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
                          G-site
--------------------------------
```

FIG. 1

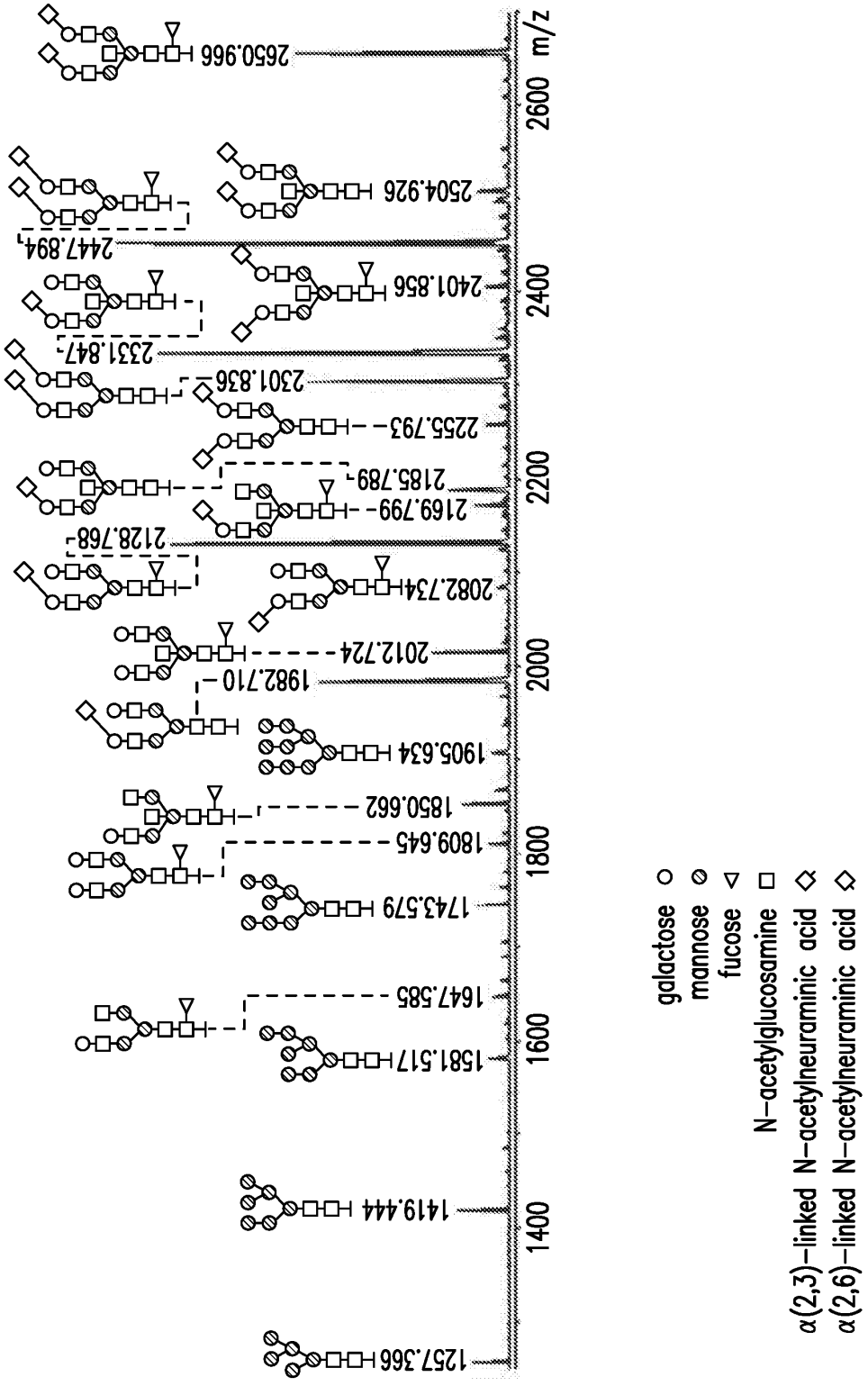

m/z
1400
1600
1800
2000
2200
2400
2600
1257.366
1419.444
1581.517
1647.585
1743.579
1809.645
1850.662
1905.634
1982.710
2012.724
2082.734
2128.768
2169.799
2185.789
2255.793
2301.836
2331.847
2401.856
2447.894
2504.926
2650.966
galactose
mannose
fucose
N-acetylglucosamine
α(2,3)-linked N-acetylneuraminic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

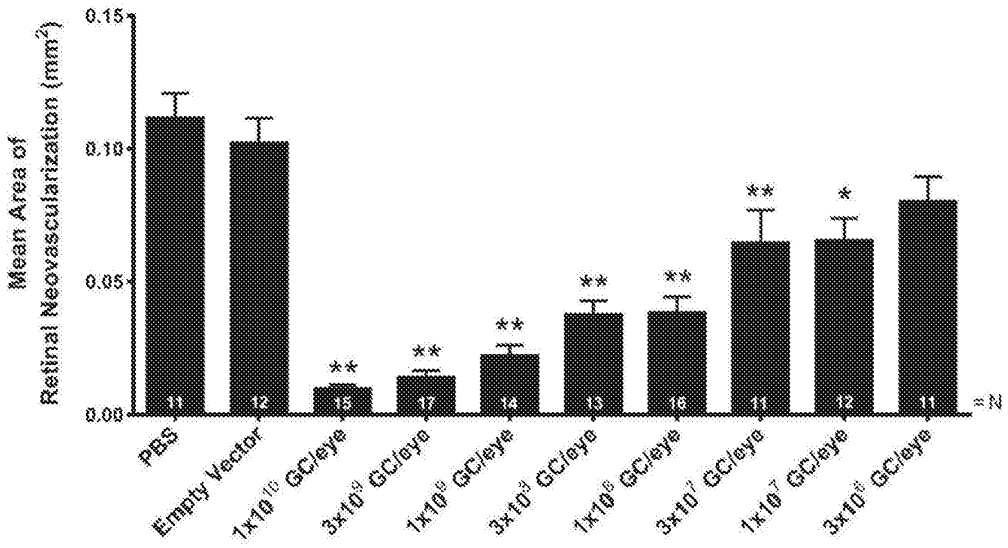

Mean Area of Retinal Neovascularization (mm²)
0.15
0.10
0.05
0.00
**
**
**
**
**
*
11
