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(54) Title: COMPOSITIONS AND METHODS FOR TREATING VASCULAR, AUTOIMMUNE AND INFLAMMATORY DISEASES

(57) Abstract: The disclosure provides methods and compositions for the treatment of vascular, autoimmune and inflammatory diseases using a combination of an inosine monophosphate dehydrogenase (IMPDH) inhibitor and a HMG CoA reductase inhibitor.

COMPOSITIONS AND METHODS FOR TREATING VASCULAR, AUTOIMMUNE AND INFLAMMATORY DISEASES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit under 35 U.S.C. § 119(e) to application Serial No. 60/651,301, filed February 8, 2005, the contents of which are incorporated herein by reference.

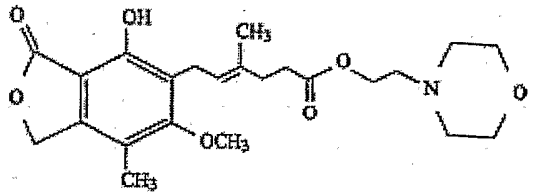
FIELD

[0002] The present invention relates generally to compositions and methods for treating vascular, autoimmune and inflammatory diseases by adjunctively administering to subjects an IMPDH inhibitor, (and/or a prodrug thereof) and an HMG-CoA reductase inhibitor (and/or a prodrug thereof).

BACKGROUND

[0003] Inosine monophosphate dehydrogenase (IMPDH) is the rate-limiting enzyme in the de novo biosynthesis of guanosine nucleotides in mammals. Both T- and B- lymphocytes rely exclusively on de novo guanosine nucleotide synthesis as they are deficient in salvage pathways.

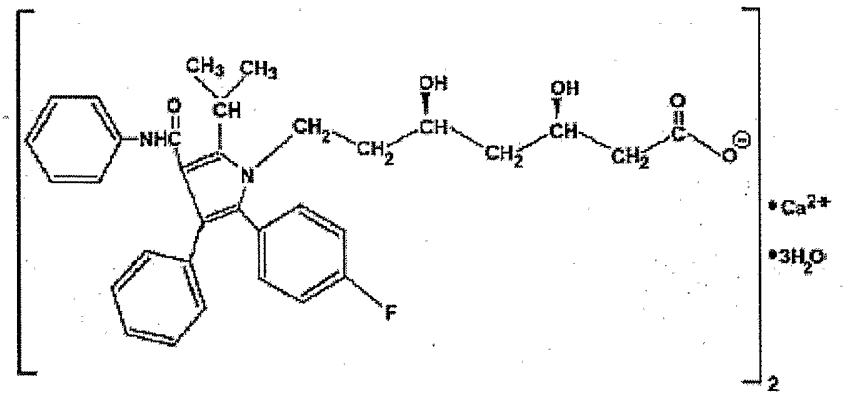
[0004] Mycophenolic acid ("MPA") is a potent inhibitor of IMPDH that has gained widespread acceptance as an immunosuppressant, particularly in the prophylactic treatment of organ rejection in patients receiving allogenic renal, cardiac or hepatic transplants. MPA treatment in the form of the 2-morpholinoethyl ester prodrug mycophenolate mofetil ("MMF"; structure illustrated below) is marketed in the US for these indications by Hoffman LaRoche under the tradename Cell Cept®:



[0005] CellCept® is currently available in capsule (250 mg), tablet (250 mg and 500 mg), oral suspension (200 mg/ml when constituted) and intravenous (6 mg/ml in 5% dextrose when reconstituted) dosage forms. Following oral or intravenous administration, the MMF is rapidly and completely metabolized to the active metabolite MPA (see, *e.g.*, *Physicians Desk Reference*, 2005 Ed., pp. 2855; "PDR").

[0006] A delayed-release, enterically coated tablet formulation of the sodium salt of mycophenolic acid (mycophenolate sodium) is marketed in the U.S. by Novartis AG under the tradename Myfortic®. Each tablet contains either 180 mg or 360 mg of mycophenolate sodium. According to the 2005 Edition of the PDR, Myfortic® is currently approved for the prophylactic treatment of organ rejection in patients receiving allogenic renal transplants.

[0007] Lipid lowering agents are another class of therapeutic agent which has achieved widespread commercial use. Major components of this class include the statins, nicotinic acid (niacin), and fibric acid derivatives. The statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. An exemplary statin is atorvastatin (Lipitor®), which is a pharmaceutical salt preparation and has the following structural formula:



[0008] Clinical and laboratory evidence indicate that statins have pleiotropic effects in addition to lipid-lowering activity. The mechanism of statins' varied effects remains poorly understood, but various hypotheses have been cited (Ehrenstein et al., 2005, *N. Engl J Med.* 352:1-3; Barilla-LaBarca et al., 2003, *Curr Opin Rheumatol.* 15(1):55-60; Carroll, M.C., 2004, *Nat Rev Immunol.* 4(10):825-31).

[0009] A need exists to identify improved therapeutic compositions that can be used for the treatment of vascular, autoimmune and inflammatory diseases. The instant disclosure provides such therapeutic compositions and methods, relying on a novel understanding of these compositions and their combined utility in treating certain vascular, autoimmune and inflammatory disease processes.

SUMMARY

[0010] In one aspect, the present disclosure provides methods for treating selected vascular, autoimmune and inflammatory diseases in a subject by adjunctively administering to the subject an IMPDH inhibitor and an HMG-CoA reductase inhibitor (including their corresponding salts, hydrates, and solvates).

[0011] The IMPDH inhibitor can be any compound that inhibits the activity of IMPDH, or a prodrug of such an IMPDH-inhibitory compound (*i.e.*, a compound that metabolizes under conditions of use to a compound that inhibits the activity of IMPDH). Such IMPDH inhibitory compounds and prodrugs are well-known, and

include, by way of example and not limitation, inhibitors 3-(1-deoxy-beta-D-ribofuranosyl)benzamide (Jayaram et al., 1992, *Biochem Biophys Res Commun.* 186(3):1600-6), mizoribine, 5-beta-D-ribofuranosylselenophene-3-carboxamide (Franchetti et al., 1997, *J Med Chem.* 40(11):1731-7), N-[2-[2-[[3-methoxy-4-(5-oxazolyl)phenyl]amino]-5-oxazolyl]phenyl]-N-methyl-4- morpholineacetamide (Dhar et al., 2002, *J Med Chem.* 45(11):2127-30), and mycophenolic acid and their various corresponding salts, hydrates, solvates and esters. Other IMPDH inhibitors include compounds disclosed in U.S. Patent Nos. 5,807.876; 5,932,600; 6,054,472; 6,344,465; 6,420,403; 6,518,291; 6,541,496; 6,596,747; 6,617,323; and 6,624,184. In some embodiments, the IMPDH inhibitory compound administered is mycophenolic acid and/or a salt, hydrate, solvate and/or ester thereof. In a specific embodiment, the compound administered is selected from a salt of mycophenolic acid, such as, for example, mycophenolate sodium, and an ester of mycophenolic acid, such as, for example, mycophenolate mofetil.

[0012] The HMG CoA reductase inhibitor can be any compound that inhibits the activity of HMG CoA reductase, or a prodrug of such a HMG CoA reductase inhibitory compound. A useful class of HMG CoA reductase inhibitors is statins, which are generally prescribed for treating a hypercholesteremic condition. Exemplary HMG CoA reductase inhibitors include, among others, mevastatin, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, pitavastatin, and rosuvastatin.

[0013] The IMPDH and HMG-CoA reductase inhibitor compounds can be administered simultaneously, either as separate dosage forms or as a single combination dosage form. Alternatively, they may be administered at different times.

[0014] The combination therapy may be practiced in patients suffering from a vascular, autoimmune and/or inflammatory disease, or a condition associated with such diseases. In some embodiments, the combination of drugs can be administered prophylactically to patients that do not currently suffer from such a disease or condition. Thus, in some embodiments, the prophylactic therapy is practiced in patients that are at risk of developing a vascular, autoimmune and/or

inflammatory disease or a condition associated with a vascular, autoimmune and/or inflammatory disease.

[0015] In some embodiments, the condition treated is associated with an autoimmune disease, such as systemic lupus erythematosus, rheumatoid arthritis, and diabetes mellitus, and includes conditions such as atherosclerosis, cardiovascular disease, and other vascular diseases, which occur at higher frequency in patients with the particular autoimmune disorder. In other embodiments, the condition associated with the autoimmune disease is an inflammatory reaction, which typically accompanies many different autoimmune reactions. In various embodiments, the combination of drugs may be administered at doses effective to treat or reduce the risk of developing the associated condition regardless of the effectiveness of the drugs on the underlying disease.

[0016] The amounts of the IMPDH and HMG CoA reductase inhibitors administered can be the standard dosages typically administered for their approved indications (as specified in The 2005 edition of The Physician's Desk Reference; "PDR"), or alternatively, the amounts administered for either or both compounds can be selectively varied. In some embodiments, it may be desirable to administer an amount of IMPDH inhibitor that provides therapeutic or prophylactic benefit for the indications described herein but that is less than the amount typically administered for the treatment or prophylaxis of allograft transplant rejection. In this way, therapeutic and/or prophylaxtic benefit may be achieved without compromising the immune system of the subject. Thus, in some embodiments, the daily amount of IMPDH inhibitor administered will correspond to a low dose, an extra-low dose or an ultra-low dose as described further herein below.

[0017] The combination therapy may utilize a single compound of each class, for example a single IMPDH inhibitor and a single HMG CoA reductase inhibitor, or multiple compounds from each class, for example, a single IMPDH inhibitor and two different HMG CoA reductase inhibitors, two different IMPDH inhibitors and a single HMG CoA reductase inhibitor, two different IMPDH inhibitors and two different HMG CoA reductase inhibitors, etc.

[0018] In another aspect, the present disclosure provides pharmaceutical compositions comprising a HMG CoA reductase inhibitor and an IMPDH inhibitor (including salts, hydrates and/or solvates of such compounds) and one or more pharmaceutically acceptable carriers, excipients and/or diluents. In some embodiments, the amounts of the compounds included in the composition are specifically suited to provide therapeutic and/or prophylactic benefit in the methods described herein. Accordingly, in some embodiments, the compositions comprise unit dosage amounts or fractional unit dosage amounts of the IMPDH inhibitor(s) that are tailored to administer low, extra-low or ultra-low daily dosages.

[0019] In another aspect, the present disclosure provides methods of treating and/or preventing restenosis, which typically arises from vascular reconstructive procedures such as the use of a stent to open clogged arteries. The methods generally comprise adjunctively administering to a subject an effective amount of an IMPDH inhibitor and a HMG CoA reductase inhibitor. The HMG CoA reductase inhibitor and IMPDH inhibitor can be administered to the subject via systemic routes of administration, or provided in the stent itself for local administration, such as in a polymer coating on the stent. Polymer coatings that allow slow or quick release of the compounds can be used.

