

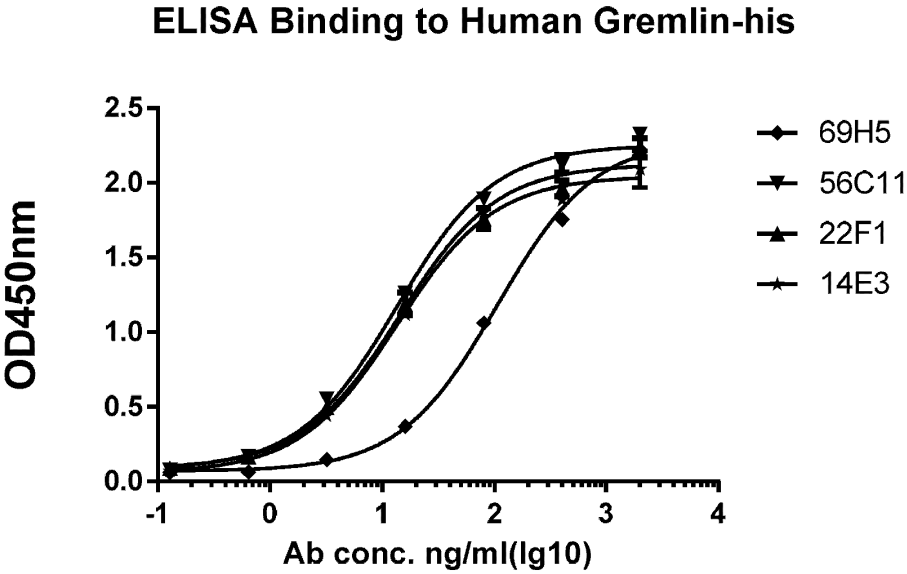


FIG. 1A

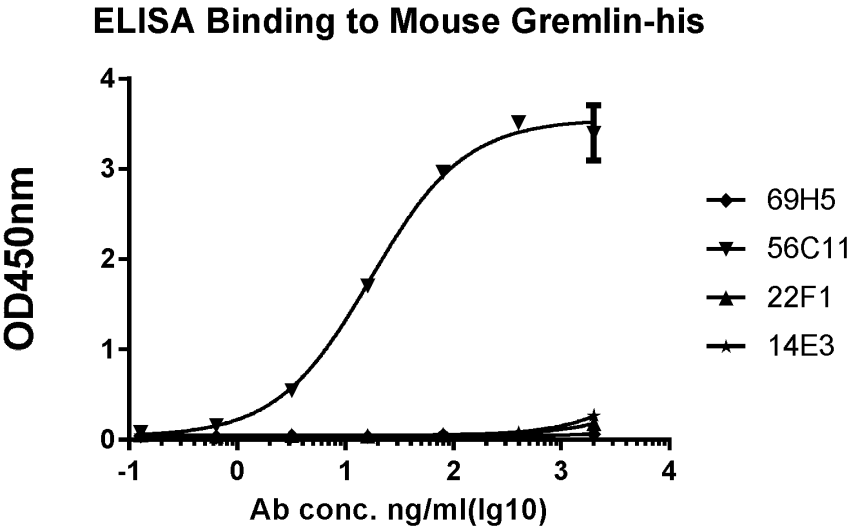


FIG. 1B

**EC50 of Binding to Human/Mouse Gremlin-1 (ng/ml)**

| Antibody | Human | Mouse |
|----------|-------|-------|
| 14E3     | 13.6  | -     |
| 69H5     | 105.9 | -     |
| 22F1     | 14.13 | -     |
| 56C11    | 13.42 | 17.2  |

FIG. 1C

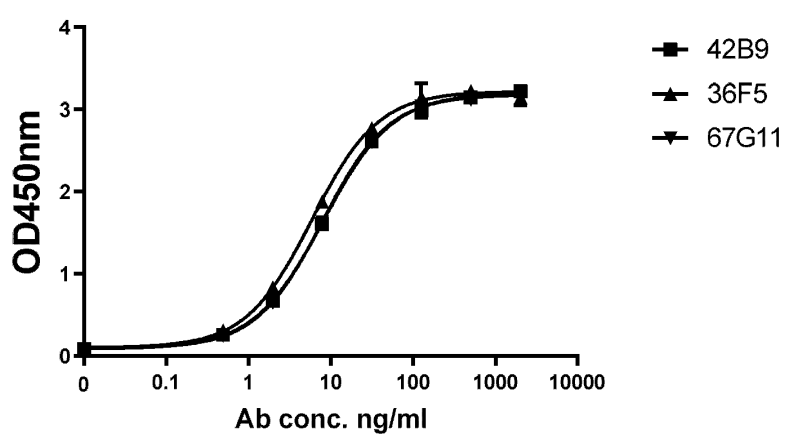
**ELISA Binding Human Gremlin-his**

FIG. 1D

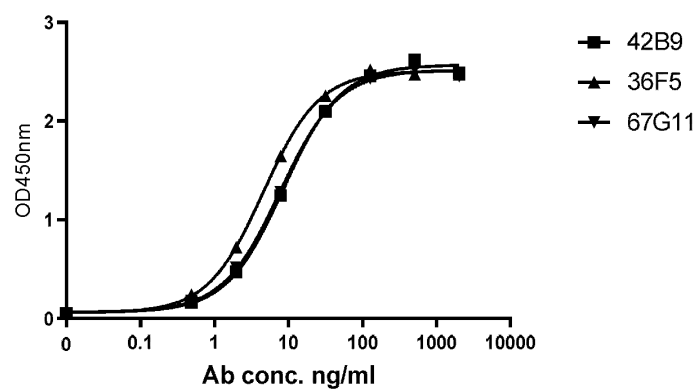
**ELISA Binding to Mouse Gremlin-his**

FIG. 1E

**EC50 of Binding to Human/Mouse Gremlin-1 (ng/ml)**

| Antibody | Human | Mouse |
|----------|-------|-------|
| 42B9     | 8.058 | 8.512 |
| 36F5     | 5.869 | 4.564 |
| 67G11    | 7.841 | 7.713 |

FIG. 1F

Binding specificity(DAN Family,R&amp;D,0.5ug/ml)

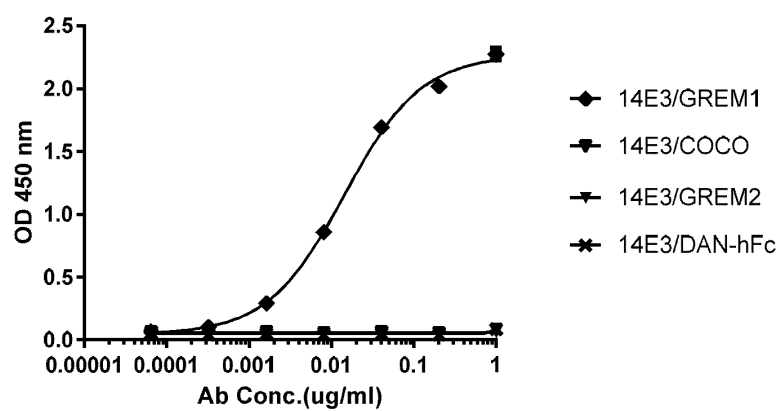


FIG. 2

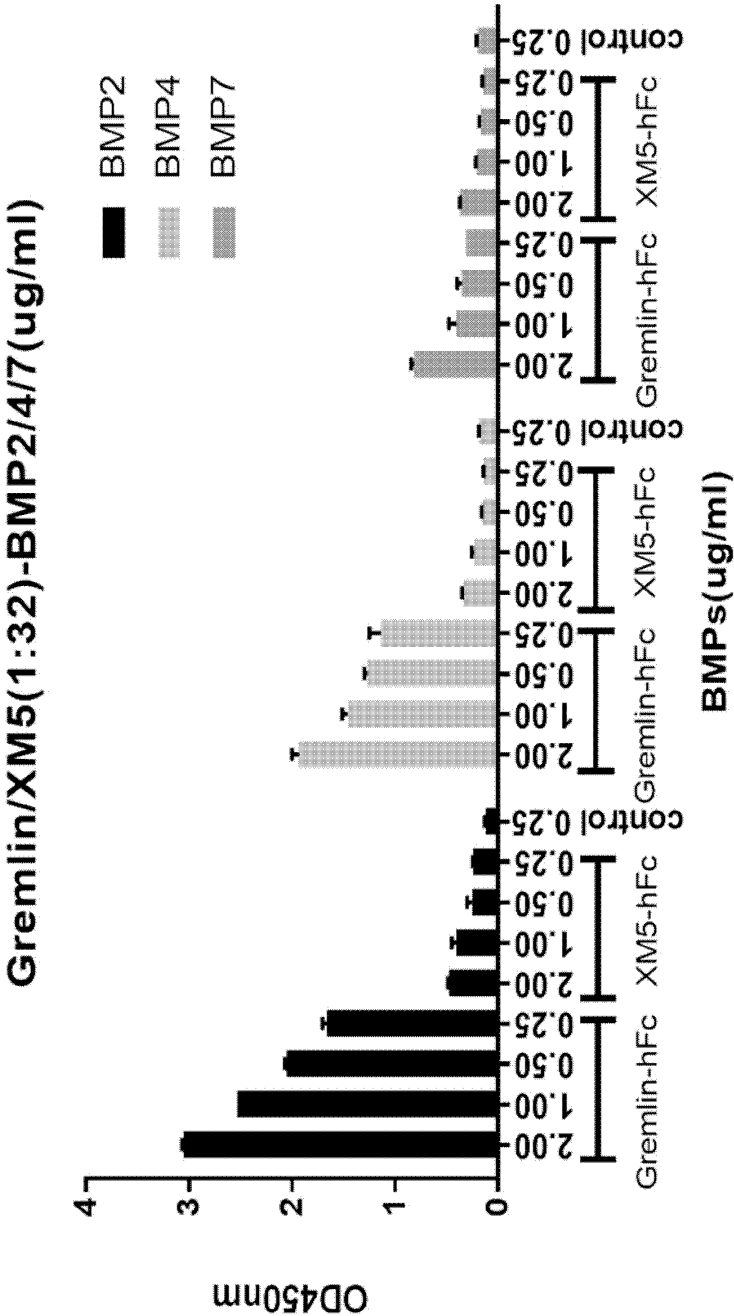


FIG. 3A

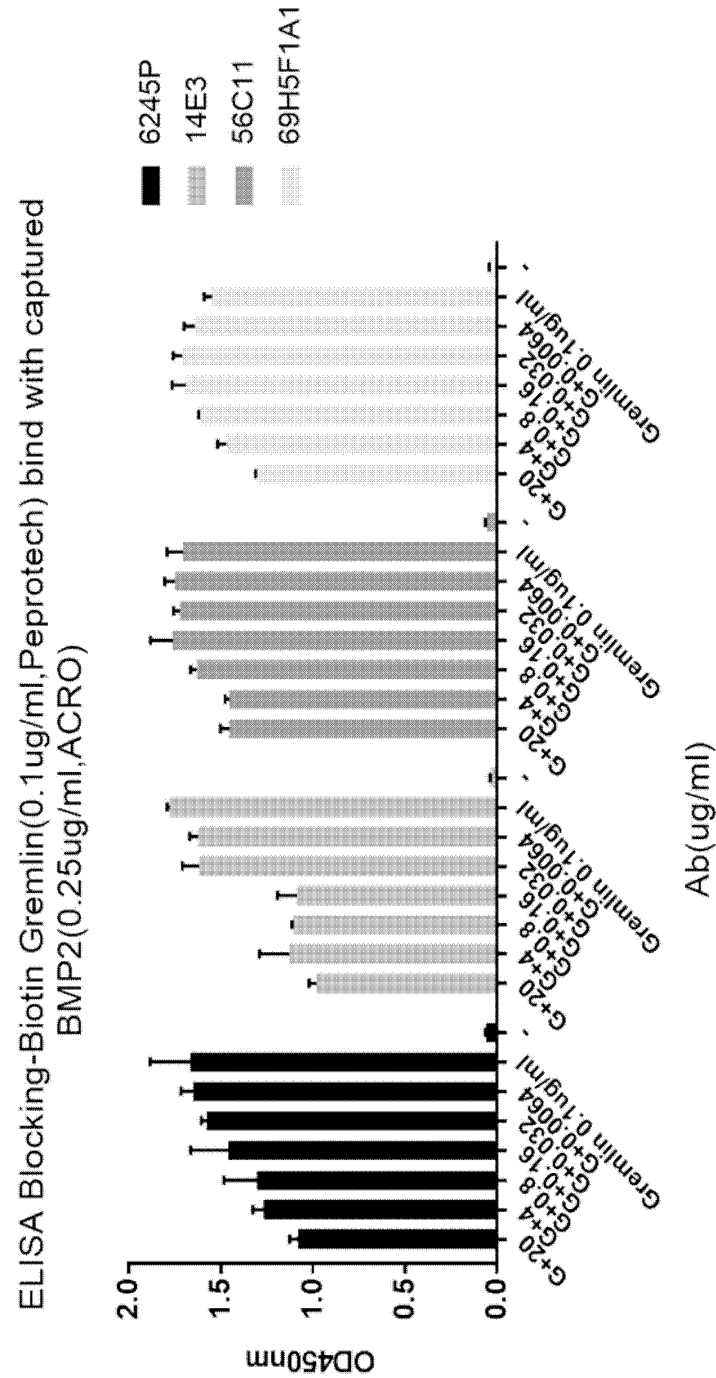
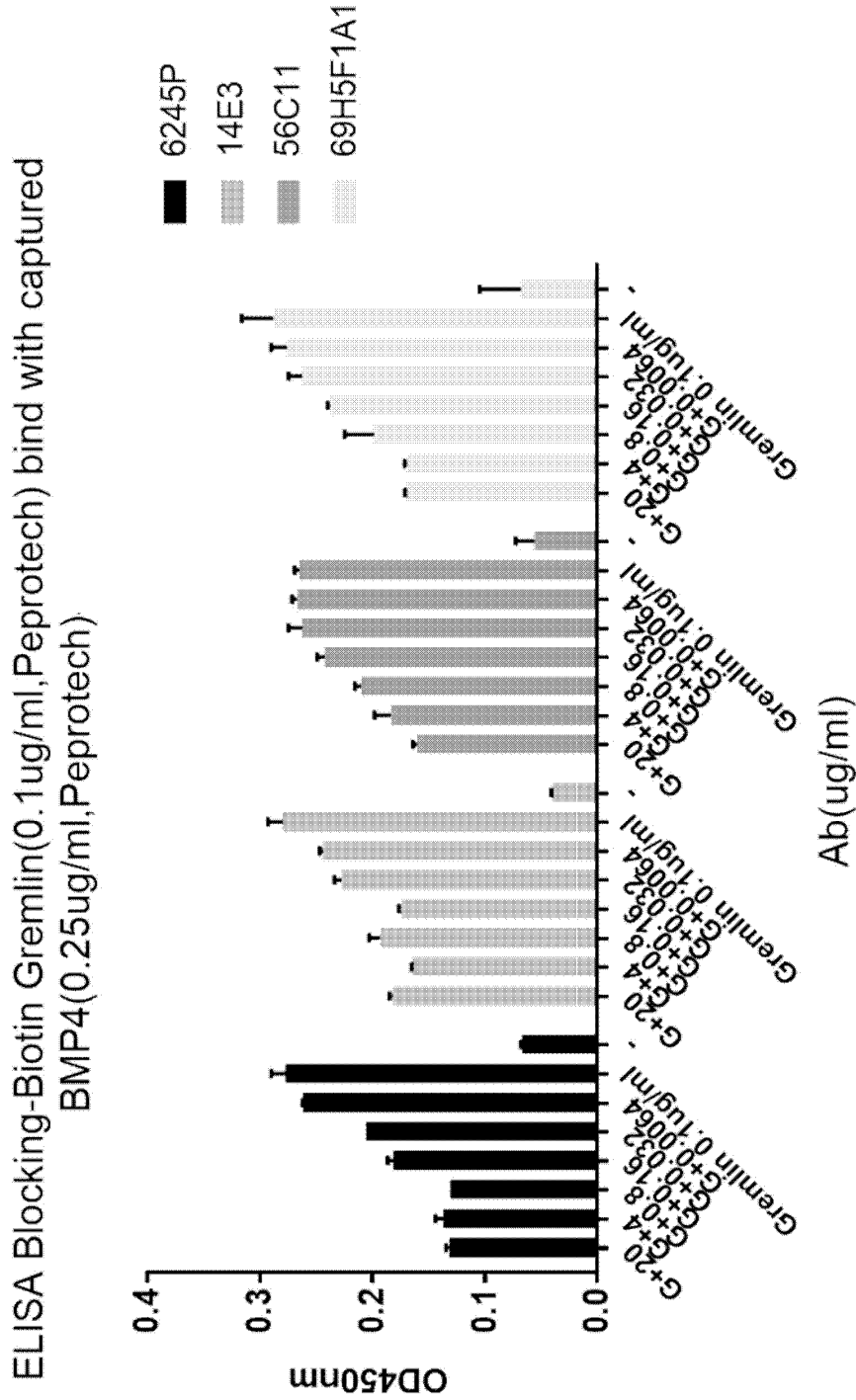