12
15
17
14
13
16
11
12
11
=N
PBS
Empty Vector
1x10¹⁰ GC/eye
3x10⁹ GC/eye
1x10⁹ GC/eye
3x10⁸ GC/eye
1x10⁸ GC/eye
3x10⁷ GC/eye
1x10⁷ GC/eye
3x10⁶ GC/eye

FIGURE 4

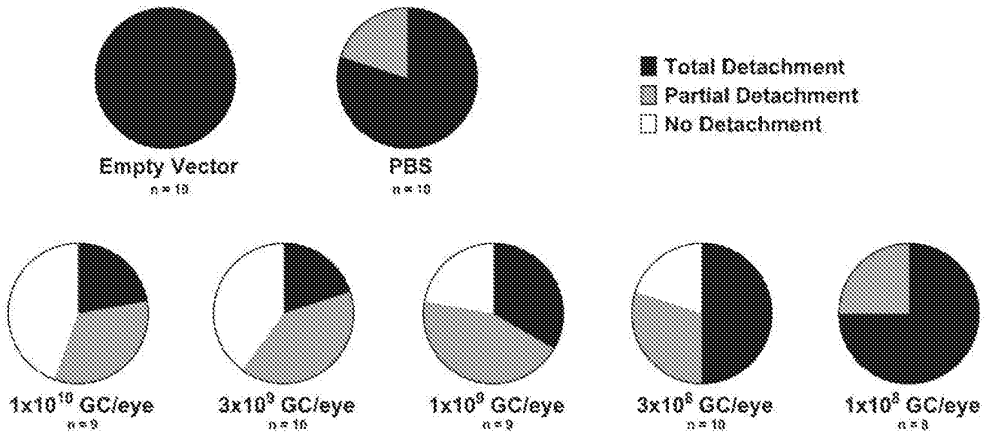

Total Detachment
Partial Detachment
No Detachment
Empty Vector
n = 19
PBS
n = 18
1x10^10 GC/eye
n = 9
3x10^9 GC/eye
n = 10
1x10^9 GC/eye
n = 9
3x10^8 GC/eye
n = 10
1x10^8 GC/eye
n = 8

FIGURE 5

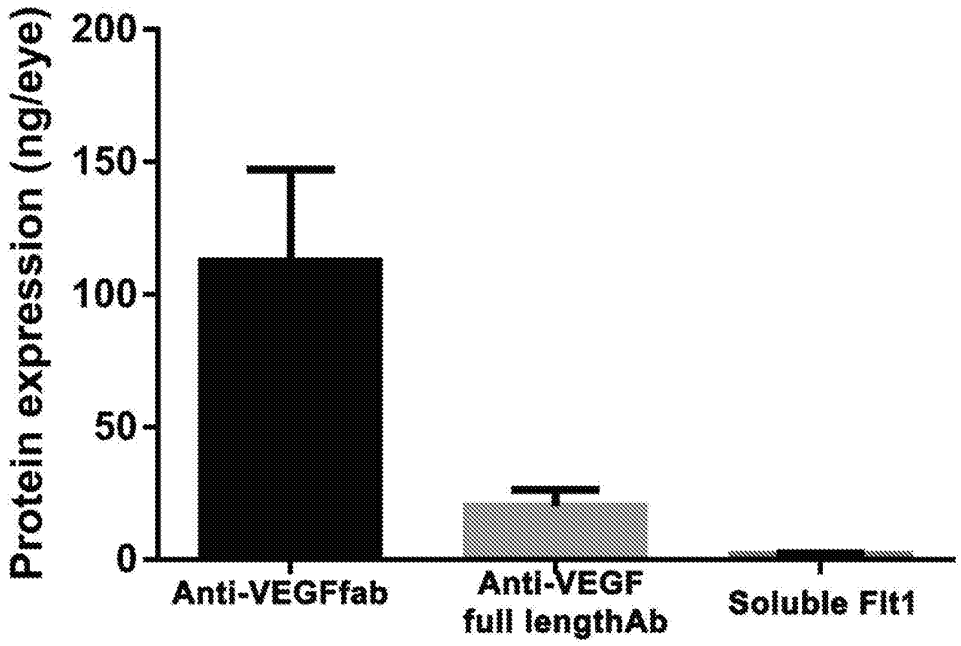

Protein expression (ng/eye)
200
150
100
50
0
Anti-VEGFfab
Anti-VEGF full lengthAb
Soluble Flt1

FIGURE 6

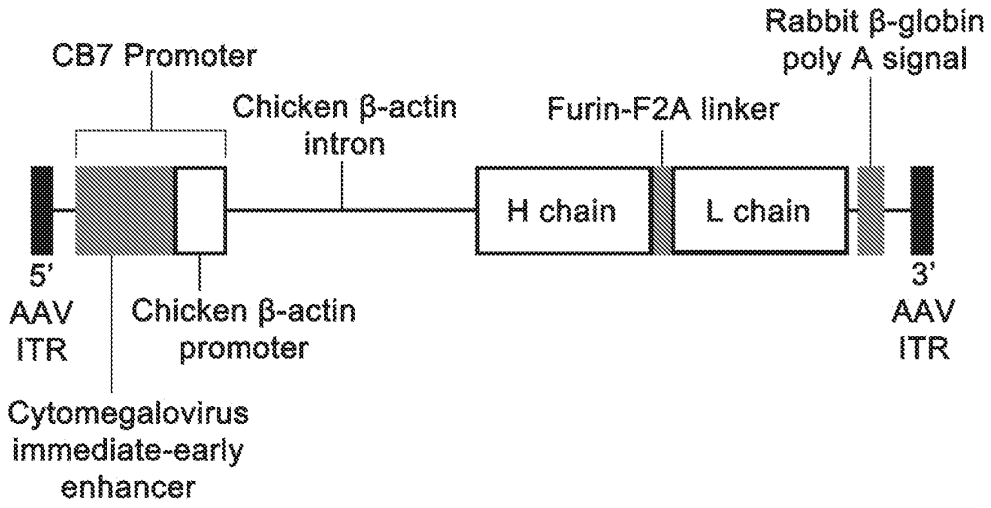


FIGURE 7A

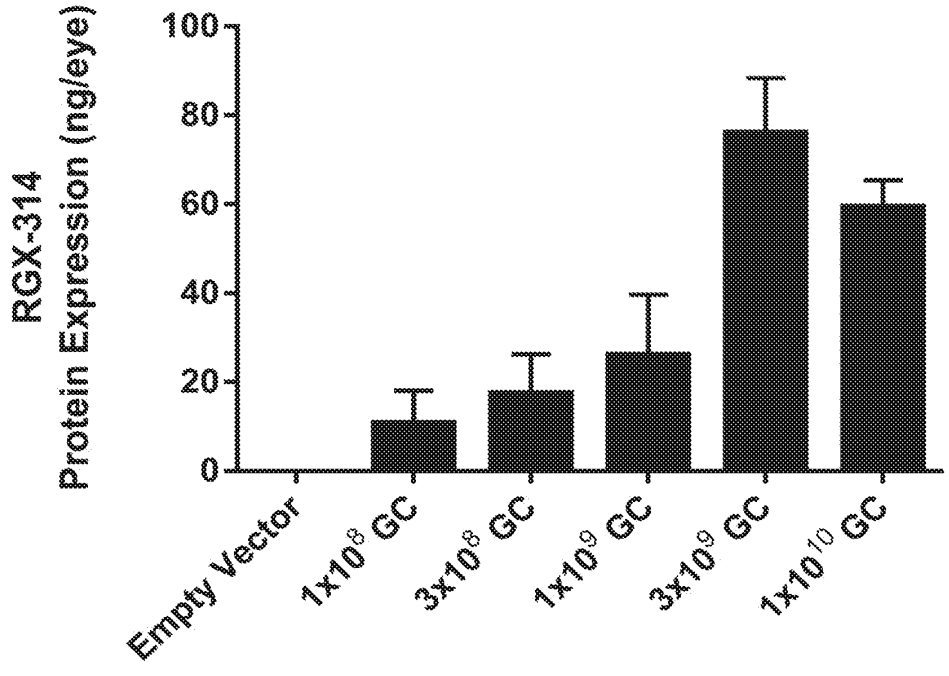


FIGURE 7B