[0020] In another aspect, the present disclosure provides kits useful for practicing the various methods described herein. In some embodiments, the kits comprise an IMPDH inhibitor and a HMG CoA reductase inhibitor in formulations suitable for administration to subjects. The compounds may be in separate containers, or provided as compositions, either as solid dosages or liquid formulations. The kits may further comprise devices for their administration and/or instructions for proper dosing.

BRIEF DESCRIPTION OF THE FIGURES

[0021] FIG. 1 shows the effect of administering mycophenolate mofetil to Ldlr -/- mice at a dosage of 15 mg/kg/day in reducing atherosclerotic plaques.

[0022] FIG. 2 illustrates the effect of mycophenolate mofetil in reducing serum triglycerides (Tgs) in male Ldlr-/- mice when given at a dosage of 15 mg/kg/day.

[0023] FIG. 3 illustrates the effect of mycophenolate mofetil in reducing serum phospholipids (PPL) in male Ldlr-/- mice when given at a dosage of 15 mg/kg/day.

[0024] FIG. 4 illustrates the effect of mycophenolate mofetil on high-density lipoprotein levels in male Ldlr-/- mice when given at a dosage of 15 mg/kg/day.

[0025] FIG. 5 illustrates the serum levels of mycophenolate mofetil in Ldlr-/- mice for corresponding dosages of 15 mg/kg/day and 100 mg/kg/day.

DETAILED DESCRIPTION

[0026] The present disclosure provides methods and compositions for treating vascular, autoimmune and inflammatory diseases in a subject. The methods comprise adjunctively administering to the subject an effective amount of a combination of an IMPDH inhibitor and a HMG-CoA reductase inhibitor. This combination therapy may provide treatment for indications not previously achieved by either drug separately.

[0027] From studies of patients afflicted with systemic lupus erythematosus (SLE), an autoimmune disease with an associated inflammatory component, the inventors recognize that the risk of myocardial infarction is increased by as much as 9-fold in patients with SLE, even after adjustment for CVD risk factors such as hypertension and high cholesterol (Esdaile et al., 2001, *Arth. & Rheum.* 44(10):2331-2337). Unstable, rupture prone plaques, which are thought to be responsible for incidences of myocardial infarction and other ischemic events, have identifiable features, including numerous inflammatory cells. These unstable plaques are characterized by active inflammation that may overwhelm the plaque's capacity for repair (Ross R., 1999, Atherosclerosis - an inflammatory disease," *N Engl J Med.* 340:115–126). Macrophages and T cells are abundant in the regions of plaque rupture, while smooth muscle cells are few. Stable plaques, conversely, contain few inflammatory cells and have abundant smooth muscle cells. Thus, a defective

inflammatory response involved in SLE may be responsible for both the underlying disease and the cardiovascular outcomes of the disease.

[0028] On the other hand, clinical and genetic studies in humans and animal models indicate a crucial protective role for the complement system in systemic lupus erythematosus (SLE). This presents a paradox because the complement system is considered to be an important mediator of the inflammation that is observed in patients with SLE. One current view is that complement provides protection by facilitating the rapid removal of apoptotic debris to circumvent an autoimmune response. (Barilla-LaBarca et al., 2003, *Curr Opin Rheumatol.* 15(1):55-60) In an alternative model, complement, together with other components of the innate immune system, participates in the 'presentation' of SLE-inducing self-antigens to developing B cells. In this way, the complement system and innate immunity may protect against responses to SLE (self) antigens by enhancing the elimination of self-reactive lymphocytes. (Carroll, MC., 2004, *Nat Rev Immunol.* 4(10):825-31).

[0029] Because the inflammatory component and the self reactive lymphocytes prominent in SLE may be responsible for the adverse physiological effects seen in patients afflicted with SLE, immunosuppressive therapy using cytotoxic agents may provide a therapeutic benefit to such patients by reducing the inflammatory reaction and attenuating the activity of self-reactive lymphocytes. A class of useful immunosuppressives for this purpose is IMPDH inhibitors, such as mycophenolic acid and its prodrug form mycophenolate mofetil, which targets the enzyme catalyzing the rate-limiting step in the de novo biosynthesis of guanine nucleotides from inosine. Since T and B-lymphocytes rely almost exclusively on the de novo pathway of purine synthesis, IMPDH inhibitors specifically target the proliferation of T and B cells, thereby inhibiting production of antibodies and generation of cytotoxic T lymphocytes. This degree of specificity is a desirable characteristic for immunosuppressive therapy when the therapeutic mechanism is cytotoxicity. In addition, it has been noted that in some disease states, such as atherosclerosis, T-regulatory cells elaborate numerous cytokines that influence the recruitment of monocyte macrophages into tissue macrophages. Thus, therapies targeted at

individual cytokines would be expected to show diminished efficacy when compared to a therapy that targets the T-cell as a complete unit (Freeman M, "Type II Diabetes and Atherosclerosis" – Oral Presentation at the Keystone Meeting on Adipogenesis, Obesity and Inflammation, Vancouver, B.C., January 25, 2006).

[0030] However, in developing effective therapeutic treatments, use of a combination of drugs (*i.e.*, drug cocktails) that act by different mechanisms but which affect the same underlying cause of the disorder may be more effective than use of a single therapeutic agent. This "multi-hit" approach to therapeutics may be more beneficial for several reasons: (1) less variability in the response of the treated population to several therapeutic agents compared to a single therapeutic agent, and (2) stricter modulation of the physiological processes responsible for the disease by targeting multiple biochemical pathways that impinge upon the disease process.

[0031] Statins, a class of HMG CoA reductase inhibitors, are generally prescribed to treat hyperlipidemic condition characterized by elevated cholesterol levels. Statins, however, have pleiotropic effects on the vasculature and the immune system, independent of statin's ability to modulate serum cholesterol.

[0032] Statins can directly upregulate endothelial nitric oxide synthase (eNOS) expression *in vitro* under cholesterol clamped conditions (Laufs et al., 1998, "Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors," *Circulation* 97:1129–1135). Both simvastatin and lovastatin upregulate eNOS expression almost fourfold, and completely prevent its downregulation by oxidized LDL. The upregulation of eNOS is reversed by the addition of mevalonate. In addition, a significant increase in endothelium-dependent vasodilation in patients with moderate hypercholesterolemia is observed after 4 weeks of treatment with simvastatin (O'Driscoll et al., 1997, "Simvastatin, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month," *Circulation* 95:1126–1131). The neuroprotective effect of statins is absent in eNOS deficient mice, suggesting that enhanced eNOS activity by statins is a main mechanism by which HMGCoA reductase inhibitors protect against cerebral injury (Endres et al., 1998, "Stroke

protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase," *Proc Natl Acad Sci USA* 95:8880–8885).

[0033] Furthermore, the statin fluvastatin appears to decrease MMP-1 expression in human vascular endothelial cells in a time- and dose-dependent manner (Ikeda et al., 2000, "Fluvastatin inhibits matrix metalloproteinase-1 expression in human vascular endothelial cells," *Hypertension* 36:325–329). This effect is also seen with lovastatin and again is completely blocked by coincubation with mevalonate. The concentration of fluvastatin required to reduce MMP-1 expression is similar to that seen in clinical practice.

[0034] Pravastatin has been shown to cause changes in the composition of atheromatous plaque independent of its cholesterol lowering effect. Pravastatin-treated monkeys have enhanced vasodilator function and favorable changes in the composition of atheromatous plaque compared with control animals with similar changes in lipid profile caused by diet alone (Williams et al., 1998, "Pravastatin has cholesterol-lowering independent effects on the artery wall of atherosclerotic monkeys," *J Am Coll Cardiol* 31:684–691). The pravastatin-treated monkeys had fewer macrophages in the intima and media, less calcification and less neovascularization in the intima. Pravastatin may thus serve to stabilize vulnerable plaques by promoting regression of fragile, rupture prone microvessels in the intima.

[0035] Numerous studies also suggest important effects of statins on macrophage and T-Cell function. Macrophages are capable of degrading the extracellular matrix and, by secreting matrix metalloproteinase (MMP), may weaken the fibrous cap and thus predispose an atheromatous plaque to rupture. Fluvastatin and simvastatin have been shown to inhibit MMP-9 (gelatinase B) activity and secretion by macrophages (Bellosta et al., 1998, "HMG-CoA reductase inhibitors reduce MMP-9 secretion by macrophages," *Arterioscler Thromb Vasc Biol.* 18:1671–1678). This effect is reversed by the addition of mevalonate, suggesting that it is mediated by HMG CoA reductase inhibition.

[0036] Hypercholesterolemic rats treated with fluvastatin have attenuated leukocyte adherence responses to platelet activation factor and leukotriene B4 (Kimura M. et al., 1997, "Effects of fluvastatin on leukocyte-endothelial cell adhesion in hypercholesterolemic rats," *Arterioscler Thromb Vasc Biol* 17:1521–1526). Statins inhibit the expression of CD-11b on the cell surface, thus reducing the adhesiveness of macrophages to the vascular endothelium (Weber et al., 1997, " HMG-CoA reductase inhibitors decrease CD11b expression and CD11b-dependent adhesion of monocytes to endothelium and reduce increased adhesiveness of monocytes isolated from patients with hypercholesterolemia," *J Am Coll Cardiol* 30:1212–1217). Atorvastatin reduces monocyte chemo-attractant protein-1 levels in the intima and media in hypercholesterolemic rabbits (Bustos et al., 1998, "HMG-CoA reductase inhibition by atorvastatin reduces neointimal inflammation in a rabbit model of atherosclerosis," *J Am Coll Cardiol* 32:2057–2064). This decrease in monocyte chemo-attractant protein-1 is related to a reduction in nuclear factor κB activation, a transcription factor involved in the induction of monocyte chemo-attractant protein-1 and other proinflammatory cytokines such as IL-1β and tumor necrosis factor-α (TNF-α).

[0037] Statins also cause a decrease in macrophage expression of soluble intercellular adhesion molecule-1 and lipopolysaccharide-induced secretion of IL-6 and TNF-α by monocytes and macrophages (Niwa et al., 1996, "Inhibitory effect of fluvastatin, an HMG-CoA reductase inhibitor, on the expression of adhesion molecules on human monocyte cell line," *Int J Immunopharmacol* 18:669–675; Ikeda et al., 1999, "Statins and monocytes," *Lancet* 353:2070; and Rosenson et al., 1999, "Inhibition of proinflammatory cytokine production by pravastatin," *Lancet* 353:983–984). Simvastatin therapy for 8 weeks reduces monocyte expression of TNF-α and IL-1β by 49 and 35%, respectively (Ferro et al., 2000, "Simvastatin inhibits the monocyte expression of proinflammatory cytokines in patients with hypercholesterolemia," *J Am Coll Cardiol* 36:427–431); this is intriguing data because elevated plasma levels of both soluble intercellular adhesion molecule-1 and IL-6 have been shown to predict risk for myocardial infarction (Ridker et al., 2000, "Plasma concentration of interleukin-6 and the risk of future myocardial

infarction among apparently healthy men," *Circulation* 101:1767–1772; Ridker et al., 1998, "Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men," *Lancet* 351:88-92). A recent analysis from the Cholesterol and Recurrent Events (CARE) trial showed that plasma concentrations of TNF-α are also persistently elevated among postmyocardial infarction patients at increased risk for coronary events (Ridker et al., 2000, "Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction," *Circulation* 101:2149–2153).

