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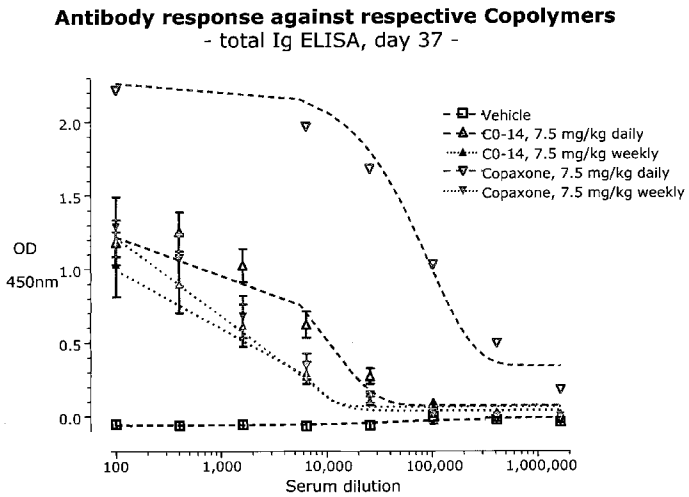

(57) Abstract: The invention relates to novel methods and kits for treating or preventing disease through the administration of random copolymers. The invention also relates to the treatment of autoimmune diseases, such as multiple sclerosis, and to the administration of random copolymers in treatment regimen comprising formulations that are administered at intervals greater than 24 hours, or to sustained release formulations which administer the copolymer over a period greater than 24 hours. The invention further relates to methods for conducting a pharmaceutical business comprising manufacturing, licensing, or distributing kits containing or relating to the formulations or dosing regimens of random copolymer described herein.

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METHODS OF TREATING DISEASE WITH RANDOM COPOLYMERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Ser. No. 60/569292 filed May 7, 2004, and to U.S. Provisional Application Ser. No. 60/663333 filed March 18, 2005.

BACKGROUND OF THE INVENTION

An autoimmune disease results from an inappropriate immune response directed against a self antigen (an autoantigen), which is a deviation from the normal state of self-tolerance. Self-tolerance arises when the production of T cells and B cells capable of reacting against autoantigens has been prevented by events that occur in the early development of the immune system. The cell surface proteins that play a central role in regulation of immune responses through their ability to bind and present processed peptides to T cells are the major histocompatibility complex (MHC) molecules (Rothbard, J.B., *et al.*, 1991, *Annu. Rev. Immunol.* 9:527). Autoimmune diseases include rheumatoid arthritis (RA), multiple sclerosis (MS), human type I or insulin-dependent diabetes mellitus (IDDM), autoimmune uveitis, primary biliary cirrhosis (PBC) and celiac disease.

One target for inhibition of an autoimmune response is the set of lymphocyte surface protein MHC molecules, particularly a protein encoded by an MHC class II gene, for example, HLA-DR, -DQ and -DP. Each of the MHC genes is found in a large number of alternative or allelic forms within a mammalian population. The genomes of subjects affected with certain autoimmune diseases, for example MS and RA, are more likely to carry one or more characteristic MHC class II alleles, to which that disease is linked.

A number of therapeutic agents have been developed to treat autoimmune diseases, including general anti-inflammatory drugs such as COX-2 inhibitors, *i.e.*, agents that can prevent formation of low molecular weight inflammatory compounds by inhibiting a cyclooxygenase; agents that can function by inhibiting a protein mediator of inflammation, for example, by sequestering the inflammatory protein tumor necrosis factor (TNF) with an anti-TNF specific monoclonal antibody or antibody fragment, or with a soluble form of the TNF receptor; and agents that target a protein on the surface of a T cell and generally prevent interaction with an

antigen presenting cell (APC) by inhibiting the CD4 receptor or the cell adhesion receptor ICAM-1. However, compositions having natural folded proteins as therapeutic agents can encounter problems in production, formulation, storage, and delivery. Several of these problems necessitate delivery to the patient in a hospital setting.

