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Papadopoulos et al.

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(54) **MODIFIED CHIMERIC POLYPEPTIDES WITH IMPROVED PHARMACOKINETIC PROPERTIES**

WO WO98/13071 4/1998
WO WO99/03996 1/1999

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OTHER PUBLICATIONS

Terman, B. I., et al, "Identification of a new endothelial cell growth factor receptor tyrosine kinase", *Oncogene* (1991) 6:1677-1683.
Terman, B.I., et al, "Identification of the KDR tyrosine kinase as a receptor for vascular endothelial cell growth factor", *Biochem Biophys Res Comm* (1992) 187(3):1579-1586.
Tsutsumi, Y., et al, "PEGylation of interleukin-6 effectively increases its thrombopoietic potency", *Thrombosis and Haemostasis* (1997) 77(1):168-173.
Dunca, R. and Spreafico, F., "Polymer Conjugates", *Drug Delivery Systems* (1994) 27(4):290-306.
Hileman, R.E., et al., "Glycosaminoglycan-protein interactions: definitions of consensus sites in glycosaminoglycan binding proteins", *BioEssays* (1998) 20:156-167.
deVries, Carlie, et al., "The *fms*-like tyrosine kinase, a receptor for vascular endothelial growth factor", *Science* (1992) 225:989-991.
Sharifi, J., et al., "Improving monoclonal antibody pharmacokinetics via chemical modification", *Quart J Nucl Med* (1998) 42:242-249.
Jensen-Pippo, K.E., et al., "Enteral bioavailability of human granulocyte colony stimulating factor conjugated with poly(ethylene glycol)", (1996) *Pharm Res* 13(1):102-107.
Tanaka, K., et al., "Characterization of the extracellular domain in vascular endothelial growth factor receptor-1 (Flt-1 Tyrosine kinase)", (1997) *Jpn J Cancer Res* 88:867-876.
Yang, J.C., et al., "The use of polyethylene glycol-modified interleukin-2 (PEG-IL-2) in the treatment of patients with metastatic renal cell carcinoma and melanoma", (1995) *Cancer* 76(4): 687-694.
Davis-Smyth, T., et al., 1996, "The second immunoglobulin-like domain of the VEGF tyrosine kinase receptor Flt-1 determines ligand binding and may initiate a signal transduction cascade", *The EMBO Journal* 15(18):4919-4927.

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 489 days.

This patent is subject to a terminal disclaimer.

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(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

5,712,380 A 1/1998 Kendall et al.
6,011,003 A 1/2000 Charnock-Jones et al.
6,100,071 A * 8/2000 Davis-Smyth et al. 435/69.7
2005/0043236 A1 * 2/2005 Daly et al. 514/12
2006/0058234 A1 * 3/2006 Daly et al. 514/12

FOREIGN PATENT DOCUMENTS

WO WO97/44453 11/1997

* cited by examiner

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(57) **ABSTRACT**

Modified chimeric polypeptides with improved pharmacokinetics are disclosed. Specifically, modified chimeric Flt1 receptor polypeptides that have been modified in such a way as to improve their pharmacokinetic profile are disclosed. Also disclosed are methods of making and using the modified polypeptides including but not limited to using the modified polypeptides to decrease or inhibit plasma leakage and/or vascular permeability in a mammal.

7 Claims, 55 Drawing Sheets

Fig.1.

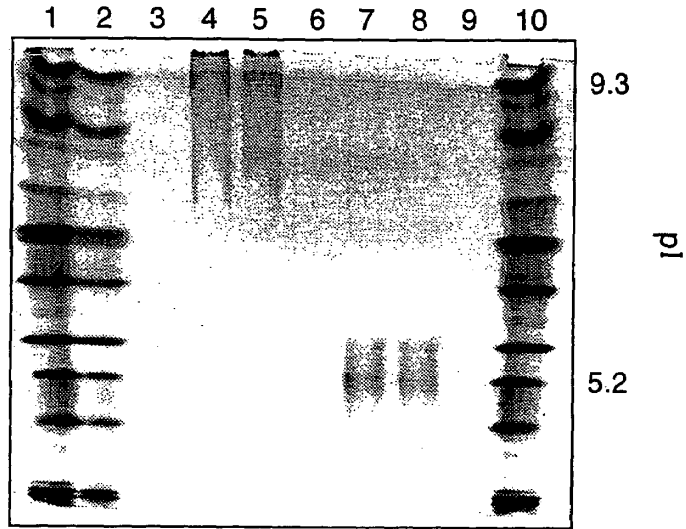


Fig.2.

