

US005922761A

United States Patent [19]

Lai

[54] METHODS FOR IN VIVO REDUCTION OF IRON LEVELS AND COMPOSITIONS USEFUL THEREFOR

[75]	Inventor:	Ching-San	Lai,	Encinitas,	Calif.
------	-----------	-----------	------	------------	--------

[73]	Assignee:	Medinox.	Inc	San	Diego.	Calif.
------	-----------	----------	-----	-----	--------	--------

[21] Appl. No.: 08/708,552

[22]	Filed:	Sep. 6,	1996

[51]	Int. Cl.6	A61K 31/27; A61K 31/40
[52]	IIS CL	514/476· 514/479· 514/480

514/481; 514/484; 514/423

[56] References Cited

U.S. PATENT DOCUMENTS

4,056,621	11/1977	Brown et al	424/273
4,160,452	7/1979	Theeuwes	128/260
4,173,644	11/1979	Brown et al	424/270
4,256,108	3/1981	Theeuwes	128/260
4,265,874	5/1981	Bonsen et al	. 424/15
4,894,393	1/1990	Nguyen et al	514/476
5,380,747	1/1995	Medford et al	514/423
5,430,058	7/1995	Shanzer et al	514/575

OTHER PUBLICATIONS

Al-Refaie et al., "Efficacy and Possible Adverse Effects of the Oral Iron Chelator 1,2-Dimethyl-3-Hydroxypyrid-4-One (L₁) in Thalassemia Major" *Blood* 80(3):593-599 (1992).

Biemond et al., "Intraarticular Ferritin–Bound Iron in Rheumatoid Arthritis" *Arthritis Rheum*. 29(10):1187–1193 (1986).

Biemond et al., "Iron Mobilization from Ferritin by Superoxide Derived from Stimulated Polymorphonuclear Leukocytes" J. Clin. Invest. 73:1576–1579 (1984).

De Sousa et al., "Iron, Iron-binding Proteins and Immune System Cells": Ann. N.Y. Acad. Sci. 526:310-323 (1988).

De Virgiliis et al., "Depletion of trace elements and acute ocular toxicity induced by desferrioxamine in patients with thalassaemia" *Arch. Dis. Chil.* 63:250–255 (1988).

Dizdaroglu and Bergtold, "Charaterization of Free Radical-Induced Base Damage in DNA at Biologically Relevent Levels" *Anal. Biochem.* 156:182–188 (1986).

Guyader et al., "Evaluation of Computed Tomography in the Assessment of Liver Iron Overload" *Gastroenterol.* 97:737–743 (1989).

Haber and Weiss, "The Catalytic Decomposition of Hydrogen Peroxide by Iron Salts" *Proc. R. Soc. Ser. A.* 147:332–351 (1934).

Halliwell and Gutteridge, in Halliwell and Gutteridge, Free Radicals in Biology and Medicine, 2nd edition. Oxford: Clarendon Press, 15–19 (1989).

Harrison and Hoare, in *Metals in Biochemistry*, Chapman and Hall, New York, (1980).

Kim et al., "Loss and Degradation of Enzyme-bound Heme Induced by Cellular Nitric Oxide Synthesis" *J. Biol. Chem.* 270(11):5710–5713 (1995).

[11] Patent Number:

5,922,761

[45] Date of Patent:

Jul. 13, 1999

Kolaric et al., "A Phase II Trial of Cardioprotection with Cardioxane (ICRF–187) in Patients with Advanced Breast Cancer Receiving 5–Fluorouracel, Doxorubicin and Cyclophosphamide" *Oncology* 52:251–255 (1995).

Komarov and Lai, "Detection of nitric oxide production in mice by spin-trapping electron paramagnetic resonance spectroscopy" *Biochim. Biophys. Acta* 1271:29–36 (1995). Kontoghiorghes, G. J., "Advances in oral iron chelation in man" *Int. J. Hematol.* 55:27–38 (1992).

Kontoghiorghes, G. J., "Comparative efficacy and toxicity of desferrioxamine, deferiprone and other iron and aluminium chelating drugs" *Toxicol. Letters* 80:1–18 (1995).

Lai and Komarov, "Spin trapping of nitric oxide produced in vivo in septic–shock mice" *FEBS Letters* 345:120–124 (1994).

Lai and Piette, "Hydroxyl Radical Production Involved in Lipid Peroxidation of Rat Liver Microsomes" *Biochem. Biophys. Res. Commun.* 78(1):51–59 (1977).

Muirden and Senator, "Iron in the Synovial Membrane in Rheumatoid Arthritis and Other Joint Diseases" *Ann. Rheum. Dis.* 27:38–48 (1968).

Myers et al., "Adriamycin: The Role of Lipid Peroxidation in Cardiac Toxicity and Tumor Response" *Science* 197:165–167 (1977).

Pippard et al., "Ferrioxamine Excretion in Iron-Loaded Man" Blood 60(2):288-294 (1982).

Proper et al., "Reassessment of the Use of Desferrioxamine B in Iron Overload" N. Engl. J. Med. 294(26):1421–1423 (1976).

(List continued on next page.)

