US006599878B2

(12) **United States Patent**
Rooney

(10) **Patent No.: US 6,599,878 B2**
(45) **Date of Patent: Jul. 29, 2003**

(54) **SUPEROXYGENATING BLOOD SUBSTITUTES BASED ON HEMOGLOBIN AND DIHYDROPYIDINE COMPOSITIONS**

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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 111 days.

(21) Appl. No.: **09/727,170**

(22) Filed: **Nov. 30, 2000**

(65) **Prior Publication Data**

US 2001/0034323 A1 Oct. 25, 2001

Related U.S. Application Data

(60) Division of application No. 08/480,189, filed on Jun. 7, 1995, now Pat. No. 6,187,744, which is a continuation-in-part of application No. 07/849,610, filed on Mar. 11, 1992, now abandoned.

(51) **Int. Cl.**[7] **A61K 38/16**; A61K 35/14

(52) **U.S. Cl.** **514/6**; 514/832; 514/833; 530/385; 530/402

(58) **Field of Search** 514/6, 832, 833; 530/385, 402

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,001,401	A		1/1977	Bonsen et al.	424/177
4,064,118	A		12/1977	Wong	530/385
4,301,144	A		11/1981	Iwashita et al.	424/78
4,401,652	A		8/1983	Simmonds et al.	424/101
4,473,494	A		9/1984	Tye	530/385
4,578,395	A		3/1986	Yamaguchi et al.	514/356
4,826,811	A		5/1989	Sehgal et al.	514/6
4,857,515	A	*	8/1989	Kimura et al.	514/89
4,925,574	A		5/1990	Hsia	530/385
5,028,627	A		7/1991	Kilbourn et al.	514/565
5,084,558	A		1/1992	Rausch et al.	530/385
5,380,758	A	*	1/1995	Stamler et al.	514/562
5,614,490	A		3/1997	Przybelski	514/6
5,661,124	A		8/1997	Hoffman et al.	514/6
6,174,917	B1	*	1/2001	McLean	514/509

OTHER PUBLICATIONS

Rooney et al. FASEB Jorunal, vol. 5, No. 4, Abstract No. 158, 1991.*
Martin, et al., J. Pharmacol. Exp. Therapeutics, vol. 232, No. 3, pp. 708–716, 1985.
Rooney, et al., Biomater, Artif. Cells Immobilization Biotechnology, 19, 477, Aug. 1991.
Katusic, et al., Gen. Pharmac., 27, 239, 1996.
Sharma, et al., Am. J. Physiol., 269, H1379–H1388, 1995.
Sheffield, et al., Biotechnology and Applied Biochemistry, 9, 230–238, 1987.
Sunder–Plassman, et al., Eur. J. Int. Care Med., 1, 37–42, 1975.
Moss, et al., Surg. Gyn. Ob., 142, 357–362, 1976.
Vlahakes, et al., J. Thorac. Cardiovasc. Surg., 100, 379–388, 1990.
Gould, et al., Ann. Surg., 211, 394–398, 1990.
Hobbahn, et al., Acta Anaestheisol. Scand., 29, 537–543, 1985.
Rooney, et al., FASEB Journal, 5(4), Abstracts 158, 1991.
Carlsson, et al., Biochem J., 173, 723–737, 1978.
Martin, et al., J. Biol. Chem., 257, 286–288, 1982.
Chatterjee, et al., J. Biol. Chem., 261, 9929–9937, 1986.
Messmer, et al., Progr. Surg., 13, 208–245, 1974.
McCarthy, et al., Editors, Controversies of Leukocyte—Poor Blood and Components, Arlington, VA, American Association of Blood Banks, 1989.
Fanelli, et al., Adv. Protein Chem., 19, 73–124, 1964.
Rabiner, et al., J. Exptl. Med, 1127–1142, 1967.
Crystal, et al., Anesth. Analg., 67, 211–218, 1988.
Van Zwieten, Handbook of Hypertension: Pharmacology of Antihypertensive Drugs, 3, 307–330, 1984.
Kass, et al., Circulation, 79, 167–178, 1989.
Hoka, et al., Anesthesiology, 66, 647–652, 1987.
Wang, et al., Anesthesiology, 46, 40–48, 1977.
Fan, et al., Anesthesiology, 53, 113–120, 1980.
Gelman, et al., Anesthesiology, 49, 182–187, 1978.
Kien, et al., Anesth. Analg., 66, 103–110, Abstract only, 1987.
Michenfelder, Anesthesiology, 46, 196–201, 1977.
Vesey, et al., Anesthesiology, 62, 415–421, 1985.
Biro, et al., American Heart Journal, vol. 99, No. 1, 64–75, Jan. 1980.
Vesey, et al., J. Pharm. Pharmacology, vol. 32, 256–261, 1990.
Wennmalm, et al., Analytical Biochemistry, vol. 187, 359–363, 1990.
Panés, et al., Gastroenterology, vol. 103, No. 2, 403–413, Aug. 1992.
Wennmalm, et al., British Journal of Pharmacology, vol. 106, No. 3, 507–508, Jul. 1992.
Lenz, et al., Chemical Abstracts, vol. 96, Ref. #210605j, 1982.

(List continued on next page.)

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(57) **ABSTRACT**

The present invention provides superoxygenating compositions that comprise hemoglobin and guanosine 3':5'-cyclic monophosphate (cyclic GMP) generating compounds, and methods for treatment of diseases or medical conditions which utilize the superoxygenating compositions as biocolloids, i.e. hemodiluents, blood substitutes, plasma expanders, or resuscitative fluids. The cardiac output-increasing compositions comprise a simple mixture of hemoglobin and the cyclic GMP generating compounds or hemoglobin physically or chemically coupled to the cyclic GMP generating compounds. The invention also provides time-controlled superoxygenating compositions of hemoglobin and cyclic GMP generating compounds that would be used for treatment of specific diseases or medical conditions requiring time-dependent use of biocolloids, i.e. hemodiluents, blood substitutes, plasma expanders, or resuscitative fluids.

5 Claims, 14 Drawing Sheets