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(12) **United States Patent**  
**Wiegand et al.**

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- (54) **USE OF VEGF INHIBITORS FOR TREATMENT OF EYE DISORDERS**
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US 2008/0220004 A1 Sep. 11, 2008
- Related U.S. Application Data**
- (60) Division of application No. 11/218,234, filed on Sep. 1, 2005, now Pat. No. 7,303,747, which is a continuation-in-part of application No. 11/089,803, filed on Mar. 25, 2005, now Pat. No. 7,306,799, which is a continuation-in-part of application No. 10/988,243, filed on Nov. 12, 2004, now Pat. No. 7,303,746, which is a continuation-in-part of application No. 10/009,852, filed as application No. PCT/US00/14142 on May 23, 2000, now Pat. No. 7,070,959, said application No. 11/218,234 is a continuation-in-part of application No. 10/880,021, filed on Jun. 29, 2004, now Pat. No. 7,279,159, which is a continuation-in-part of application No. 10/609,775, filed on Jun. 30, 2003, now Pat. No. 7,087,411.
- (60) Provisional application No. 60/138,133, filed on Jun. 8, 1999.
- (51) **Int. Cl.**  
**A61K 38/18** (2006.01)  
**C07K 14/71** (2006.01)  
**C12N 15/62** (2006.01)

- (52) **U.S. Cl.** ..... **424/134.1**; 424/192.1; 514/2; 514/12; 530/350; 536/23.4
- (58) **Field of Classification Search** ..... None  
See application file for complete search history.

- (56) **References Cited**  
U.S. PATENT DOCUMENTS  
6,100,071 A 8/2000 Davis-Smyth et al.  
6,897,294 B2 5/2005 Davis-Smyth et al.  
2005/0281831 A1 12/2005 Davis-Smyth et al.

- FOREIGN PATENT DOCUMENTS  
WO WO97/44453 11/1997  
WO WO98/13071 4/1998  
WO WO99/03996 1/1999

- OTHER PUBLICATIONS  
Terman, B.I., et al., (1991) Oncogene 6:1677-1683.  
Terman, B.I., et al., (1992) Biochem. Biophys. Res. Comm. 187(3):1579-1586.  
Davis-Smyth, T., et al., (1996) The EMBO Journal 15(18):4919-4927.  
Holash, J., et al., (2002) PNAS 99(17):11393-11398.  
Heidaran, M.A., et al., (1990) J. Bio. Chem. 265(31):18741-18744.  
Cunningham, S.A., et al., (1997) Biochem. Biophys. Res. Comm. 231:596-599.  
Fuh, G., et al., (1998) J. Bio. Chem. 273(18):11197-11204.  
Wiesmann, C., et al., (1997) Cell 91:695-704.  
Barleon, B., et al., (1997) J. Bio. Chem. 272(16):10382-10388.  
Davis-Smyth, T., et al., (1998) J. Bio. Chem. 273(6):3216-3222.

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- (57) **ABSTRACT**  
Modified chimeric polypeptides with improved pharmacokinetics and improved tissue penetration are disclosed useful for treating eye disorders, including age-related macular degeneration and diabetic retinopathy.

**15 Claims, 11 Drawing Sheets**

**Mylan v. Regeneron**  
**IPR2021-00880**  
**U.S. Pat. 9,669,069**  
**Exhibit 2035**

Figure 1

Binding Stoichiometry of hVEGF165 to Flt1D2Flk1D3. FcΔC1(a) & VEGFR1R2- FcΔC1(a)		
hVEGF165 (nM)	VEGF/Flt1D2Flk1D3.FcΔC1(a)	VEGF/VEGFR1R2- FcΔC1(a)
1	0.93	0.98
10	0.97	0.94
50	1	0.99
Average ± StDev	0.96 ± 0.03	0.97 ± 0.02