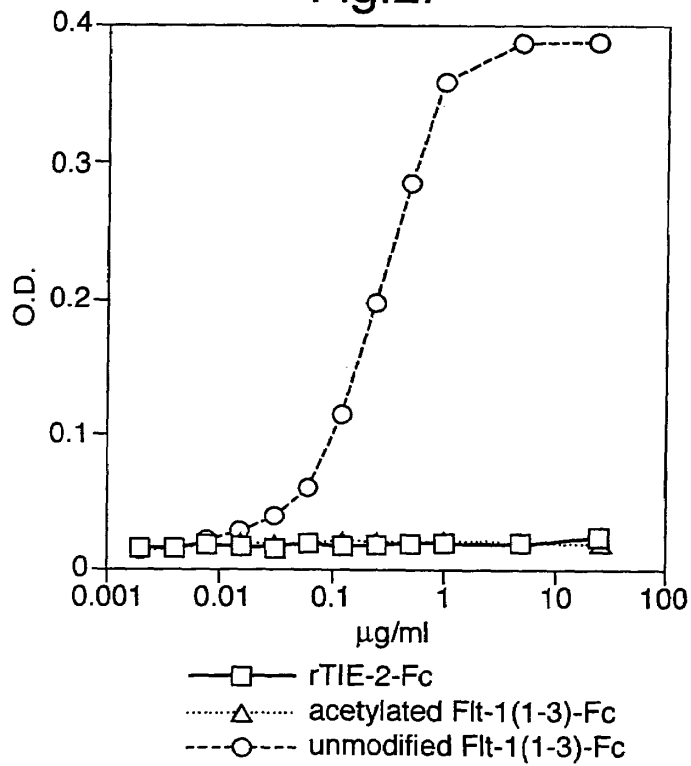
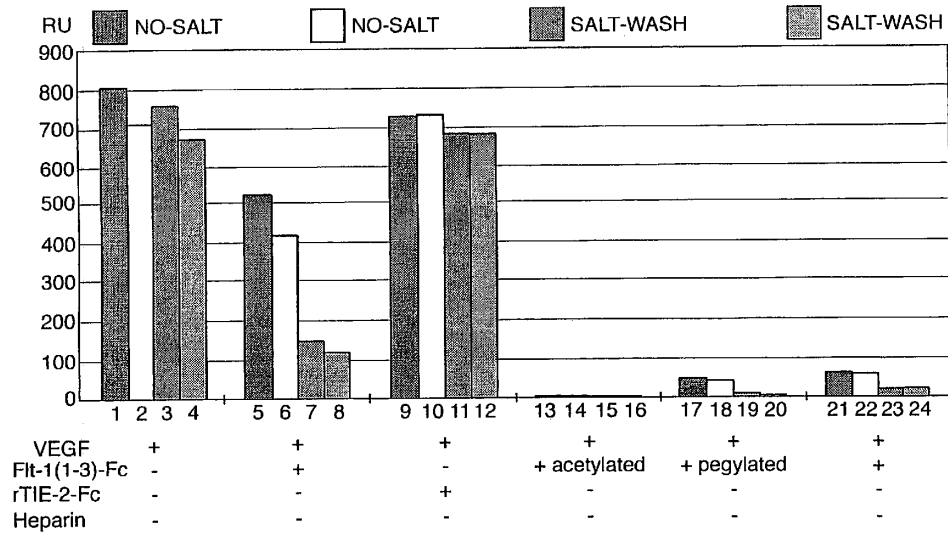


Fig.3.