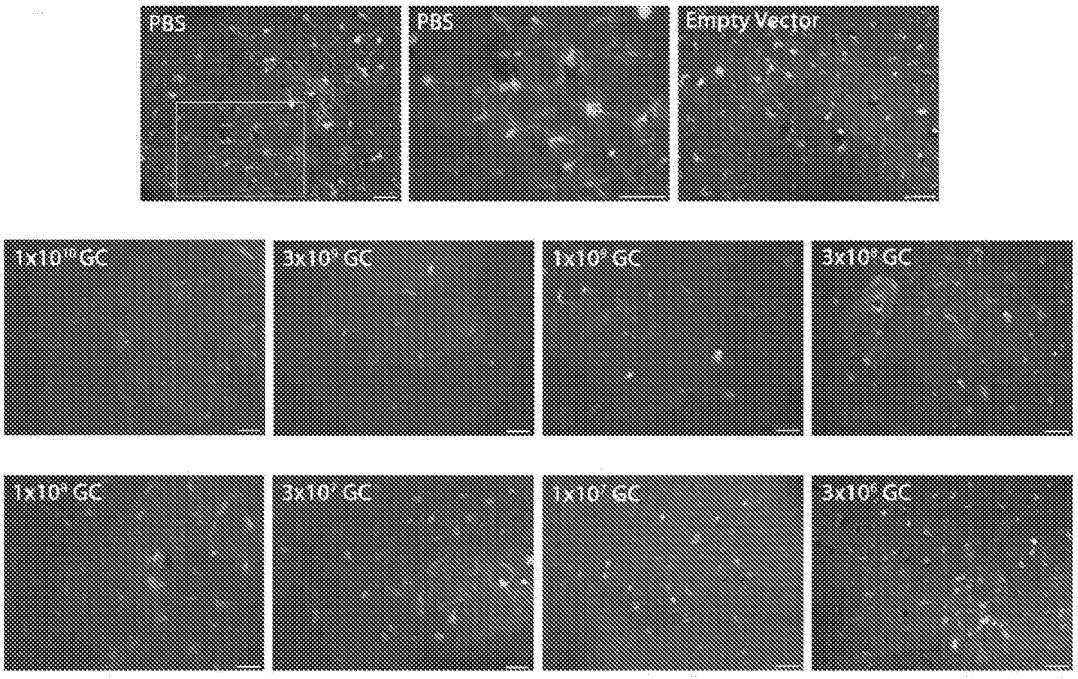


FIGURE 8A

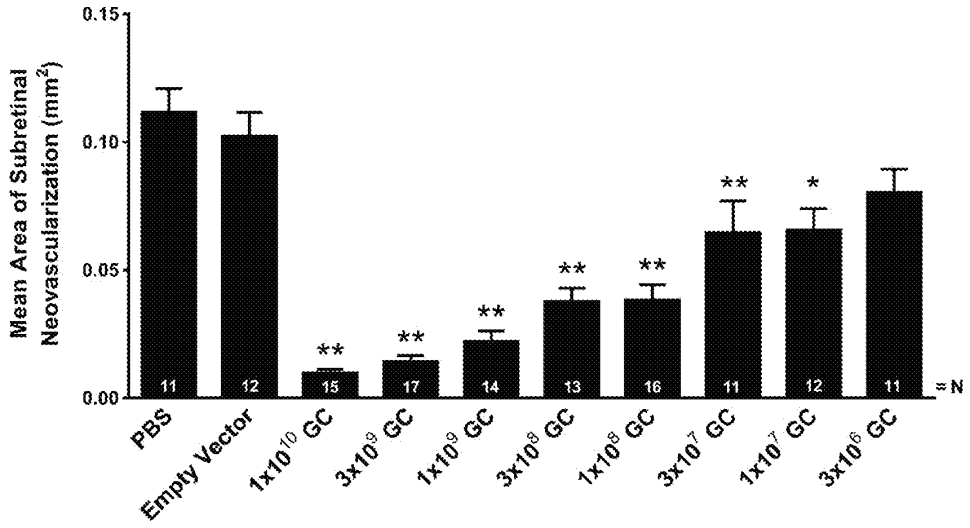


FIGURE 8B

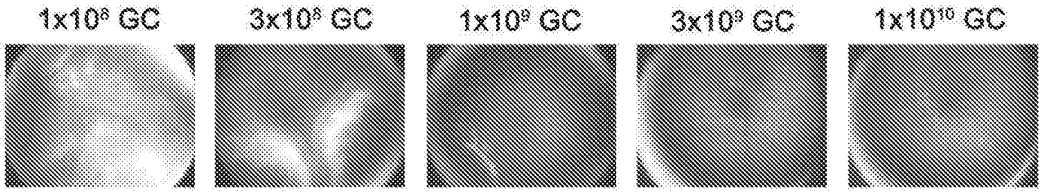


FIGURE 9A

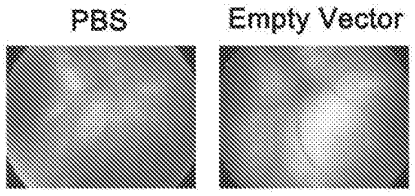


FIGURE 9B

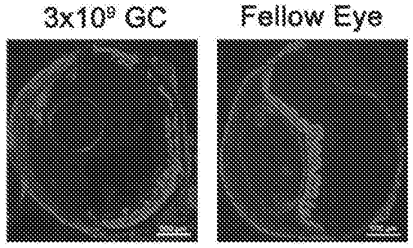


FIGURE 9C

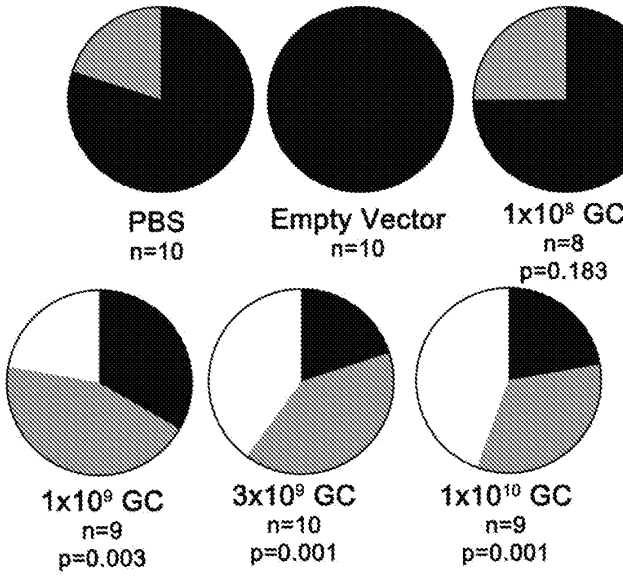


FIGURE 9D

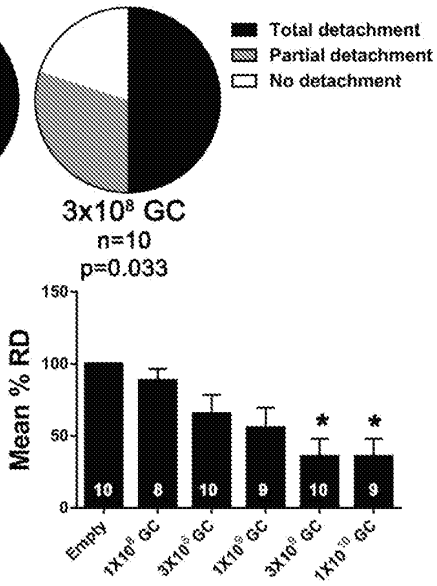


FIGURE 9E

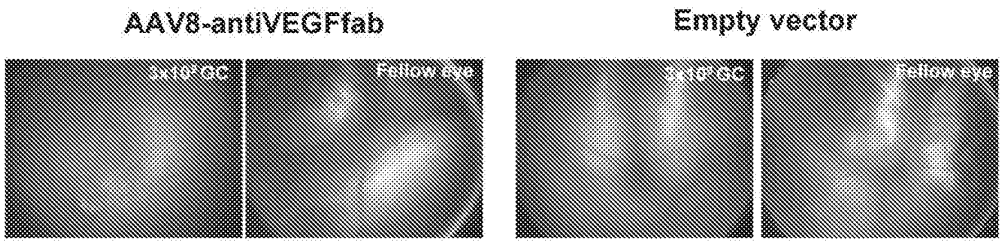


FIGURE 10A

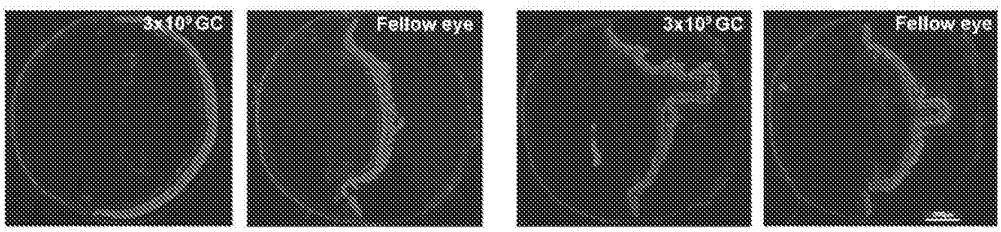


FIGURE 10B

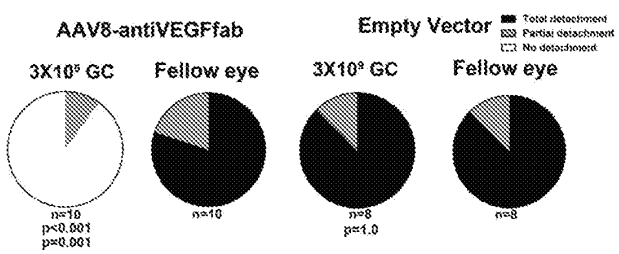


FIGURE 10C

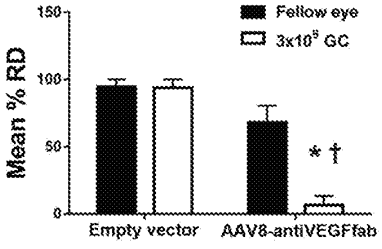


FIGURE 10D

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