FIG. 3B



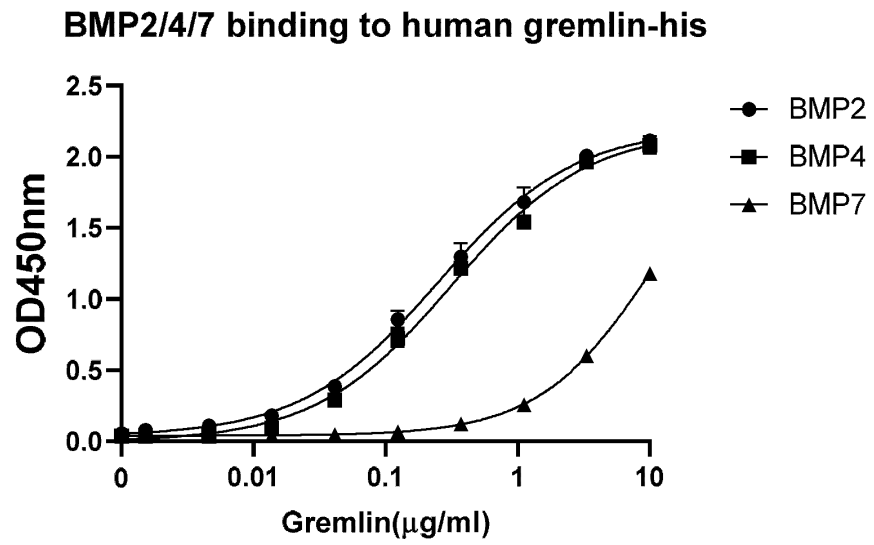
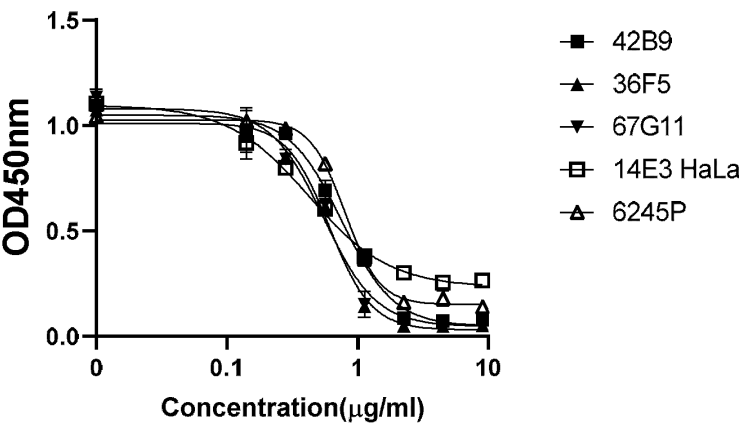


FIG. 3D

Ab blocking human gremlin binding to BMP2



Elisa blocking gremlin binding to BMP2

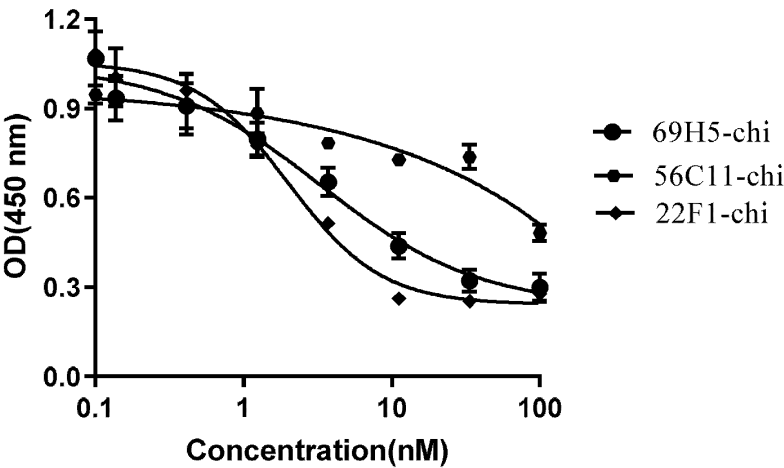
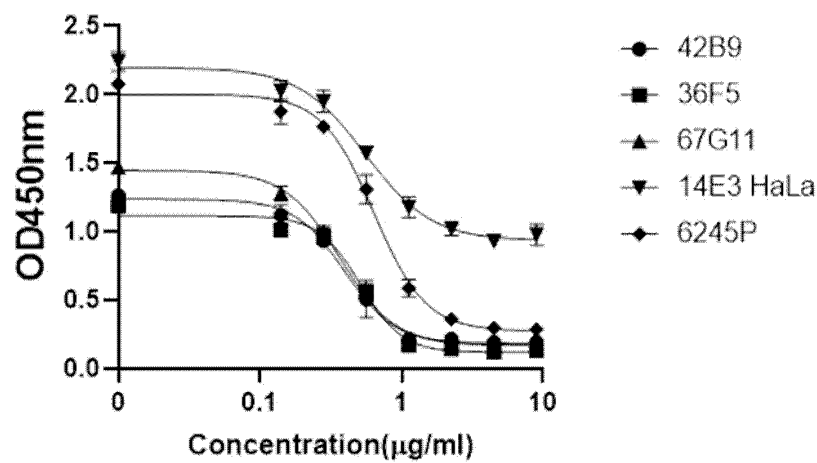


FIG. 3E

Ab blocking human gremlin binding to BMP4



Elisa blcking gremlin binding to BMP4

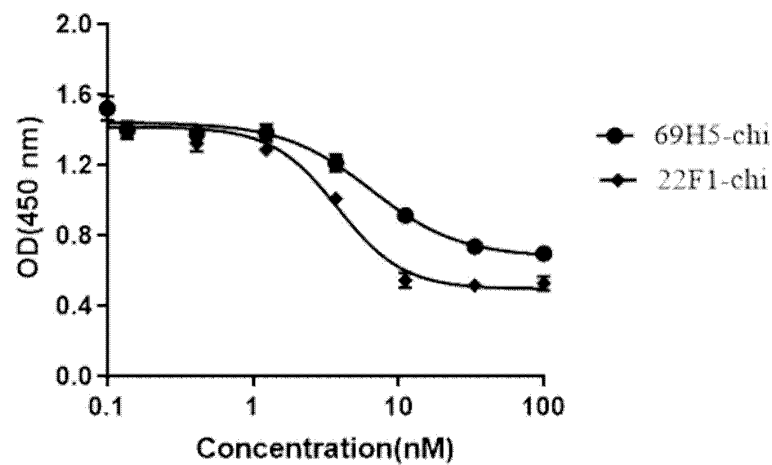


FIG. 3F

Ab blocking human gremlin binding to BMP7

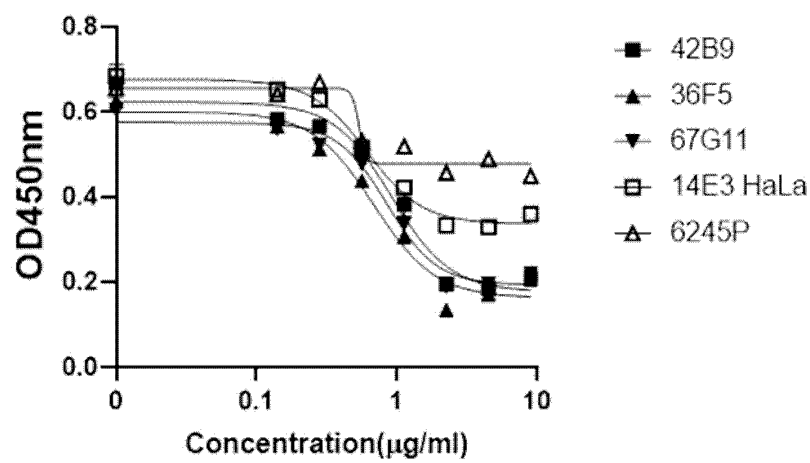


FIG. 3G

IC50 of Binding Ab blocking Human Gremlin-1 binding to BMPs ( $\mu$ g/ml)

| Type                 | BMP2               |            | BMP4               |            | BMP7               |            |
|----------------------|--------------------|------------|--------------------|------------|--------------------|------------|
| Parameter            | IC50 ( $\mu$ g/ml) |            | IC50 ( $\mu$ g/ml) |            | IC50 ( $\mu$ g/ml) |            |
| Group                | OD450              | Percentage | OD450              | Percentage | OD450              | Percentage |
| <b>42B9</b>          | 0.7521             | 0.7523     | 0.3965             | 0.3964     | 0.9164             | 0.9281     |
| <b>36F5</b>          | 0.6042             | 0.6042     | 0.5122             | 0.512      | 0.6835             | 0.6835     |
| <b>67G11</b>         | 0.5471             | 0.5478     | 0.3673             | 0.3673     | 0.8476             | 0.8476     |
| <b>14E3<br/>HaLa</b> | 0.4232             | 0.4233     | 0.5551             | 0.5548     | 0.6085             | 0.6106     |
| <b>6245P</b>         | 0.7971             | 0.7971     | 0.6377             | 0.6377     | 0.5363             | 0.5362     |

FIG. 3H

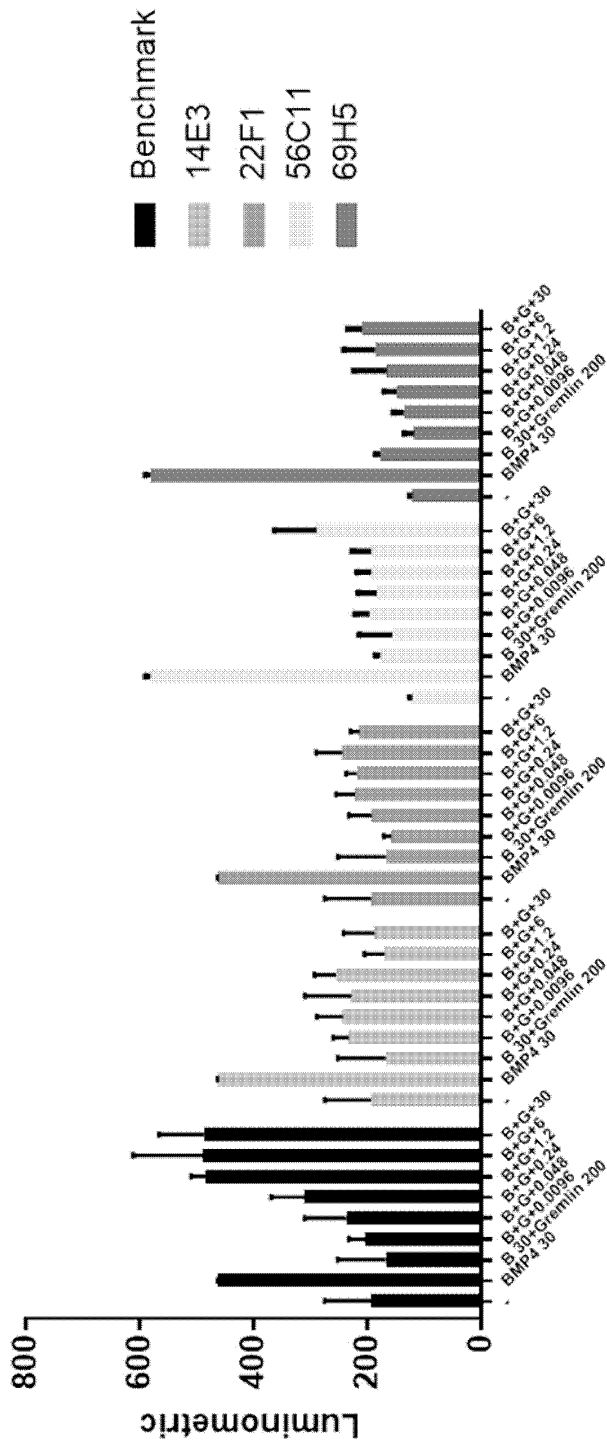


FIG. 4

Effect of Ab in ATDC-5 cell differentiation assay  
(BMP4,Peptech,100ng/ml;Gremlin,Acro,400ng/ml)