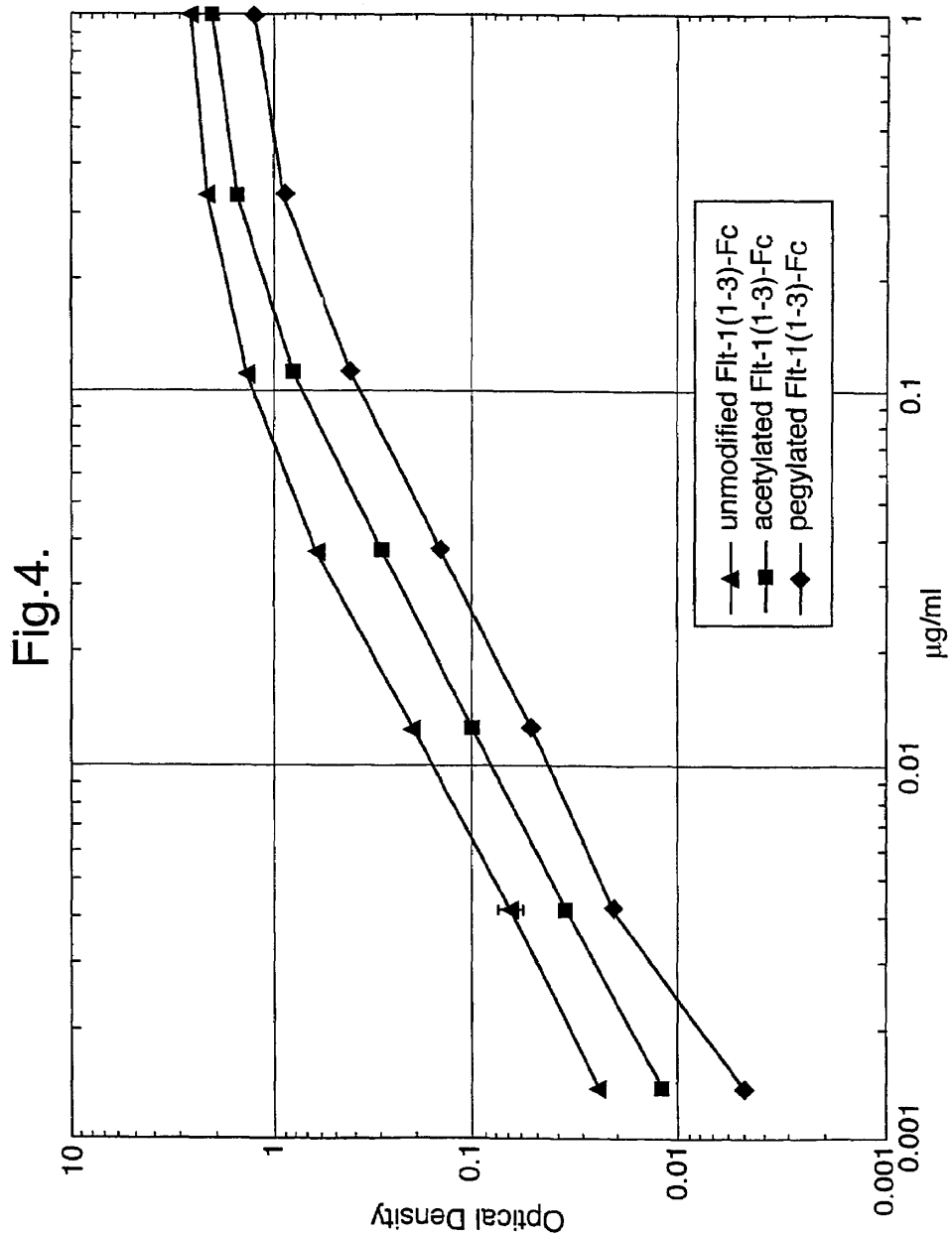
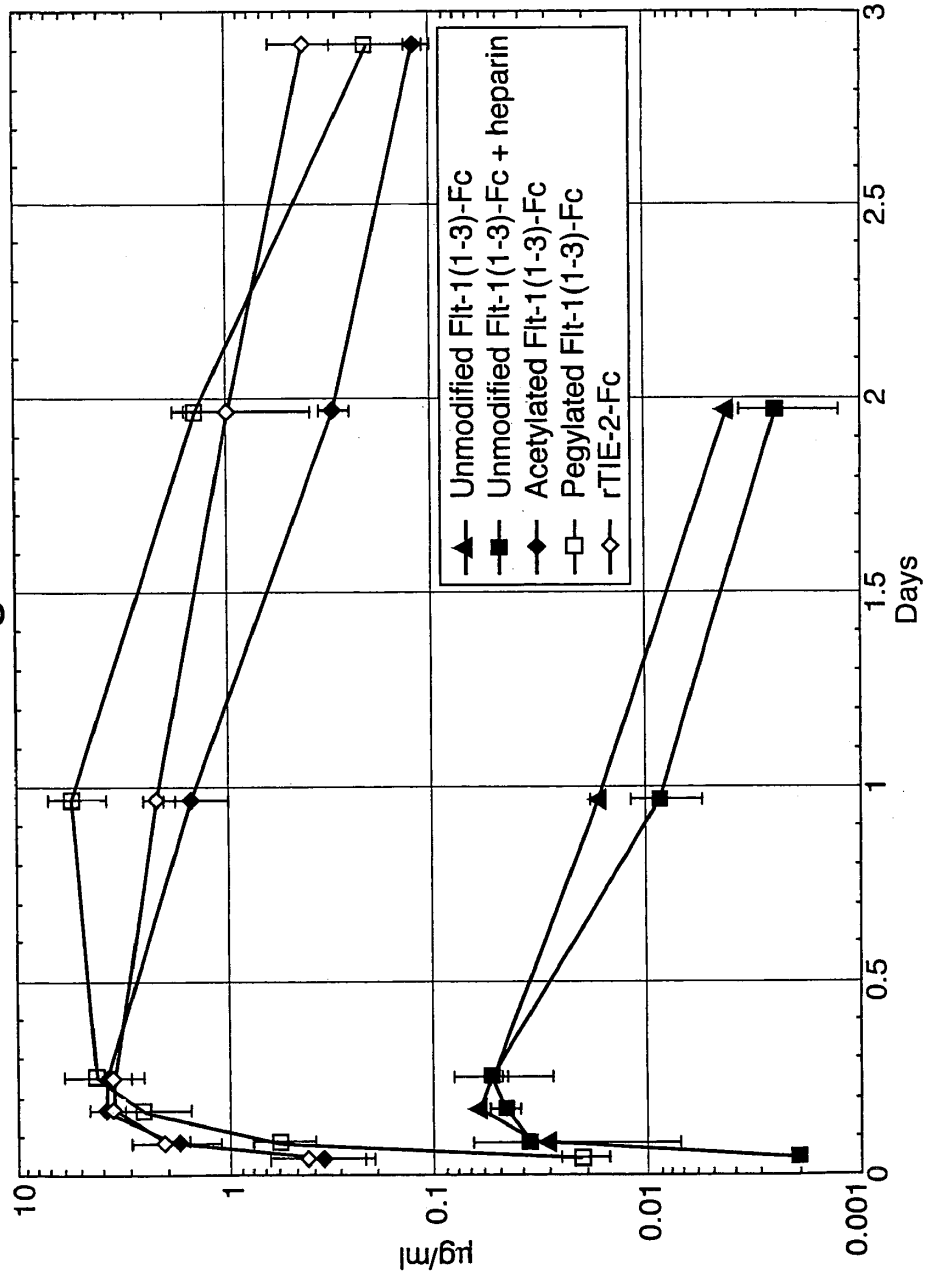


Fig.5.



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