



US007374757B2

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

(10) **Patent No.:** **US 7,374,757 B2**
(45) **Date of Patent:** ***May 20, 2008**

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

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

(75) Inventors: **Nicholas J. Papadopoulos**, Lagrangeville, NY (US); **Samuel Davis**, New York, NY (US); **George D. Yancopoulos**, Yorktown Heights, NY (US)

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.

(73) Assignee: **Regeneron Pharmaceuticals, Inc.**, Tarrytown, NY (US)

(*) 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.

(21) Appl. No.: **11/016,097**

(22) Filed: **Dec. 17, 2004**

(65) **Prior Publication Data**
US 2005/0163798 A1 Jul. 28, 2005

Related U.S. Application Data

(62) Division of application No. 10/009,852, filed as application No. PCT/US00/14142 on May 23, 2000, now Pat. No. 7,070,959.

(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

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

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

7 Claims, 55 Drawing Sheets

Fig. 1.

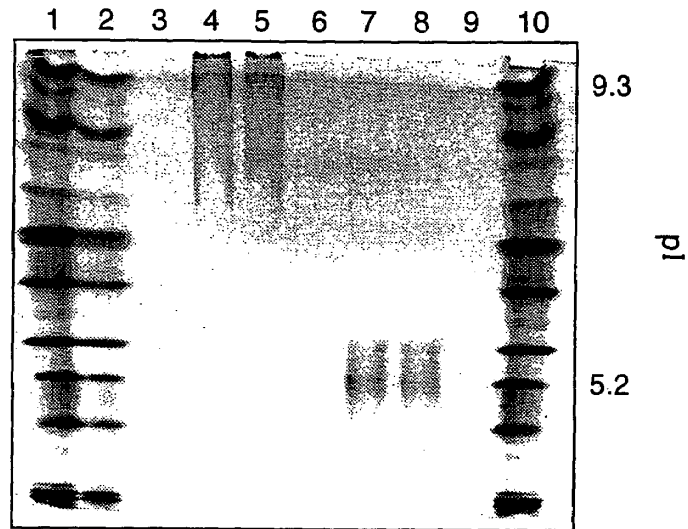


Fig. 2.

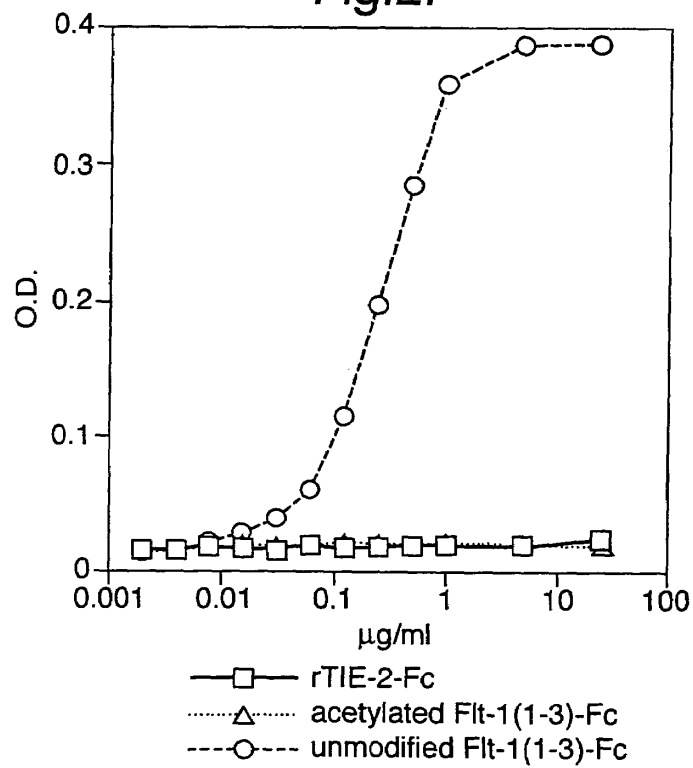
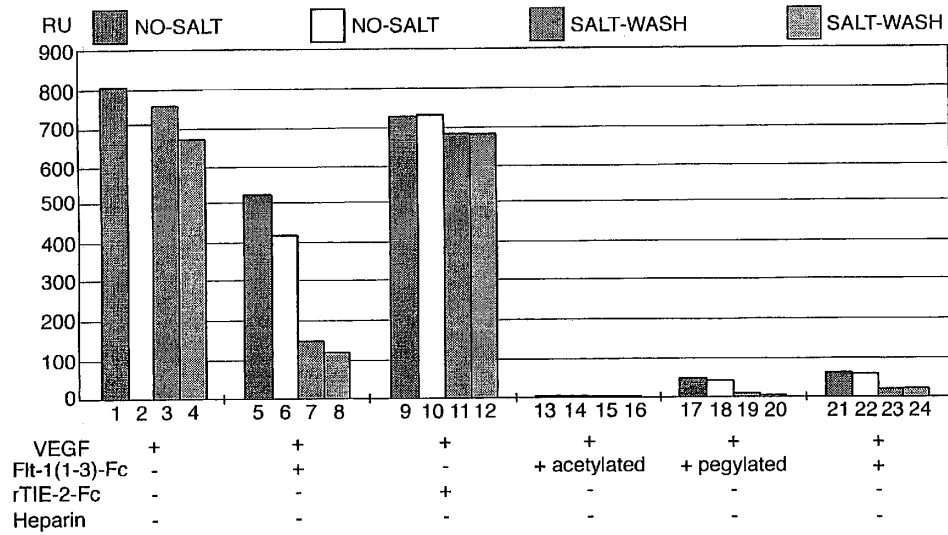


