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ning of each regular issue of the PCT Gazette.

(54) Title: METHODS FOR GENERATING ENHANCED ANTIBODY-PRODUCING CELL LINES WITH IMPROVED
GROWTH CHARACTERISTICS

(57) Abstract: The use of mismatch repair (MMR) defective antibody producer cells offers a method to generate subclone variants with elevated protein production such as antibodies. Using MMR defective cells and animals, new cell lines and animal varieties with novel and useful properties such as enhanced protein production can be generated more efficiently than by relying on the natural rate of mutation. These methods are useful for generating genetic diversity within host cells to alter endogenous genes that can yield increased titer levels of protein production. By employing this method, two genes were discovered whose suppressed expression is associated with enhanced antibody production. Suppressed expression of these genes by a variety of methods leads to increased antibody production for manufacturing as well as strategies for modulating antibody production in immunological disorders. Moreover, the suppression of these two genes in host cells can be useful for generating universal high titer protein production lines.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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 US CL : 435/4,5,6,7, 70.21, 320.1, 325, 326, 455, 463; 514/44; 800/6, 21

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/4,5,6,7, 70.21, 320.1, 325, 326, 455, 463; 514/44; 800/6, 21

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2002/0055106 A1 (NICOLAIDES et al.) 09 May 2002 (09.05.2002), see entire document.	1-18
Y	WINTER, D. B. et al. Altered spectra of hypermutation in DNA repair-deficient mice. Phil. Trans. R. Soc. Lond. B. 2001, Vol. 356, pages 5-11, see entire document.	1-18
Y	KIM, N. et al. The role of DNA repair in somatic hypermutation of immunoglobulin genes. J. Exp. Med. 1998, Vol. 187, No. 11, pages 1729-1733, see entire document.	1-18
X	SIFERS, R. N. et al. A frameshift mutation results in a truncated alpha 1 antitrypsin that is retained within the rough endoplasmic reticulum. J. Biol. Chem. 25 May 1988, Vol. 263, No. 15, pages 7330-7335, see entire document.	56,58
Y	SCOBIE, G. et al. Non-specific effects of anti-sense oligonucleotides on alpha-1-antitrypsin expression in Cos cells transfected with alpha-1 antitrypsin cDNA constructs. Biochem. Soc. Trans. 1992, Vol. 20, No. 4, page 319S, see entire document.	19-25, 36-38, 57
Y	OZAKI, L. ^{et al.} Inhibition of alpha-1-antitrypsin (alpha1-AT) gene expression by a hammerhead ribozyme in hepatoma cells. Gastroenterology. 1996, Vol. 110, No. 4, page A1288, see abstract.	19-27, 36-38, 43-46, 56,59
Y		19-25, 29, 36-38, 43-46, 56, 60

☒ Further documents are listed in the continuation of Box C.

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Continuation of B. FIELDS SEARCHED Item 3:

DIALOG-Medline, Embase, Cancerlit, Scisearch, Biosis; BRS/EAST-USPatful, EPO, JPO, Derwint, PG-Pubs
search terms: alpha antitrypsin, antisense, ribozyme, knock-out, transgenic, monocyte activating polypeptide 1, MAP1, emap1,
mismatch repair