PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/445	A1	(11) International Publication Number: WO 98/03174
		(43) International Publication Date: 29 January 1998 (29.01.98)

(21) International Application Number: PCT/US97/12158

(22) International Filing Date: 14 July 1997 (14.07.97)

(30) Priority Data:
60/022,863 24 July 1996 (24.07.96) US

(71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(72) Inventor: FIRESTONE, Raymond, A.; 59 Barnes Road, Stamford, CT 06902 (US).

(74) Agents: RODNEY, Burton et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: METHOD FOR TREATING TUMORS HAVING HIGH LDL REQUIREMENTS EMPLOYING MTP INHIBITORS

(57) Abstract

A method is provided for treating hematologic tumors and solid tumors, including certain types of leukemias and metastatic tumors, having high LDL requirements employing a delipidating agent such as an MTP inhibitor to substantially reduce LDL blood levels. In addition, a method is provided for treating tumors of the above types having high LDL requirements, especially hematologic tumors such as certain leukemias, employing a delipidating compound to substantially remove native LDL, and then administering a cytotoxic agent carried in reconstituted LDL.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

METHOD FOR TREATING TUMORS HAVING HIGH LDL REQUIREMENTS EMPLOYING MTP INHIBITORS

Field of the Invention

The present invention relates to a method for treating cancers having high LDL requirements employing a delipidating agent, which preferably is an MTP inhibitor, alone or in combination with a cytotoxic agent.

Background of the Invention

It is known that cancer cells need cholesterol to make new cell membrane. The cholesterol is supplied by either de novo synthesis or from low-density lipoprotein (LDL), or both, Firestone, R.A. et al, "Selective Delivery of Cytotoxic Compounds to Cells by the LDL Pathway, J. Med. Chem., 1984, 27, 1037-1043. Firestone et al describe a series of cytotoxic compounds that are compatible with reconstituted LDL and may be delivered with reconstituted LDL against cancers that copiously internalize LDL.

Firestone, R.A., "Low-Density Lipoprotein as a Vehicle for Targeting Antitumor Compounds to Cancer Cells", Bioconjugate Chemistry, 1994, 5, pp 105-113, at page 105, in the "Introduction", discusses problems associated with cancer treatment as follows:

"It is difficult to eradicate cancer cells in vivo because they share with normal cells, for the most part, the same biochemical machinery. There is no cytotoxic substance that is completely selective for malignant cells, and all those presently in use cause dose-limiting toxic side effects. For this reason there is a growing emphasis on targeting, i.e., selective delivery of

drugs to tumors in ways that bypass normal body tissues.

"Among the vehicles that can be used for this purpose is low-density lipoprotein (LDL), a normal blood constituent that is the body's principal means for delivery of cholesterol to tissues. Cholesterol, a major constituent of mammalian cell membranes, is obtained by cells either by making it themselves or by picking it up from LDL or both. Cancer cells, like all dividing ones, need large amounts of cholesterol because they are making new membrane. There is ample evidence that many types of cancer cells indeed have unusually great LDL requirements. The evidence is 2-fold: measurements of LDL uptake by tumor cells and depletion of LDL in the blood of cancer patients resulting from high uptake by the tumor (*vide infra*). Thus. if LDL could be made to carry antitumor drugs, it would serve as a targeting vehicle. This concept was proposed in 1981-2 (*1,2*) and has been reviewed several times since then (*3-7*)."

(1) Gal, D., Ohashi, J., MacDonald, P.C., Buchsbaum, H.J., and Simpson, E.R. (1981) Low-density lipoprotein as a potential vehicle for chemotherapeutic agents and radionucleotides in the management of gynecologic neoplasms. *Am. J. Obstet. Gynecol.* 139, 877.

(2) Counsell, R.E., and Pohland, R.C. (1982) Lipoproteins as potential site-specific delivery systems for diagnostic and therapeutic agents. *J. Med. Chem. 25*, 1115.

(3) van Berkel, T.J.C. (1993) Drug targeting: application of endogenous carriers for site-specific delivery of drugs. *J. Controlled Release 24*, 145.

(4) Vitols, S. (1991) Uptake of low-density lipoprotein by malignant cell--possible therapeutic applications. *Cancer Cells 3*, 488.

(5) deSmidt, P.C., and Van Berkel, T.J.C. (1990) LDL-mediated drug targeting. *Crit. Revs. Thera. Drug Carrier Syst. 7*, 99.

(6) Peterson, C., Masquelier, M., Rudling, M., Söderberg, K., and Vitols, S. (1991) Lipoproteins, malignancy and anticancer agents. *Targeted Diagn. Ther. (U.S.) 5*, 175.

(7) Catapano, A.L. (1987) Transport of cytotoxic compounds to cells via the LDL receptor pathway. *Med. Sci. Res. 15*, 411.

At page 105 under the topic "LDL Uptake...", Firestone, supra, lists numerous tumor types that have especially high LDL requirements including acute myeloid leukemia (AML), human monocytic (FAB-M5) and myelomonocytic (FAB-M4) leukemias, chronic myeloid leukemia in blast crisis, solid tumors such as epidermoid cervical cancer EC-50, endometrial adenocarcinoma AC-258, gastric carcinoma and parotid adenoma, G2 heptoma, squamous lung cancer, choriocarcinoma, brain tumors such as medulloblastoma, oligodendroglioma, glioma V-251MG, and malignant menigioma, as well as tumor cells that are exceptionally metastatic (Schroeder, F., Kier, A.B. Olson, C.D., and Dempsey, N.E. (1984) Correlation of tumore metastasis with sterol carrier protein and plasma membrane sterol levels. *Biochem. Biophys. Res. Commun. 124*, 283, and Cambien, F., Ducimetiere, P., and Richard, J. (1980) Total serum cholesterol and cancer mortality in a middle-aged male population. *Am. J. Epidemiol. 112*, 388), tumor cells that are exceptionally aggressive (Rudling, M.J., Stahle, L., Peterson,

DOCKET ALARM

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.