Fig.3.



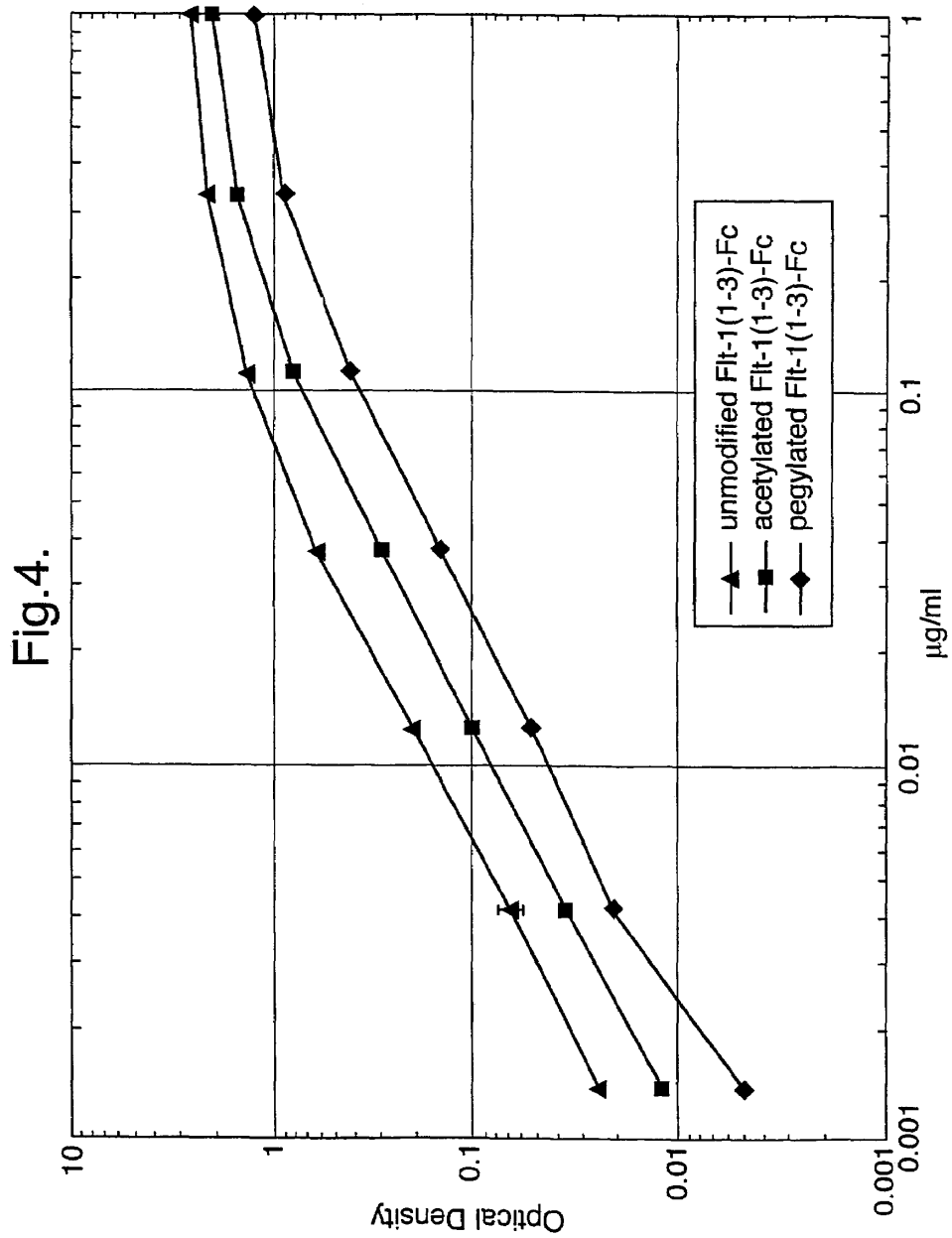
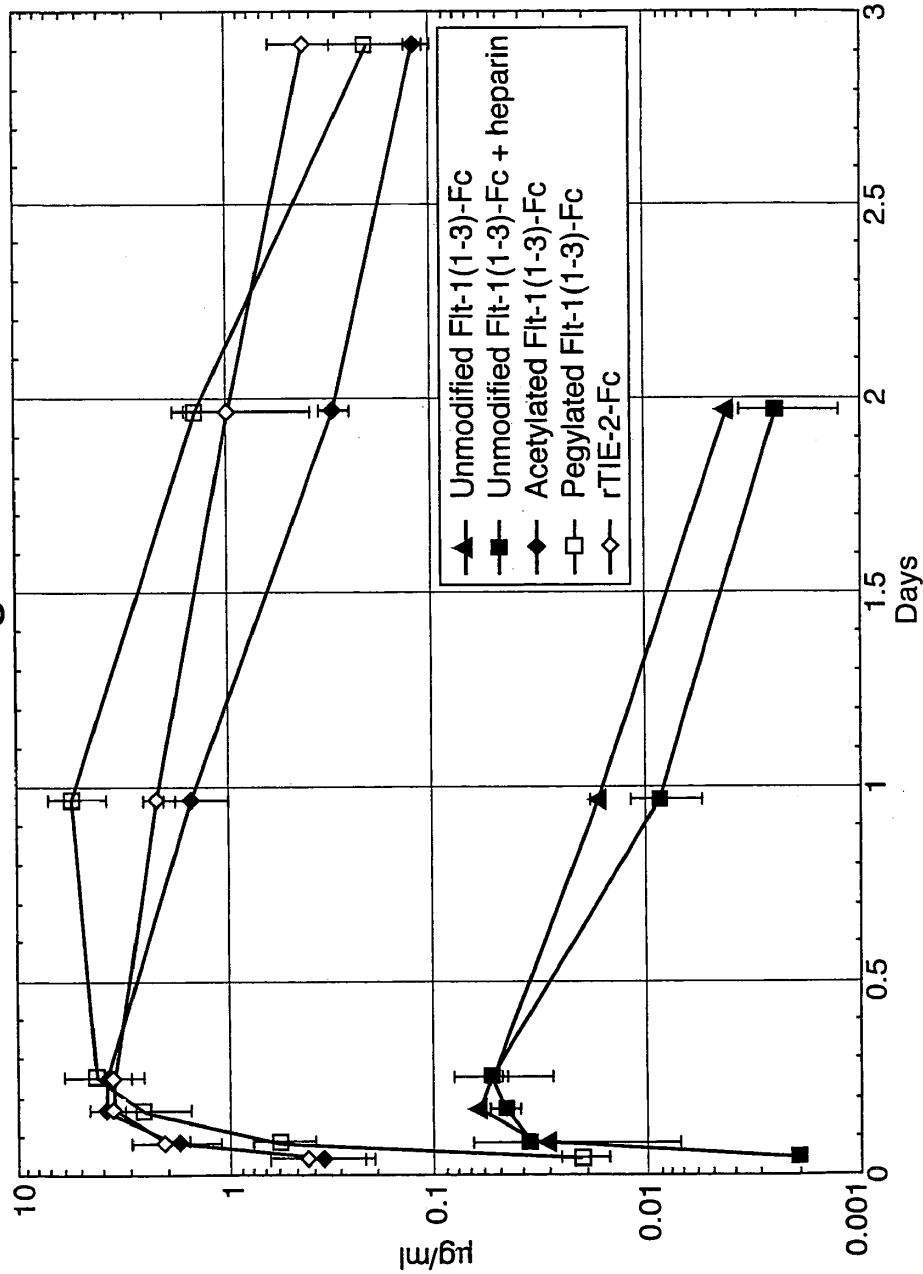


Fig.5.



Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.