[0038] The anti-inflammatory activity of statins may also be explained based on the role of oxidized LDL in the atherogenic pathway. The uptake of oxidized LDL by macrophages generates lipid rich foam cells. Oxidized LDL causes monocyte tissue factor expression, and the proliferation and apoptosis of smooth muscle cells (Bjorkerud et al., 1996, "Contrary effects of lightly and strongly oxidized LDL with potent promotion of growth versus apoptosis on arterial smooth muscle cells, macrophages, and fibroblasts," *Arterioscler Thromb Vasc Biol* 16:416–424; Broze, GJ, 1992, "The role of tissue factor pathway inhibitor in a revised coagulation cascade," *Semin Hematol* 29:159–169). Oxidized LDL also inhibits nitric oxide synthase activity and hence impairs endothelium-dependent vasodilation (Laufs et al., 1998, "Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors," *Circulation* 97:1129–1135). Statins reduce the susceptibility of LDL to oxidation by a variety of mechanisms. Statins reduce the cholesterol content of lipoproteins through their hypocholesterolemic effects, and thus lower the amount of substrate available for oxidation (Hoffman et al., 1992, "Hypolipidemic drugs reduce lipoprotein susceptibility to undergo lipid peroxidation: in vitro and ex vivo studies," *Atherosclerosis* 93:105–113). Simvastatin also reduces macrophage superoxide formation, thereby decreasing cell oxygen production (Giroux et al., 1993, "Simvastatin inhibits the oxidation of low-density lipoproteins by activated human monocyte-derived macrophages," *Biochim Biophys Acta* 1165:335–338). Fluvastatin and lovastatin bind to phospholipid on the surface of LDL and thus prevent diffusion into the lipoprotein core of free radicals generated under oxidative stress (Aviram et al., 1998, "Interactions of platelets, macrophages, and lipoproteins in

hypercholesterolemia: antiatherogenic effects of HMG-CoA reductase inhibitor therapy," *J Cardiovasc Pharmacol* 31:39–45). Atorvastatin and fluvastatin have also been shown to have direct antioxidant potential (Aviram et al., 1998, "Atorvastatin and gemfibrozil metabolites, but not the parent drugs, are potent antioxidants against lipoprotein oxidation," *Atherosclerosis* 138:271–280; Suzumura et al., 1999, "Protective effect of fluvastatin sodium (XU-62-320), a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, on oxidative modification of human low-density lipoprotein in vitro," *Biochem Pharmacol* 57:697–703).

[0039] Pravastatin therapy is associated with a reduction in the number of episodes of rejection following cardiac transplantation. The inhibition of natural killer T cell activity by pravastatin may explain, in part, this beneficial effect (Kobashigawa et al., 1995, *N Engl J Med.* 333(10):621-7). Although transplant vasculopathy is an entity distinct from atherosclerotic disease, similar inflammatory mediators may contribute to plaque instability.

[0040] There is also an indication that statins may be beneficial for multiple sclerosis and other Th1-mediated autoimmune disease. (Yousseff et al. 2002, *Nature*. 420(6911):78-84). This conclusion was based on the finding of direct effects of atorvastatin (Lipitor®) on differentiation of Th0 cells into Th2 cells in the mouse model of chronic and relapsing experimental autoimmune encephalomyelitis (EAE). Atorvastatin can induce STAT6 phosphorylation and secretion of Th2 cytokines (interleukin (IL)-4, IL-5 and IL-10) and transforming growth factor (TGF)-beta. Conversely, STAT4 phosphorylation was inhibited and secretion of Th1 cytokines (IL-2, IL-12, interferon (IFN)-gamma and tumour necrosis factor (TNF)-alpha) was suppressed. Thus, atorvastatin has pleiotropic immunomodulatory effects involving both APC and T-cell compartments.

[0041] The pleiotropic biological properties of statins may be attributable to their effect on the synthesis of intermediates used as lipid attachments for the modification and membrane localization of proteins. Farnesyl and geranylgeranyl groups are found on a variety of proteins, including heterotrimeric G proteins, nuclear lamins, and small GTP-binding proteins, such as ras, rho, rab rac, ral and rap.

Inhibiting lipid attachment results in protein mislocalization in the cytoplasm, thereby disrupting proper protein function. The pleiotropic effects of statins may arise from the critical role played by many of these lipidated proteins (*e.g.*, ras and rho) in signal transduction pathways.

[0042] Given the pleiotropic effects of statins and its posited mechanism of action, treatment with a combination of a HMG CoA reductase inhibitor and an IMPDH inhibitor may provide a greater therapeutic benefit in patients afflicted with autoimmune and/or inflammatory diseases, since these agents appear to work via different mechanisms in influencing inflammatory and immune responses. Accordingly, the present disclosure provides a method of treating vascular, autoimmune, or inflammatory diseases, or a condition associated with such diseases, with a combination of an IMPDH inhibitor and a HMG CoA reductase inhibitor.

[0043] As used herein, an "HMG-CoA reductase inhibitor" includes any compound that inhibits or reduces the biological activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. One important class of HMG CoA reductase inhibitors is statins, various embodiments of which are known in the art. Atorvastatin, and derivatives thereof, are described in U.S. Patent No. 5,273,995 and EP 409281 and are available commercially under the tradenames Lipitor®, Sortis®, Torvast®, Totalip®, and Xarator®. Cerivastatin is described in U.S. Patent Nos. 5,006,530 and 5,177,080, and EP 325130, and is available under the tradenames Rivastatin®, Baycol®, and Lipobay®. Although the levels of cerivastatin prescribed for hyperlipidemia has resulted in toxic side effects, lower non-toxic levels may be appropriate for treatments described herein. Lovastatin and derivatives thereof are described in U.S. Patent No. 4,231,938 and are available under the tradenames Altocar®, Lovalip®, Mevacor®, Mevinacor®, Nevlor®, and Sivlor®. Pitavastatin and derivatives thereof are described in EP65835 and U.S. Patent No. 6,162,798, and are available under the tradenames Itabastatin®, Livalo®, Nisvastatin®, Itavastatin®, and Zomaril®. Pravastatin and derivatives thereof are described in U.S. Patent No. 4,346,227 and DE 3122499 and are available under the tradenames Elisor®, Lipostat®, Liprevil®, Mevalotin®, Oliprevin®, Pravachol®,

Pravasin®, Selectin®, and Vasten®. Rosuvastatin and derivatives thereof are described in U.S. Patent Nos. 5,128,366; 5,260,440; and 6,589,959; and patent EP 521471. Simvastatin and derivatives thereof are described in U.S. Patent No. 4,444,784 and EP 33538 and are available under the tradenames Denan®, Liponorm®, Simovil®, Sinvacor®, Sivastin®, Zocor®, and Zocord®. Fluvastatin and derivatives thereof are described in U.S. Patent No. 4,739,073 and WO 84/02131 and are available under the tradenames Fluindostatin®, XU 62-320®, Lescol®, Lipaxan® and Primexin®. Mevastatin is described in, among others, Fears et al., 1980, *Atherosclerosis* 35(4):439-49, and is also known as compactin. The statins may be used individually, or as compatible mixtures to enhance efficacy and/or reduce toxicity of the HMG CoA reductase inhibitors.

[0044] In some embodiments, the combination therapy may also include other lipid lowering drugs, such as fibric acid derivatives. Exemplary fibric acid derivatives include, among others, clofibrate, colestipol, and gemfibrozil. Clofibrate is described in U.S. Patent No. 3,262,850 and GB 860303 and is available under the tradenames Amotril®, Anparton®, Apolan®, Artevil®, Claripex®, Liprinal®, Normet®, Regelen®, Serotinex®, and Xyduril®. Colestipol and derivatives thereof are described in U.S. Patent Nos. 3,692,895 and 3,803,237, and patents DE 1927336 and DE 2053585. Gemfibrozil and derivatives thereof are described in U.S. Patent Nos. 3,674,836 and 4,126,637, and patent DEL 1925423 and are available under the tradenames Decrelip®, Genlip®, Gevilon®, Lipozid®, and Lopid®.

[0045] As used herein, "IMPDH inhibitory compound" or "IMPDH inhibitor" refers to any compound that inhibits or reduces the activity of inosine monophosphate dehydrogenase (IMPDH), the rate-limiting enzyme in the de novo biosynthesis of guanosine nucleotides. Also included within the definition are prodrugs of such IMPDH inhibitory compounds (for example, esters of such compounds) that metabolize under their conditions of use to an active metabolite that is an IMPDH inhibitory compound.

[0046] Significant members of the class of IMPDH inhibitory compounds are mycophenolic acid ("MPA") and its corresponding salts, hydrates, solvates and

esters, and mycophenolate mofetil ("MMF") and its corresponding salts, hydrates and solvates. MMF is the 2-morpholinoethyl ester prodrug of MPA. When administered orally or intravenously, MMF rapidly and completely metabolizes to MPA. MPA is a selective, non-competitive and reversible inhibitor of IMPDH (in particular the type II isoform) and strongly inhibits both T- and B lymphocyte proliferation. MMF has been used in the prevention of acute and chronic allograft rejection since the mid 1990s under the trade name CellCept® (F. Hoffman-La Roche, AG). An enterically coated formulation of the sodium salt of MPA (mycophenolate sodium) has been approved for prophylaxis of rejection in allogenic renal transplants under the tradename Myfortic® (Novartis AG). Specific embodiments of salts and analogs of MMF, as well as methods of making the salts and analogs, are described in U.S. Patents Nos. 4,686,234; 4,725,622; 4,727,069; 4,748,173; 4,753,935; 4,786,637; 4,808,592; 4,861,776; 4,868,153; 4,948,793; 4,952,579; 4,959,387; and 4,922,467; the disclosures of which are incorporated herein by reference.

[0047] Other IMPDH inhibitors are known and include compounds disclosed in U.S. Patent Nos. 5,807,876; 5,932,600; 6,054,472; 6,344,465; 6,420,403; 6,518,291; 6,541,496; 6,596,747; 6,617,323; and 6,624,184; the disclosures of which are incorporated herein by reference.

[0048] In various embodiments, disease areas where the disclosed combination therapy is expected to be applicable include vascular, autoimmune and/or inflammatory diseases, or conditions associated with such diseases.

[0049] As such, in various embodiments, the combination therapy can be used to treat patients who manifest clinical indications of the disease. In some embodiments, the compositions and methods are used to treat vascular diseases that include, by way of example and not limitation, atherosclerosis, coronary heart disease (CHD), cardiovascular disease (CVD), coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease.

[0050] In other embodiments, the combination therapy is used to treat autoimmune diseases that include, by way of example and not limitation, systemic lupus erythematosus (SLE), multiple sclerosis (MS), diabetes mellitus, and rheumatoid arthritis (RA).