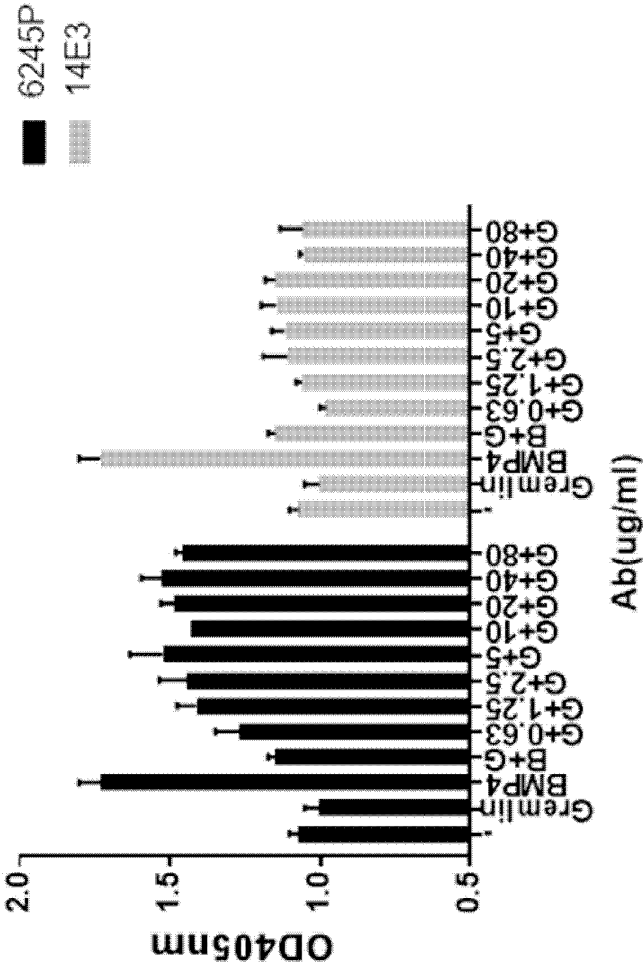


FIG. 5A

Effect of Ab in A TDC-5 cell differentiation assay  
(BMP4, Peprotech, 100ng/ml; Gremlin, Acro, 400ng/ml)

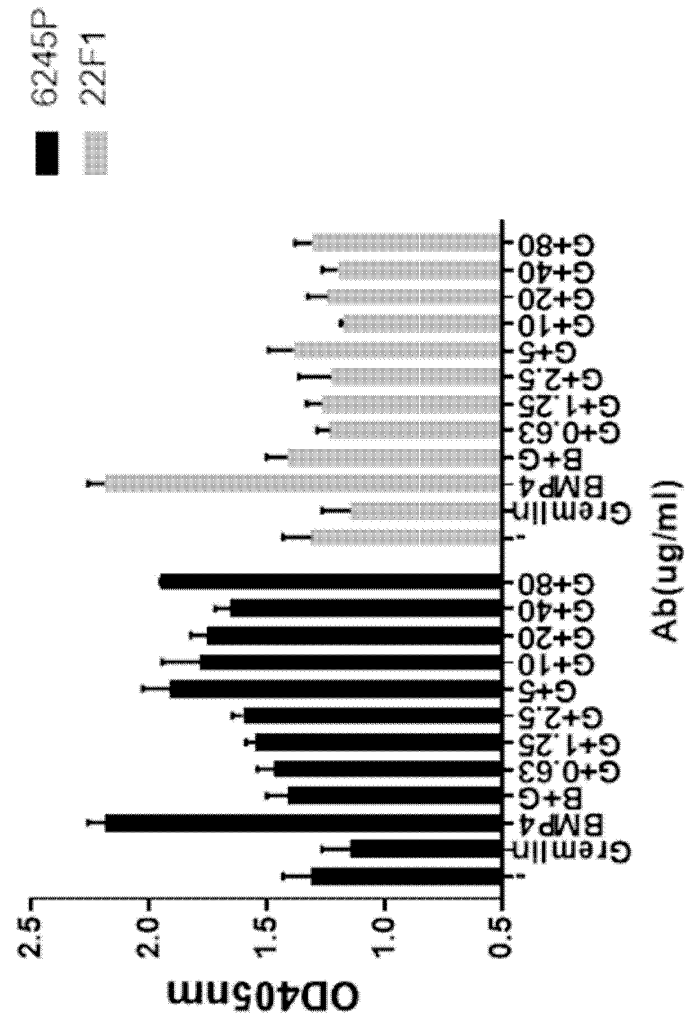


FIG. 5B

Effect of Ab in ATDC-5 cell differentiation assay  
(BMP4, Peprotech, 100ng/ml; Gremlin, Acro, 400ng/ml)

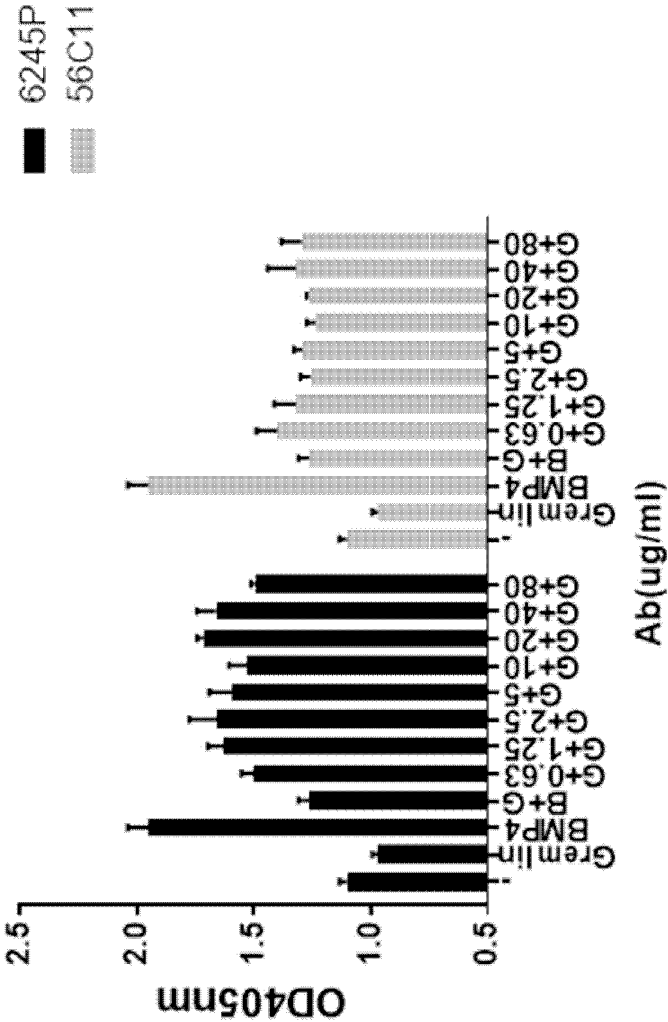


FIG. 5C

Effect of Ab in A TDC-5 cell differentiation assay  
(BMP4, Peprotech, 100ng/ml; Gremlin, Acro, 400ng/ml)

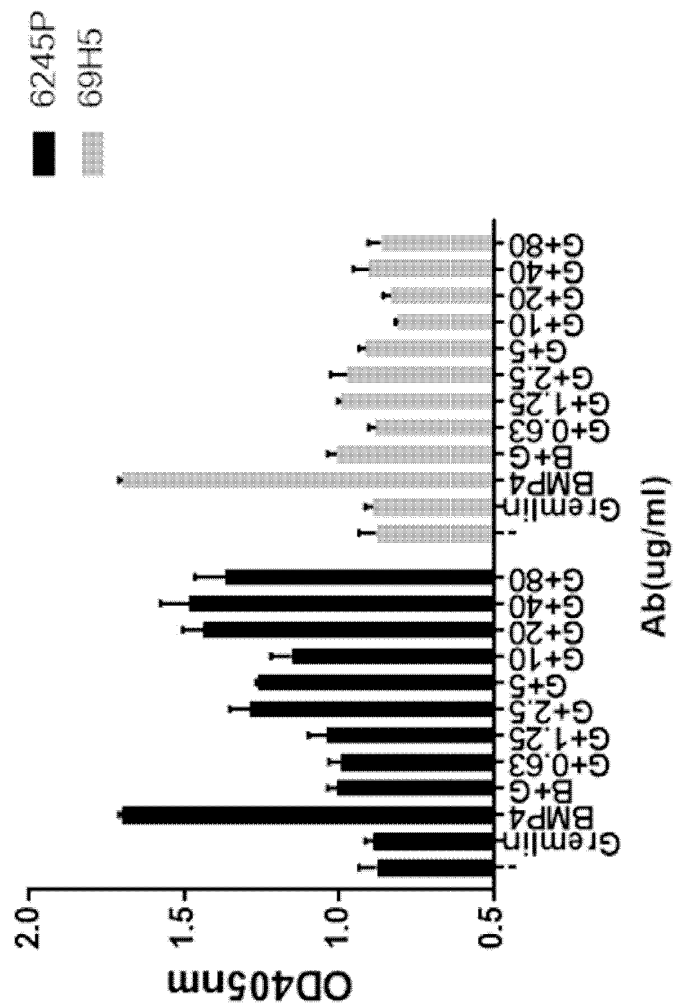


FIG. 5D

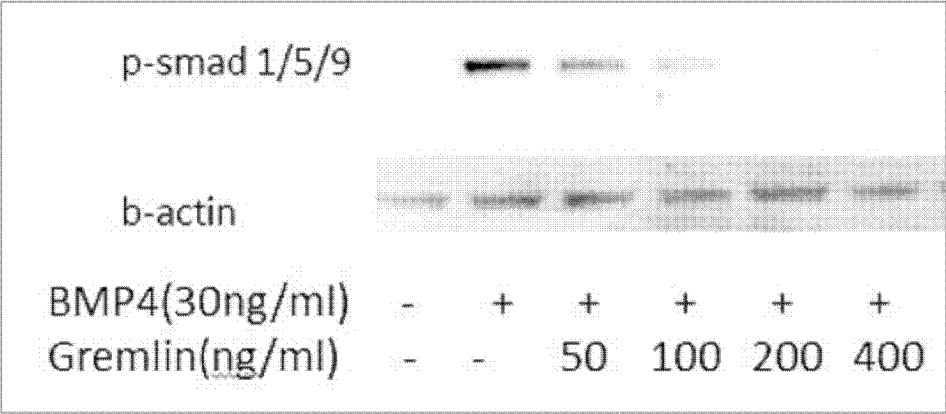
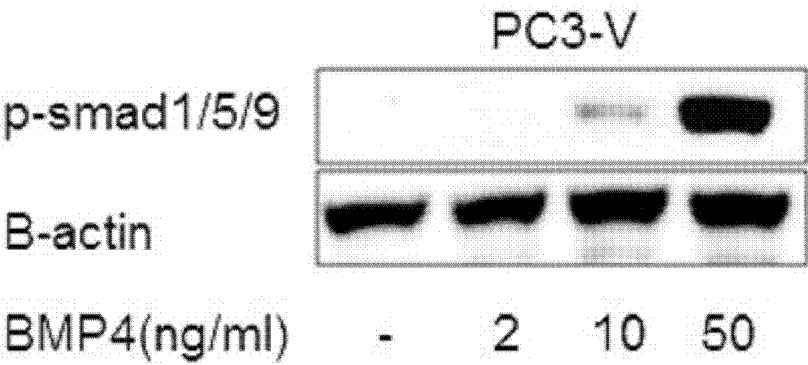