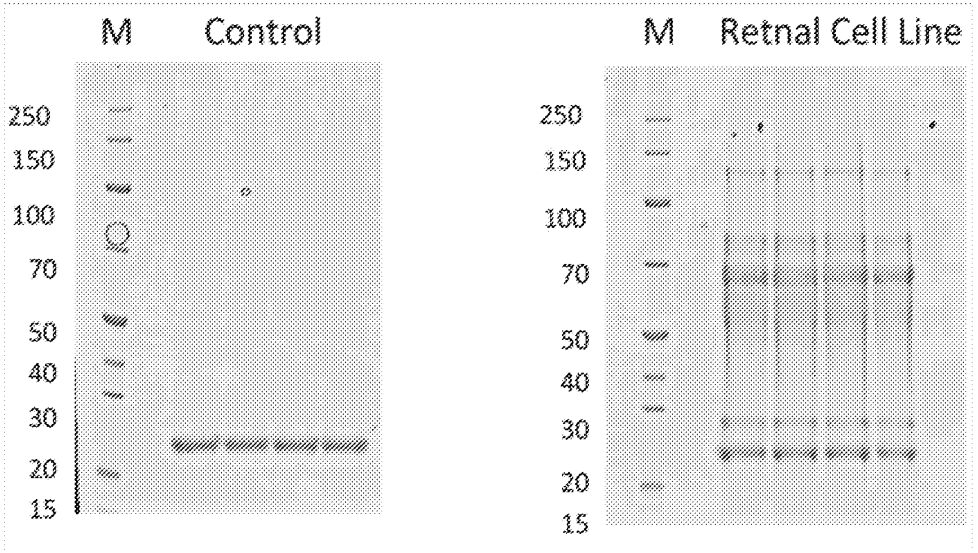


FIGURE 12

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

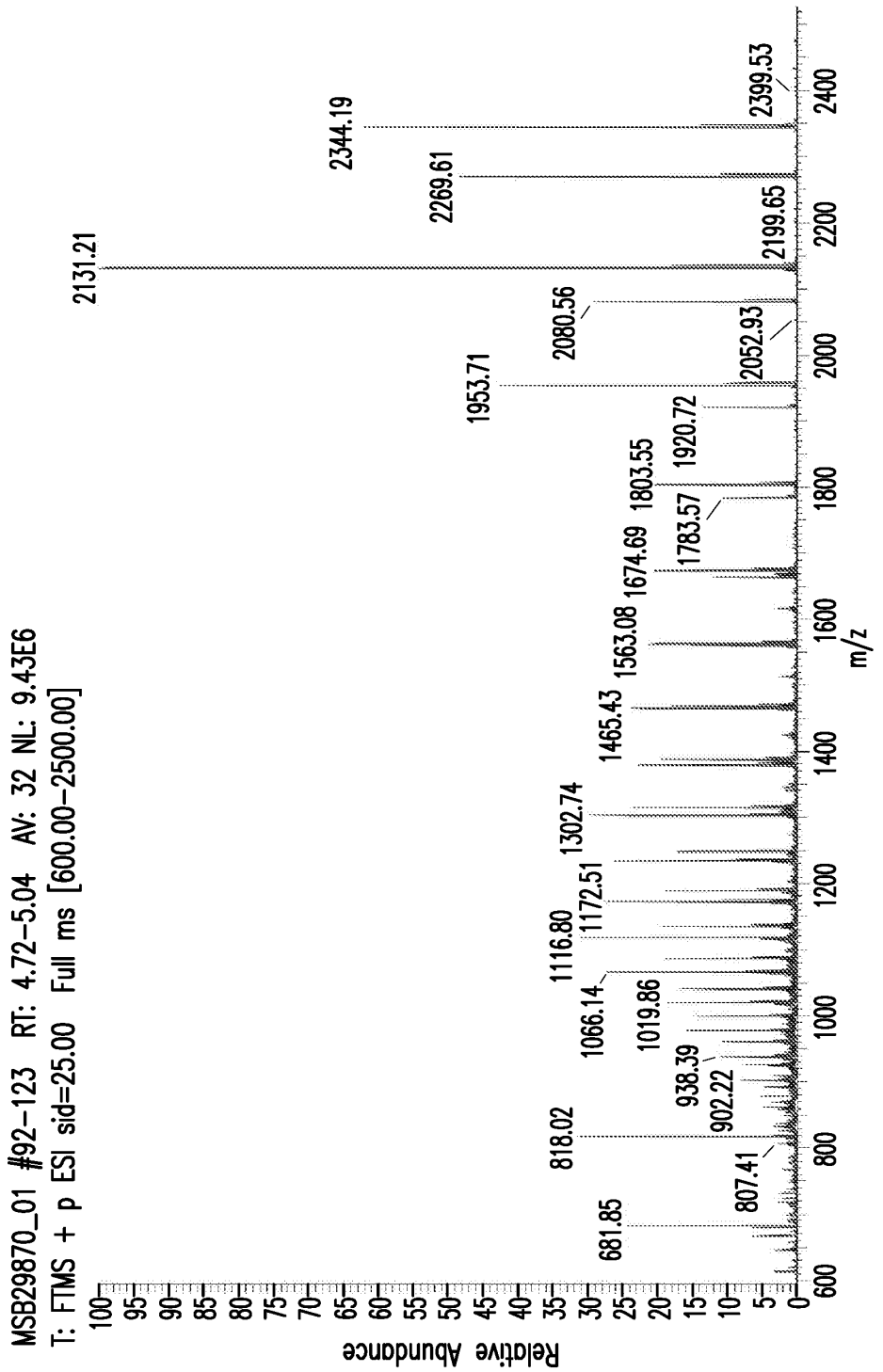
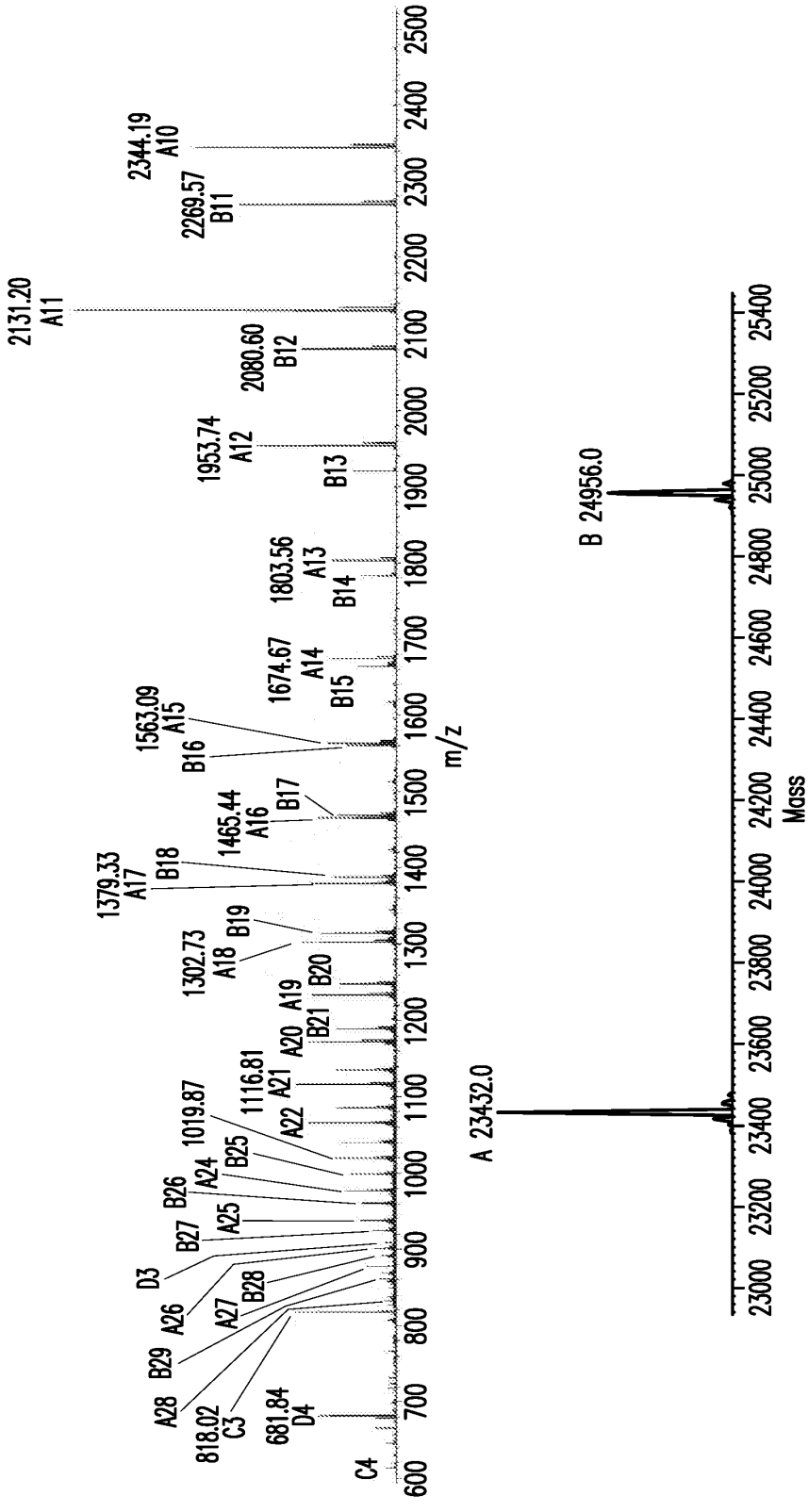

MSB29870_01 #92-123 RT: 4.72-5.04 AV: 32 NL: 9.43E6
T: FTMS + p ESI sid=25.00 Full ms [600.00-2500.00]
Relative Abundance
m/z
2131.21
2344.19
2269.61
2399.53
2199.65
2080.56
2052.93
1953.71
1920.72
1803.55
1783.57
1674.69
1563.08
1465.43
1302.74
1172.51
1116.80
1066.14
1019.86
938.39
902.22
818.02
807.41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

FIG. 15A



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

* 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
