



US007414026B2

(12) **United States Patent**
Beyaert et al.

(10) **Patent No.:** **US 7,414,026 B2**
(45) **Date of Patent:** **Aug. 19, 2008**

(54) **INHIBITORS OF NF-KAPPAB ACTIVATION**

(75) Inventors: **Rudi Beyaert**, Zingem (BE); **Karen Heyninck**, Sint-Martens-Latem (BE); **Walter Fiers**, Destelbergen (BE)

(73) Assignee: **Vlaams Interuniversitair Instituut voor Biotechnologie VZW**, Zwijnaarde (BE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 361 days.

(21) Appl. No.: **10/680,998**

(22) Filed: **Oct. 8, 2003**

(65) **Prior Publication Data**

US 2004/0092430 A1 May 13, 2004

Related U.S. Application Data

(60) Division of application No. 09/702,953, filed on Oct. 31, 2000, now Pat. No. 6,673,897, which is a continuation of application No. PCT/BE99/00055, filed on May 5, 1999.

(51) **Int. Cl.**
A61K 38/00 (2006.01)

(52) **U.S. Cl.** **514/12**

(58) **Field of Classification Search** 514/12
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,186,183 A	1/1980	Steck et al.
4,217,344 A	8/1980	Vanlerberghe et al.
4,235,871 A	11/1980	Papahadjopoulos et al.
4,261,975 A	4/1981	Fullerton et al.
4,485,054 A	11/1984	Mezei et al.
4,501,728 A	2/1985	Geho et al.
4,774,085 A	9/1988	Fidler
4,797,368 A	1/1989	Carter et al.
4,837,028 A	6/1989	Allen
4,897,355 A	1/1990	Eppstein et al.
4,946,787 A	8/1990	Eppstein et al.
5,049,386 A	9/1991	Eppstein et al.
5,173,414 A	12/1992	Lebkowski et al.

FOREIGN PATENT DOCUMENTS

WO	WO 91/16024	10/1991
WO	WO 91/17424	11/1991
WO	WO 93/24641	12/1993
WO	WO 97/37016	10/1997
WO	WO 99/57133	11/1999

OTHER PUBLICATIONS

Song et al., The tumor necrosis factor-inducible zinc finger protein A20 interacts with TRAF1/TRAF2 and inhibits NF- κ B activation, Proc. Natl. Acad. Sci. USA, 1996, vol. 93, p. 6721-6725.*
Jaattela et al., A20 zzzzzinc finger protein inhibits YNF and IL-1 signaling, The Journal of Immunology, 1996, 156, p. 1166-1173.*

Ferran et al., A29 inhibits NF- κ B activation in endothelial cells without sensitizing to tumor necrosis factor-mediated apoptosis, Blood, 1998, vol. 91, p. 2249-2258.*

Heyninck et al., The zinck finger protein A20 inhibits TNF-induced NF- κ B-dependent gene expression by interfering with an RIP- or TRAF2-mediated transactivation signal and directly binds to a novel NF- κ B-inhibiting protein ABIN, The Journal of Cell Biology, 1999, vol. 145, p. 1471-1482.*

De Valck et al., "A20, an inhibitor of cell death, self-associates by its zinc finger domain," 384 FEBS Letters 61-64 (1996).

Fukushi, M., Homosapiens mRNA for HIV-1, Nef-associated factor 1 beta (Naf1 betas),: EMHUM Database Entry HSA011896, Accession No. AJ011896, Oct. 14, 1998, XP002124741.

Fukushi, M., et al., "NAF1 alpha protein (KIAA0113 protein)," TREMBL Database Entry A15025, Accession No. Q15025, Nov. 1, 1996, XP02124740.

Hendrick, B.D., et al., "An X-linked homologue of the autosomal imprinted gene NF127 escapes X chromosome inactivation," EMHUM Database Entry HS4131510; Accession No. U41315, May 19, 1996, XP002125387.

Heyninck et al., "The Zinc Finger Protein A20 Inhibits TNF-induced NF- κ B-dependent Gene Exp[ression by interfering with an RIP- or TRAF2-mediated Transactivation Signal and Directly Binds to a Novel NF- κ B-inhibiting Protein ABIN," 145 The Journal of Cell Biology 1471-1482 (1999).

Miyajima, N., et al., "Human mRNA for KIAA 0133 gene, partial coding sequence," EMHUM Databse Entry HSORFA2, Accession No. D30755, May 21, 1994, XP002124739.

Nomura et al., "mRNA for ORF, partial CDS (fragment)," TRHUM Database Entry Q15025; Nov. 1, 1996, Accession No. Q15025, XP002080989.

Song et al., "The tumor necrosis factor-inducible zinc finger protein A20 interacts with TRAF1/TRAF2 and inhibits NF- κ B activation," 93 Proc. Natl. Acad. Sci. USA 6721-6725 (1996).

Yen, R.W.C., et al., "DNA-methyltransferase," SWISSPROT Database Entry MTDM_Human; May 1, 1992, Accession No. P26358, XP002080990.

PCT International Search Report, PCT/BE99/00055, dated Dec. 31, 1999 (9 pages).

PCT International Preliminary Examination Report, PCT/BE99/00055, dated Aug. 10, 2000.

(Continued)

Primary Examiner—Karen Cochrane Carlson

Assistant Examiner—Agnes B. Rooke

(74) *Attorney, Agent, or Firm*—TraskBritt

(57) **ABSTRACT**

The present invention relates to novel inhibitors of the Nuclear factor kappa B (NF- κ B) activating pathway useful in the treatment of NF- κ B related diseases and/or in the improvement of anti-tumor treatments. These inhibitors interfere early in the TRAF induced signaling pathway and are therefore more specific than I κ B.

6 Claims, 10 Drawing Sheets