FIG. 6A

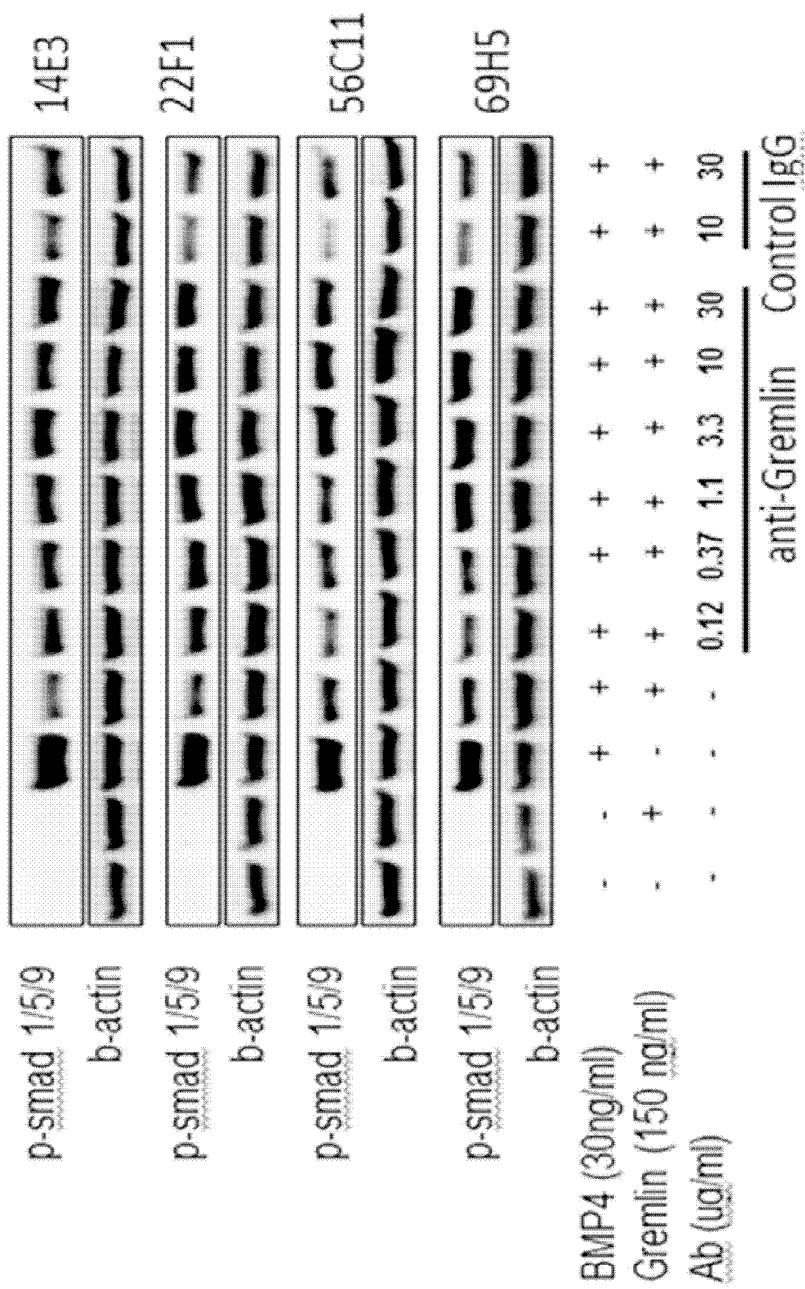


FIG. 6B

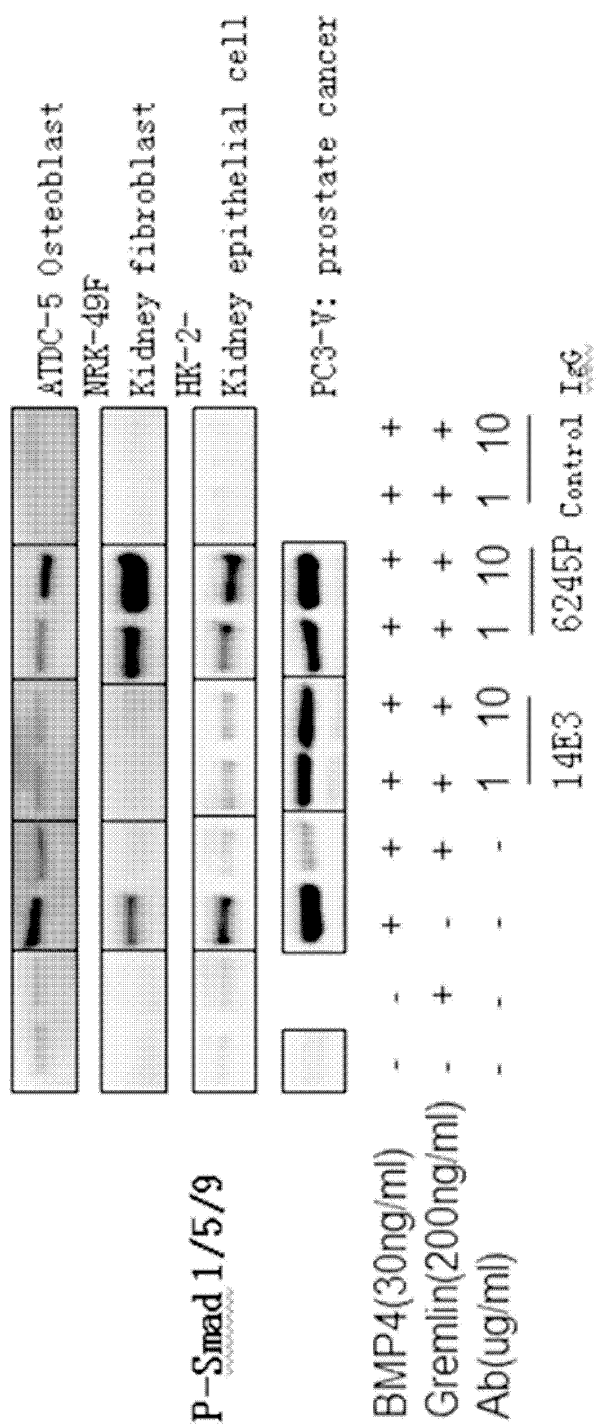


FIG. 7

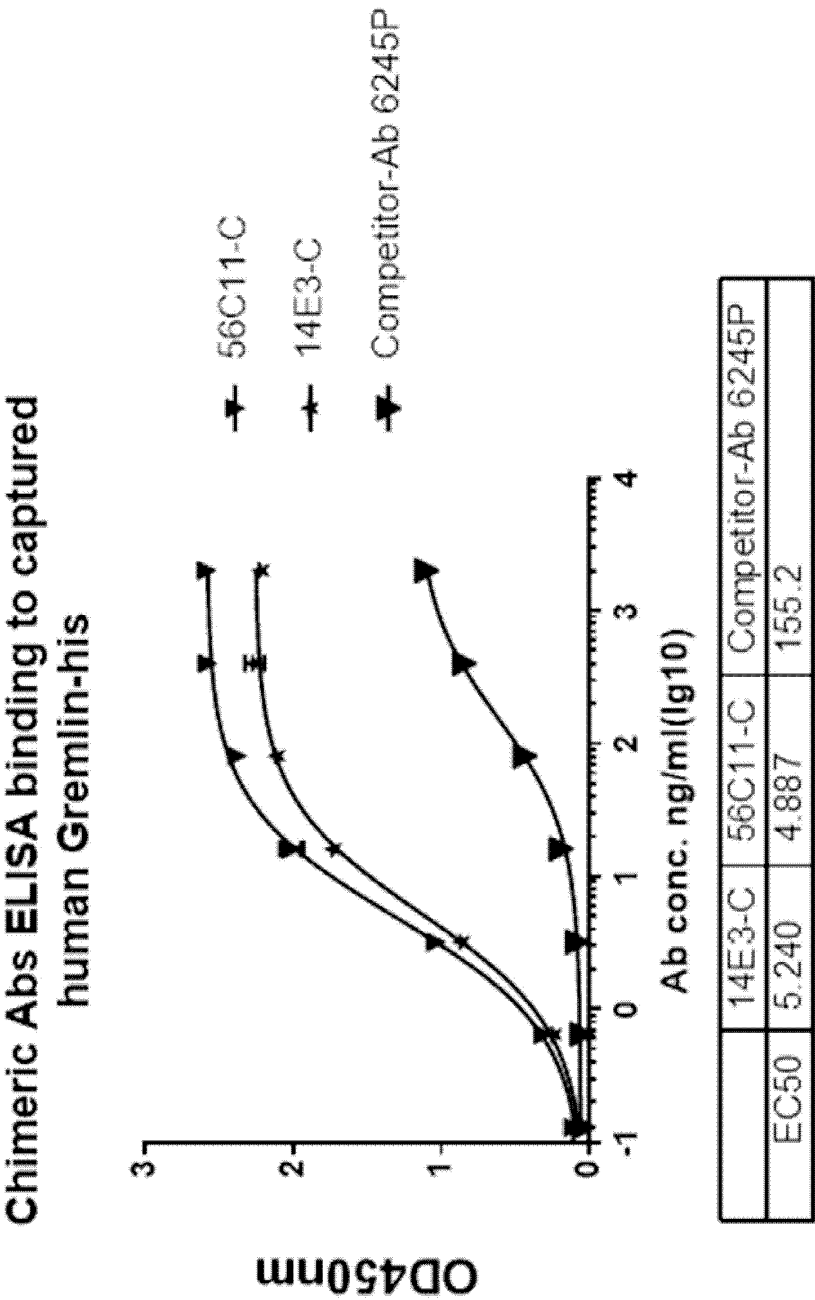
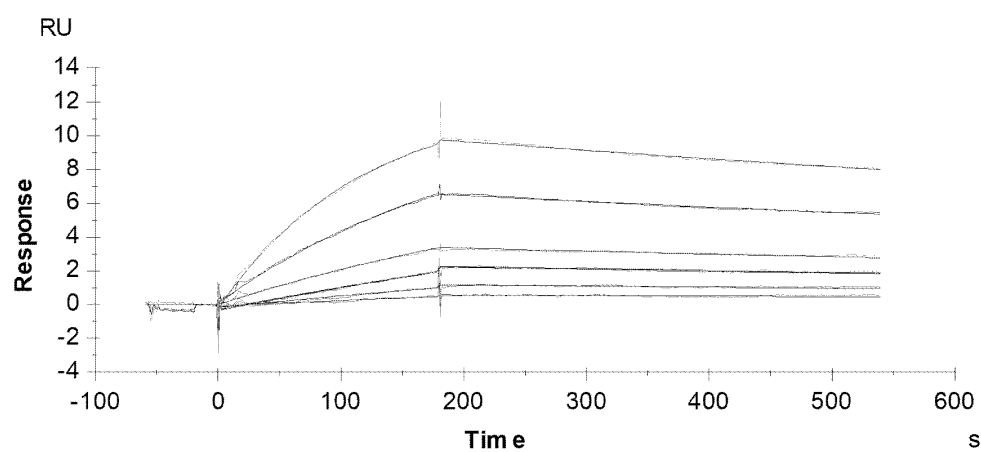
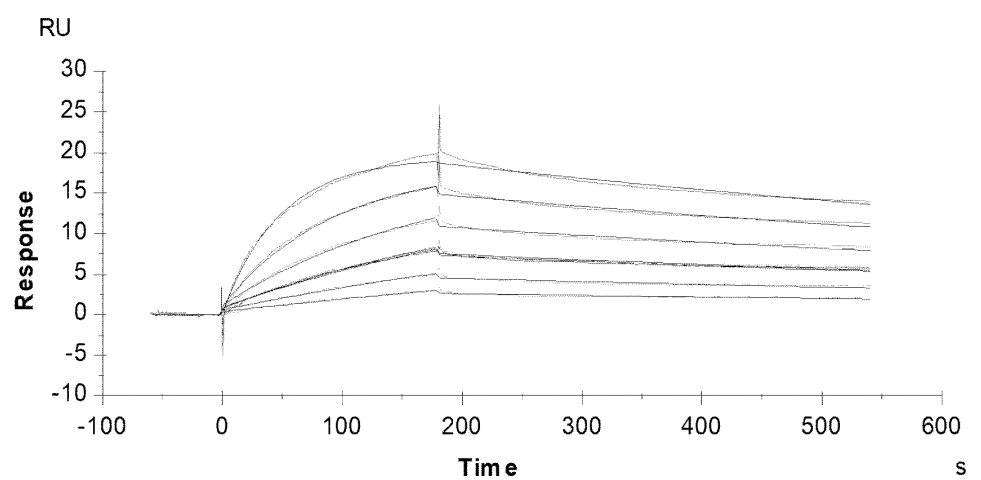


FIG. 8



**Biacore affinities at 25°C for antibodies binding to captured human Gremlin-1**

| Captured               | Antibody | $k_a$ (1/Ms) | $k_d$ (1/s) | KD (M)   |
|------------------------|----------|--------------|-------------|----------|
| Gremlin<br>(Peprotech) | 14E3-C   | 4.988E+4     | 8.821E-4    | 1.768E-8 |
|                        | 22F1-C   | 2.038E+4     | 5.561E-4    | 2.728E-8 |

FIG. 9

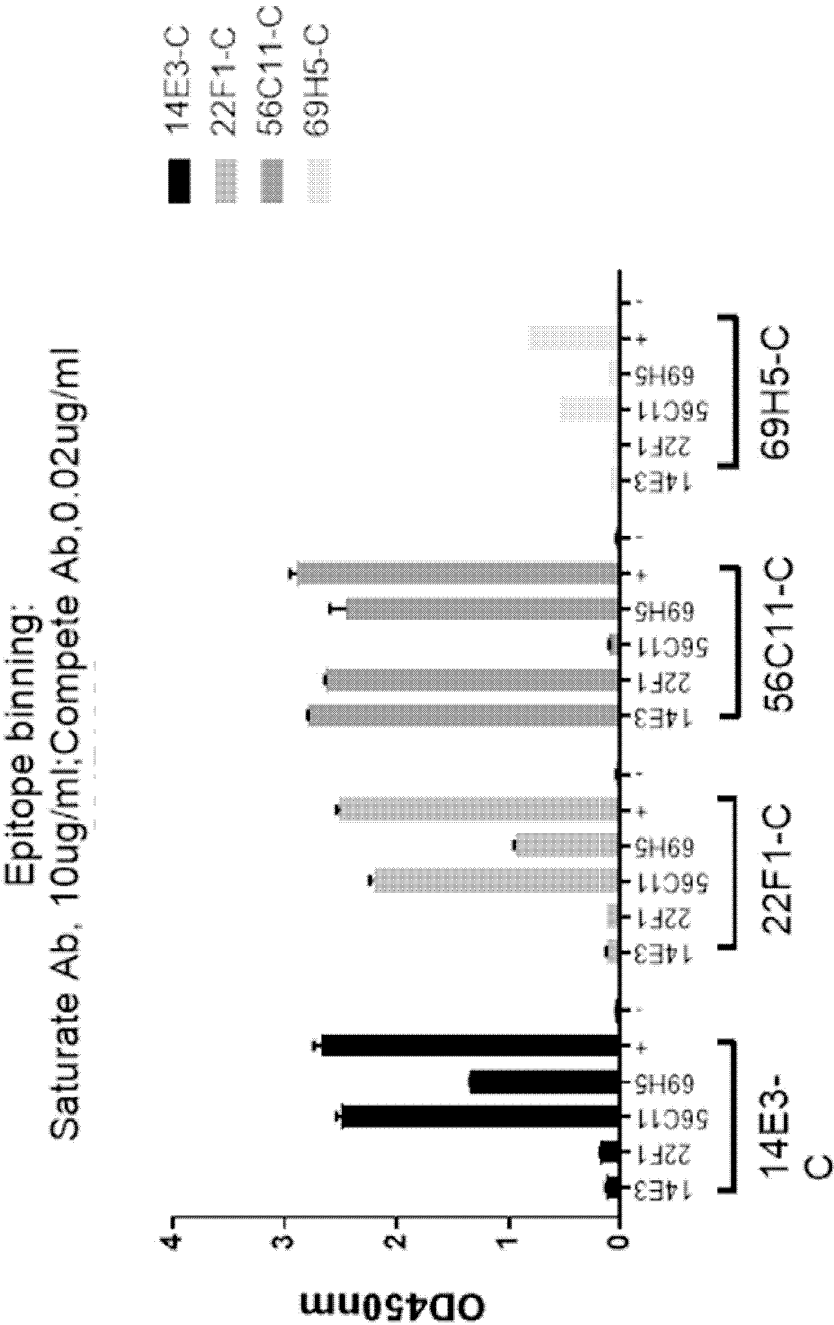
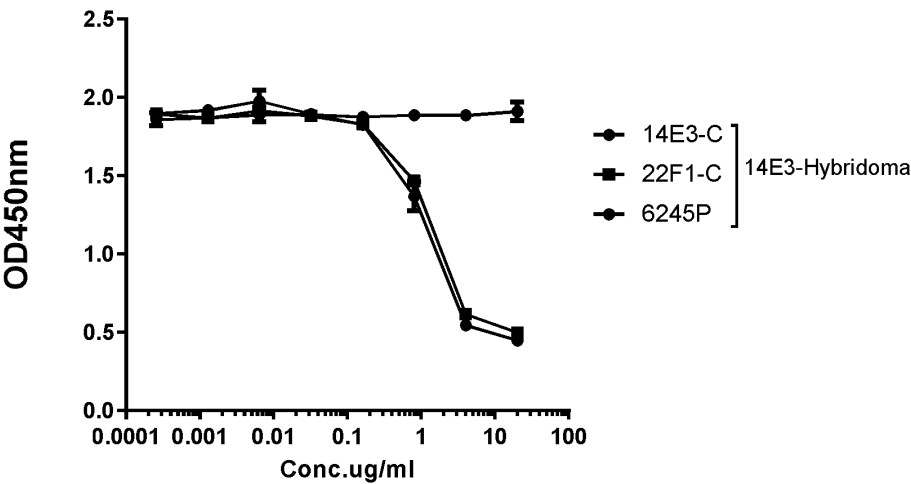


FIG. 10A

Binding to captured human gremlin(Acro,0.5ug/ml)



Binding to captured human gremlin(Acro,0.5ug/ml)

