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(12) United States Patent

Papadopoulos et al.

(54) MODIFIED CHIMERIC POLYPEPTIDES WITH IMPROVED PHARMACOKINETIC PROPERTIES AND METHODS OF USING THEREOF

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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.

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- (51) Int. Cl.

A61K 38/18	(2006.01)
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C12N 15/62	(2006.01)

- (58) **Field of Classification Search** None See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,712,380	Α	1/1998	Kendall et al.	
6,011,003	Α	1/2000	Charnock-Jones et al.	
2004/0265309	A1 $*$	12/2004	Kandel et al	424/145.1
2005/0175610	A1 $*$	8/2005	Wiegand et al	424/145.1
2005/0260203	A1 $*$	11/2005	Wiegand et al	424/145.1
2005/0281822	A1 $*$	12/2005	Cedarbaum et al	424/145.1
2005/0281831	A1 $*$	12/2005	Davis-Smyth et al	424/178.1
2006/0210566	A1 $*$	9/2006	Holash et al	424/145.1
2007/0037748	A1*	2/2007	Stahl et al.	514/12

FOREIGN PATENT DOCUMENTS

WO	WO97/44453	11/1997
WO	WO98/13071	4/1998
WO	WO99/03996	1/1999

(10) Patent No.: US 7,374,758 B2 (45) Date of Patent: *May 20, 2008

OTHER PUBLICATIONS

Wells, J.A. (1990). Additivity of mutational effects in proteins. Biochemistry. 29(37):8509-8517.*

Ngo et al. (1994). Computational complexity, protein structure prediction, and the Levinthal paradox. In Merz and Le Grand (Eds.) The Protein Folding Problem and Tertiary Structure Prediction. Birkhauser:Boston, pp. 491-495.*

Herley et al. (1999). Characterization of the VEGF binding site on the Flt-1 receptor. Biochemical and Biophysical Research Communications. 262:731-738.*

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.

de Vries, Carlie, et al., "The *fins*-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.

* cited by examiner

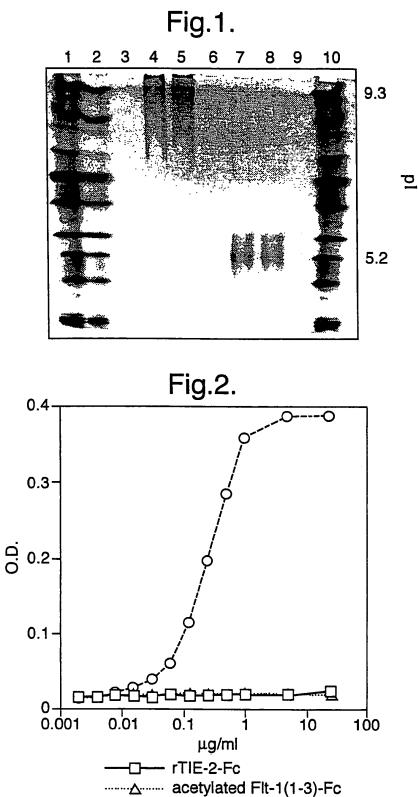
Primary Examiner—Christine J Saoud Assistant Examiner—Jon M Lockard (74) Attorney, Agent, or Firm—Valeta Gregg, Esq.

(57) ABSTRACT

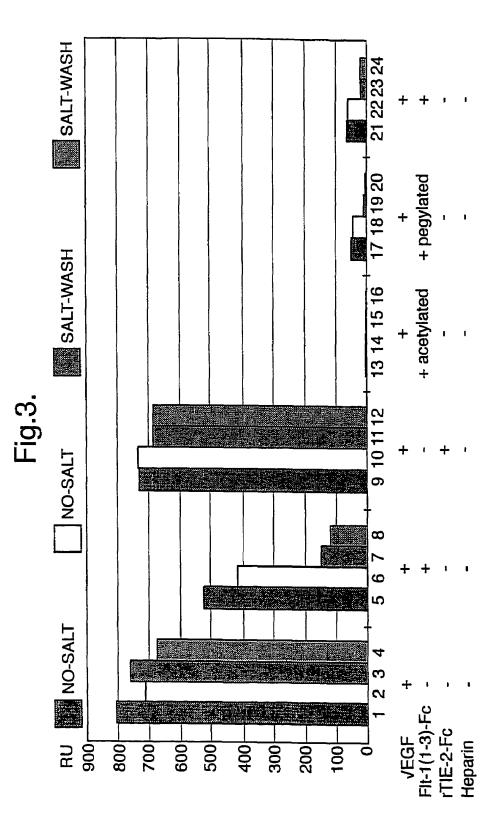
Modified chimeric polypeptides with improved pharmacokinetics are disclosed. Specifically, modified chimeric Flt1 receptor polypeptides that have been modified in such a way as to improve their pharmacokinetic profile are disclosed. Also disclosed are methods of making and using the modified polypeptides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

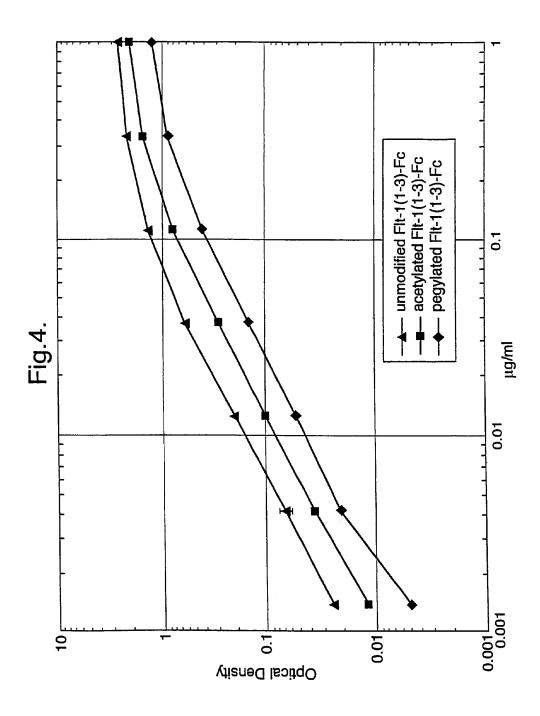
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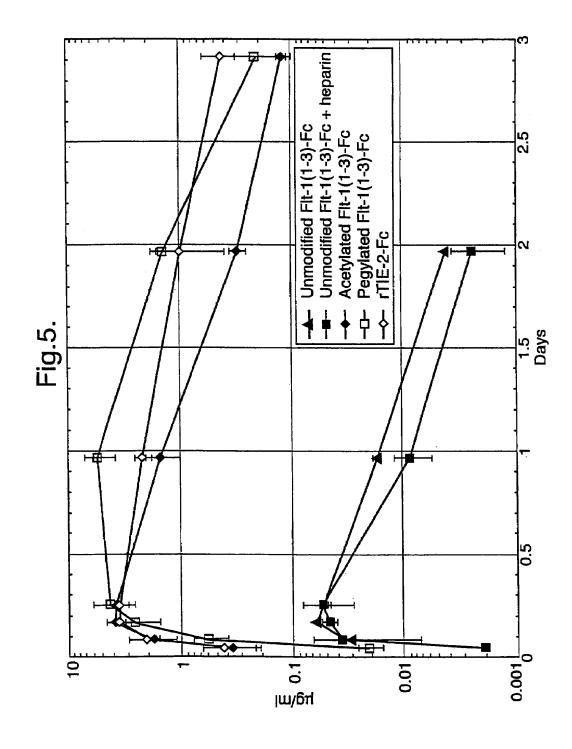


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