Primary Examiner—Theodore J. Criares Attorney, Agent, or Firm—Gray Cary Ware & Freidenrich LLP; Stephen E. Reiter

[57] ABSTRACT

In accordance with the present invention, there are provided methods for the in vivo reduction of free iron ion levels in a mammalian subject. The present invention employs a scavenging approach whereby free iron ions are bound in vivo to a suitable physiologically compatible scavenger. The resulting complex renders the free iron ions harmless, and is eventually excreted in the urine of the host. Further in accordance with the present invention, there are provided compositions and formulations useful for carrying out the above-described methods. An exemplary scavenger contemplated for use in the practice of the present invention is a dithiocarbamate-containing composition. This material binds to free iron ions, forming a stable, water-soluble dithiocarbamate-iron complex. The present invention relates to methods for reducing in vivo levels of free iron ions as a means of treating subjects afflicted with iron overload and non-iron overload diseases and/or conditions, such as thalassemia, anemia hereditary hemochromatosis, hemodialysis, stroke and rheumatoid arthritis. Dithiocarbamate-containing scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo forming a stable dithiocarbamate-metal complex, which is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject, thereby reducing in vivo levels of free iron ions.

40 Claims, 3 Drawing Sheets



OTHER PUBLICATIONS

Rowley et al., "Lipid peroxidation in rheumatoid arthritis: thiobarbituric acid-reactive material and catalytic iron salts in snyovial fluid from rheumatoid patients" *Clin. Sci.* 66:691–695 (1984).

Shinobu et al., "Sodium N-Methyl-D-glucamine Dithiocarbamate and Cadmium Intoxication" *Acta Pharmacol et Toxicol.* 54:189–194 (1984).

Singal et al., "Subcellular Effects of Adriamycin in the Heart: A Concise Review" J. Mol. Cell. Cardiol. 19:817–828 (1987).

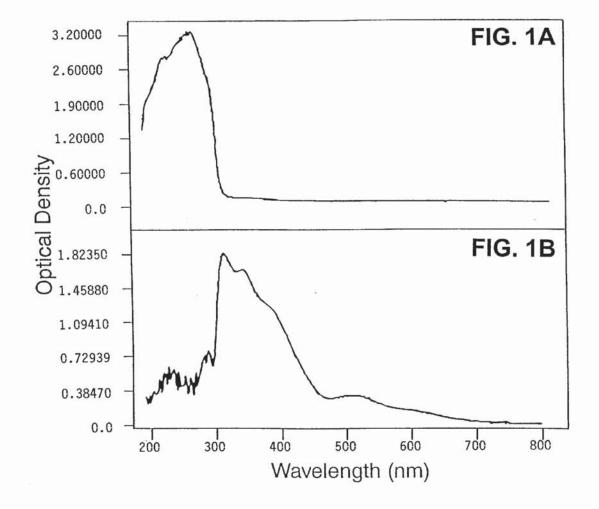
St. Louis et al., "Comparison of oral iron chelator L1 and desferrioxamine in iron-loaded patients" *Lancet* 336:1275–1279 (1990).

Thomas et al., "The Hydrolysis Product of ICRF-187 Promotes Iron-Catalysed Hydroxyl Radical Production via the Fenton Reaction" *Biochem. Pharmacol.* 45(10):1967-72 (1993).

Voest et al., "Iron-Chelating Agents in Non-Iron Overload Conditions" Ann. Intern. Med. 120(6):490-499 (1994).

Vreugdenhil et al., "Efficacy and Safety of Oral Iron Chelator L_1 in Anaemic Rheumatoid Arthritis Patients" *Lancet* 8:1398–1399 (1989).







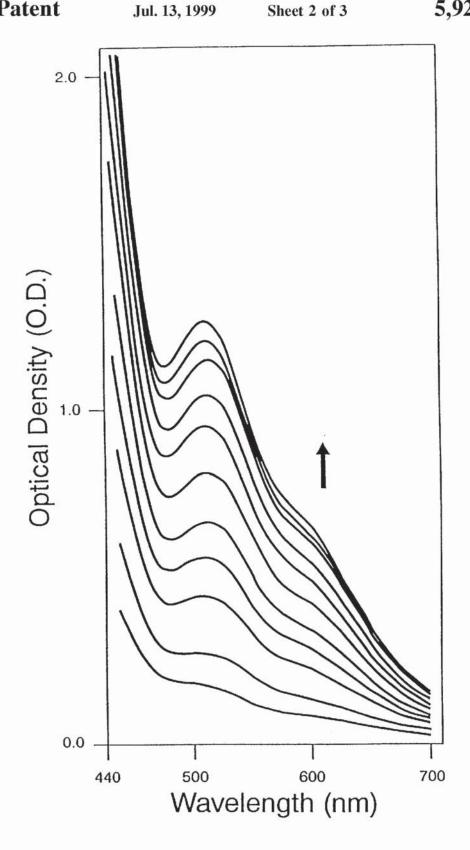


FIG. 2



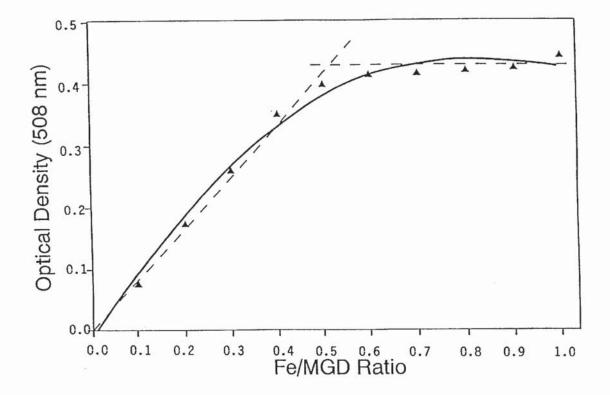


FIG. 3

DOCKET

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.