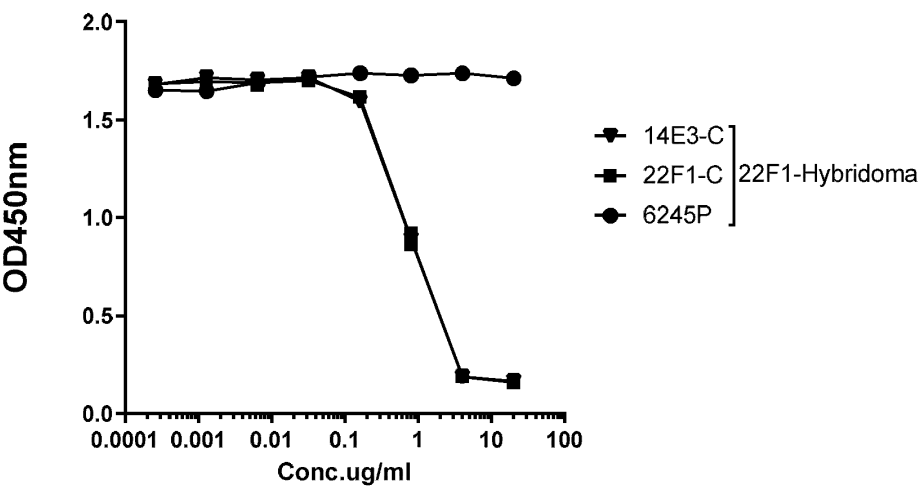


FIG. 10B

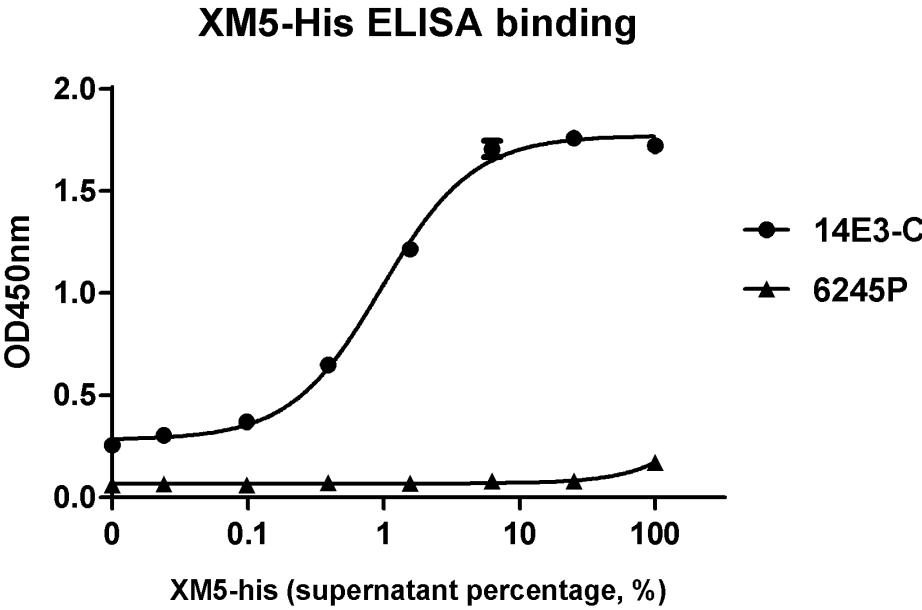
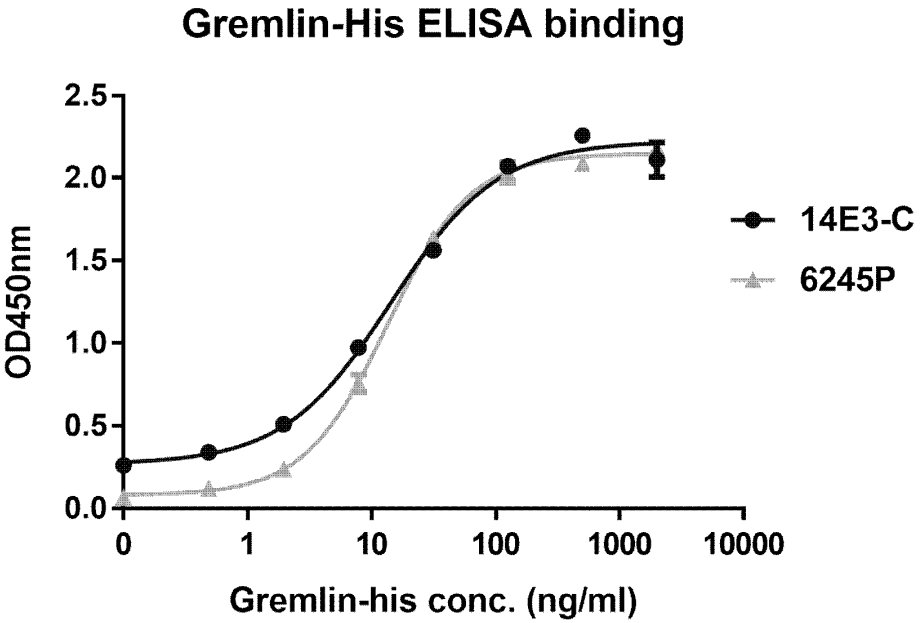


FIG. 10C

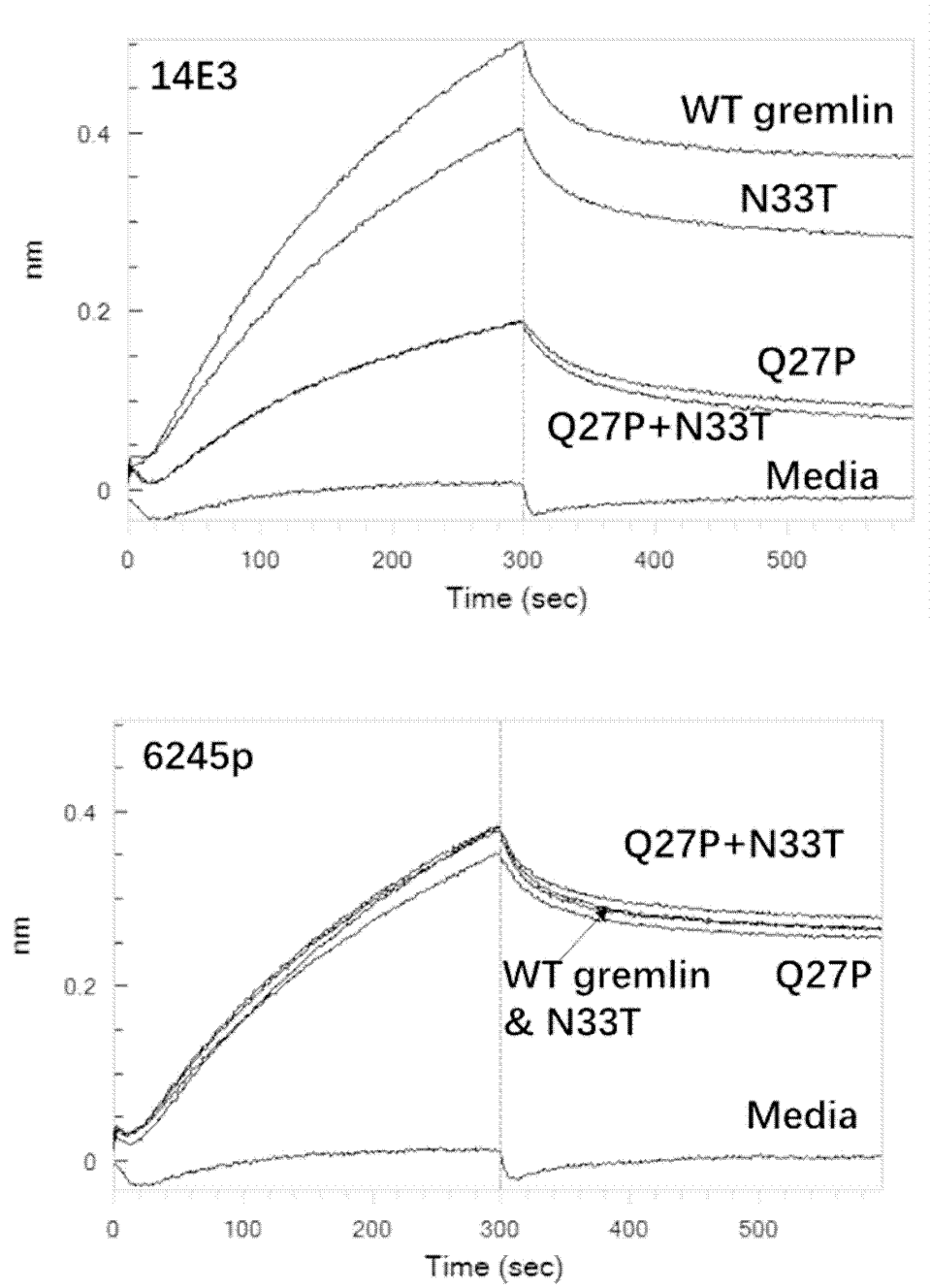


FIG. 10D

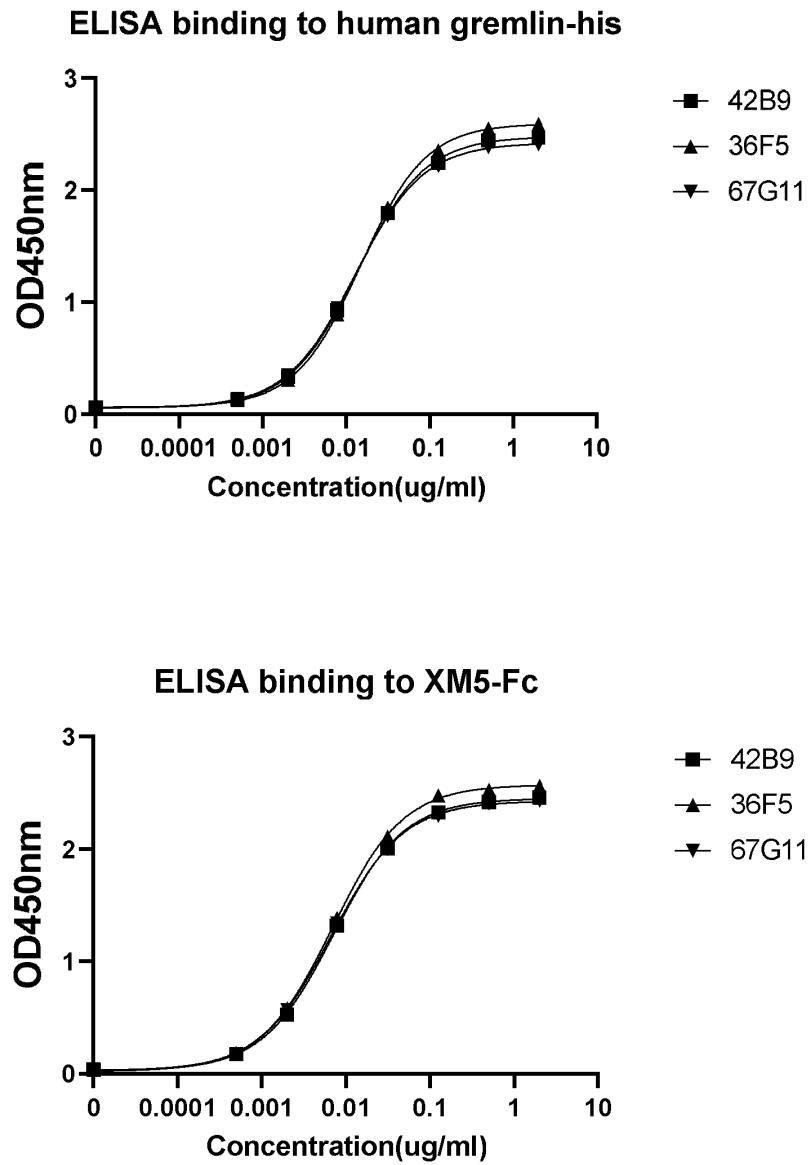


FIG. 10E

**EC50 of Binding to Human Gremlin-1 and XM5 (  $\mu$  g/ml)**

| Antibody | Gremlin | XM5      |
|----------|---------|----------|
| 42B9     | 0.01339 | 0.007121 |
| 36F5     | 0.01475 | 0.006918 |
| 67G11    | 0.01262 | 0.006646 |

