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(54) **CYTOKINE-BASED FUSION PROTEINS FOR TREATMENT OF MULTIPLE SCLEROSIS**

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(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,858,980	A *	1/1999	Weiner et al.	514/21.4
6,942,853	B2 *	9/2005	Chernajovsky et al.	424/85.1
2002/0038002	A1 *	3/2002	Zaghouani	530/388.22
2003/0017550	A1	1/2003	Pang	
2005/0025744	A1 *	2/2005	Lane	424/85.6

FOREIGN PATENT DOCUMENTS

EP	0326120 A2	8/1989
WO	WO 91/01146 A	2/1991
WO	WO 91/01146 A1	2/1991
WO	WO 99/32141 A1	7/1999
WO	WO 01/68896 A	9/2001
WO	WO 03/024404 A	3/2003
WO	WO 2004/020405 A2	3/2004
WO	WO 2004/028472 A2	4/2004
WO	WO 2004/092210 A	10/2004
WO	WO 2006/000448 A2	1/2006
WO	WO 2006/063800 A	6/2006
WO	WO 2006/063800 A1	6/2006

OTHER PUBLICATIONS

Kim, 1997, Arch. Pharm. Research, vol. 20, No. 5, pp. 396-403.*

Mannie, 2007, Journal of Immunology, vol. 178, pp. 2835-2843.*

Kuerten, 2006, Journal of Neuroimmunology, vol. 177, pp. 99-111.*

Calabresi, 1998, Neurology, vol. 51, pp. 289-292.*

Tuohy, 1989, The Journal of Immunology, vol. 142, issue 5, pp. 1523-1527.*

Yu, 1996, Journal of Experimental Medicine, vol. 183, pp. 1777-1788.*

Kim et al. "An ovalbumin-IL-12 fusion protein is more effective than ovalbumin plus free recombinant IL-12in inducing a T helper cell type 1-dominated immune response and inhibiting antigen-specific IgE production", *J. of Immunology* 158(9):4137-4144 (1997).

Lim et al. "Potentiation of antigen-specific, Th1 immune responses by multiple DNA vaccination with an ovalbumin/interferon-gamma hybrid construct", *Immunology* 94(2):135-141 (1998.

Kim et al. "Efficient induction of antigen-specific T helper type 1-mediated immune responses by intramuscular injection with ovalbumin/interleukin-18 fusion DNA", *Vaccine, Butterworth Scientific* 19(30):4107-4114 (2001).

Maecker et al. "Vaccination with allergen-IL-18 fusion DNA protects against, and reverses established, airway hyperreactivity in a murine asthma model", *J. of Immunology* 166(2):959-965 (2001).

Martin et al. "Protective effect of the interleukin-1 receptor antagonist (IL-1ra) on experimental allergic encephalomyelitis in rats", *J. of Neuroimmunology*, 61(2):241-245 (1995).

(Continued)

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(57) **ABSTRACT**

The present invention provides fusion proteins including an autoimmune antigen, an allergen antigen or an alloantigen, and an anti-inflammatory cytokine. Compositions and methods including the fusion proteins are also provided.

10 Claims, 21 Drawing Sheets