Figure 2

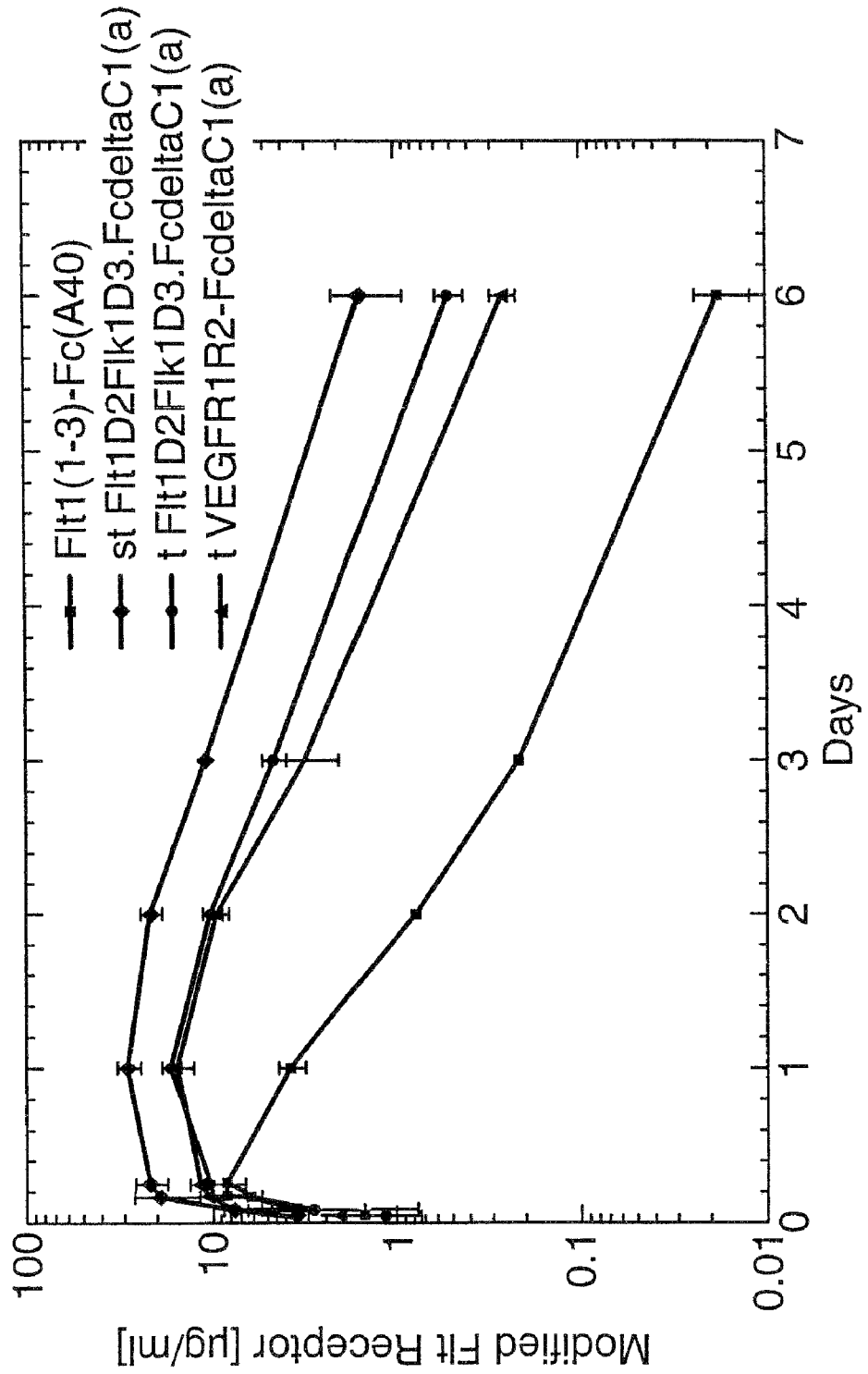


Figure 3