FIG. 10F

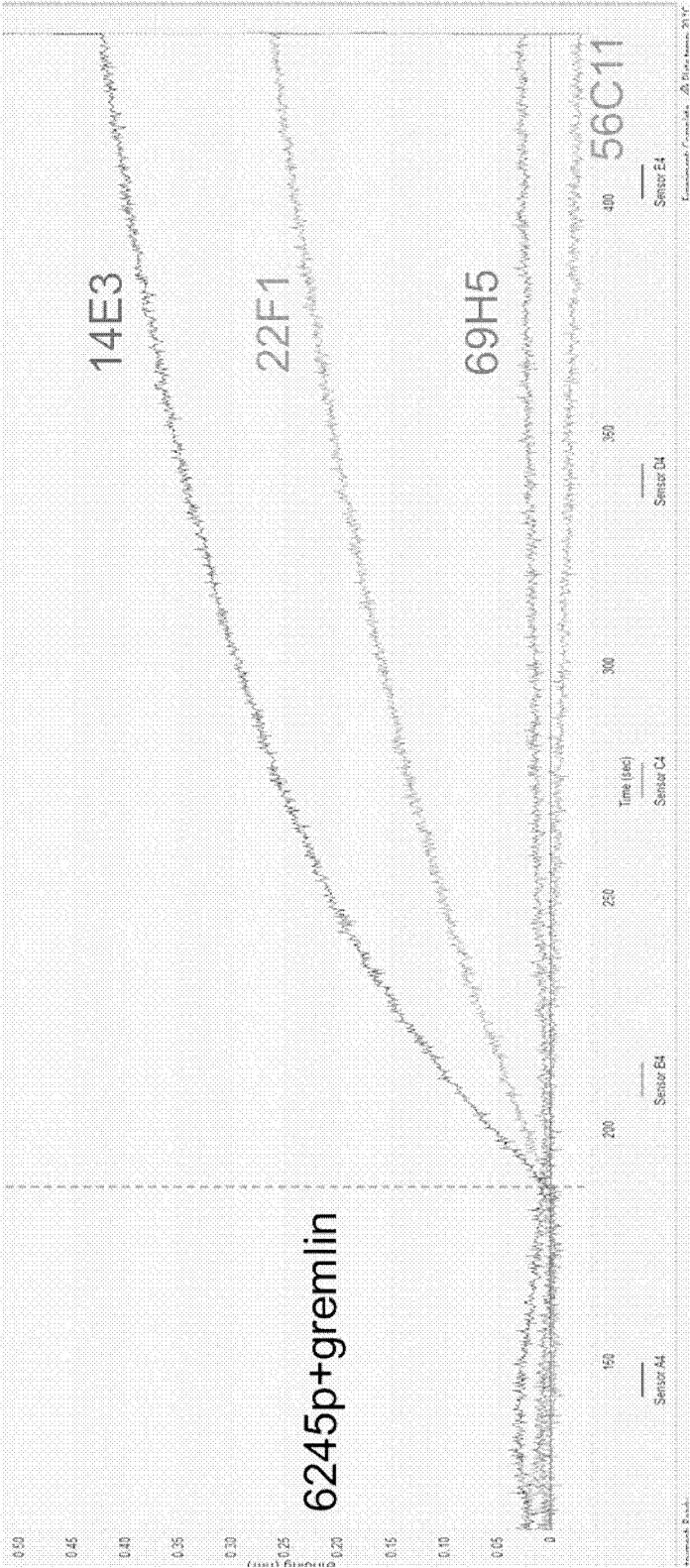


FIG. 11A

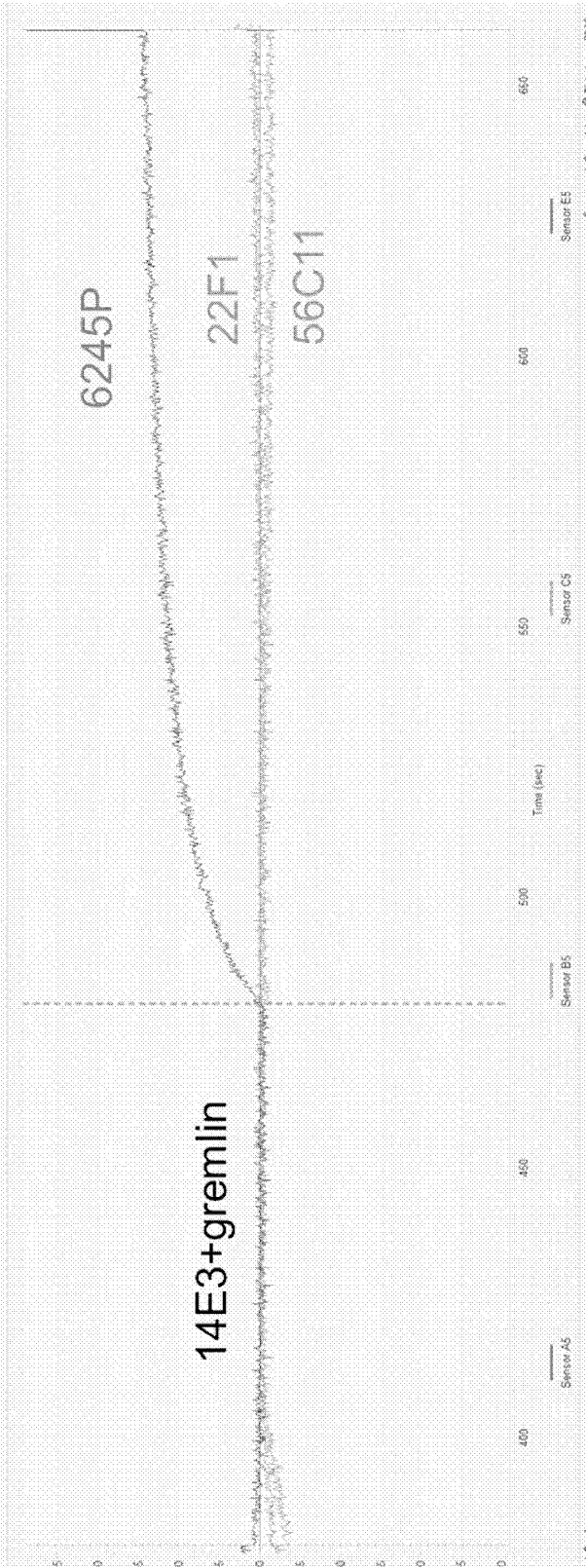


FIG. 11B

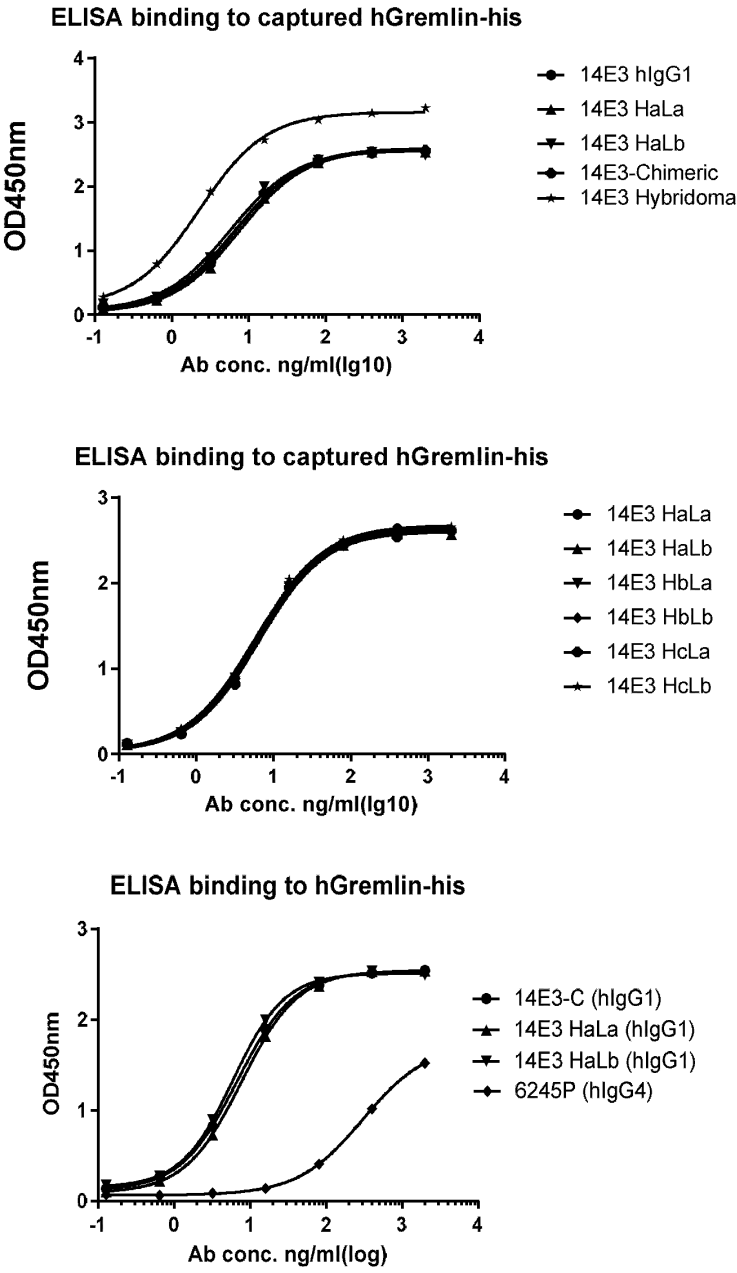
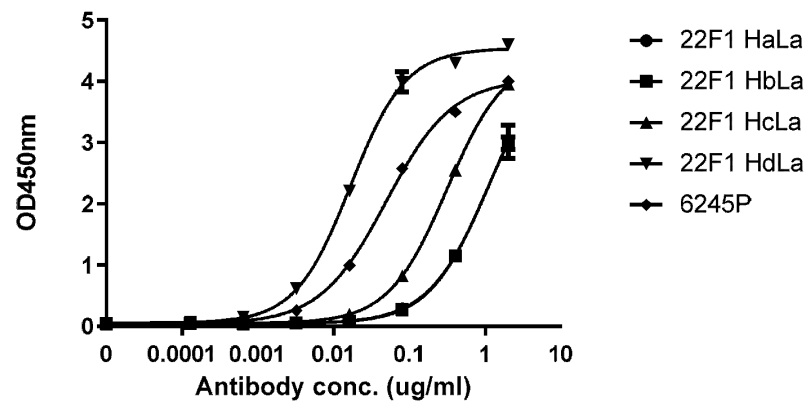


FIG. 12A

22F1 humanized antibodies binding with hGremlin-his



22F1 humanized antibodies binding with hGremlin-his

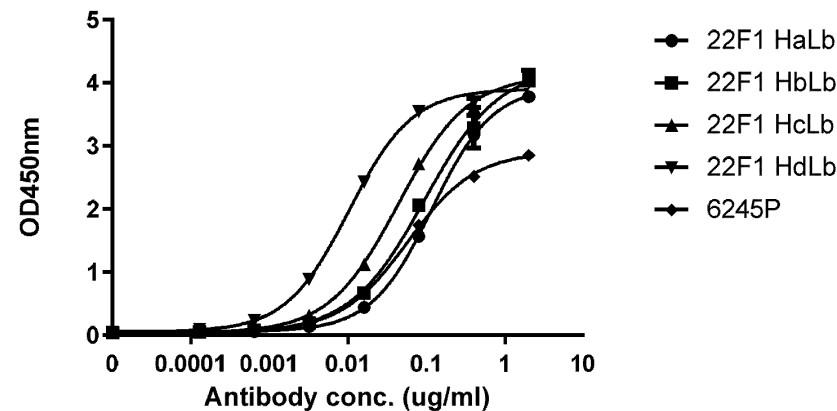
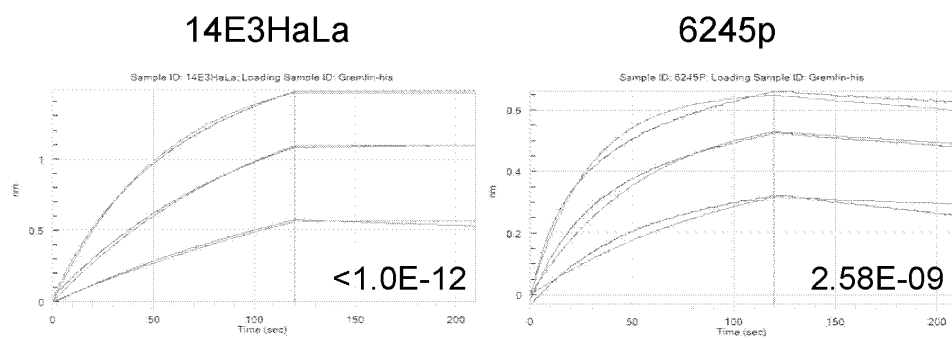


FIG. 12B

**EC50 of Binding to hGremlin-his**

| Antibody      |          | EC50 (ng/ml) |
|---------------|----------|--------------|
| 14E3 (hIgG1)  | HaLa     | 6.9          |
|               | HaLb     | 5.6          |
|               | HbLa     | 6.0          |
|               | HbLb     | 6.2          |
|               | HcLa     | 6.6          |
|               | HcLb     | 6.1          |
|               | chimeric | 6.8          |
| 22F1 (hIgG1)  | HaLa     | 1167.0       |
|               | HaLb     | 117.4        |
|               | HbLa     | 1038.0       |
|               | HbLb     | 94.0         |
|               | HcLa     | 312.2        |
|               | HcLb     | 43.5         |
|               | HdLa     | 16.7         |
|               | HdLb     | 10.3         |
| 6245P (hIgG4) |          | 57.5         |

FIG. 12C



| Loading(2ug/ml) | Sample ID | Conc. (nM) | Response | KD (M)   | kon(1/Ms) | kdis(1/s) |
|-----------------|-----------|------------|----------|----------|-----------|-----------|
| Gremlin-his     | 6245P     | 100        | 0.6488   | 2.58E-09 | 3.38E+05  | 8.70E-04  |
| Gremlin-his     | 6245P     | 50         | 0.5126   |          |           |           |
| Gremlin-his     | 6245P     | 25         | 0.3132   |          |           |           |
| Gremlin-his     | 14E3HaLa  | 100        | 1.4344   | <1.0E-12 | 1.82E+05  | <1.0E-07  |
| Gremlin-his     | 14E3HaLa  | 50         | 1.0436   |          |           |           |
| Gremlin-his     | 14E3HaLa  | 25         | 0.5469   |          |           |           |

FIG. 12D

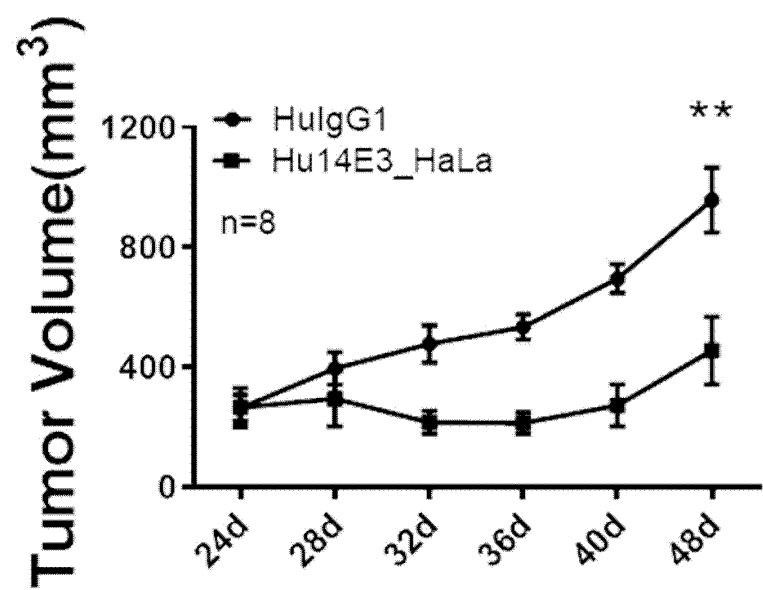


FIG. 13A

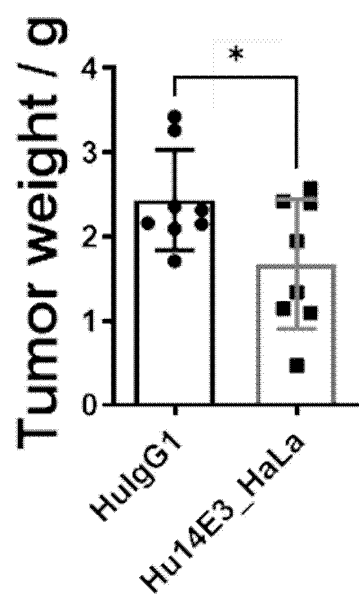


FIG. 13B

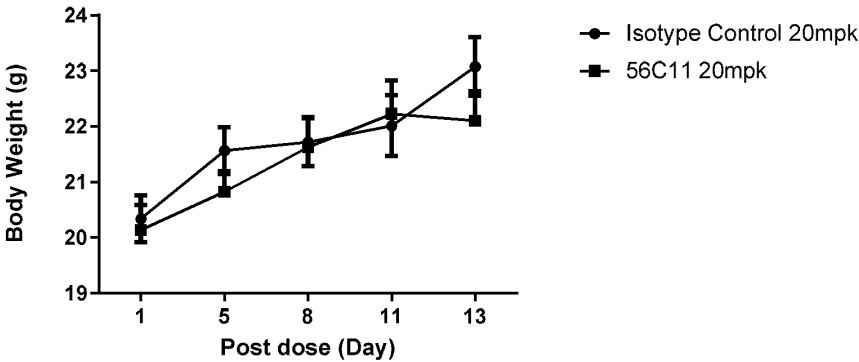
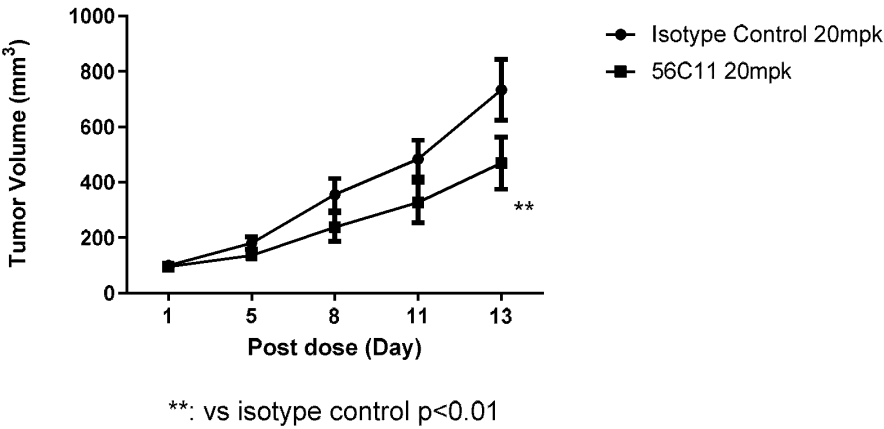