WIMTYTGEPT YAADFKRRFT FSLDTSKSTA YLQMNSLRAE DTAVYYCAKY
PYYYGTSHWY FDVWGQGTLV TVSSASTKGP SVFPLAPSSK STSGGTAALG
CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL
GTQTYICNVN HKPSNTKVDK KVEPKSCDKT HLRKRR (SEQ ID NO. 39)

FIGURE 16

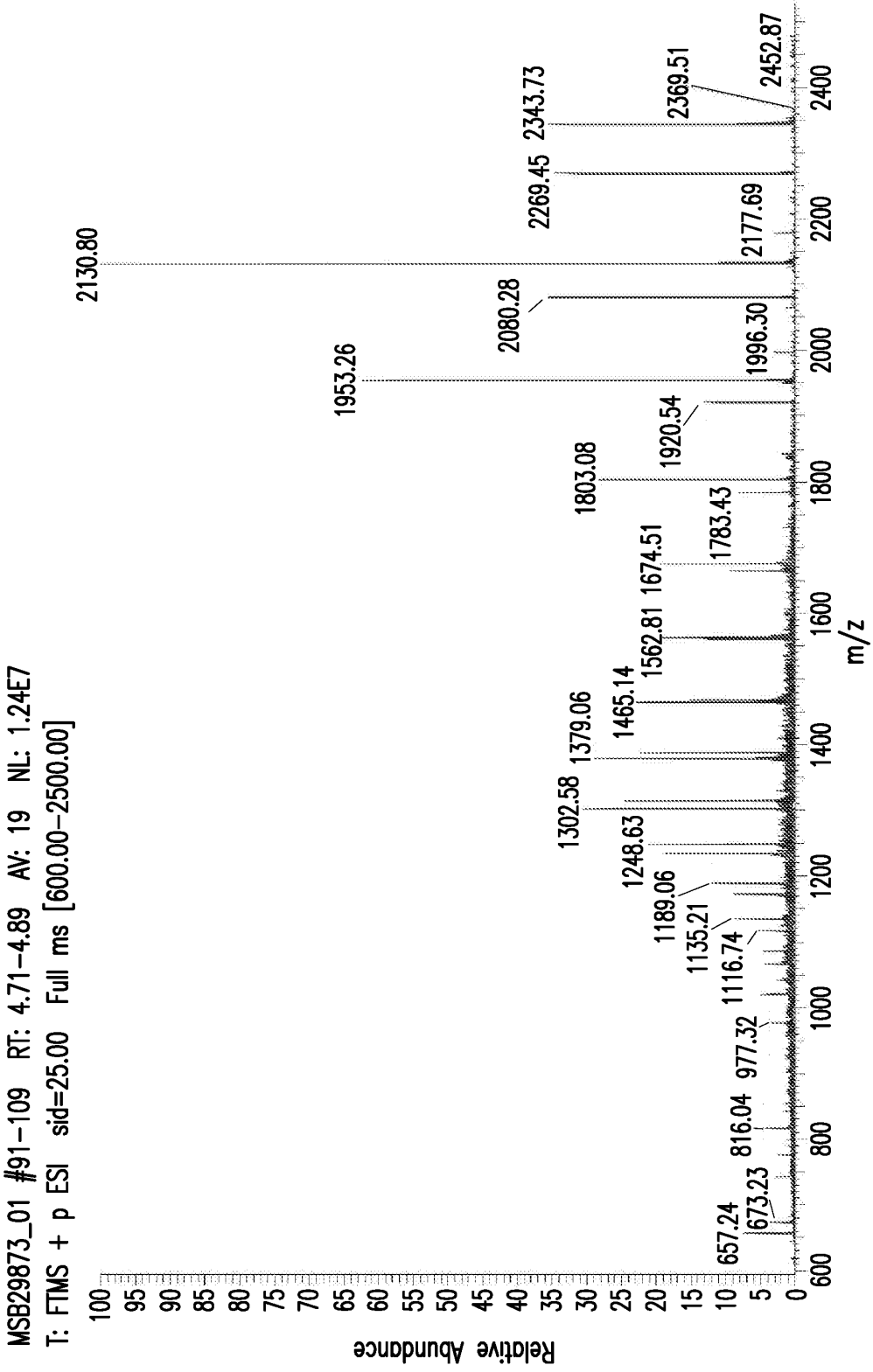
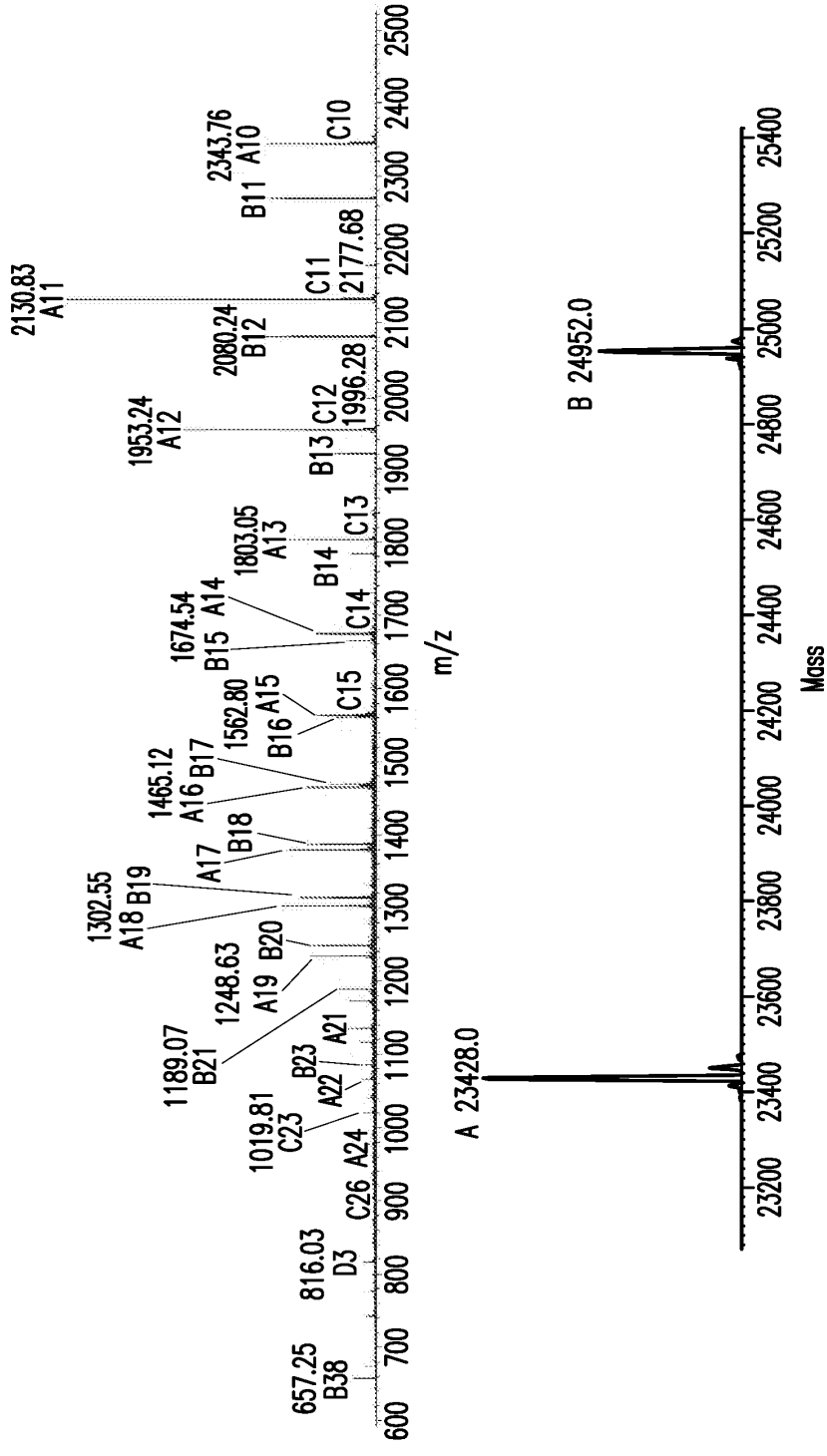

MSB29873_01 #91-109 RT: 4.71-4.89 AV: 19 NL: 1.24E7
T: FTMS + p ESI sid=25.00 Full ms [600.00-2500.00]
Relative Abundance
m/z
2130.80
1953.26
2080.28
2269.45
2343.73
2369.51
2452.87
2177.69
1996.30
1920.54
1803.08
1783.43
1674.51
1562.81
1465.14
1379.06
1302.58
1248.63
1189.06
1135.21
1116.74
977.32
816.04
673.23
657.24