[0051] In still other embodiments, the combination therapy is used to treat inflammatory diseases that include, by way of example and not limitation, Crohn's disease, ulcerative colitis, pelvic inflammation, and vasculitis. An exemplary inflammatory disease treatable with the compositions is vasculitis, a vascular inflammatory disease arising from inflammation of the blood vessel system, which includes the veins, arteries, and capillaries. Vasculitis may affect blood vessels of any type, size, or location, and therefore can cause dysfunction in any organ system, including the central and peripheral nervous systems.

[0052] In some embodiments, the compositions and methods herein are used to treat or reduce the risk of a condition associated with a vascular, autoimmune and/or inflammatory disease. In these embodiments, doses of the combination therapy can be administered to treat the associated condition regardless of whether the underlying disease is treated. For example, as noted above, the autoimmune disease SLE is associated with increased atherosclerosis and cardiovascular disease such that it is one of the leading causes of death in SLE patients. The risk of myocardial infarction increases by as much as 9 fold in patients with SLE. Hence, the combination therapy disclosed herein can be administered to treat or reduce the risk of atherosclerosis and cardiovascular disease associated with SLE, regardless of whether the doses are effective in treating the SLE. Other autoimmune diseases manifesting an increased vascular disease occurrence include, among others, diabetes mellitus (*i.e.*, type I diabetes) and rheumatoid arthritis. Thus, in some embodiments, the combination therapy can be used in a method to treat or reduce the risk of atherosclerosis, cardiovascular disease, or other vascular disease in a subject with a pre-existing autoimmune disease, such as, for example, SLE, diabetes mellitus, or rheumatoid arthritis.

[0053] In some embodiments, the associated condition is an inflammatory condition associated with autoimmune disease. For example, chronic inflammation accompanies many forms of autoimmune disease, such as rheumatoid arthritis, systemic lupus, and diabetes mellitus. The inflammatory cascade activated by the autoimmune reaction can exacerbate the damage caused by the autoimmune activity. In some cases, a patient with an underlying autoimmune disease may not display clinical signs of an inflammatory reaction, but have levels of biochemical markers indicative of inflammatory reactions (*e.g.*, inflammatory cytokine levels). As such, the compositions and methods herein can be used to treat or reduce the risk of such inflammatory conditions associated with autoimmune disease.

[0054] In some embodiments, the combination therapy can be used in a method to lower serum triglyceride levels. The studies herein indicate that MMF can lower triglyceride levels in a mouse model of atherosclerosis. In some embodiments, the elevated triglyceride level may be a condition associated with a pre-existing disease or be present in a otherwise healthy subject but have increased risk of vascular disease, such as atherosclerosis and cardiovascular disease, because of the elevated triglyceride levels.

[0055] In some embodiments, the subjects treated are healthy but have an increased risk or susceptibility to the diseases or associated conditions. In some embodiments, the subjects may have a genetic predisposition to the disease, as indicated by family history or genetic testing. In other embodiments, the subject may display one or more indications associated with an increased risk or susceptibility to the disease. Exemplary embodiments of markers or indications for increased risk of vascular disease include, among others, obesity, low HDL level, elevated cholesterol level, high fasting glucose, elevated blood pressure, and elevated levels of C-reactive protein, serum amyloid A, homocysteine, and inflammatory cytokines (*e.g.*, interleukin-6, tumor necrosis factor-alpha, interleukin-8, etc.). Exemplary embodiments of markers for increased risk of autoimmune disease include, among others, presence of immuno reactive autoantibodies and corresponding autoantigens (see, *e.g.*, Lernmark, A., 2001, *J Clin Invest.* 108:1091-1096), and an MHC type

associated with autoimmune disease (see, e.g., Weyand and Goronzy, 2000, *Arthritis Res.* 2(3):203-4).

[0056] In various embodiments, the combination therapies herein are directed to adult subjects. As used herein, "adult" in the context of human subjects refers to a person of about 18 years or older. As further described below, in some embodiments, the dosages administered are less than the dosages required to suppress the immune system for reducing the risk of organ rejection in an adult transplant patient. In some embodiments, the adult subjects may be further grouped into various age groups for purposes of treatment. For example, it is understood that as a human ages, there is an increased incidence of certain diseases that are "age related," such as atherosclerosis, cardiovascular disease, arthritis, rheumatoid arthritis, and type II diabetes. Thus, older age groups can benefit from therapy with the combination therapy as compared to subjects in younger age groups. Grouping of adult subjects may also be useful for taking into consideration differences in metabolism of the statin and IMPDH inhibitory compounds by different age groups. Thus, in some embodiments, treatments with combination therapy can be directed to those in the group of about 65 years or older, in the group of about 50 to about 64 years of age, in the group of about 40 to about 49 years of age, and in the group of about 18 years to about 39 years of age. In some embodiments, the low dose, extra low dose, or ultra low doses of IMPDH inhibitor in combination with statins can be used to delay the onset of such disease or lessen its severity in older patient populations that are at increased risk for such age related diseases, for example, patients who are 50 years or older.

[0057] In other embodiments, the treatments are directed to children and adolescents of about 18 years or younger, of about 12 years or younger, of about 6 years or younger, or of about 4 years or younger. Thus, in some embodiments, the low dose, extra low dose, or ultra low dose may be administered to children and adolescents diagnosed with or at increased risk for vascular, autoimmune, and/or inflammatory diseases, and conditions associated therewith. For example, nearly a quarter of all systemic lupus cases are diagnosed in children, which may warrant

early treatment to limit the risk of developing atherosclerosis, cardiovascular disease, and other vascular diseases associated with SLE.

[0058] The combination therapy may be administered therapeutically to subjects who are suffering from the particular indication to achieve a therapeutic benefit. As used herein, therapeutic benefit includes, in addition to treating the underlying indication, reducing and/or ameliorating the overall number and/or severity of its associated symptoms and/or halting or slowing the progression of the indication and/or its symptoms. For example, as described above, the combination of IMPDH and HMG CoA reductase inhibitors may be administered therapeutically to individuals afflicted with an indication to avoid the onset of symptoms or side-effects associated with the indication, regardless of whether the underlying the indication is treated. In other embodiments, the combination therapy may be administered prophylactically to subjects that are not suffering from the particular indication to achieve prophylactic benefit.

[0059] Generally, the compounds are administered in amounts that, in combination, provide therapeutic and/or prophylactic benefit. The actual dosage of each class of compound will vary, depending upon, among other factors, the individual, the condition being treated, the state of the disease, and other factors that will be apparent to the prescribing physician. Those skilled in the art will be able to select a proper amounts of the compounds based on Table 1, below, on the rest of this disclosure, and on the disease to be treated. An important practical effect of such combinations is to facilitate patient compliance. Thus, the dose of HMG CoA reductase inhibitor may use a dose sufficient to provide the desired anti-inflammatory, immunomodulatory, and therapeutic effect, which in some embodiments are the dosages normally used to treat hypercholesterolemia. For instance, simvastatin in oral dosage from is prescribed at 5–40 mg/day while fluvastatin is prescribed at 20-80 mg/day for an adult. It is to be understood, however, that lower dosages may be used since the effect of statins on inflammation and the immune system may occur in the absence of lowering, significant lowering, or substantial lowering of serum cholesterol level. As used herein, a "lowering" of serum cholesterol level refers to a decrease of about 5% or more serum cholesterol

level as compared to levels in untreated subjects. A "significant lowering" refers to a decrease of about 25% or more serum cholesterol level as compared to levels in untreated subjects. A "substantial lowering" refers to a decrease of about 40% or more of serum cholesterol levels as compared to levels in untreated subjects.

[0060] Similarly, the dose of the IMPDH inhibitor used is an amount sufficient to effect treatment of the specified disorder in combination with the HMG CoA reductase inhibitor. In some embodiments, the dose of the IMPDH inhibitor is an amount sufficient to reduce the risk of allograft rejection. The recommended dose of CellCept® is 1 g administered orally or intravenously twice daily for renal transplant (*i.e.*, a daily dose of 2 g; corresponding to a daily dose in the range of about 20-45 mg/kg for a patient body mass in the range of 45-100 kg) and 1.5 g administered orally or intravenously twice daily for hepatic and cardiac transplant (*i.e.*, a daily dose of 3 g; corresponding to a daily dose of about 30-67 mg/kg for a patient body mass in the range of 45-100 kg). The recommended dose of Myfortic® is 720 mg administered orally twice daily (*i.e.*, a daily dose of 1.44 g; corresponding to a daily dose in the range of about 14-32 mg/kg for a patient body mass in the range of 45-100kg).

[0061] In other embodiments, the dose of the IMPDH inhibitor used may be lower than the standard dosage typically administered to reduce the risk of allograft rejection. At these lower dosages, therapeutic and/or prophylactic benefit can be achieved while avoiding or minimizing the adverse consequences of severe immunosuppression that occurs with standard doses of such compounds. In some embodiments, the amount of IMPDH inhibitor administered is an amount effective to achieve a low, extra-low or ultra-low daily dose when taken once or more per day.

[0062] As used herein, a "low dose" of MMF or MPA is less than 2.0 g/day. In some embodiments, a "low dose" of MMF or MPA ranges from about 0.5 to 1.75 g/day (e.g., 0.5, 0.75, 1.0, 1.25, 1.5 and 1.75 g/day). These doses correspond to 5-39 mg/kg/day, depending on patient body mass, including 5 to 11, 5 to 17, 5 to 22, 5 to 28, and 5 to 33 mg/kg/day. In some embodiments, a "low dose" of MMF or MPA is about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26,

27, 28, 29, or 30 mg/kg/day. In other embodiments, a low dose is in the range of about 10-15 mg/kg/day.

[0063] An "extra-low dose" of MMF or MPA is 1.0 g/day or less. In some embodiments, an "extra-low dose" of MMF or MPA ranges from about 100 to 500 mg/day (*e.g.*, 100, 125, 150, 175, 200, 225, 250, 300, 350, 400 and 500 mg/day). These doses correspond to about 1 to 11 mg/kg/day, depending on patient body mass, including 1 to 2, 1 to 3, 1 to 4, 1 to 5, 1 to 6, 1 to 7, 1 to 8, 1 to 9, and 1 to 10 mg/kg/day. In some embodiments, an extra-low dose is about 1, 2, 3, 4, or 5 mg/kg/day.

[0064] An "ultra-low dose" of MMF or MPA is 0.5 g/day or less. In some embodiments, an "ultra-low dose" of MMF or MPA ranges from about 5 to 100 mg/day, (*e.g.*, 5, 10, 20, 25, 30, 40, 50, 60, 70, 75, 80, 90, and 100 mg/day). These doses correspond to about 0.05 to 2.2 mg/kg/day, depending on patient body mass, including 0.05 to 0.10, 0.05 to 0.20, 0.05 to 0.30, 0.05 to 0.50, 0.05 to 0.70, 0.05 to 0.90. 0.05 to 1.10, 0.05 to 1.30, 0.05 to 1.50, 0.05 to 1.80, and 0.05 to 2.00 mg/kg/day. In some embodiments, an ultra-low dose is about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1.0 mg/kg/day.

