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Clare-Salzler

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(54) **MATERIALS AND METHODS FOR DETECTION AND TREATMENT OF IMMUNE SYSTEM DYSFUNCTIONS**

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(56) **References Cited**

U.S. PATENT DOCUMENTS

4,409,243	A		10/1983	Lieb	424/330
4,490,385	A		12/1984	Lieb	424/272
5,008,240	A	*	4/1991	Bentz et al.	514/2
5,449,515	A		9/1995	Hamilton et al.	424/85.2
5,449,688	A	*	9/1995	Wahl et al.	514/546
5,466,823	A	*	11/1995	Talley et al.	548/377.1
5,474,995	A	*	12/1995	Ducharme et al.	514/241
5,476,659	A		12/1995	Goodman et al.	424/278.1
5,512,447	A		4/1996	Baekkeskov et al.	435/7.4
5,538,854	A		7/1996	Faustman	435/7.24
5,601,815	A		2/1997	Powrie et al.	424/85.2
5,604,260	A		2/1997	Guay et al.	514/605
5,643,786	A		7/1997	Cohen et al.	435/325
5,681,842	A		10/1997	Dellaria et al.	514/367
5,827,513	A	*	10/1998	Bond et al.	424/85.2
6,048,850	A	*	4/2000	Young et al.	514/183
6,168,792	B1	*	1/2001	Clare-Salzler	424/184.1
6,403,562	B1	*	6/2002	Johnson et al.	514/21

FOREIGN PATENT DOCUMENTS

EP	0436333	7/1991
WO	9220811	* 11/1992
WO	9408606	* 4/1994
WO	9518799	* 7/1995
WO	9523599	9/1995
WO	95/27500	* 10/1995
WO	9621654	7/1996

OTHER PUBLICATIONS

The Merck Index, Thirteenth Edition, pp. 336, 1481.*
Science, 294, 1638–1639, 2003.*
Ibelgaufts, Dictionary of Cytokines, pp. 393–398, 416–419, 423–425, 685–693, Pub. 1995.*
Coffey, R.G., V.A. Alberts, L.L. Weakland (1990) "Prostaglandin–Dependent Desensitization of Human Monocyte cAMP Responses" *J. Leukocyte Biol.* 48:557–564.
Crofford et al. (1994) "Cyclooxygenase–1 and –2 Expression in Rheumatoid Synovial Tissues" *J. Clin. Invest.* 93:1095–1101.
Endres, S. et al., (1991) "Cyclic nucleotides differentially regulate the synthesis of tumor necrosis factor–α and interleukin–1β by human mononuclear cells" *Immunology* 72:56–60.
Farber, Joshua M. (1992) "A Collection of mRNA Species That Are Inducible In The RAW 264.7 Mouse Macrophage Cell Line by Gamma Interferon and Other Agents" *Molecular and Cellular Biology* 12(4):1535–1545.
Hafler, David A., Marion Buchsbaum, Howard L. Weiner (1985) "Decreased Autoogous Mixed Lymphocyte Reaction In Multiple Sclerosis" *Journal of Neuromimmunology* 9:339–347.
Howard, M. et al. (1992) "Biological Propeties of Interleukin 10" *Journal of Clinical Immunology* 12(4):239–247.
Kujubu, D.A. et al. (1991) "TIS10, a Phorbol Ester Tumor Promoter–inducible mRNA from Swiss 3T3 Cells, Encodes a Novel Prostaglandin Synthase/Cyclooxygenase Homologue" *Journal of Biological Chemistry* 266(20):12866–12872.
Mertz, Prema M., David L. DeWitt, William G. Stetler-Stevenson, Larry M. Wahl (1994) "Interleukin 10 Suppression of Monocyte Prostaglandin H Synthase–2" *Journal of Biological Chemistry* 269(33):21322–21329.
Rasanen, L. et al. (1988) "Defective autologous mixed leukocyte reaction in newly diagnosed type 1 diabetes mellitus" *Clin. Exp. Immunol.* 71:470–474.
Ristimaki, Ari, Susan Garfinkel, Jorg Wessendorf, Thomas Maciag, Timothy Hla (1994) "Induction of Cyclooxygenase–2 by Interleukin– 1α" *Journal of Biological Chemistry* 269(16):11769–11775.
Seldon, Paul M., Peter J. Barnes, Koremu Meja, Mark A. Giembycz (1995) "Suppression of Lipopolysaccharide–Induced Tumor Necrosis Factor–α Generation from Human Peripheral Blood Monocytes by Inhibitors of Phosphodiesterase 4:Interaction with Stimulants of Adenylyl Cyclase" *Molecular Pharmacology* 48:747–757.

(Continued)

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(57) **ABSTRACT**

The subject invention concerns novel materials and methods for the treatment and/or prevention of autoimmune disease. In a specific embodiment, elevated production of prostaglandin synthase-2 (PGS-2) is correlated with autoimmune dysfunction.

2 Claims, 3 Drawing Sheets