FIG. 14

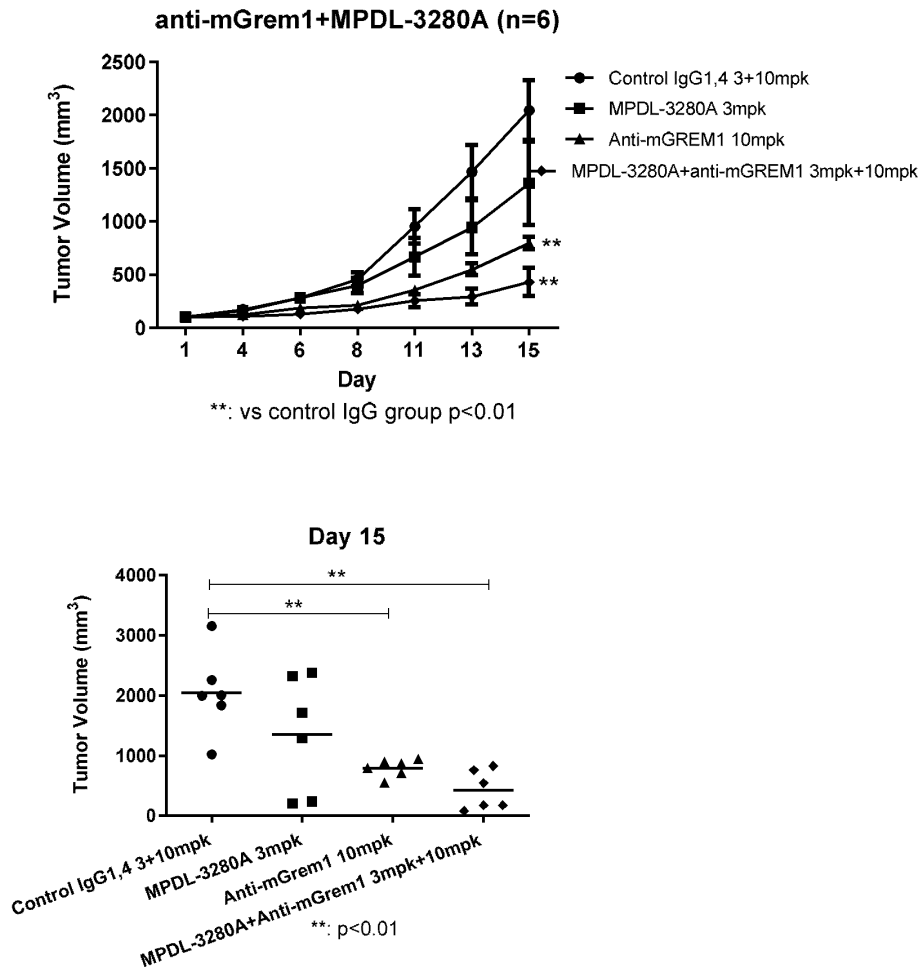


FIG. 15A

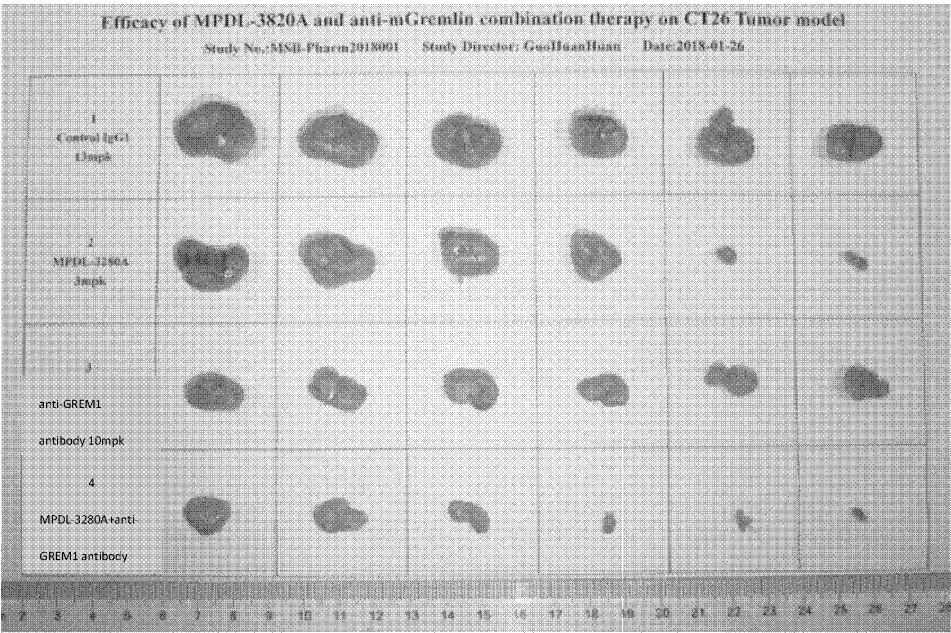
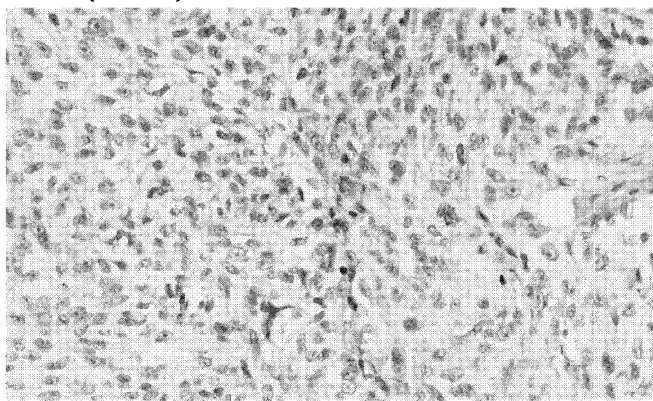


FIG. 15B

**PD-L1(22C3)**



**Gremlin(14E3)**

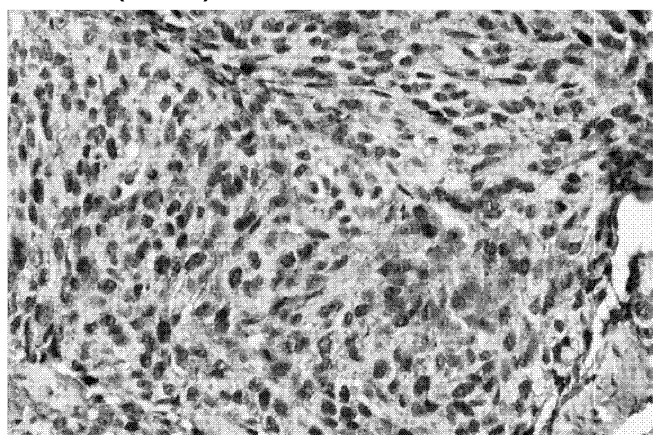
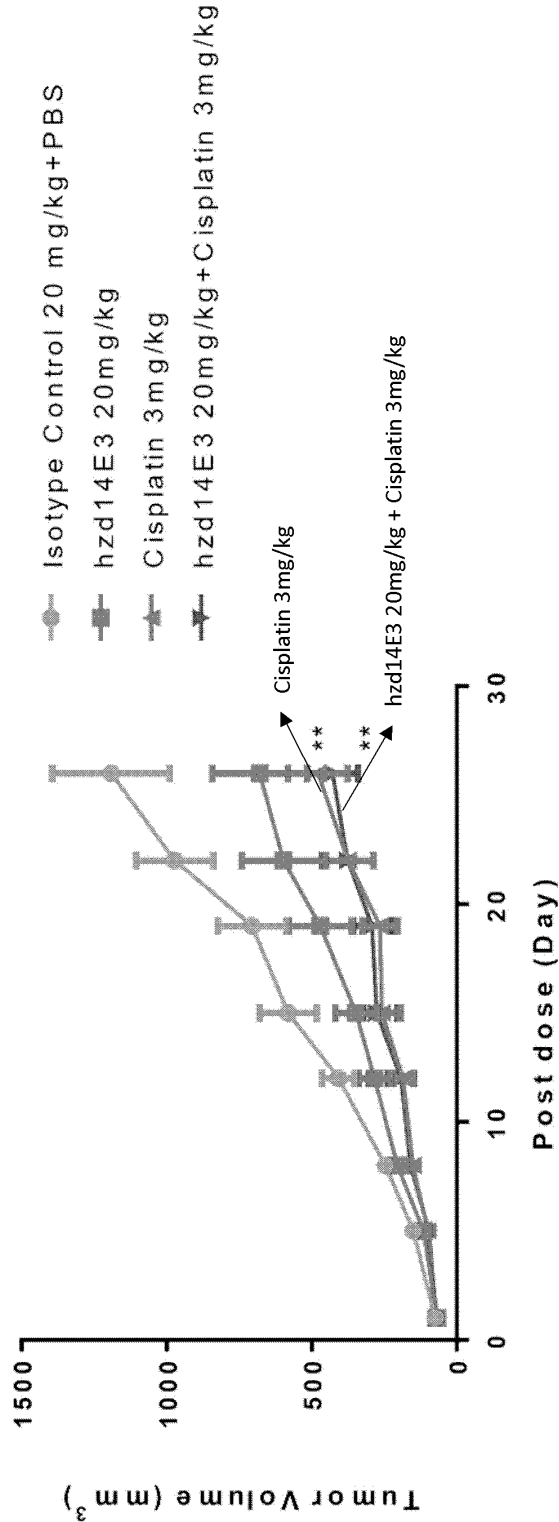


FIG. 16

Day 26 Tumor Growth Inhibition of hzd14E3 combination with Cisplatin on esophageal cancer PDX model

| Treatment<br>(n=8)                    | Tumor size<br>(mm <sup>3</sup> , mean±S.E.M.) | TGI (%) | p value vs.<br>Isotype control |
|---------------------------------------|-----------------------------------------------|---------|--------------------------------|
| Isotype control                       | 1192.40±203.22                                | /       | /                              |
| 20mg/kg+PBS                           |                                               |         |                                |
| hzd14E3 20mg/kg                       | 680.59±163.73                                 | 42.92   | 0.0701                         |
| Cisplatin 3mg/kg                      | 479.41±104.05                                 | 59.79   | 0.0075                         |
| hzd14E3 20mg/kg<br>+ Cisplatin 3mg/kg | 429.65±86.99                                  | 63.97   | 0.0039                         |

FIG. 17A



\*\* : vs Isotype Control+ PBS group p<0.01

FIG. 17B

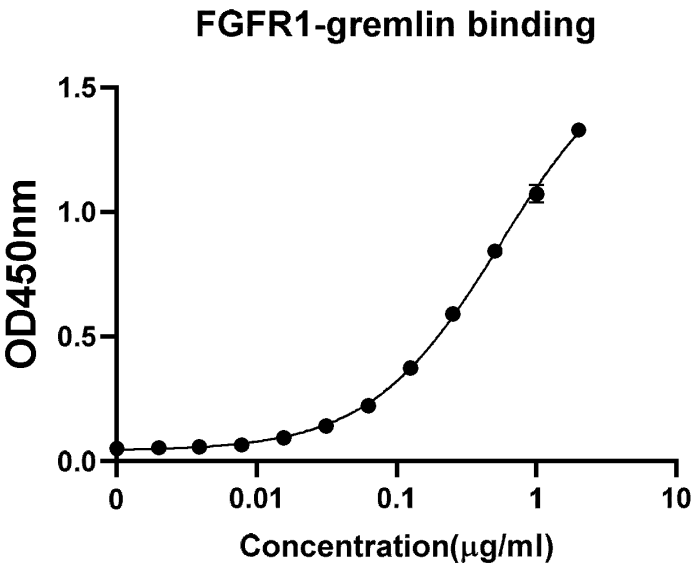
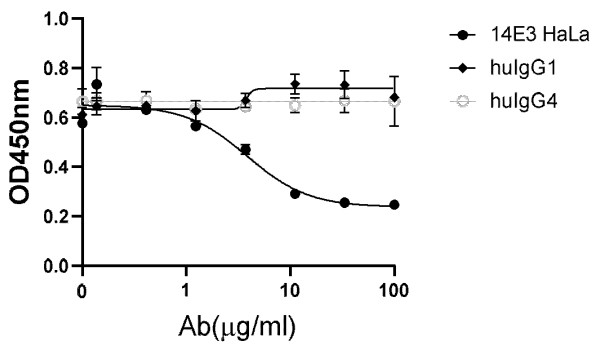
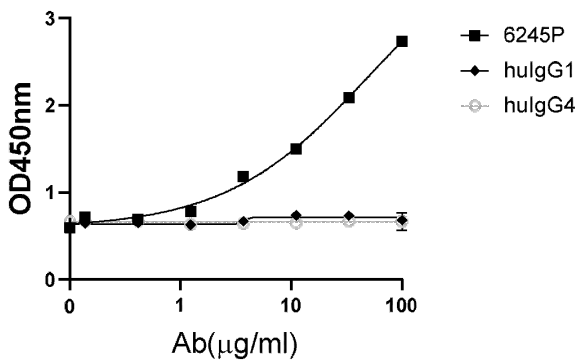