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   VITTSTRTWALPTYNNHLYKQISSAST-GASNDNHYFGYSTPWGYFDFNRFHCHFSPRDW 297
AAV7   VITTSTRTWALPTYNNHLYKQIS-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 (CONT)

```
                                    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-----NNSNFFWTAASKYHLNGRDSLVNPGPAMASHK 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  QIFIKNTPVPANPATTFSSTPVNSFITQYSTGQVSVQIDWEIQKERSKRWNPEVQFTSNY 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 (CONT)

```
        ┌-----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)

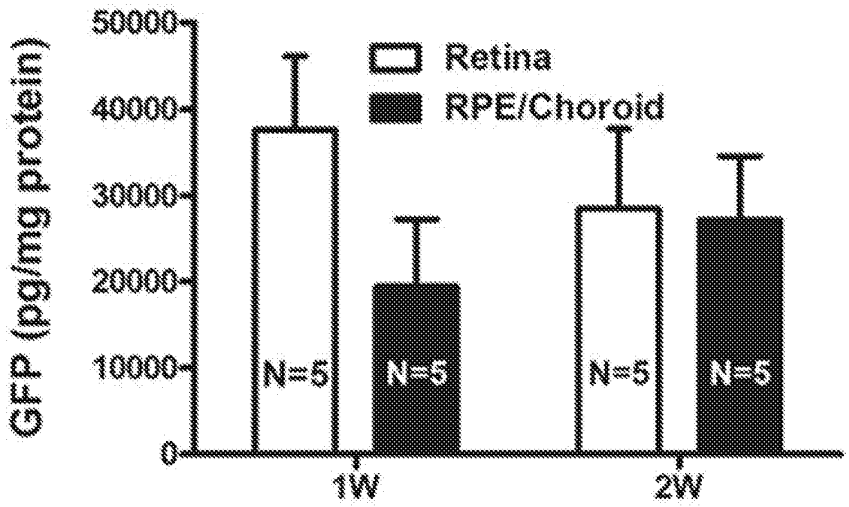

GFP (pg/mg protein)
50000
40000
30000
20000
