

*Replaced by new set of
claims.*

We claim.

1. A method for suppressing the expression of VCAM-1 comprising administering an effective amount of a substance that prevents or minimizes the oxidation of a polyunsaturated fatty acid.

2. A method for suppressing the expression of a redox-sensitive gene comprising administering an effective amount of a substance that prevents or minimizes the oxidation of a polyunsaturated fatty acid.

3. A method for activating a gene that is suppressed by the oxidation of a polyunsaturated fatty acid, comprising administering an effective amount of a substance that prevents or minimizes the oxidation of a polyunsaturated fatty acid.

4. A method for suppressing the expression of VCAM-1 comprising administering an effective amount of a substance that prevents the interaction between a polyunsaturated fatty acid and a protein that mediates the expression of VCAM-1.

5. The method of claims 1-4, wherein the polyunsaturated acid is selected from the group consisting of oxidized linoleic ($C_{18} \Delta^{9,12}$), linolenic ($C_{18} \Delta^{6,9,12}$), arachidonic ($C_{20} \Delta^{5,8,11,14}$) and eicosatrienoic ($C_{20} \Delta^{8,11,14}$) acid.

6. The method of claim 2 or 3, wherein the redox-sensitive gene is selected from the group consisting of those expressing cytokines involved in initiating the immune response (e.g., IL-1 β), chemoattractants that promote the migration of inflammatory cells to a point of injury (e.g., MCP-1), growth factors (e.g., IL-6 and the thrombin receptor), and adhesion molecules (e.g., VCAM-1 and E-selectin).

7. The method of claims 1-4, wherein the substance is pyrrolidine dithiocarbamate, or its pharmaceutically acceptable salt.

8. A method for the prediction or assessment of disorders mediated by VCAM-1 in vivo, comprising quantifying the level of oxidized polyunsaturated fatty acid in the tissue or blood.

9. A method for the prediction or assessment of redox-sensitive gene mediated disease in vivo, comprising quantifying the level of oxidized polyunsaturated fatty acid in the tissue or blood.

11. A method for the prediction or assessment of disorders mediated by VCAM-1 in vivo, comprising quantifying a surrogate marker for the level of oxidized polyunsaturated fatty acid in the tissue or blood.

12. A method for the prediction or assessment of redox-sensitive gene mediated disease in vivo, comprising quantifying a surrogate marker for the level of oxidized polyunsaturated fatty acid in the tissue or blood.

13. The method of claim 11, wherein the surrogate marker is circulating or cell-surface VCAM-1.

14. A method for the evaluation of the sensitization of a host's vascular endothelial cells to polyunsaturated fatty acids or their oxidized counterparts, comprising challenging a host with a PUFA or ox-PUFA and comparing the resulting concentration of cell-surface or circulating VCAM-1 or other surrogate marker to a population norm.

15. A method to screen compounds for their ability to treat disorders mediated by VCAM-1 comprising evaluating the ability of the compound to inhibit the oxidation of a polyunsaturated fatty acid.

16. A method to screen compounds for their ability to treat disorders mediated by VCAM-1 comprising evaluating the ability of the compound to inhibit the interaction of a PUFA or ox-PUFA with a protein target.

17. A method for the treatment of a cardiovascular disease in humans comprising administering an effective amount of a dithiocarbamate of the formula A-SC(S)-B;

wherein A selected from the group consisting of hydrogen, a pharmaceutically acceptable cation, and a physiologically cleavable leaving group;

and B is selected from the group consisting of alkyl, alkenyl, alkynyl, alkaryl, aralkyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, alkaryl, hydrogen, C₁₋₆ alkoxy-C₁₋₁₀ alkyl, C₁₋₆ alkylthio-C₁₋₁₀ alkyl, NR²R³, -(CHOH)_nCH₂OH, wherein n is 0, 1, 2, 3, 4, 5, or 6, -(CH₂)_nCO₂R¹, including alkylacetyl, alkylpropionyl, and alkylbutyryl, and hydroxy(C₁₋₆)alkyl-.

18. The method of claim 17, wherein A is hydrogen or a pharmaceutically acceptable cation selected from the group consisting of sodium, potassium, calcium, magnesium, aluminum, zinc, bismuth, barium, copper, cobalt, nickel, or cadmium.

19. The method of claim 17, wherein A is a salt-forming organic acid.

20. The method of claim 19, wherein A is selected from the group consisting of choline, acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid.

21. The method of claim 17, wherein A is a cation formed from ammonia or other nitrogenous base.

22. The method of claim 21, wherein A is a nitrogenous heterocycle, or a moiety of the formula $NR^4R^5R^6R^7$, wherein R^4 , R^5 , R^6 , and R^7 are independently hydrogen, C_{1-6} alkyl, hydroxy(C_{1-6})alkyl, aryl, N,N-dibenzylethylene-diamine, D-glucosamine, tetraethylammonium, or ethylenediamine.

