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

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patent is extended or adjusted under 35
U.S.C. 154(b) by 489 days.

This patent is subject to a terminal dis-
claimer.

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(51) **Int. Cl.**

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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

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 pro-
teins", *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., "Enterol bioavailability of human granu-
locyte 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.

* cited by examiner

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(57) **ABSTRACT**

Modified chimeric polypeptides with improved pharmaco-
kinetics 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 modi-
fied 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.

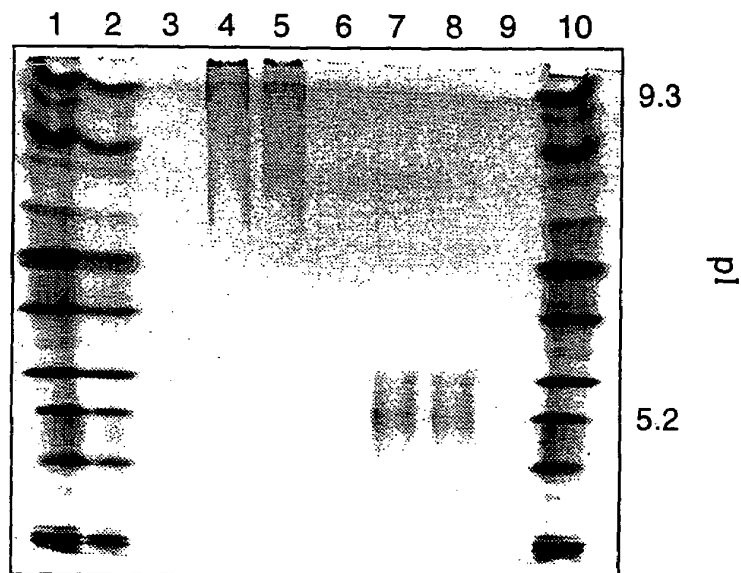


Fig. 2.

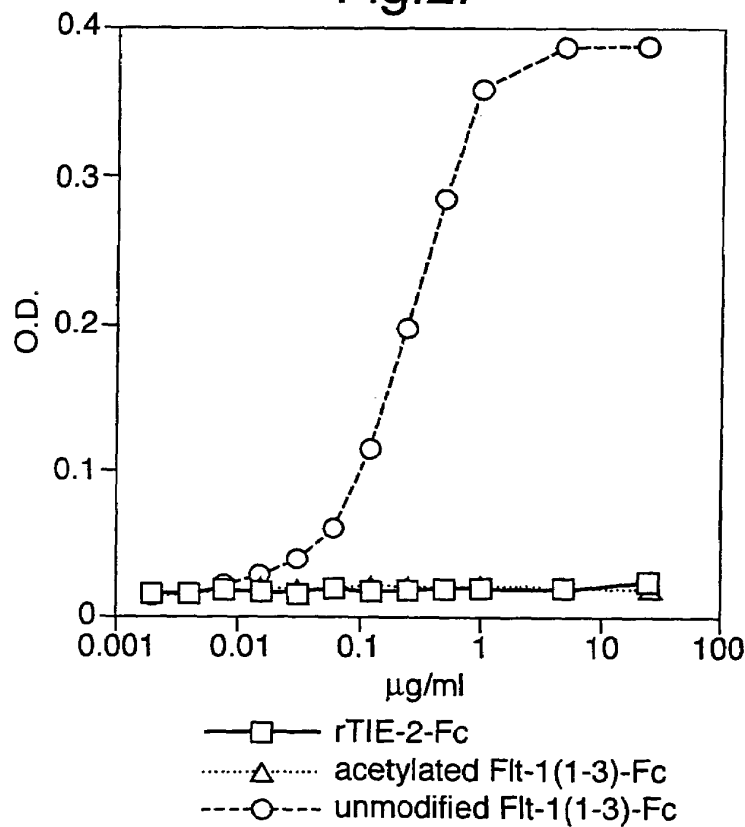
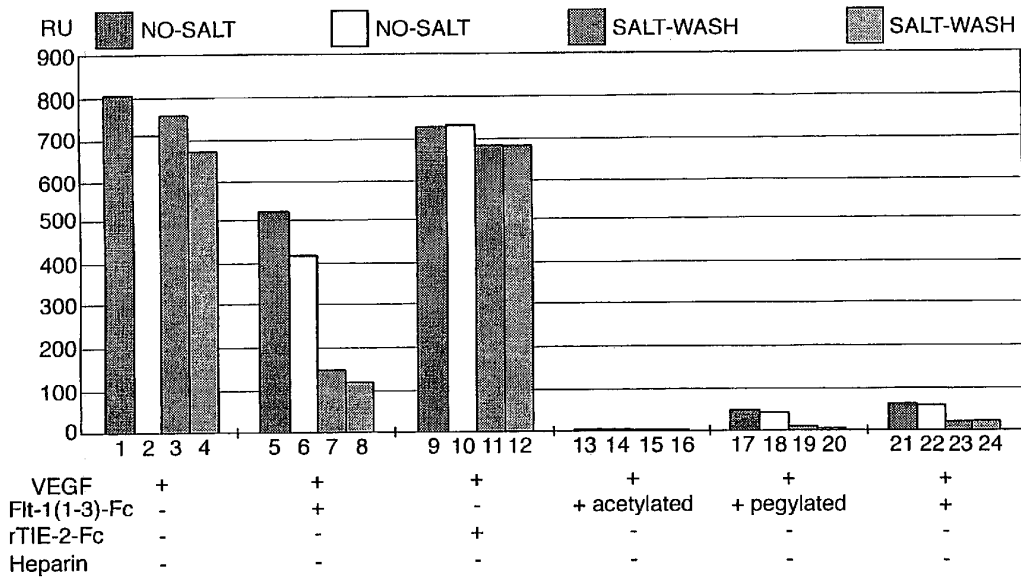