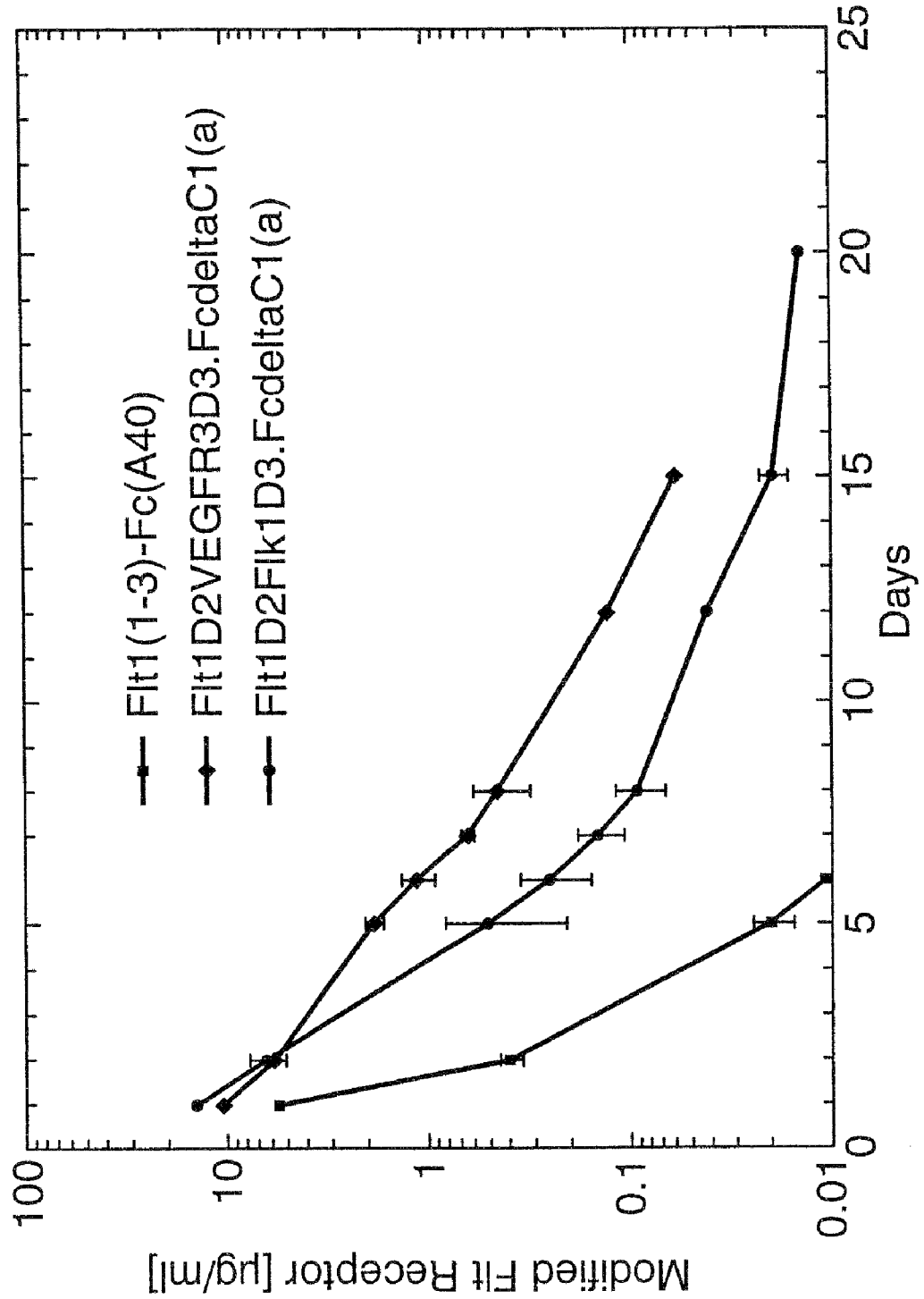
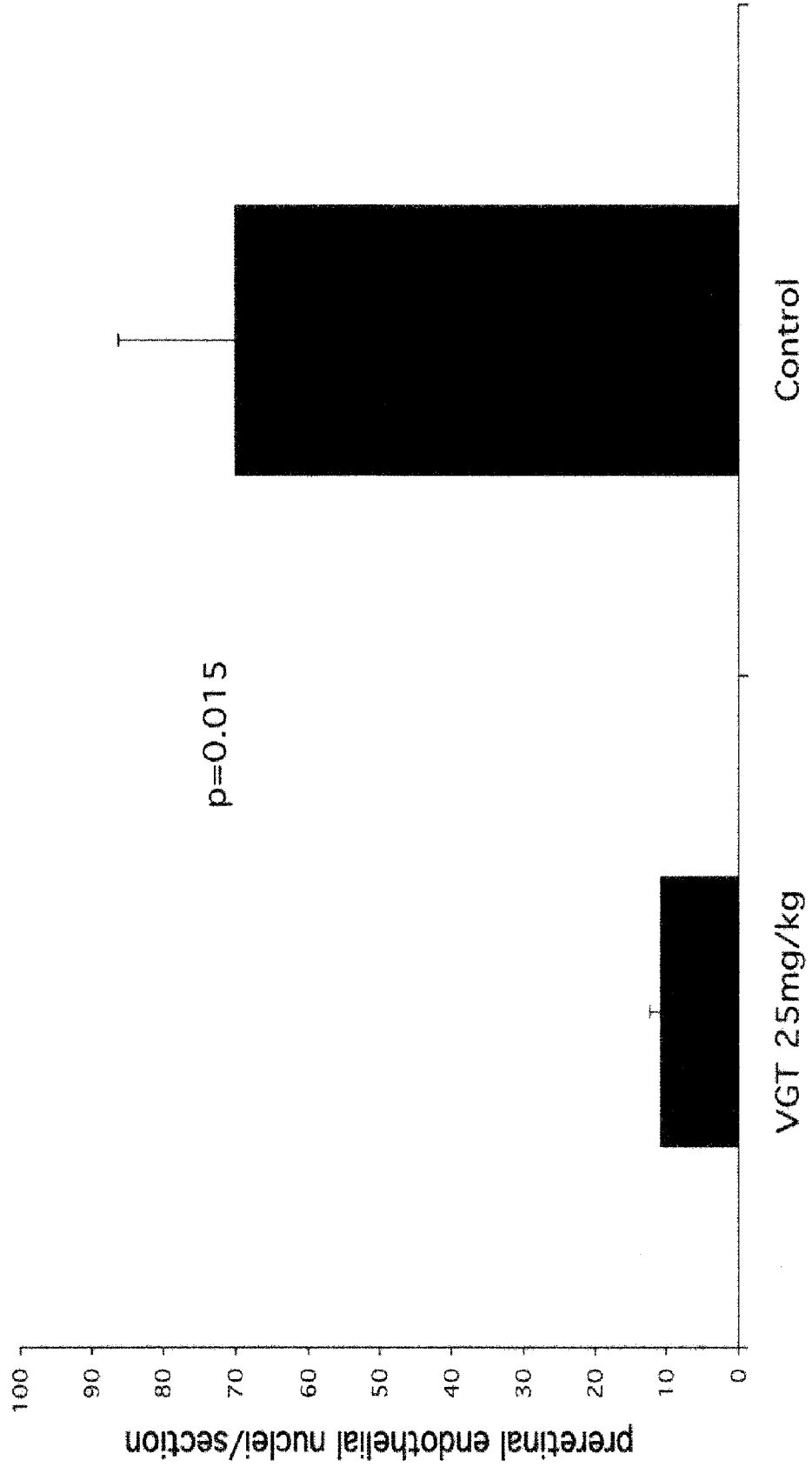


Figure 4



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