



US007101990B2

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

(10) **Patent No.:** **US 7,101,990 B2**
(45) **Date of Patent:** **Sep. 5, 2006**

(54) **BAX-RESPONSIVE GENES FOR DRUG TARGET IDENTIFICATION IN YEAST AND FUNGI**

(75) Inventors: **Roland Henri Contreras**, Schelderode/Merelbeke (BE); **Ines Eberhardt**, Zwalm (BE); **Walter Herman Maria Luyten**, Turnhout (BE); **Rieka Josephina Reekmans**, Zwijnaarde (BE)

(73) Assignee: **Janssen Pharmaceutica N.V.**, Beerse (BE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 359 days.

(21) Appl. No.: **10/451,467**
(22) PCT Filed: **Dec. 21, 2001**
(86) PCT No.: **PCT/EP01/15398**

§ 371 (c)(1),
(2), (4) Date: **Jun. 19, 2003**

(87) PCT Pub. No.: **WO02/064766**
PCT Pub. Date: **Aug. 22, 2002**

(65) **Prior Publication Data**
US 2004/0161840 A1 Aug. 19, 2004

(30) **Foreign Application Priority Data**
Dec. 22, 2000 (EP) 00870318
Jan. 4, 2001 (EP) 01870002
Jan. 9, 2001 (EP) 01870003

(51) **Int. Cl.**
C07H 21/04 (2006.01)

(52) **U.S. Cl.** **536/23.7**; 536/24.1; 536/23.1;
435/320.1; 435/69.1; 435/254.2; 435/243;
435/252.3

(58) **Field of Classification Search** 536/23.1,
536/23.7, 24.1; 435/320.1, 69.1, 254.2, 243,
435/252.3
See application file for complete search history.

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

GB	2326413	12/1998
WO	WO 9505750	3/1995
WO	WO 9916787	4/1999
WO	WO 9932514	7/1999
WO	WO 0023083	4/2000
WO	WO 0102550	1/2001

OTHER PUBLICATIONS

Ligr, M. et al. "Mammalian Bax triggers apoptotic changes in yeast". Federation of Biochemical Societies (FEBS) Letters 438 (1998) pp. 61–65. XP-000857722.

Marzo, I. et al. "Bax and Adenhe Nucleotide Translocaton Cooperate in the Mitochondrial Control of Apoptosis". SCIENCE vol. 281, Sep. 25, 1998, pp. 2027–2031, XP-000982449.

Tao, W. et al. "Modulation of Cell Death in Yeast by the Bci-2 Family of Proteins". Journal of Biological Chemistry 1997, vol. 272, Issue of Jun. 13, pp. 15547–15552, XP-000982450.

Greenhalf, W. et al. "A Secltion System for Human Apoptosis Inhibitors Using Yeast". Oncology Research, Novartis Pharma AG, Basel, Switzerland. Yeast 15 (1999), pp. 1307–1321. XP-002174101.

Brown, A. et al. "Codon utilisation in the pathogenic yeast, Candida albicans". Nucleic Acids Research, vol. 19, No. 15, Submitted May 28, 1991. p. 4298. Oxford University Press. XP-00100538. (Abstract).

Matsuyama, S. et al. "The Mitochondrial FOF1-ATPase Proton Pump Is Required for Function of the Prospoptotic Protein Bax in Yeast and Mammalian Cells". Molecular Cell, vol. 1, pp. 327–336, Feb. 1998, XP-000987219.

Martinet, W. et al. "Bax-induced cell death in Pichia pastoris" Biotechnology Letters 21: pp. 821–829, 1999. XP-001106921.

Frohlich, K. et al. "Apoptosis in yeast—a monocellular organism exhibits atrulstic behaviour" FEBS Letters 473 (2000) pp. 6–9.

Oitvai, Z. et al. "Bci-2 Heterodimertzes in Vivo with a Conserved Homolog, Bax, That Accelerates Programmed Cell Death" Cell, vol. 74, pp. 609–619, Aug. 27, 1993. XP-002018918.

Torgler, C.N. et al. "Exploiting the utility of yeast in the context of programmed cell death". Medthe Methods Enzymol 2000, 297–322, XP-002174102. (Abstract).

Xu, Q. et al. "Methods of Assaying Bci-2 and Bax Family Proteins in Yeast". A Companion to Methods in Enzymology 17, pp. 292–304 (1999).

Primary Examiner—Jennifer E. Graser
(74) Attorney, Agent, or Firm—Laura Donnelly

(57) **ABSTRACT**

The use of nucleic acids and polypeptides which are involved in a pathway eventually leading to programmed cell death of yeast or fungi for the preparation of a medicament for treating diseases associated with yeast or fungi or for the treatment of proliferative disorders or for preventing apoptosis in certain diseases is disclosed. Methods are provided to identify compounds which selectively modulate the expression or functionality of said polypeptides in the same or a parallel pathway. Also provided are compounds as well as pharmaceutical compositions, medicaments and vaccines. New nucleic acid sequences, probes and primers derived thereof, expression vectors and host cells transformed with said vectors, polypeptides and antibodies raised against said polypeptides are also disclosed.

13 Claims, 251 Drawing Sheets