Fig.3.



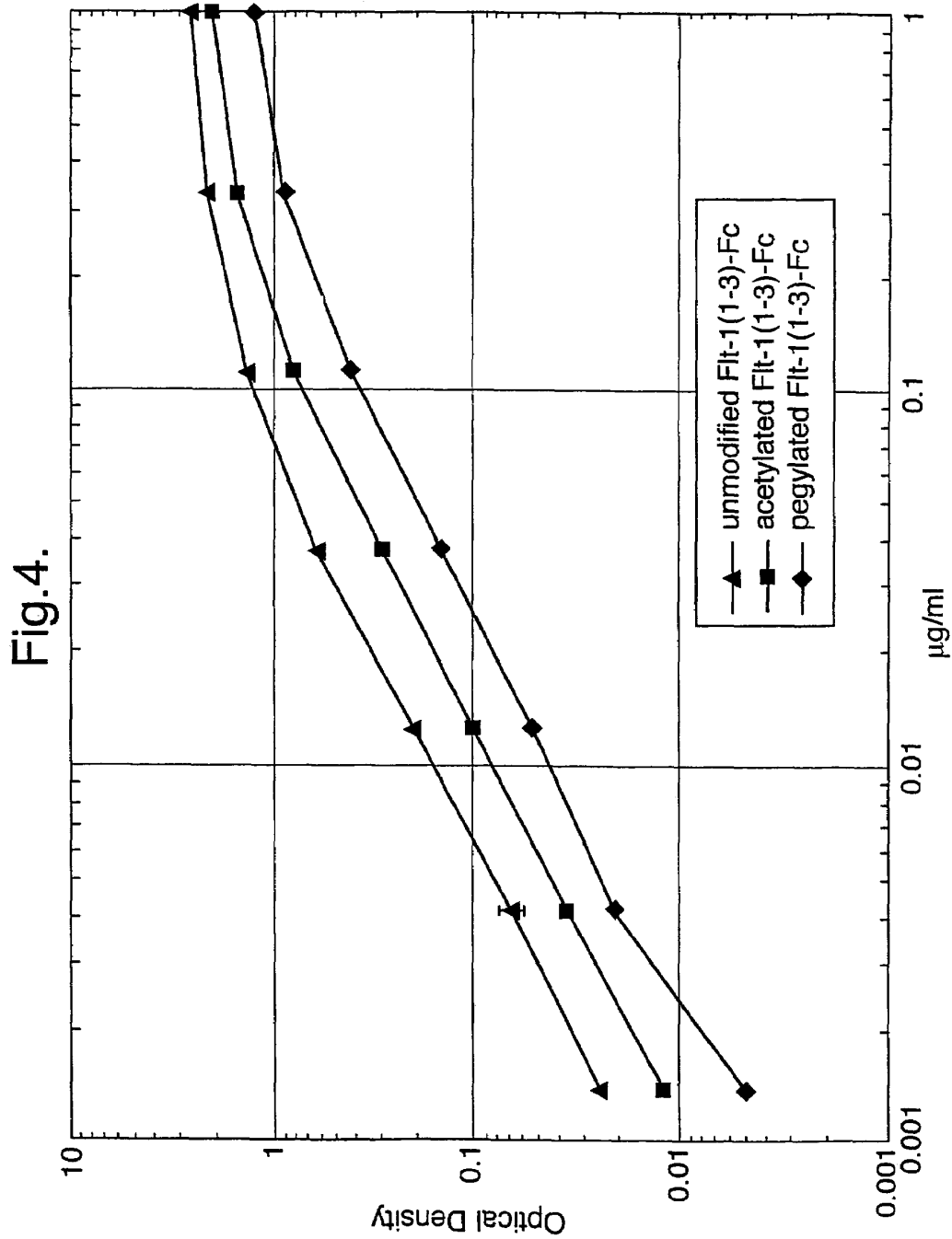
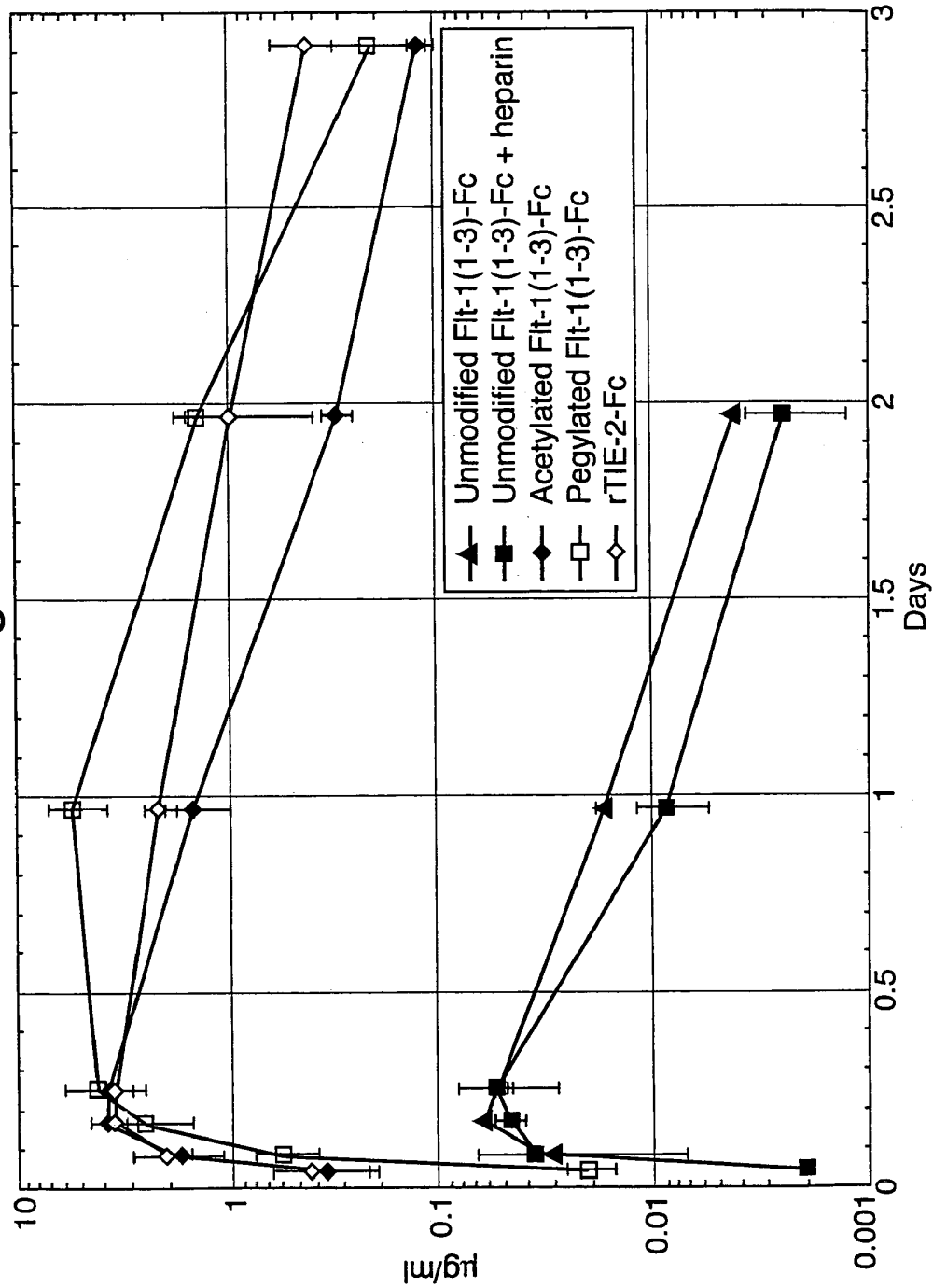


Fig.5.



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