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(54) Title: THE USE OF PLP WITH PEG-RMETASE *IN VIVO* FOR ENHANCED EFFICACY

(57) Abstract: This invention relates to methods of modifying pyridoxal 5' phosphate (PLP) dependent enzymes to extend the serum half-life of the enzyme, extend the *in vivo* period of methionine depletion in a host, and decrease the immunogenicity of the enzyme. A preferred PLP-dependent enzyme to be modified is a methioninase, preferably a recombinant methioninase (rMETase). The invention further relates to compositions comprising a modified PLP-dependent enzyme and methods of using the same.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/22769

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **A61K 38/46**(2006.01)

USPC: 424/94.6
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/94.6

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 practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SUN X. et al, Pyridoxal 5'-phosphate (PLP)-infusion extends plasma methionine depletion in mice treated with the PLP enzyme recombinant methioninase. Proc. Am. Assoc. Canc. Res., March 2002, vol 43, page 1093, Meeting abtsract # 5415, entire abstract.	1-50
Y	US 5,888,506 (TAN) 30 March 1999 (30.03.1999), abstract, columns 11-13, figures 6-19, and example 7, in particular.	1-50
Y	YOSHIOKA T. et al. Anticancer efficacy in vivo and invitro, synergy with 5-fluorouracil, and safety of recombinant methioninase. 1998, vol 58, pages 2583-2587, especially abstract, materials & methods, page 2583.	22-23 AND 49-50
Y	KOKKINAKIS D.M. et al. Synergy between methioninase stress and chemotherapy in the treatment of brain tumor xenografts in athymic mice. Cancer Research, May 2001, vol 61, pages 4017-4023, especially abstract, materials & methods, pages 4018, and discussion, pages 4022.	1-50

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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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.
Y	TAN Y. et al. Efficacy of recombinant methioninase in combination with cisplatin on human colon tumors in nude mice, Clinical Cancer Research, August 1999, vol 5, pages 2157-2163, especially abstract, materials & methods, page 2158, and figure 3.	22-23 and 49-50
Y	TAN Y. et al. Polyethylene glycol conjugation of recombinant methioninase for cancer therapy. Protein Expression and Purification, 1998, vol 12, pages 45-52, especially page 45, materials & methods, pages 46, 48, and results & discussion.	1-50
A	US 5,690,929 (LISHKO et al) 25 Nov 1997 (25.11.1997), especially abstract, columns 7-11, and claims.	1-50
A	US 6,524,571 B1 (XU et al) 25 Feb 2003 (25.02.2003), especially abstract and cited publications.	1-50

INTERNATIONAL SEARCH REPORT

International application No.
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Continuation of B. FIELDS SEARCHED Item 3:
EAST:
USPAT, USOCR, PG-PUB, JPO, EPO, DERWENT
STN:
REGISTRY, CAPLUS, MEDLINE, BIOSIS, SCISEARCH

SEARCH STRATEGY:
methioninase and polyethyleneglycol or peg or ?glycol
pyridoxal or b6 and methioninase
methioninase and cancer or neoplasm or tumor or tumour