[0065] The "low," "extra-low" and "ultra-low" daily doses described above may be achieved by administering the MMF or MPA in unit dosage amounts, or, alternatively, the daily doses may be achieved by administering MMF or MPA in two or more equal or unequal dosage amounts during the course of the day, such that the total amount of MMF or MPA administered per day equals the total amount desired (for example, a "low," "extra-low" or "ultra-low" dose).

[0066] According to the methods described herein, the IMPDH and HMG CoA reductase inhibitors are adjunctively administered to the subject. Relative to the administration of the IMPDH inhibitor, the adjunctive administration of the HMG-CoA reductase inhibitor can occur before, at the same time (*e.g.*, contemporaneously), subsequent to, or on an irregular basis. Those skilled in the art are able to identify a suitable temporal relationship between the agents which will achieve the desired

treatment result, several examples of which are set out below. Treatment may continue until the disease process is resolved, until the symptoms of the disease are reduced to a satisfactory level, or until otherwise determined by the physician and patient. In some cases, treatment may be chronic.

[0067] When administered non-contemporaneously (*e.g.*, sequentially) the active agents may typically be formulated separately, using off-the shelf formulations. When administered contemporaneously, it may be advantageous to provide the HMG-CoA reductase inhibitor in a dosage form in combination with the IMPDH inhibitor, as disclosed in the compositions described below, to improve patient compliance and the effect of the therapy, although off-the-shelf formulations may be used.

[0068] An embodiment of the disclosure is a convenient dosage form of an IMPDH inhibitor and an HMG-CoA reductase inhibitor. The composition may take the form of a pill, capsule or tablet that comprises an effective amount of both active ingredients. Effective amounts of a variety of combinations are set out in Table 1, below. Based on this disclosure, those skilled in this art are able to identify further effective dosage combinations, all of which are included in the instant disclosure.

[0069] In some embodiments, the combination composition includes amounts of IMPDH and HMG CoA reductase inhibitors that correspond to unit or fractional amounts of their standard daily dosages. Standard daily dosages recommended for specific IMPDH and HMG CoA reductase inhibitors can be obtained from The 2005 Edition of The Physician's Desk Reference ("PDR"), incorporated herein by reference. In some embodiments, the combination composition includes an amount of an IMPDH inhibitor that corresponds to a unit or fractional unit amount of a low dose, extra-low dose or ultra-low dose of the specified inhibitor.

[0070] The pill, capsule or tablet may optionally contain, along with an effective amount of both active ingredients, a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof like pregelatinized starch (corn); a lubricant such as magnesium stearate and the like;

and a binder such as starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose and derivates thereof, and the like. Additional inactive ingredients may include butylated hyrdoxyanisole NF, citric acid monohydrate USP, croscarmellose sodium NF, hydroxypropyl cellulose; hydroxypropyl methylcellulose USP, iron oxides, lactose monohydrate NF, magnesium stearate NF, potassium bicarbonate, povidone, povidone K-90, ammonium hydroxide, microcrystalline cellulose NF, Opadry White YS-1-7040, polyethylene glycol, PEG 8000, sodium lauryl sulfate, polysorbate 80 NF, simethicone emulsion, talc, titanium dioxide, calcium carbonate USP, candelilla wax FCC; FD&C Blue 2, D&C Yellow 10, ethyl alcohol, methyl alcohol, n-butyl alcohol, propylene glycol, shellac and propyl gallate NF.

[0071] Non-limiting examples of excipiating agents ingredients include benzyl alcohol, black iron oxide, butylparaben, edentate calcium disodium, methylparaben, propylparaben, and sodium propionate.

[0072] Compositions that are in the form of tablets may include optional coatings designed, for example, to be resistant to the acid environment of the stomach and remain undissolved until they reach the alkaline environment of the small intestine. Films that dissolve between pH 5.5 and 6.5 are generally preferred. A wide variety of such coatings are known to those skilled in the art.

[0073] Liquid pharmaceutically administrable compositions can be prepared by dissolving, dispersing, etc. the active compounds (each about 0.5% to about 40%), as described above, and optional pharmaceutical adjuvants in a carrier, such as for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to form a solution or suspension. In 5% dextrose solution, MMF has a solubility of 65.8 mg/ml and a pH of 2.4 to 4.1. Inactive ingredients in liquid formulation may further include aspartame, citric acid anhydrous, colloidal silicon dioxide, mixed fruit flavour, sodium citrate dehydrate, sorbitol, soybean lecithin and xanthan gum.

[0074] If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or

emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

[0075] Methods of preparing the various dosage forms discussed are known, or will be apparent, to those skilled in this art; for example, see *Remington's Pharmaceutical Sciences*, 2000, 20th edition (Mack Publishing Company, Easton, PA).

[0076] Mycophenolate mofetil, or morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate, can be made as described in U.S. Patent No. 4,753,935. The pharmaceutically acceptable salts or derivatives of mycophenolate mofetil can be made as described in U.S. Patents Nos. 4,686,234; 4,725,622; 4,727,069; 4,748,173; 4,753,935; 4,786,637; 4,808,592; 4,861,776; 4,868,153; 4,948,793 4,952,579; 4,959,387; and 4,922,467. The methods for synthesis of HMG CoA reductase inhibitors are described in the references disclosed above. Formulating the combination of the active and inactive ingredients into the desired pill, tablet, capsule or liquid can be achieved according to known methods standard in the art.

[0077] Also provided are kits containing an IMPDH inhibitor packaged alone or together with an HMG-CoA reductase inhibitor. The kits may comprise one or more containers filled with solid compositions or aqueous solutions of an IMPDH inhibitor and an HMG-CoA reductase inhibitor, optionally in a combined container. For example, a kit may comprise one bottle containing a dosage form of an IMPDH inhibitor, and a separate bottle comprising a dosage form of an HMG-CoA reductase inhibitor. Alternatively, the kit may comprise a device for administering the active therapeutic agents in combination with each other, such as in a combination pill. In this case, the kit would comprise, for example, a single bottle or a blister pack comprising a dosage form comprising a combination of a an IMPDH inhibitor and HMG-CoA reductase inhibitor. Other devices for administration include, among others, a graduated cup or cylinder, a dropper, or a syringe. A kit may optionally include instructions for proper dosing use and information on the drug. Mediums for

this information include printed forms, compact disc, flash memory, videotape, or other as is known in the art.

[0078] In some embodiments, the combination therapies may be directed to prevention of restenosis, which is a form of chronic vascular injury leading to vessel wall thickening and loss of blood flow to the tissue supplied by the blood vessel. It typically occurs in response to vascular reconstructive procedures, including virtually any manipulation which attempts to relieve vessel obstructions.

[0079] The combination therapy may be provided to prevent restenosis in a subject undergoing vascular reconstructive procedures, either by oral administration or by local administration to the site of the procedure, either by injection or other direct application, or in conjunction with a stent.

[0080] In some embodiments, the therapy is administered in conjunction with stents, which comprise a generally tubular structure (which includes for example, spiral or coil shapes), the surface of which is coated with the IMPDH and HMG-CoA reductase inhibitors. Typically, a stent is a scaffolding, usually cylindrical in shape, that may be inserted into a body passageway (*e.g.*, bile ducts) or a portion of a body passageway, which has been narrowed, irregularly contoured, obstructed, or occluded by a disease process (*e.g.*, ingrowth by an atherosclerotic plaque) in order to prevent closure or reclosure (restenosis) of the passageway. Stents act by physically holding open the walls of the body passage into which they are inserted.

[0081] A variety of stents may be used with the therapeutic combination disclosed herein, including for example, esophageal stents, vascular stents, biliary stents, pancreatic stents, ureteric and urethral stents, lacrimal stents, Eustachian tube stents, fallopian tube stents, and tracheal/bronchial stents. Stents may be readily obtained from commercial sources, or constructed in accordance with well-known techniques. Representative examples of stents are described in U.S. Patent Nos. 4,768,523; 4,776,337; 5,041,126; 5,052,998; 5,064,435 ; 5,089,606; 5,147,370; 5,176,626; 5,213,580; and 5,328,471; the disclosures of which are incorporated herein by reference.

[0082] The stents may be coated with the IMPDH inhibitor and HMG-CoA reductase inhibitor in a variety of manners, including for example: (a) by directly affixing to the stent these therapeutic agents (*e.g.*, by either spraying the stent with a polymer/drug film, or by dipping the stent into a polymer/drug solution), (b) by coating the stent with a substance such as a hydrogel which will in turn absorbs the therapeutic agents, (c) by interweaving a thread coated with the therapeutic agents (or the polymer itself formed into a thread) into the stent structure, (d) by inserting the stent into a sleeve or mesh which is comprised of or coated with the therapeutic agents, or (e) constructing the stent itself from a composition comprising the therapeutic agents. In some embodiments, the composition should firmly adhere to the stent during storage and at the time of insertion, and should not be dislodged from the stent when the diameter is expanded from its collapsed size to its full expansion size. The therapeutic agents should not degrade during storage, prior to insertion, or when warmed to body temperature after expansion inside the body. In addition, it should preferably coat the stent smoothly and evenly, with a uniform distribution of therapeutic agent, while not changing the stent contour. Embodiments of therapeutic agents in the stent should provide a uniform, predictable, prolonged release of the therapeutic agents into the tissue surrounding the stent once it has been deployed. For vascular stents, in addition to the above properties, the composition should not render the stem thrombogenic (causing blood clots to form), or cause significant turbulence in blood flow (more than the stent itself would be expected to cause if it was uncoated). Standard methods for coating stents are generally known and examples can be found in U.S. Patent Nos. 6,153,252; 6,258,121; and 5,824,048, herein incorporated by reference.

[0083] For each of the therapeutic compounds listed in the present application, the amount of therapeutic agent used will be dependent upon the particular drugs employed. Typically, the amount of drug can represent about 0.001% to about 70%, about 0.00 1 % to about 60%, or about 0.00 1 % to about 45% by weight of the coating.

[0084] To achieve therapeutic and/or prophylactic benefit, an effective amount of the IMPDH inhibitor and HMG-CoA reductase inhibitor should be applied to the site

of vascular reconstruction such that restenosis is prevented. In general, for treating humans or animals, between approximately 0.1 mg/kg to 500 mg/kg body weight, between approximately 1 mg/kg to 50 mg/kg body weight, or between approximately from 1 mg/kg to 25 mg/kg body weight of the therapeutic compound can be used. Depending upon the half-life of the compound in the particular animal or human, the compound can be administered on a variety of schedules, including once (*e.g.*, in conjunction with a delayed release stent), several times per day, once a week or as otherwise desired. The methods disclosed herein provide for single as well as multiple administrations, given either simultaneously (*e.g.*, in conjunction with a stent implant procedure) or over an extended period of time.

[0085] Within another aspect of the present disclosure, methods are provided for expanding the lumen of a body passageway, comprising inserting a stent into the passageway, the stent having a generally tubular structure, the surface of the structure being coated with an IMPDH inhibitor and HMG-CoA reductase inhibitor such that the passageway is expanded. In various embodiments, the lumen of a body passageway is expanded in order to eliminate a vascular obstruction.