An agent that interacts and binds relatively nonspecifically to several MHC class II molecules is Copolymer 1 (Cop 1), a synthetic amino acid heteropolymer that was shown to be capable of suppressing experimental allergic encephalomyelitis (EAE; Sela, M. *et al.*, 1990, Bull. Inst. Pasteur (Paris)), which can be induced in the mouse and is a model for MS. Copolymer 1, which is poly(Y,E,A,K) also known as glatiramer acetate or "YEAK" using the one letter amino acid code (see infra; Y represents tyrosine, E glutamic acid, A alanine, and K lysine), has been used to treat relapsing forms of MS but does not suppress the disease entirely (Bornstein, M.B., *et al.*, 1987, *N. Engl. J. Med.* 317:408; Johnson, K.P. *et al.*, 1995, *Neurology* 45:1268).

Although random copolymers may be effective for the treatment of autoimmune diseases (Simpson, D. *et al.*, 2003, *BioDrugs* 17(3):207-10), their repeated administration may cause undesired side effects. Accordingly, there is a need for improved methods for the treatment of autoimmune diseases with random copolymers which result in fewer side effects.

BRIEF SUMMARY OF THE INVENTION

The invention provides methods and kits for the treatment or prevention of disease in a subject, preferably in a human. One aspect of the invention provides methods of treating or preventing a disease, the method comprising administering to said subject a dosing regimen of an effective amount of a random copolymer for the amelioration of a disease treatable with the random copolymer, said effective amount delivered to said subject at time intervals greater than 24 hours, 36 hours, or more preferably greater than 48 hours. A related aspect of the invention provides a method for the treatment of a subject in need thereof, comprising administering to said subject a dosing regimen of an effective amount of a random copolymer for the amelioration of a disease treatable with the random copolymer, said effective amount delivered to the subject using a sustained-release formulation which administers the random copolymer over a period of at least 2 days, at least 4 days, or at least 6 days, wherein the effective amount is an amount that is effective if delivered daily. In some embodiments, the disease of the methods

of the present invention is mediated by T-cells, and in particular T_H1 cells or cells with T_H1 immune posture, or is a disease which is exacerbated by an excess of inflammatory cytokines. In some embodiments, the disease is an autoimmune disease, such as multiple sclerosis. In some preferred embodiments, the random copolymer comprises tyrosine (Y), phenylalanine (F), alanine (A) and lysine (K) (YFAK copolymer). In other embodiments, the random copolymer is Copolymer 1 (YEAK). The invention is not limited to any particular random copolymer or mode of administration.

The invention also provides kits for the treatment of disease. One aspect of the invention provides a kit for the treatment of an autoimmune disease comprising (i) a composition comprising a random copolymer and (ii) instructions for administering the composition to a subject at time intervals of at least 24 hours, or more preferably 36 or 48 hours or longer. In preferred embodiments, the composition is formulated for subcutaneous injection, the random copolymer is YFAK or Copolymer 1, and the disease is an autoimmune disease, such as multiple sclerosis, particularly relapsing-remitting multiple sclerosis.

The invention further provides agents for the manufacture of medicaments to treat diseases. Any methods disclosed herein for treating or preventing a disease by administering a random copolymer to a subject may be applied to the use of the random copolymer in the manufacture of a medicament to treat that disease. Accordingly, one aspect of the invention provides the use of a random copolymer for the treatment of a disease in a subject, wherein the random copolymer is formulated to be administered to the subject at intervals greater than 24 hours, 36 hours, and more preferably of at least 48 hours. In preferred embodiments, the random copolymer is Copolymer 1 (YEAK), and the disease is an autoimmune disease, such as multiple sclerosis, particularly relapsing-remitting multiple sclerosis.

The invention further provides methods of conducting a pharmaceutical business.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the effect of copolymer administration on the disease progression of EAE.

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