23. The method of claim 17, wherein A is a physiologically cleavable leaving group.

24. The method of claim 17, wherein A is an acyl group.

25. The method of claim 17, wherein B is NR^2R^3 , wherein R^2 and R^3 are selected from the group consisting of alkyl; $-(CHOH)_n(CH_2)_nOH$, wherein n is 0, 1, 2, 3, 4, 5, or 6; $-(CH_2)_nCO_2R^1$, $-(CH_2)_nCO_2R^4$; hydroxy(C_{1-6})alkyl-; alkenyl; alkyl(CO_2H), alkenyl(CO_2H), alkynyl(CO_2H), or aryl, or R^2 and R^3 can together constitute a bridge of the formula $-(CH_2)_m-$, wherein m is 3, 4, 5, or 6, and wherein R^4 is selected from the group consisting of aryl, alkaryl, or aralkyl, including acetyl, propionyl, and butyryl.

26. The method of claim 17, wherein B is a heterocyclic or alkylheterocyclic group.

27. The method of claim 26, wherein the heterocycle is partially or totally hydrogenated.

28. The method of claim 17, wherein B is the residue of a pharmaceutically-active compound or drug which is directly linked to A-SC(S)- or linked through a divalent linking moiety.

29. The method of claim 17, wherein B is selected from the group consisting of probucol, nicotinic acid, aspirin, coumadin, varapamil, diltiazem, nifedipine, captopril, enalapril, propanalol, terbutalol, labetalol, ibuprofen,

indomethacin, fenoprofen, mefenamic acid, flufenamic acid, sulindac, and a corticosteroid.

30. The method of claim 17, wherein the dithiocarbamate is an amino acid derivative of the structure $\text{AO}_2\text{C-R}^9\text{-NR}^{10}\text{-C(S)SA}$, wherein R_9 is B or the internal residue of an amino acid and R^{10} is hydrogen or lower alkyl.

31. The method of claim 17, wherein B is a polymer to which one or more dithiocarbamate groups are attached, either directly, or through any suitable linking moiety.

32. The method of claim 17, wherein the polymer is biodegradable.

33. The method of claim 32, wherein the polymer is selected from the group consisting of peptides, proteins, nucleoproteins, lipoproteins, glycoproteins, synthetic and natural polypeptides and polyamino acids, polyorthoesters, poly(α -hydroxy acids), polyanhydrides, polysaccharides, and polycaprolactone.

34. The method of claim 1, wherein B-C(S)S- is pyrrolidine-N-carbodithioate.

35. The method of claim 17 wherein the cardiovascular disease is atherosclerosis.

36. The method of claim 17, wherein the cardiovascular disease is post-angioplasty restenosis.

37. The method of claim 17, wherein the cardiovascular disease is coronary artery disease.

38. The method of claim 17, wherein the cardiovascular disease is angina.

39. The method of claim 17, wherein the cardiovascular disease is a small vessel disease.

40. The method of claim 17, wherein the dithiocarbamate is administered in a dosage of between 0.5 and 500 mg/kg body weight.

41. The method of claim 17, wherein the dithiocarbamate is administered by perfusion balloon catheter.

42. The method of claim 17, wherein the dithiocarbamate is administered in combination with a pharmaceutical agent selected from the group consisting of a lipid lowering agent, a platelet aggregation inhibitor, an antithrombotic agent, a calcium channel blocker, an angiotensin converting enzyme (ACE) inhibitor, a β -blocker, a nonsteroidal antiinflammatory, and a corticosteroid.

43. A method for the suppression of VCAM-1 expression in human cells comprising administering an effective amount of the dithiocarbamate described in claim 17.

44. A method for the treatment of an inflammatory skin disease that is mediated by VCAM-1 comprising administering an effective amount of the dithiocarbamate described in claim 17.

45. A method for the treatment of a human endothelial disorder that is mediated by VCAM-1 comprising administering an effective amount of the dithiocarbamate described in claim 17.

46. The method of claim 45, wherein the disorder is selected from the group consisting of asthma, psoriasis, eczematous dermatitis, Kaposi's sarcoma, multiple sclerosis, and proliferative disorders of smooth muscle cells.

47. A method for the treatment of an inflammatory condition that is mediated by a mononuclear leucocyte comprising administering an effective amount of the dithiocarbamate described in claim 17.

48. The dithiocarbamate disclosed in any of claims 17-34.

49. A pharmaceutical composition comprising an effective amount to treat cardiovascular disease of a compound disclosed in any of claims 17-34.

50. A pharmaceutical composition comprising an effective amount to treat a disorder mediated by VCAM-1 of a compound disclosed in any of claims 17-34.