US009636381B2

(12) **United States Patent**
Basile

(10) **Patent No.: US 9,636,381 B2**
(45) **Date of Patent: *May 2, 2017**

(54) **METHODS FOR RADIATION PROTECTION BY ADMINISTERING IL-12**

(71) Applicant: **Neumedicines, Inc.**, Pasadena, CA (US)

(72) Inventor: **Lena A. Basile**, Tujunga, CA (US)

(73) Assignee: **NEUMEDICINES, INC.**, Pasadena, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/745,698**

(22) Filed: **Jan. 18, 2013**

(65) **Prior Publication Data**

US 2013/0243722 A1 Sep. 19, 2013

Related U.S. Application Data

(60) Provisional application No. 61/588,098, filed on Jan. 18, 2012, provisional application No. 61/734,364, filed on Dec. 6, 2012.

(51) **Int. Cl.**
A61K 36/19 (2006.01)
A61K 38/20 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 38/208*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 38/208
USPC 424/85.2; 530/351
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,179,337	A	12/1979	Davis et al.
4,301,144	A	11/1981	Iwashita et al.
4,485,045	A	11/1984	Regen
4,496,689	A	1/1985	Mitra
4,544,545	A	10/1985	Ryan et al.
4,640,835	A	2/1987	Shimizu et al.
4,670,417	A	6/1987	Iwasaki et al.
4,791,192	A	12/1988	Nakagawa et al.
5,013,556	A	5/1991	Woodle et al.
5,573,764	A	11/1996	Sykes et al.
5,648,072	A	7/1997	Trinchieri et al.
5,648,467	A	7/1997	Trinchieri et al.
5,744,132	A	4/1998	Warne et al.
5,756,085	A	5/1998	Sykes et al.
5,853,714	A	12/1998	Deetz et al.
6,683,046	B1	1/2004	Gately et al.
7,052,685	B1	5/2006	Rook
7,939,058	B2	5/2011	Chen et al.
2003/0147849	A1	8/2003	Warne et al.
2005/0136034	A1	6/2005	Chen
2010/0015134	A1	1/2010	Parren et al.
2011/0206635	A1	8/2011	Chen et al.
2012/0010229	A1	1/2012	MacDougall et al.

FOREIGN PATENT DOCUMENTS

WO	WO 2011/005406		1/2011
WO	WO-2011/022339	A1	2/2011
WO	WO-2011/146574	A1	11/2011

OTHER PUBLICATIONS

Ahmed et al., "Cytokine-induced expansion of human CD34^{+} stem/progenitor and CD34^{+}CD41^{+} early megakaryocytic marrow cells cultured on normal osteoblasts," *Stem Cells*, 1999, 17:92-99.
Akimoto et al., "Erythropoietin regulates vascular smooth muscle cell apoptosis by a phosphatidylinositol 3 kinase-dependent pathway," *Kidney Int.*, 2000, 58:269-282.
Anagnostou et al, "Erythropoietin receptor mRNA expression in human endothelial cells," *Proc. Natl. Acad. Sci. USA*, 1994, 91:3974-3978.
Barker et al., "Identification of stem cells in small intestine and colon by marker gene *Lgr5," Nature*, Oct. 25, 2007, 449:1003-1008.
Barker et al., "Lgr5($^{+ve}$) stem cells drive self-renewal in the stomach and build long-lived gastric units in vitro," *Cell Stem Cell.*, Jan. 8, 2010, 6:25-36.
Basile et al., "Multilineage hematopoietic recovery with concomitant antitumor effects using low dose Interleukin-12 in myelo suppressed tumor-bearing mice," *J. Transl. Med.*, May 19, 2008, 6:26, 27 pages.
Bekaii-Saab et al., "A phase I trial of paclitaxel and trastuzumab in combination with interleukin-12 in patients with HER2/neu-expressing malignancies," *Mol. Cancer Ther.*, Nov. 2009, 8(11):2983-2991.
Bellone et al., "Dual stimulatory and inhibitory effect of NK cell stimulatory factor/IL-12 on human hematopoiesis," *J. Immunol.*, 1994, 153:930-937.
Brines et al., "Emerging biological roles for erythropoietin in the nervous system," *Nat. Rev. Neurosci.*, Jun. 2005, 6:484-494.
Broxmeyer et al., "Comparative analysis of the influences of human gamma, alpha and beta interferons on human multipotential (CFU-GEMM), erythroid (BFU-E) and granulocyte-macrophage (CFU-GM) progenitor cells," *J. Immunol.*, Sep. 1983, 131(3):1300-1305.
Buemi et al., "The pleiotropic effects of erythropoietin in the central nervous system," *J. Neuropathol. Exp. Neurol.*, Mar. 2003, 62(3):228-236.
Burdelya et al., "An agonist of toll-like receptor 5 has radioprotective activity in mouse and primate models," *Science*, Apr. 11, 2008, 320:226-230.
Cetin et al., "Novel evidence suggesting an anti-oxidant property for erythropoietin on vancomycin-induced nephrotoxicity in a rat model," *Clin. Exp. Pharmacol. Physiol.*, 2007, 34:1181-1185.
Chao, "Accidental or intentional exposure to ionizing radiation: biodosimetry and treatment options," *Exp. Hematol.*, 2007, 35:24-27.

(Continued)

Primary Examiner — Prema Mertz
(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

(57) **ABSTRACT**

Aspects and embodiments of the instant disclosure provide therapeutic methods and compositions comprising interleukin 12 (IL-12) useful for treating radiation-induced damage in a subject. In particular, the instant disclosure provides methods and compositions for radiation protection and/or radiation toxicity mitigation for the treatment of acute radiation syndrome and radiation induced toxicity associated with the treatment of cutaneous T-cell lymphoma.

40 Claims, 43 Drawing Sheets