[0086] Generally, stents are inserted in a similar fashion regardless of the site or the disease being treated. Briefly, a preinsertion examination, usually a diagnostic imaging procedure, endoscopy, or direct visualization at the time of surgery, is generally performed in order to determine the appropriate positioning for stent insertion. A guidewire is then advanced through the lesion or proposed site of insertion, and over this is passed a delivery catheter which allows a stent in its collapsed form to be inserted. Typically, stents are capable of being compressed, so that they can be inserted through tiny cavities via small catheters, and then expanded to a larger diameter once they are at the desired location. Once expanded, the stent physically forces the wails of the passageway apart and holds them open. As such, they are capable of insertion via a small opening, and yet are still able to hold open a large diameter cavity or passageway. The stent may be self-expanding (*e.g.*, the Wallstent and Gianturco stents), balloon expandable (*e.g.*, the Palmaz stent and Strecker stent), or implanted by a change in temperature (*e.g.*, the Nitinol stent).

[0087] To enhance its drug carrying and drug eluting properties, the stent may be coated with a wide variety of polymeric carriers, including for example both biodegradable and non-biodegradable compositions. Representative examples of biodegradable compositions include albumin, gelatin, starch, cellulose, dextrans, polysaccharides, fibrinogen, poly(D,L lactide), poly(D,L-lactide-co-glycolide), poly(glycolide), poly(hydroxybutyrate), poly(alkylcarbonate) and poly(orthoesters) (see generally, Illium, L. and Davids, S. S., 1987, "Polymers in controlled Drug Delivery" Wright, Bristol; Arshady, 1991, *J. Controlled Release* 17:1-22; Pitt, 1990, *Int. J. Phar.* 59:173-196; and Holland et al., 1986, *J. Controlled Release* 4:155-0180). Representative examples of nondegradable polymers include EVA copolymers, silicone rubber and poly (methylmethacrylate). Exemplary polymeric carriers include poly (ethylene-vinyl acetate)(40% cross-linked), poly(D,L-lactic acid) oligomers and polymers, poly(L-lactic acid) oligomers and polymers, poly(glycolic acid), copolymers of lactic acid and glycolic acid, poly(caprolactone), poly (valerolactone), polyanhydrides, copolymers of poly(caprolactone) or poly(lactic acid) with polyethylene glycol and blends thereof.

[0088] Polymeric carriers may be fashioned in a variety of forms, including for example, coils, expandable coils, rod-shaped devices, pellets, slabs, or capsules (see, *e.g.*, Goodell et al., 1986, *Am J Hosp Pharm.* 43:1454-1461; Langer et al., 1980, "Controlled release of macromolecules from polymers", in *Biomedical polymers, Polymeric materials and pharmaceuticals for biomedical use* (Goldberg, E. and Nakagim, A. eds.) Academic Press, pp. 113-137; Rhine et al., 1980, *J. Pharm. Sci.* 69:265-270; Brown et al., 1983, *J. Pharm. Sci.* 72:1181-1185; and Bawa et al., 1985, *J. Controlled Release* 1:259-267). The IMPDH and/or HMG CoA reductase inhibitors may be linked to the polymeric carrier by occlusion in the matrices of the polymer, bound by covalent linkages, or encapsulated in microcapsules. Within certain embodiments, compositions are provided in non-capsular formulations such as microspheres (ranging from nanometers to micrometers in size), pastes, threads of various sizes, coils, films and sprays.

[0089] The composition should be biocompatible, and release the inhibitors over a period of several days to months. For example, "quick release" or "burst"

compositions are provided that release greater than 10%, 20%, or 25% (w/v) of the loaded inhibitors over a period of 7 to 10 days. Such "quick release" compositions should, within certain embodiments, be capable of releasing chemotherapeutic levels (where applicable) of the therapeutic agents. Within other embodiments, "low release" compositions are provided that release less than 1% (w/v) of the loaded therapeutic agents over a period of 7 to 10 days. Further, compositions should preferably be stable for several months and capable of being produced and maintained under sterile conditions.

EXAMPLES

Example 1: Doses of combination therapies

[0090] Treatment regimens comprising combination therapy likely will be most effective by approximately daily dosing of the two active agents, although other dosing schedules are possible. The preferred manner of administration, for the conditions detailed herein, is oral using a convenient daily dosage regimen that can be adjusted according to the degree of the disease. Preferred combinations, which are not intended to limit the scope of options set out herein, are listed in Table 1.

Table 1: Therapeutically Effective Combination Doses

Combination	Dosage frequency/Dose Amount
MMF	Standard dose, low dose, extra-low dose or ultra-low dose
atorvastatin (Lipitor®)	10, 20, 40, 80 mg/day
MMF	Standard dose, low dose, extra-low dose or ultra-low dose
fluvastatin (Lescol®)	20 to 40 mg/day
MMF	Standard dose, low dose, extra-low dose or ultra-low dose
lovastatin (Mevacor®)	10, 20, 40 mg/day
MMF	Standard dose, low dose, extra-low dose or ultra-low dose
pravastatin (Pravachol®)	10, 20, 40, 80 mg/day

Table 1: Therapeutically Effective Combination Doses	
Combination	**Dosage frequency/Dose Amount**
MMF	Standard dose, low dose, extra-low dose or ultra-low dose
simvastatin (Zocor®)	Single daily dose in evening, with or without food 10, 20, 40, 80mg / day
MMF	Standard dose, low dose, extra-low dose or ultra-low dose
rosuvastatin (Crestor®)	10, 20, 40mg / day

[0091] In the above chart, the dose of MMF is selected to be in the range of from 0.1 to 5.0 g/day, in particular, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, or 3.5 g/day, which may be alternatively divided into equal or unequal doses during the course of the day, such that the combination of doses per day equals the total amount desired per day.

[0092] In an embodiment of a combination composition, the composition is a tablet comprising MMF (0.5 g) and simvastatin (Zocor®) (10, 20, 40 or 80 mg). In another embodiment, the tablet comprises MMF (0.25 g) and simvastatin (Zocor®) (5, 10, 20, 40 or 80 mg). Alternatively, the embodiment comprises MMF (0.5 g) and atorvastatin (Lipitor®) (10, 20, 40 or 80 mg). Each embodiment may be administered from one to four times per day. Each embodiment may have inactive ingredients or an enteric coating as provided herein. An important practical effect of the compositions and methods described herein is that it overcomes the challenge faced by clinicians who are hesitant to use statins in lupus patients as they may have the adverse effects of worsening fibromyalgia or cause complications through the adverse effect of fibromyositis. The combination therapy described herein provides relief from the concerns about these side-effects.

[0093] In some methods or compositions described herein, it may be desirable to employ a dose of a statin which falls below the regularly accepted dosages (listed in Table 1). The disclosure thus contemplates doses of the statins which are as low as 5% of the lowest approved dosage for the statin.

Example 2: Effect of Simvastatin, combined with either low-dose MMF or high-dose MMF, on a mouse model of atherosclerosis

[0094] This example illustrates the effect of low-dose MMF on mice lacking the low-density lipoprotein receptor B6.129S7-Ldlr^{tm1Her}/J (hereinafter referred to as LDLRKO mice) obtained from Jackson Labs. When placed on a high-fat, high-cholesterol "Western-type" diet, these mice develop severe atherosclerosis (Ishibashi et al., 1994, *J Clin Invest.* 93(5):1885-93).

[0095] Study Design: Male mice will be fed a high-fat, high-cholesterol "Western-type" diet (15% cocoa butter, 0.25% cholesterol by weight, 34% of calories from fat ("Diet W" Hope Farms, Woerden, Nertherlands)) for 12 weeks, a time which has been shown to be sufficient for the mice to develop significant atherosclerosis, as assessed by the appearance of atheromatous lesions at the aortic root.

[0096] Studies show that male LDLRKO mice consume, on average, 3.3 grams of Diet W per mouse per day. Diet W will be formulated with CellCept® incorporated directly into the chow, at concentrations of 0.04% or 0.26% mycophenolate mofetil by weight. When administered in this way, the mice will be expected to consume 15 mg/kg/day ("low dose") or 100 mg/kg/day ("high-dose") of the MMF. Additional diets will be formulated to include MMF as above, with Simvastatin at a concentration of 0.25% (w/w), such that the mice will be expected to consume 300 mg/kg/day ("high-dose") of the MMF. Mice are sacrificed 12 weeks after feeding on the study diet, and the endpoints determined.

[0097] The primary endpoint will be evaluated using histological analysis of plaque area at the aortic root. The total lesion area in oil red O-stained cryostat sections of the aortic root will be quantified using the Leica image analysis system. Mean lesion area (in square millimetres) will be calculated from 10 oil red O-stained sections, beginning at the appearance of the tricuspid valves.

[0098] Plaque composition will be analysed as a secondary endpoint using oil red O staining (for lipid content – see above), Movat's pentachrome staining (for lesion complexity including extracellular matrix and glycosaminoglycans) and haematoxylin

and eosin (for macrophage content). The average atherosclerotic area will be compared between the groups using the two-way ANOVA test. Additional secondary endpoints will be plasma levels of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and glucose, as well as *en face* visualization of the thoracic and abdominal aortas stained with oil red O.

[0099] Predicted Results: It is expected that mycophenolate mofetil, at either low or high dose, in combination with simvastatin, in the LDLRKO mice will attenuate atherosclerosis through suppression of the T-cell mediated arm of the inflammatory response in addition to inhibition of cholesterol biosynthesis. It is expected that the size, composition and/or maturity of the lesions will be reduced by the combination therapy. Measures of outcome which will improve include, but are not limited to, maturity of the lesion (as judged by histological analysis by a qualified cardiovascular pathologist, blinded to treatment), reduction in the percentage of the aortic sinus occluded by atheroma from 21.1 +/- 4.5% to 16.6 +/- 4.5%, reduction in the amount of degenerative tissue present within the lesion and reduction in lesion complexity. A decrease in lesion maturity is also expected, indicative of an attenuation in the initiation of the atheromatous process ("younger lesions"). Also expected is a reduction in serum and tissue inflammatory mediators, such as, but not limited to, CRF, VCAM-1, ICAM-1 and matrix metalloproteases

[0100] Results of administering 15 mg/kg/day of MMF: Figure 1 shows the effect of mycophenolate mofetil given at a dosage of 15 mg/kg/day in reducing atherosclerosis (AS), as assessed by percentage of aortic sinus occluded by plaque, in male Ldlr-/- mice. Low-dose therapy (15 mg/kg/day, a dosage equivalent to approximately 1 gram per day in a 70 kg human) reduced AS by 31% (from 16% to 11% of the sinus) whereas high-dose therapy reduced AS by 61% (from 16% to 6.2%). The response was dose-dependent. Quantification was performed by a single, trained observer blinded to treatment group.

[0101] Figure 2 shows the effect of mycophenolate mofetil given at a dosage of 15 mg/kg/day in reducing serum triglyceride (Tgs) levels in male Ldlr-/- mice. Low-dose therapy reduced Tgs from 1198+137 mg/dL to 994+149 mg/dL whereas high-

dose therapy reduced Tgs to 452+180 mg/dL. The response was dose-dependent. Quantification was performed by a single, trained observer blinded to treatment group. Mouse groups are the same as for Figure 1.