FIG. 18A

ELISA blocking gremlin binding to FGFR1



ELISA blocking gremlin binding to FGFR1



ELISA blocking gremlin binding to FGFR1

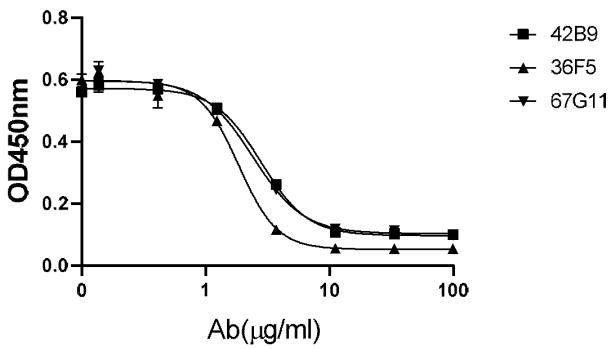


FIG. 18B

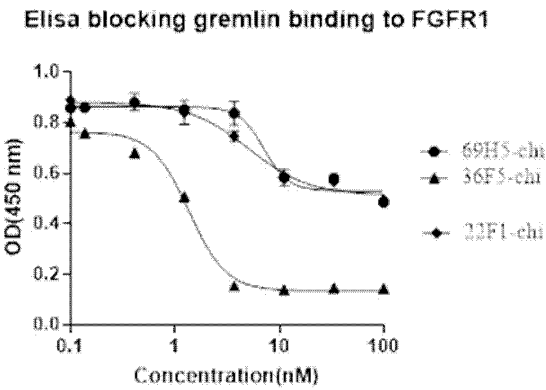


FIG. 18B (Continued)

IC<sub>50</sub> of Binding Ab blocking Human Gremlin-1 binding to FGFR1  
( $\mu$ g/ml)

| Clone#    | IC <sub>50</sub> ( $\mu$ g/ml) |
|-----------|--------------------------------|
| 42B9      | 2.795                          |
| 36F5      | 1.844                          |
| 67G11     | 2.411                          |
| 14E3 HaLa | 3.853                          |

FIG. 18C

ELISA Binding activity of hybridoma 36F5 to Gremlin-his and DAN-his

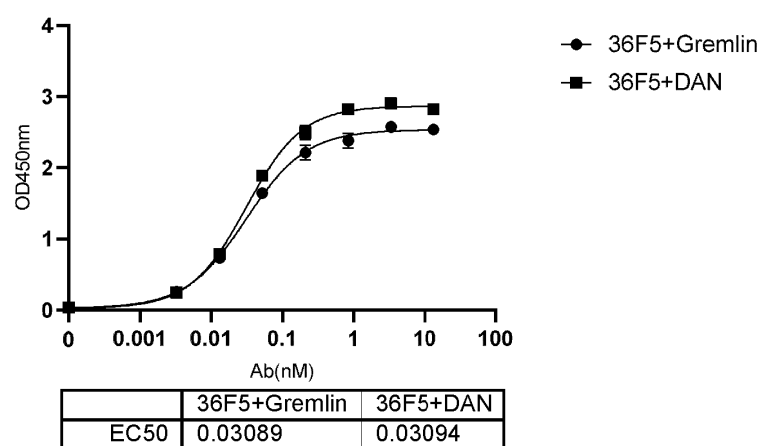


FIG. 19A

ELISA Binding activity of chiemric 36F5 to Gremlin-his and DAN-his

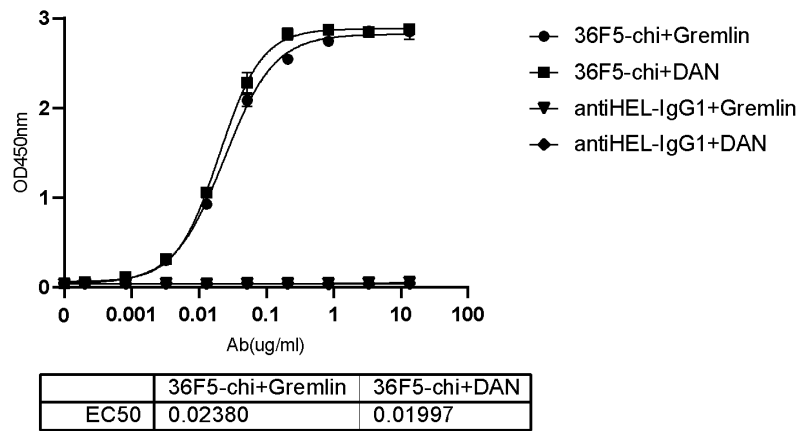


FIG. 19B

ELISA Binding activity of chimeric Abs to human Gremlin-his and DAN-his

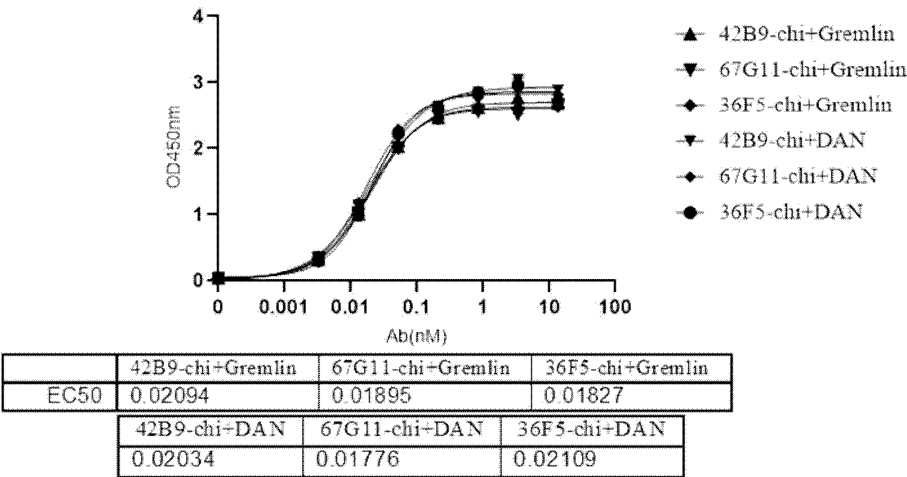


FIG. 20A

Anti-gremlin blocking BMP4 binding to DAN protein

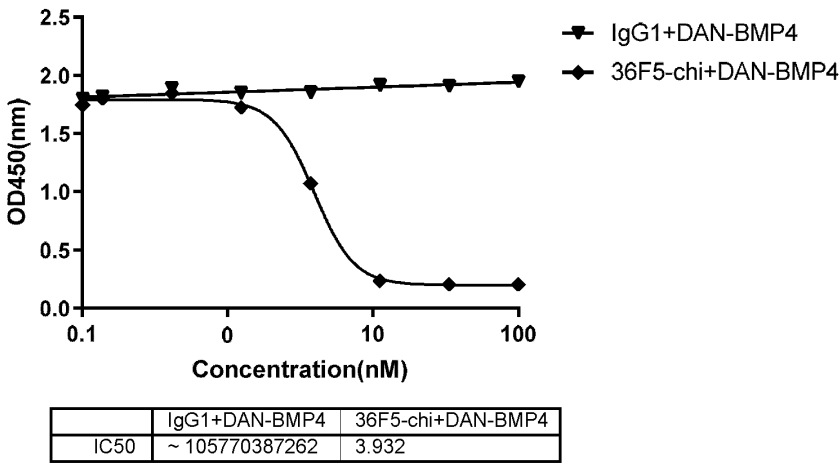


FIG. 20A (Continued)

Anti-gremlin blocking BMP2 binding to DAN protein

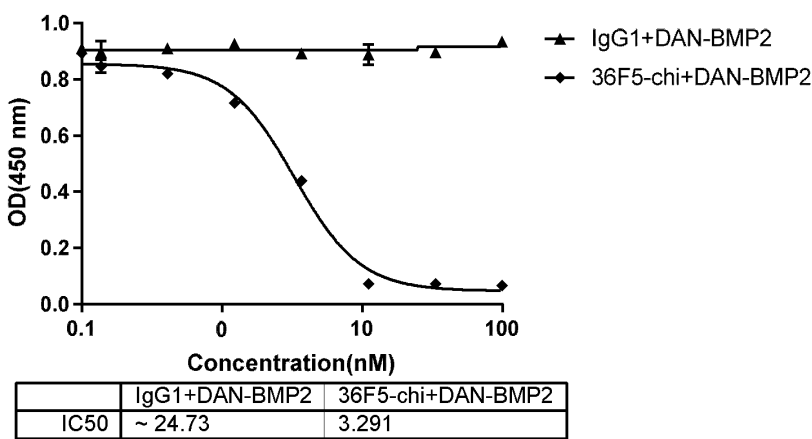


FIG. 20B

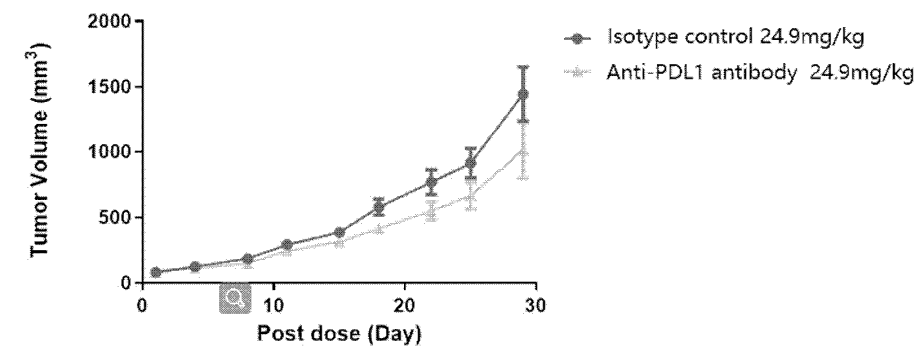


FIG. 21A

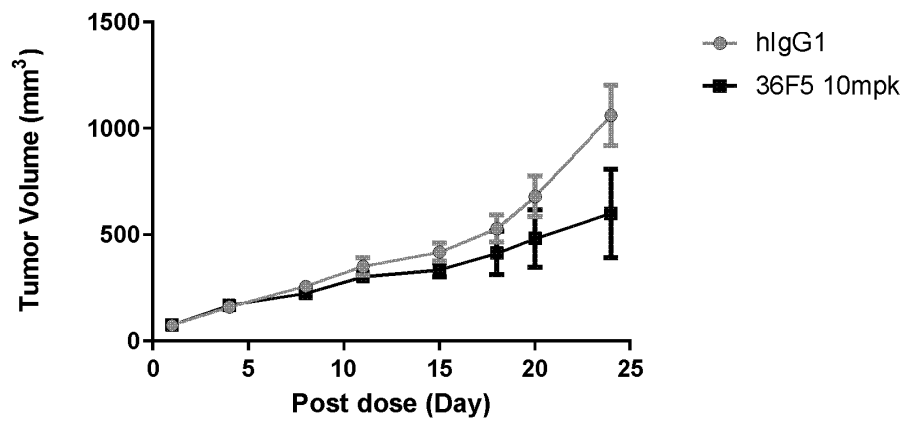


FIG. 21B

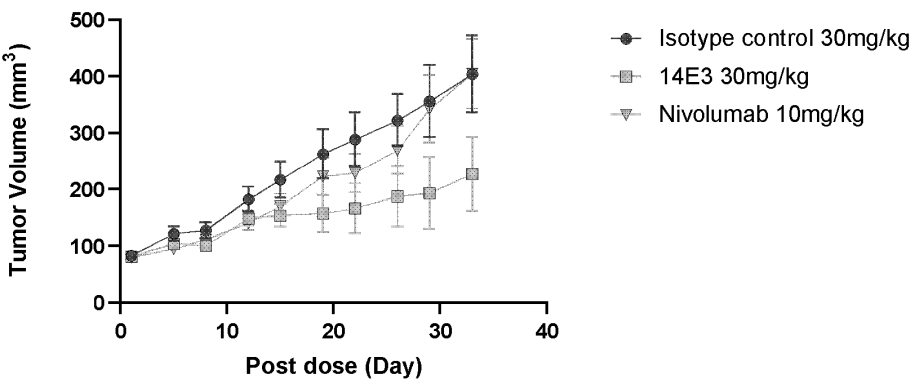


FIG. 22A

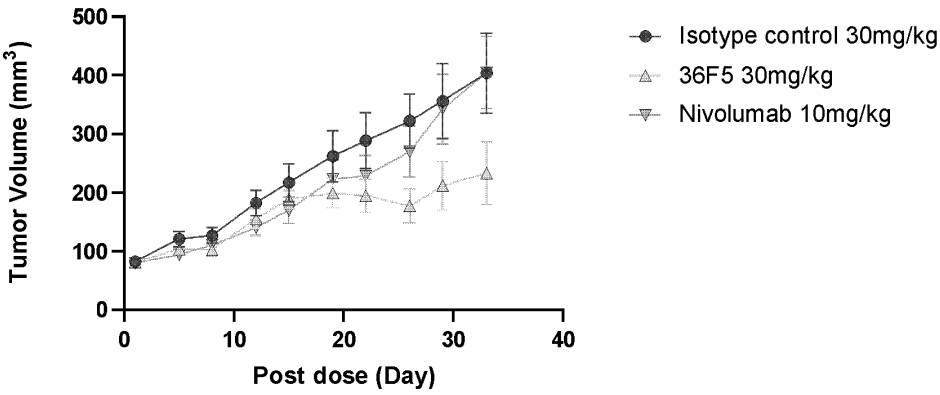


FIG. 22B

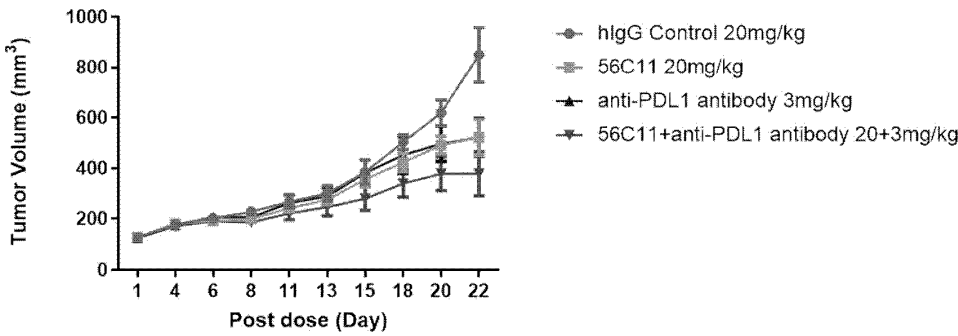


FIG. 23