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[54] **METHOD OF INHIBITING CANCER GROWTH**

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[58] **Field of Search** 514/152, 154, 514/153

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,308,839	5/1994	Golub et al.	514/152
5,321,017	6/1994	Golub et al.	514/152
5,563,130	10/1996	Backer	514/152
5,567,693	10/1996	Backer et al.	514/154
5,574,026	11/1996	Backer et al.	514/152
5,668,122	9/1997	Fife et al.	514/152

FOREIGN PATENT DOCUMENTS

12717 8/1992 WIPO .

OTHER PUBLICATIONS

Bassett P, Okada A, Chenard M–P, Kannan R, Stoll I, Anglard P, Bellocq J–P, Rio M–C, "Matrix Metalloproteinases as Stromal Effectors of Human Carcinoma Progression: Therapeutic Implications", *Matrix Biology* 15:535–541 (1997).

Golub LM, Ramamurthy NS, Leungt M, McNamara TF, "Low–Dose Doxycycline Thrapy: Effect on Gingival and Crevicular Fluid Collagenase Activity in Humans", *J. Periodont Res* 25:321–330 (1990).

Golub LM, Lee HM, Lehrer G, Nemiroff A, McNamara TF, Kaplan R, Ramamurthy NS, "Minocycline Reduces Gingival Collagenolytic Activity During Diagetes", *Journal of Periodontal Research* 18:516–526 (1983).

Hatsu M, Sasaki T, Watabe H–O, Miyadoh S, Nagasawa M, Shomura T, Sezaki M, Inouye S, Kondo S, "A New Tetracycline Antibiotic with Antitumor Activity", *The Journal of Antibiotics* 45(3):320–324 (1992).

Hatsu M, Sasaki T, Gomi S, Kodama Y, Sezaki M, Inouye S, Kondo S, "A New Tetracycline Antibiotic with Antitumor Activity", *The Journal of Antibiotics* 45(3):325–330 (1992).

Johnson RK, Goldin A, "The Clinical Impact of Screening and Other Experimental Tumor Studies", *Cancer Treatment Reviews* 2:1–31 (1975).

Okada A, Bellocq J–P, Rouyer N, Chenard M–P, Rio M–C, Chambon P, Basset P, "Membrane–Type Matrix Metalloproteinase (MT–MMP) Gene is Expressed in Stromal Cells of Human Colon, Breast, and Head and Neck Carcinoma", *Proc. Natl. Acad. Sci. USA* 92:2730–2734 (1995).

Okada A, Tomasetto C, Lutz Y, Bellocq J–P, Rio M–C, Basset P, "Expression of Matrix Metalloproteinases During Rat Skin Wound Healing: Evidence that Membrane Type–1 Matrix Metalloproteinase is a Stromal Activator of Pro–Gelatinase A", *The Journal of Cell Biology* 137(1):67–77 (1997).

Sotomayor EA, Teicher BA, Schwartz GN, Holden SA, Menon K, Herman TS, Frei III E, Minocycline in Combination with Chemotherapy or Radiation Therapy in Vitro and in Vivo, *Cancer Chemother Pharmacol* 30:377–384 (1992).

Uitto V–J, Firth JD, Nip L, Golub LM "Doxycycline and Chemically Modified Tetracyclines Inhibit Gelatinase A (MMP–2) Gene Expression in Human Skin Keratinocytes", *Annals of the New York Academy of Sciences* 732:140–151 (1994).

Zeng ZS, Huang Y, Cohen AM, Guillem JG, "Prediction of Colorectal Cancer Relapse and Survival via Tissue RNA Levels of Matrix Metalloproteinase–9", *Journal of Clinical Oncology* 14(12):3133–3140 (1996).

Zucker S. Lysik RM, Ramamurthy NS, Golub LM, Wieman JM, Wilkie DP, "Diversity of Melanoma Plasma Membrane Proteinases: Inhibition of Collagenolytic and Cytolytic Activities by Minocycline", *JNCI* 75(3):517–525 (1985).

Zucker S, Turpeenniemi–Hujanen, T, Ramamurthy N, Wieman J, Lysik R, Gorevic P, Liotta LA, Simon SR, Golub LB, "Purification and Characterization of a Connective–Tissue–Degrading Metalloproteinase from the Cytosol of Metastatic Melanoma Cells", *Biochem. J* 245:429–437 (1987).

Zucker S, Weiman J, Lysik RM, Imhof B, Nagase H, Ramamurthy N, Liotta LA, Golub LM, "Gelatin–Degrading Type IV Collagenase Isolated from Human Small Cell Lung Cancer", *Invasion Metastasis* 9:167–181 (1989).

Johnson et al, Cancer Treatment Reviews vol. 2 p. 1, 1975.

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[57] **ABSTRACT**

The invention is a method of inhibiting cancer growth, including cellular proliferation, invasiveness, or metastasis in mammals. The method employs 6-demethyl-6-deoxy-4-dedimethylaminotetracycline (CMT-3) and other functionally related chemically modified, preferably non-antibacterial, tetracycline compounds to inhibit cancer growth. The method is particularly effective to inhibit the establishment, growth, and metastasis of solid tumors, such as tumors derived from colon cancer cells, breast cancer cells, melanoma cells, prostatic carcinoma cells, or lung cancer cells.

13 Claims, 8 Drawing Sheets