[0102] Figure 3 shows the effect of mycophenolate mofetil given at a dosage of 15 mg/kg/day on serum phospholipids (PPL) in male Ldlr-/- mice. Low-dose therapy reduced PPL from 1078+91 mg/dL to 964+87 mg/dL whereas high-dose therapy reduced PPL to 696+115 mg/dL. The response was dose-dependent. Quantification was performed by a single, trained observer blinded to treatment group. Mouse groups are the same as for Figure 1.

[0103] Figure 4 shows that mycophenolate mofetil does not appear to affect HDL levels, thus indicating that MMF reduces atherosclerosis through mechanisms independent of raising high-density lipoprotein. Importantly, levels of serum HDL-cholesterol are not lowered by MMF treatment. Quantification was performed by a single, trained observer blinded to treatment group. Mouse groups are the same as for Figure 1.

[0104] Figure 5 shows Data Quality Assurance in which serum mycophenolic acid (MPA) levels were measured by commercial assay at the Vancouver General Hospital Special Chemistry laboratory. No MPA was detected in the serum of control mice (data not shown). The average serum level in the low-dose group was 1.16+0.09 mg/L, and in the high-dose group 3.65+0.3 mg/L, indicating that the drug remained stable and active after incorporation into the high-fat mouse chow.

[0105] The data presented herein on the efficacy of MMF in reducing AS in Ldlr-/- mice suggests that MMF can lower triglyceride levels, in addition to an inhibitory effect on function of immune system cells. Simvastatin can decrease AS in Ldlr -/- male mice but has no observed effect on triglyceride levels (see, *e.g.*, Wang et al., 2002, "Anti-atherosclerotic effect of simvastatin depends on the presence of apolipoprotein E," *Atherosclerosis* 162(1): 23-32. Therefore, the combination of an IMPDH inhibitor and a HMG CoA reductase inhibitor, *e.g.*, MMF in combination with

statins, may have a beneficial effect on the reduction of atherosclerosis by a mechanism that includes lowering of triglyceride levels by action of MMF or MPA.

Example 3: Effect of Low dose MMF in high-cholesterol rabbit model.

[0106] This example illustrates the use of combination MMF and statin therapy in an animal model of atherogenesis.

[0107] Study Design: Studies are done in 30 male New Zealand White (NZW) rabbits weighing 1.0-1.5 kg at the beginning of the experiment. After obtaining baseline blood samples, rabbits are fed *ad libitum* a 1% cholesterol diet for 12 weeks. This diet is prepared by dissolving cholesterol (Sigma, St. Louis, MO) in 100% ethanol at a temperature of 60° C, mixing this solution with standard rabbit chow (Purina), and allowing the complete evaporation of the ethanol.

[0108] The rabbits are divided into three groups and treated as indicated: (1) CHOL + MMF (extra-low) + simvastatin group (n=10) receives by gastric gavage 5 mg/kg of MMF and 0.5 mg/kg simvastatin in 0.4 ml of water; (2) CHOL + MMF (ultra-low) + atorvastatin group (n=10) receives by gastric gavage 1 mg/kg of MMF and 0.5 mg/kg atorvastatin in 0.4 ml of water; and (3) CHOL group (n=10), which receives by the same route daily 0.4 ml water. Since the MMF is insoluble in water, the drug is individually prepared as a suspension by vigorous shaking immediately before administration. The MMF, statin (*i.e.*, simvastain or atorvastatin) and vehicle are given daily throughout the 12 experimental weeks.

[0109] Blood samples for determination of plasma cholesterol and triglyceride are taken every 2 weeks.

[0110] A separate set of rabbits of similar weight is kept for 12 weeks on a standard rabbit chow not supplemented with cholesterol and then sacrificed to determine normal values.

[0111] Animals are sacrificed at the end of the 12th week. The aorta is rapidly dissected and cut from the beginning of the aortic arch to the bifurcation of the iliac vessels. Then, thoracic and abdominal segments of the aorta are separated using

the diaphragm as a reference point. Aortic rings of about 1 mm width are cut at the initiation of the aortic arch for histologic and immunohistologic analysis. Then, thoracic and abdominal segments of the aorta are opened longitudinally and photographed for evaluation of the extension of atherosclerotic plaques. The adventitia is then carefully separated and the aortic segments weighed and used for determination of the total cholesterol content.

[0112] Determination of aortic cholesterol content: Lipids are isolated from the aortic segments as described by Folch et al., 1957, *J Biol Chem.* 266:497-509. Briefly, tissue is homogenized in a mixture of chlorophorm-methanol 2:1 (v:v) in a final volume 20 times the mixture volume. Homogenates are centrifuged at 2500 rpm for 15 min and the supernatant is washed in ionic 0.017% $MgCl_2$ solution and then centrifuged for 20 min. Lipids are extracted from the lower layer. Cholesterol is determined in the lipid extract by the method of Zlatikis et al., 1953, *J. Lab. Clin. Med.*41:486-492.

[0113] Expected Results: The size and severity of the atherosclerotic lesion, as measured by the intima/media ratio, and by aortic cholesterol content, are expected to be significantly reduced in the rabbits treated with the MMF/Statin combination therapy. Size and severity of atherosclerotic lesions in rabbits of group (1) are expected to be similar to those of the group (2) group.

Example 4: Effect of low-dose MMF in combination with statin on a mouse model of SLE

[0114] This example will illustrate the effect of the combination therapy on the mouse model of the W/B F1 cross (New Zealand White x BXSB F1), recognized as the closest model to the human disease SLE. W/B F1 mice are bred according to previous protocols (Hang et al.,1981, *J Exp Med.* 154:216-221) and obtained from Jackson Labs. Eighty percent of W/B F1 males are expected to develop a degenerative vascular disease confined predominantly to the coronary artery system, which is often associated with myocardial infarction.

[0115] Male W/B F1 mice are divided in three groups and treated as indicated: (1) MMF (extra-low) and simvastatin group (n=10) receives by gastric gavage 5 mg/kg of MMF and 0.5 mg/kg simvastatin in 0.1 ml of water; (2) MMF (ultra-low) and atorvastatin group (n=10) receives by gastric gavage 1 mg/kg of MMF and 0.5 mg/kg atorvastatin in 0.1 ml of water; and (3) control group (n=10) which receives by the same route daily 0.1 ml water. Since the MMF is insoluble in water, the drug is individually prepared as a suspension by vigorous shaking immediately before administration. The MMF and statin (*i.e.*, simvastatin or atorvastatin) and vehicle are given daily throughout the 20 experimental weeks.

[0116] Survival of control animals is expected to be approximately 50% at the end of 20 weeks. At the end of 20 weeks of treatment, MMF and statin treated animals are expected to demonstrate improved survival and reduced evidence of disease as compared to MMF treatment alone.

[0117] All publications, patents, patent applications and other documents cited in this application are hereby incorporated by reference in their entireties for all purposes to the same extent as if each individual publication, patent, patent application or other document were individually indicated to be incorporated by reference for all purposes.

[0118] While various specific embodiments have been illustrated and described, it will be appreciated that various changes can be made without departing from the spirit and scope of the invention(s).

What is claimed is:

1. A method for treating a vascular, autoimmune, and/or inflammatory disease, or a condition associated therewith, comprising adjunctively administering to a human subject an amount of an IMPDH inhibitor and a HMG-CoA reductase inhibitor that is effective to treat or reduce the risk of the vascular, autoimmune and/or inflammatory disorder or the condition associated therewith.

2. The method of claim 1 in which the amount of the IMPDH inhibitor administered is less than the amount necessary to reduce the risk of allograft rejection in the subject.

3. The method of claim 1 in which the subject is not an allograft transplant recipient.

4. The method of claim 1 in which the IMPDH inhibitor is selected from MPA, MMF, and combinations thereof.

5. The method of claim 1 in which the daily amount of IMPDH inhibitor administered corresponds to a low dose.

6. The method of claim 1 in which the daily amount of IMPDH inhibitor administered corresponds to an extra-low dose.

7. The method of claim 1 in which the daily amount of IMPDH inhibitor administered corresponds to an ultra-low dose.

8. The method of claim 1 in which the HMG-CoA reductase inhibitor is a statin.

9. The method of claim 8 in which the statin is selected from mevastatin, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, pitavastatin, rosuvastatins and combinations thereof.

10. The method of claim 8 in which the statin is administered at a dose that is less than an amount effective to lower serum cholesterol levels.

11. The method of claim 1 in which the disease is vascular disease.

12. The method of claim 11 in which the vascular disease is atherosclerosis, coronary heart disease (CHD), cardiovascular disease (CVD), coronary artery disease (CAD), cerebrovascular disease, or peripheral vascular disease.

13. The method of claim 1 in which the disease is an autoimmune disease.

14. The method of claim 13 in which the autoimmune disease is lupus erythematosus, diabetes mellitus, multiple sclerosis, or rheumatoid arthritis.

15. The method of claim 1 in which the disease is an inflammatory disease.

16. The method of claim 15 *in* which the inflammatory disease is Crohn's disease, ulcerative colitis, inflammatory bowel disease, pelvic inflammatory disease, and vasculitis.

17. The method of claim 1 in which the condition is associated with autoimmune disease.

18. The method of claim 17 in which the condition associated with the autoimmune disease is atherosclerosis.

19. The method of claim 17 in which the condition associated with the autoimmune disease is an inflammatory condition.

20. The method of claim 1 in which the HMG CoA reductase inhibitor and the IMPDH inhibitor are administered sequentially.

21. The method of claim 1 in which the HMG CoA reductase inhibitor and the IMPDH inhibitor are administered simultaneously.

22. A pharmaceutical composition comprising an IMPDH inhibitor and a HMG-CoA reductase inhibitor.

23. The pharmaceutical composition of claim 22 in which the IMPDH inhibitor is selected from MPA, MMF, and combinations thereof.

24. The pharmaceutical composition of claim 22 in which the HMG CoA reductase inhibitor is a statin.

25. The pharmaceutical composition of claim 24 in which the statin is selected from the group consisting of mevastatin, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin and combinations thereof.

26. The pharmaceutical composition of claim 22 in which the IMPDH inhibitor is MMF and the HMG-CoA reductase inhibitor is simvastatin.

27. The pharmaceutical composition of claim 22 in which the amount of IMPDH inhibitor is effective to achieve a low, extra-low or ultra-low daily dose when taken once or more per day.

28. The pharmaceutical composition of claim 22 in which the amount of IMPDH inhibitor is effective to achieve a low, extra-low or ultra-low daily dose when taken once per day.

29. The pharmaceutical composition of claim 22 in which the amount of IMPDH inhibitor is effective to achieve a low, extra-low or ultra-low daily dose when taken twice per day.

30. A stent coated with a composition comprising an IMPDH inhibitor and an HMG-CoA reductase inhibitor.

31. The stent of claim 30 in which the IMPHD inhibitor is selected from MPA, MMF and combinations thereof.

32. The stent of claim 30 in which the HMG CoA reductase inhibitor is a statin.

33. The stent of claim 32 in which the statin is selected from the group consisting of mevastatin, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin and combinations thereof.