10000
0
Retina
RPE/Choroid
N=5
N=5
N=5
N=5
1W
2W

FIGURE 19

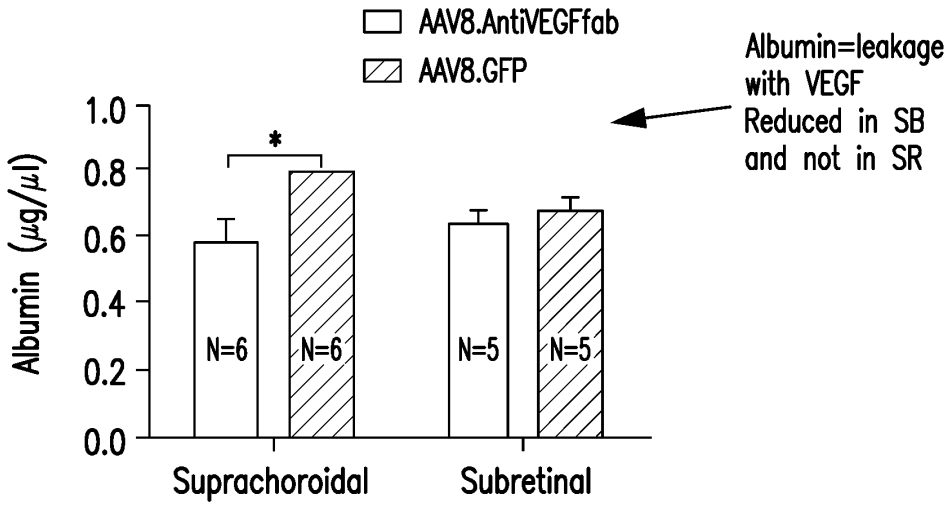


FIG. 20A

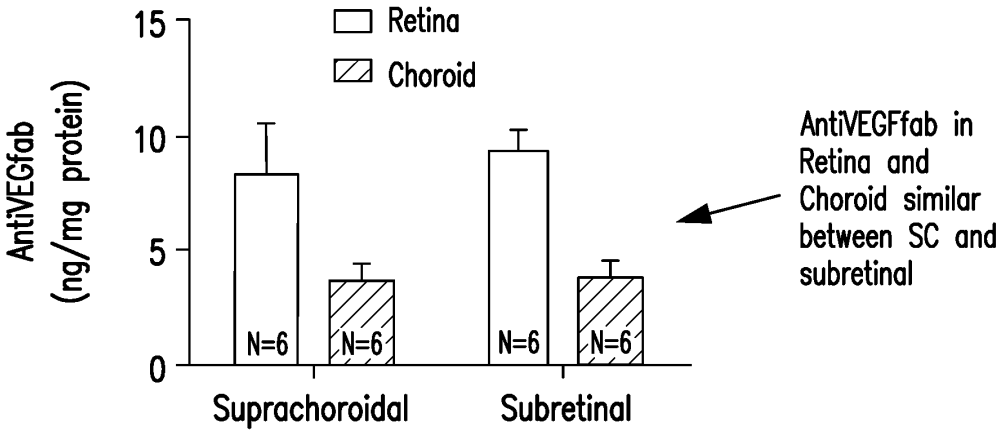


FIG. 20B

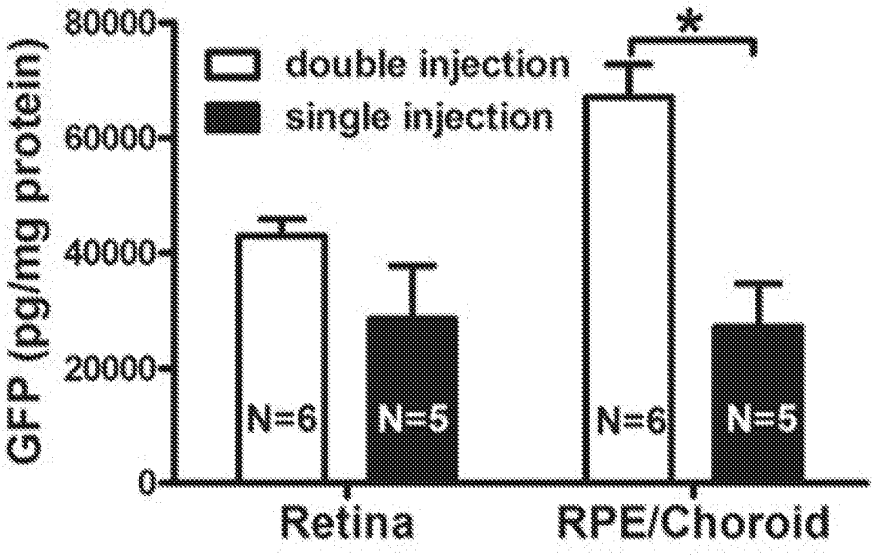

80000
60000
40000
20000
0
GFP (pg/mg protein)
double injection
single injection
*
N=6
N=5
N=6
N=5
Retina
RPE/Choroid

FIGURE 21

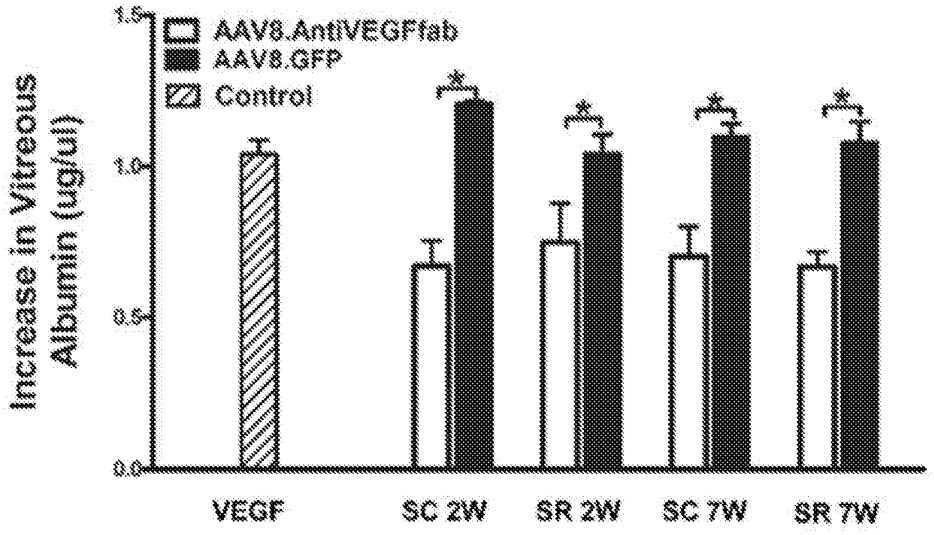

AAV8.AntiVEGFfab
AAV8.GFP
Control
Increase in Vitreous Albumin (ug/ul)
1.5
1.0
0.5
0.0
*
*
*
*
VEGF
SC 2W
SR 2W
SC 7W
SR 7W

FIGURE 22

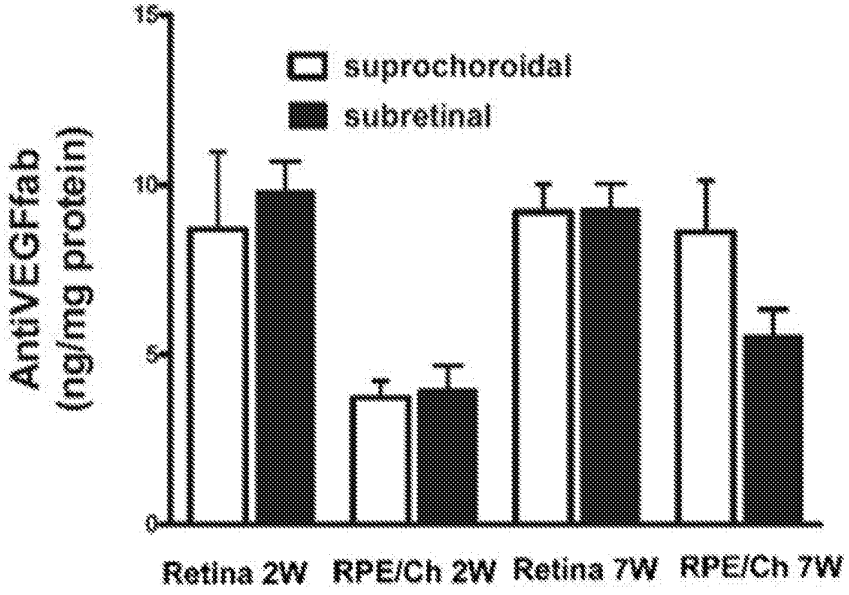

15
10
5
0
AntiVEGFfab
(ng/mg protein)
suprochoroidal
subretinal
Retina 2W
RPE/Ch 2W
Retina 7W
RPE/Ch 7W

