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(54) TREATMENT OF SICKLE CELL DISEASE

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See application file for complete search history.

(56)**References Cited**

U.S. PATENT DOCUMENTS

5,399,363	Α		Liversidge et al.
5,466,468	A	11/1995	Schneider et al.
5,543,158	Α	8/1996	Gref et al.
5,580,579	A	12/1996	Ruddy et al.
5,641,515	A	6/1997	Ramtoola
5,725,871	Α	3/1998	Illum

5,756,353 A 5,780,045 A 5,792,451 A		Debs McQuinn et al. Sarubbi et al.
5,804,212 A 6,613,308 B2 6,737,514 B1	9/1998 9/2003	
2007/0185045 A1		Ratcliffe

FOREIGN PATENT DOCUMENTS

WO WO-2004106325 A1 12/2004

OTHER PUBLICATIONS

Charache et al., "Treatment of sickle cell anemia with 5-azacytidine results in increase fetal hemoglobin production and is associated with nonrandom hypomethylation of DNA around the γ-σ-β-globin gene complex", The Proceeding of the National Academy of Sciences of the USA, vol. 80, No. 15, pp. 4842-4846 (1983).*

Fibach et al., "Enhanced Fetal Hemoglobin Production by Phenylacetate and 4-Phenylbutyrate in Erythroid Precursors Derived From Normal Donors and Patients With Sickle Cell and β-Thalassemia", Blood, vol. 82, No. 7, pp. 2203-2209 (1993).* Chokchaisiri et al., "Labdane diterpenes from the aerial parts of Curcuma comosa enhance fetal hemoglobin production in an

erythroid cell line", Journal of Natural Products, Apr. 23, 2010, vol. 73, No. 4, pp. 724-728.

Cokic et al., "Hydroxyurea induces fetal hemoglobin by the nitric oxide-dependent activation of soluble guanylyl cyclase", J Clin Invest, 2003, vol. 111, pp. 231-239.

Olnes et al, "Improvement in hemolysis and pulmonary arterial systolic pressure in adult patients with sickle cell disease during treatment with hydroxyurea" Am J Hematol, Aug. 2009, vol. 84, No. 8, pp. 530-532.

Brawley et al., "National Institutes of Health Consensus Development Conference Statement: Hydroxyurea Treatment for Sickle Cell Disease", Ann Intern Med, Jun. 17, 2008, vol. 148, No. 12., pp. 932-938.

Haynes et al., "Hydroxyurea attenuates activated neutrophil-mediated sickle erythrocyte membrane phosphatidylserine exposure and adhesion to pulmonary vascular endothelium", American Journal of Physiology — Heart and Circulatory Physiology, Jan. 1, 2008, vol. 294, No. H379-H385.

Abraham et al., "Asymmetric synthesis of N,O,O,O-tetra-acetyl d-lyxo-phytosphingosine, jaspine B (pachastrissamine), 2-epijaspine B, and deoxoprosophylline via lithium amide conjugate addition", Org. Biomol. Chem., 6:1665-1673, 2008.

Arita et al., "Rho kinase inhibition by fasudil ameliorates diabetesinduced microvascular damage", Diabetes, 58:215-226, 2009. Barabino et al., "Sickle cell biomechanics", Annu. Rev. Biomed. Eng., 12:345-367, 2010.

(Continued)

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ABSTRACT (57)

The present invention includes embodiments for treatment and/or prevention of sickle cell disease that employ Hydroxyfasudil or Isocoronarin D alone or either in conjunction with each other or an inducer of HbF production. The compounds may act synergistically, and the compounds employed circumvent the side effects seen with Hydroxyurea.

8 Claims, No Drawings