34. A method of preventing restenosis comprising administering to a subject an IMPDH inhibitor and an HMG-CoA reductase inhibitor.

35. The method of claim 34 in which the IMPDH inhibitor and the HMG-CoA reductase inhibitor are administered from a drug eluting stent.

36. A kit useful for treating a disease selected from among vascular, autoimmune and inflammatory disease, in a subject, the kit comprising:

an effective amount of an IMPDH inhibitor;

an effective amount of an HMG-CoA reductase inhibitor; and

means for administering the IMPDH inhibitor and HMG-CoA reductase inhibitor in combination.

37. The kit of claim 36 further comprising instructions for determining proper dosing and administration of the IMPDH and HMG CoA reductase inhibitors.

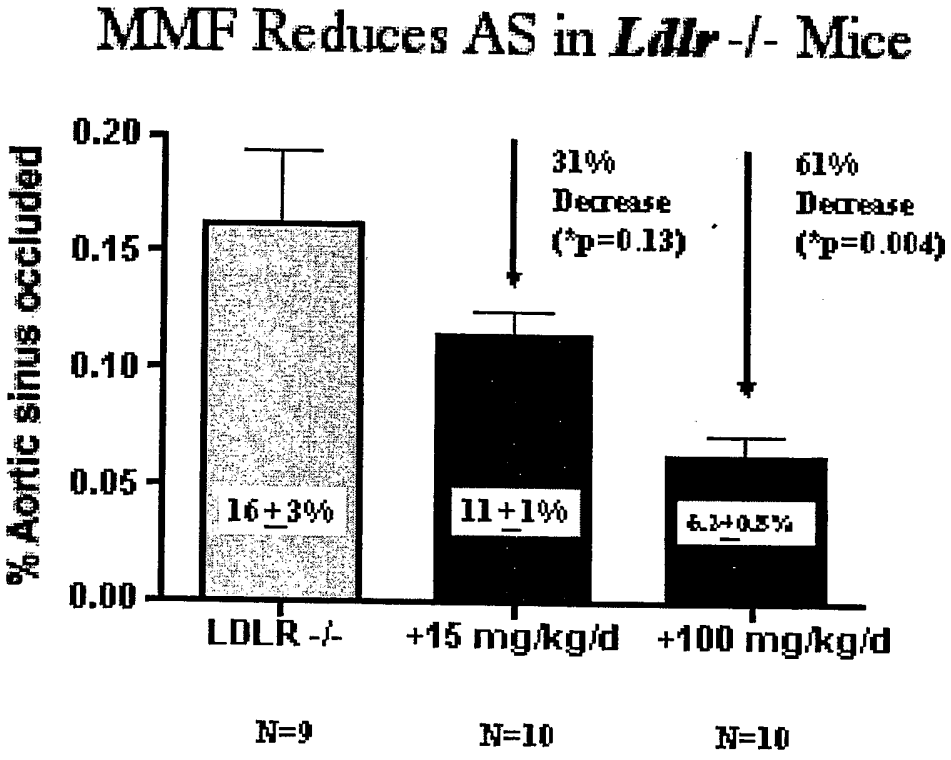

MMF Reduces AS in Ldlr -/- Mice
% Aortic sinus occluded
0.20
0.15
0.10
0.05
0.00
16±3%
11±1%
6.2±0.8%
31% Decrease (*p=0.13)
61% Decrease (*p=0.004)
LDLR -/-
+15 mg/kg/d
+100 mg/kg/d
N=9
N=10
N=10

FIG. 1

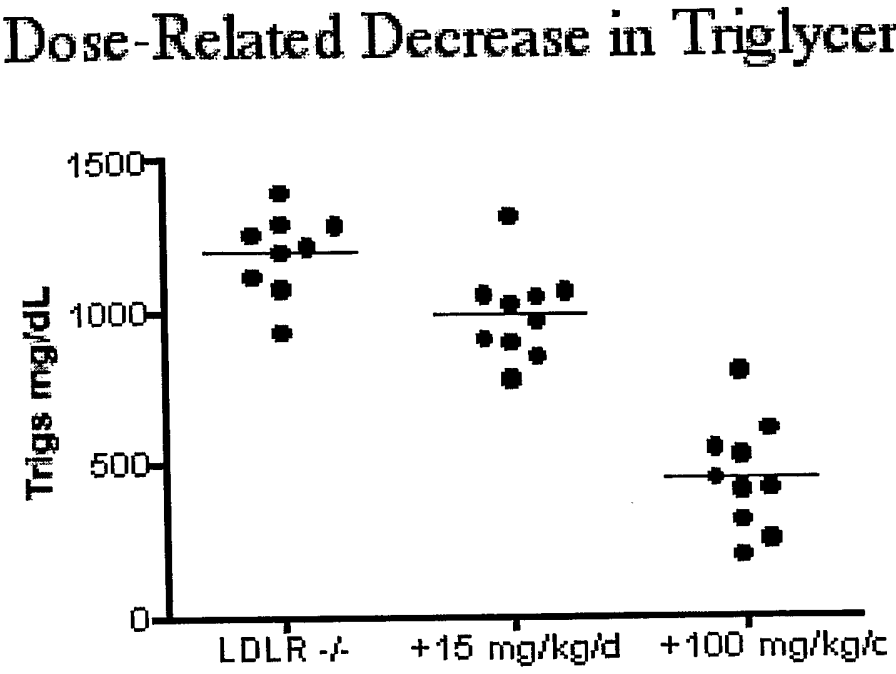

Dose-Related Decrease in Triglycerides
1500
1000
500
0
Trigs mg/dL
LDLR -/-
+15 mg/kg/d
+100 mg/kg/c

FIG. 2

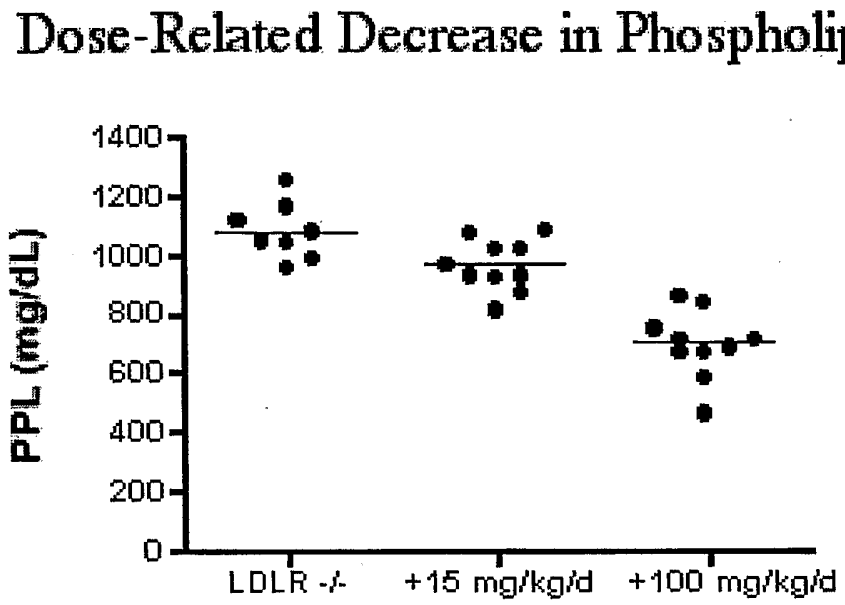

Dose-Related Decrease in Phospholipids
PPL (mg/dL)
1400
1200
1000
800
600
400
200
0
LDLR -/-
+15 mg/kg/d
+100 mg/kg/d

FIG. 3

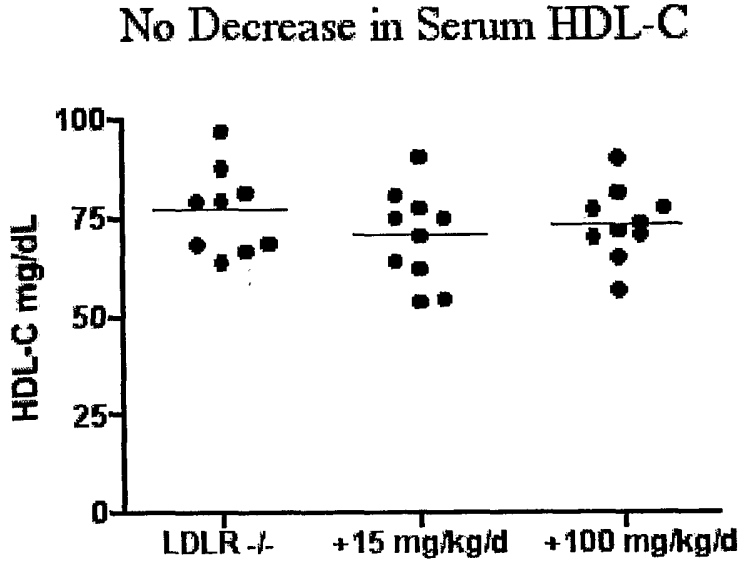

No Decrease in Serum HDL-C
HDL-C mg/dL
100
75
50
25
0
LDLR -/-
+15 mg/kg/d
+100 mg/kg/d

FIG. 4

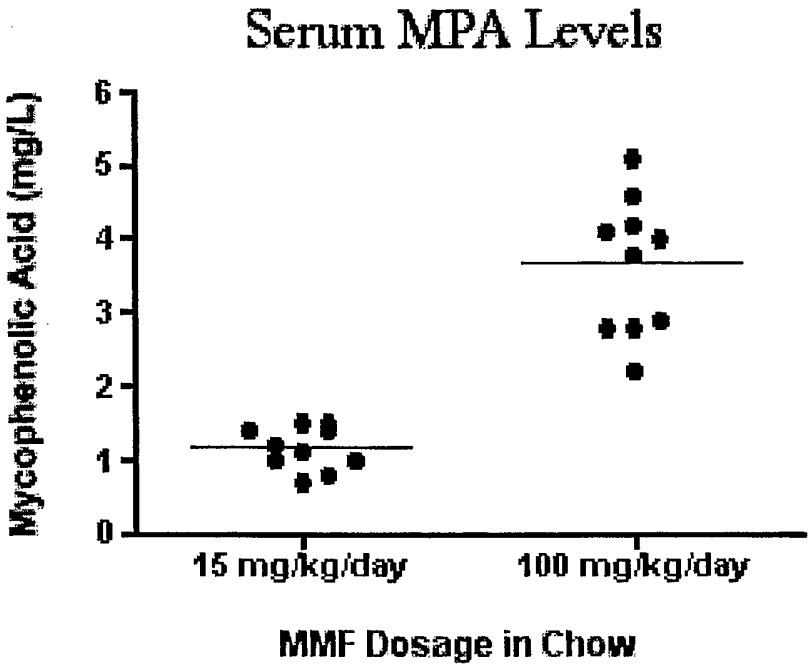

Serum MPA Levels
Mycophenolic Acid (mg/L)
0
1
2
3
4
5
6
15 mg/kg/day
100 mg/kg/day
MMF Dosage in Chow

FIG. 5