FIGURE 23

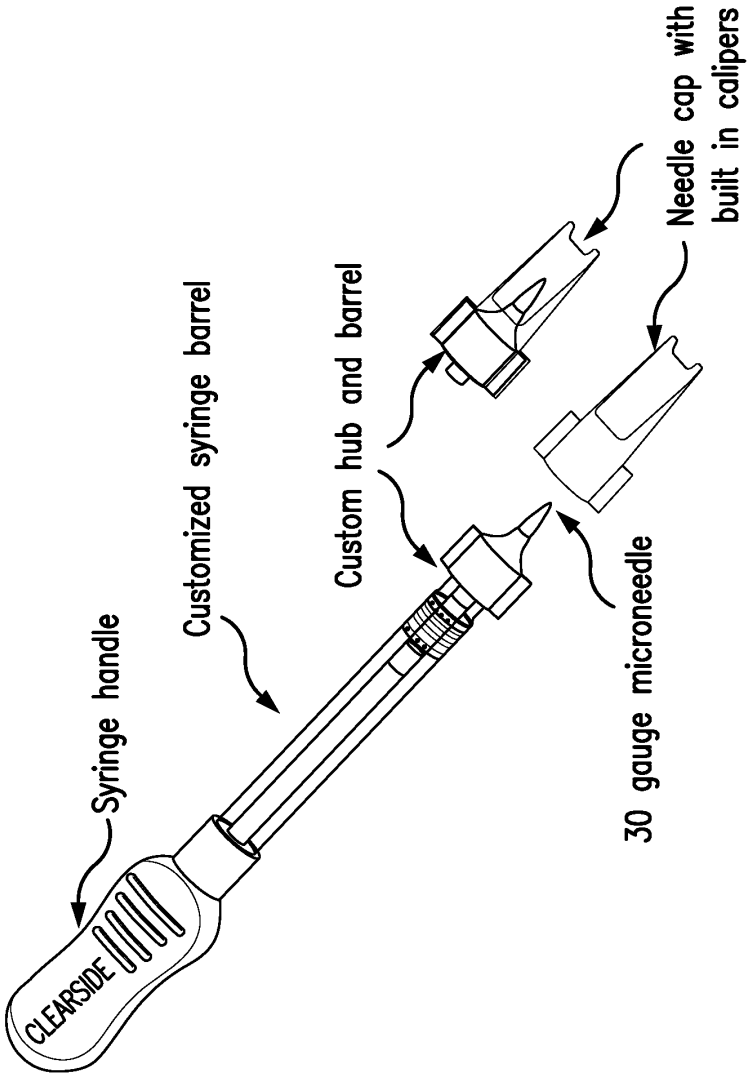

Needle cap with built in calipers
Custom hub and barrel
Customized syringe barrel
Syringe handle
30 gauge microneedle
CLEARSIDE

FIG. 24

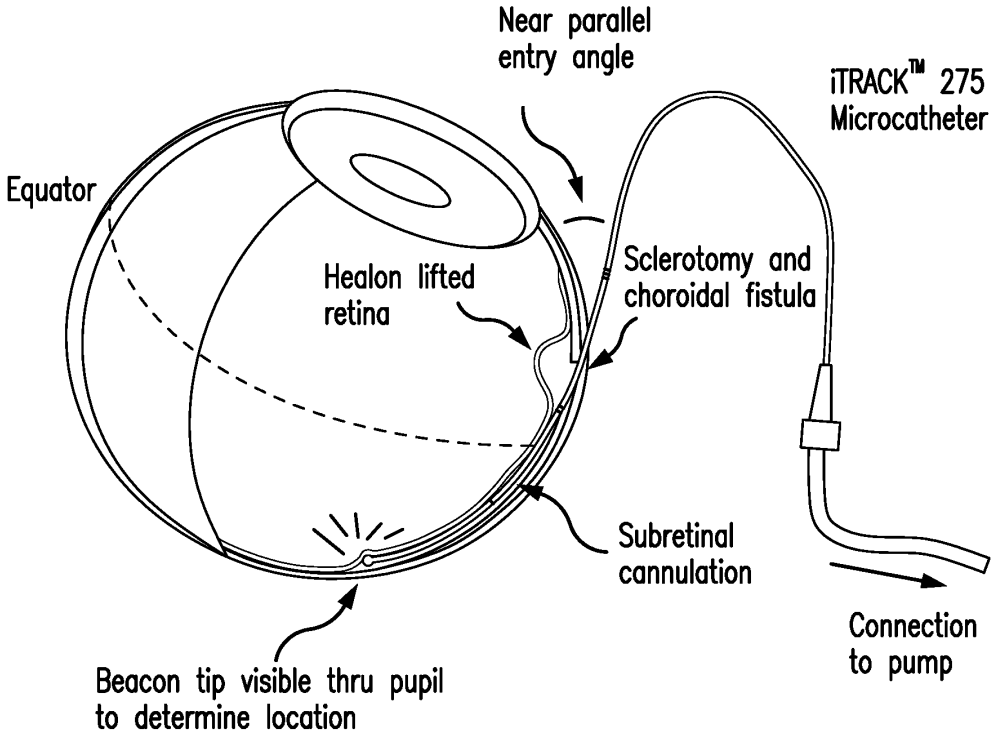

Near parallel
entry angle
iTRACK™ 275
Microcatheter
Equator
Healon lifted
retina
Sclerotomy and
choroidal fistula
Subretinal
cannulation
Connection
to pump
Beacon tip visible thru pupil
to determine location

FIG. 25

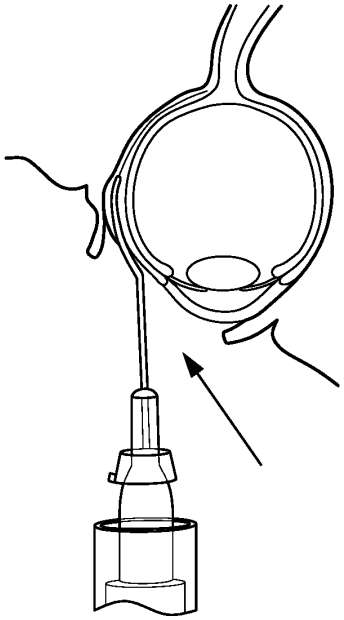


FIG. 26B

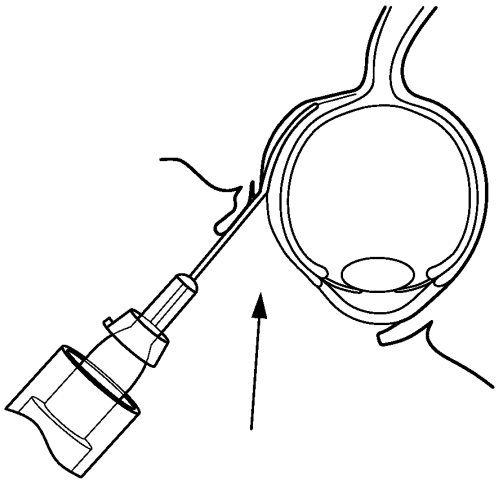


FIG. 26D

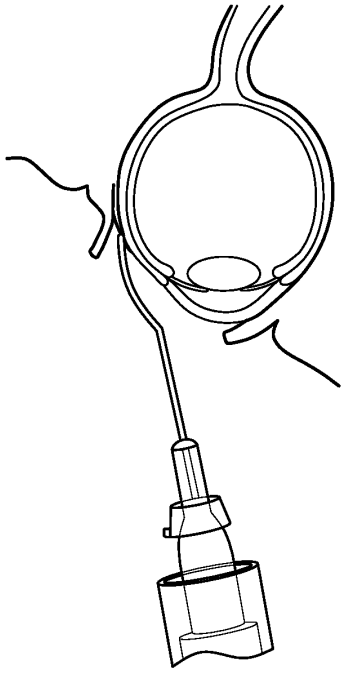


FIG. 26A

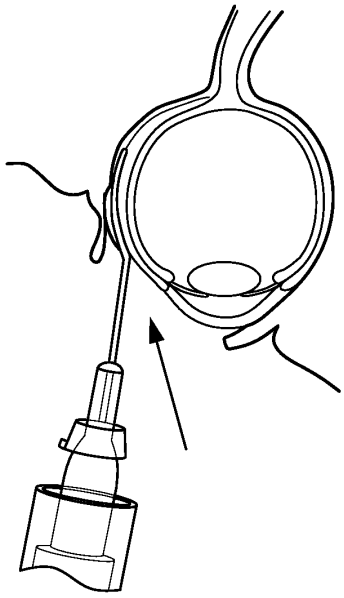


FIG. 26C