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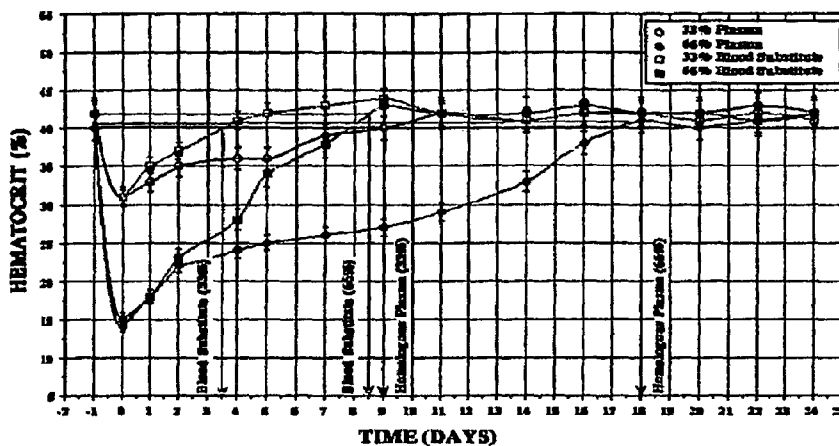
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(54) Title: METHODS OF TREATING ACUTE BLOOD LOSS ANEMIA WITH A CROSS-LINKED HEMOGLOBIN BLOOD SUBSTITUTE



(57) Abstract: The present invention relates to novel methods of using blood substitutes to treat acute blood loss and novel pharmaceutical compositions comprising blood substitutes. Blood substitutes useful for the methods of the present invention can (1) induce expression of erythropoietin as tested in a cell culture under normoxic conditions, and/or (2) induce erythropoiesis under normoxic conditions as measured by (a) a decrease in the doubling time of the subject's hematocrit or hemoglobin, and/or (b) an increase in the subject's circulating erythropoietin level. Blood substitutes useful for the pharmaceutical compositions of the present invention can (1) stabilize HIF-1 alpha expression, and/or (2) down regulate NF-kappa B. Preferably, the blood substitutes are cross-linked hemoglobin blood substitutes, or more preferably, cross-linked hemoglobins that comprise a hemoglobin that is cross-linked intramolecularly with periodate-oxidized ATP5 cross-linked intermolecularly with periodate-oxidized adenosine, and conjugated with reduced glutathione.

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A. CLASSIFICATION OF SUBJECT MATTER
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 439 882 A (FEOLA MARIO [US] ET AL) 8 August 1995 (1995-08-08) cited in the application column 5, lines 50-61 examples 8,9,19	35-121
Y	claims 1-4,12-15	23-110
A	US 5 631 219 A (ROSENTHAL GARY J [US] ET AL) 20 May 1997 (1997-05-20) cited in the application claim 1 example 7	

Further documents are listed in the continuation of Box C.

See patent family annex.

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LUTTON J D ET AL: "Pharmacologic effects of the red blood cell substitutes cross-linked and non-cross-linked hemoglobins on hematopoiesis in rabbits." PHARMACOLOGY JUN 1999, vol. 58, no. 6, June 1999 (1999-06), pages 319-324, XP009091012 ISSN: 0031-7012 cited in the application abstract figure 1	
X	KLEIN H G: "Blood substitutes: how close to a solution?" DEVELOPMENTS IN BIOLOGICALS 2005, vol. 120, 2005, pages 45-52, XP009091022 ISSN: 1424-6074 cited in the application abstract table 1	35-58, 72-93
Y	page 50, paragraph 2	59-71, 94-105
X	US 2002/120098 A1 (BELL DAVID [CA] ET AL) 29 August 2002 (2002-08-29) paragraphs [0088] - [0090], [0103], [0107]	35-58, 72-93
Y	paragraphs [0073], [0107]	23-34
X	US 2004/242464 A1 (TYE ROSS WALDEN [US]) 2 December 2004 (2004-12-02) paragraphs [0001], [0019], [0127], [0158], [0159]	35-58, 72-93, 106-110
Y	paragraphs [0001], [0019], [0159] - [0161]	23-34, 57-71, 94-105
Y	FEOLA M ET AL: "CLINICAL TRIAL OF A HEMOGLOBIN BASED BLOOD SUBSTITUTE IN PATIENTS WITH SICKLE CELL ANEMIA" SURGERY, GYNECOLOGY AND OBSTRETRICS, vol. 174, no. 5, May 1992 (1992-05), pages 379-386, XP000939099 ISSN: 0039-6087 cited in the application abstract table III page 384, column 2	35-110
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International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZUCALI J R ET AL: "Erythropoiesis and artificial blood substitution with a perfluorocarbon-polyol." THE JOURNAL OF LABORATORY AND CLINICAL MEDICINE NOV 1979, vol. 94, no. 5, November 1979 (1979-11), pages 742-746, XP009091008 ISSN: 0022-2143 abstract page 745, paragraph 4 - page 746, paragraph 1 -----	1-11, 35-46, 72-82

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2007/011697

Patent document cited in search report	Publication date	Publication date	Patent family member(s)	Publication date
US 5439882	A	08-08-1995	NONE	
US 5631219	A	20-05-1997	AU 699671 B2	10-12-1998
			AU 2227095 A	25-09-1995
			CA 2182800 A1	14-09-1995
			EP 0749318 A1	27-12-1996
			FI 963482 A	05-09-1996
			HU 74846 A2	28-02-1997
			JP 10500105 T	06-01-1998
			NO 963742 A	07-11-1996
			PL 316145 A1	23-12-1996
			WO 9524213 A1	14-09-1995
US 2002120098	A1	29-08-2002	NONE	
US 2004242464	A1	02-12-2004	US 6894150 B1	17-05-2005