CLAIMS

1. A composition comprising one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and one or more gap junction inhibitors for use in a method of treating or preventing (i) necrosis, (ii) tissue damage, (iii) organ damage, or (iv) cell death, in a subject.

2. An endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use in a method of treating or preventing (i) necrosis, (ii) tissue damage, (iii) organ damage, or (iv) cell death in a subject, wherein said endoplasmic/sarcoplasmic reticulum calcium channel inhibitor is to be administered in combination with one or more gap junction inhibitors.

3. A gap junction inhibitor for use in a method of treating or preventing (i) necrosis, (ii) tissue damage, (iii) organ damage, or (iv) cell death in a subject, wherein said gap junction inhibitor is to be administered in combination with one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors.

4. A method of treating or preventing (i) necrosis, (ii) tissue damage, (iii) organ damage, or (iv) cell death in a subject, the method comprising:

administering one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and one or more gap junction inhibitors to the subject to treat or prevent necrosis, tissue damage, organ damage, or cell death,

wherein the one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and the one or more gap junction inhibitors are administered simultaneously, separately or sequentially.

5. A method of preventing (i) necrosis or (ii) cell death in a cell or tissue, the method comprising:

contacting the cell or tissue with one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and one or more gap junction inhibitors to prevent necrosis or cell death in the cell or tissue.

6. The composition for use according to claim 1, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to claim 2, the gap junction inhibitor for use according to claim 3, or the methods according to any one of claims 4-5, wherein there are one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and two or more gap junction inhibitors.

7. The composition for use according to claim 1 or 6, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to claim 2 or 6, the gap junction inhibitor for use according to

claim 3 or 6, or the methods according to any one of claims 4-6, wherein there are two or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and two or more gap junction inhibitors.

8. The composition for use according to any one of claims 1 or 6-7, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to any one of claims 2 or 6-7, the gap junction inhibitor for use according to any one of claims 3 or 6-7, or the methods according to any one of claims 4-7, wherein the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor is a ryanodine receptor antagonist;

optionally wherein the ryanodine receptor antagonist is selected from one or more of dantrolene, DHBP dibromide, cis-Ned 19, trans-Ned 19, ryanodine, SKF 86365 hydrochloride, ruthenium red, procaine, and tetracaine;

optionally wherein the ryanodine receptor antagonist is selected from dantrolene and/or ryanodine.

9. The composition for use according to any one of claims 1 or 6-8, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to any one of claims 2 or 6-8, the gap junction inhibitor for use according to any one of claims 3 or 6-8, or the methods according to any one of claims 4-8, wherein the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor is dantrolene.

10. The composition for use according to any one of claims 1 or 6-9, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to any one of claims 2 or 6-9, the gap junction inhibitor for use according to any one of claims 3 or 6-9, or the methods according to any one of claims 4-9, wherein the gap junction inhibitor is selected from (i) one or more of a fatty acid, a polyamine and a cyclodextrin, optionally wherein the fatty acid contains 13-21 carbons, or (ii) a connexin inhibitor and/or a pannexin inhibitor, preferably a connexin inhibitor.

11. The composition for use according to any one of claims 1 or 6-10, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to any one of claims 2 or 6-10, the gap junction inhibitor for use according to any one of claims 3 or 6-10, or the methods according to any one of claims 4-10, wherein the gap junction inhibitor is selected from one or more of 18α-glycyrrhetinic acid, 18β-glycyrrhetinic acid, carbenoxolone disodium, heptanol, octanol, halothane, oleic acid, oleamide, linoleic acid, arachidonic acid, palmitoleic acid, flufenamic acid, myristic acid, lauric acid, quinine, quinidine, dihydroquinidine, mefloquine, meclofenamic acid, probenecid, niflumic acid, flufenamic acid, astaxanthin, and retinoic acid.

12. The composition for use according to claim 11, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to claim 11, the gap junction inhibitor for use according to claim 11, or

the method according to claim 11, wherein the gap junction inhibitor is one or more of retinoic acid, oleic acid, linoleic acid, octanol, heptanol, arachidonic acid, palmitoleic acid, flufenamic acid, myristic acid, halothane, astaxanthin and quinine.

13. The composition for use according to claim 12, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to claim 12, the gap junction inhibitor for use according to claim 12, or the method according to claim 12, wherein the gap junction inhibitor is one or more of retinoic acid, oleic acid, and linoleic acid.

14. The composition for use according to any one of claims 1 or 6-13, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to any one of claim 2 or 6-13, the gap junction inhibitor for use according to any one of claims 3 or 6-13, or the methods according to any one of claims 4-13, wherein the gap junction inhibitor is selected from two or more of oleic acid, linoleic acid, palmitoleic acid, quinine, astaxanthin, and retinoic acid.

15. The composition for use according to claim 14, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to claim 14, the gap junction inhibitor for use according to claim 14, or the methods according to claim 14, wherein the gap junction inhibitor is selected from (i) retinoic acid and linolic acid, (ii) retinoic acid and oleic acid, and (iii) linoleic acid and oleic acid.

16. The composition for use according to any one of claims 1 or 6-15, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to any one of claim 2 or 6-15, the gap junction inhibitor for use according to any one of claims 3 or 6-15, or the methods according to any one of claims 4-15, further comprising one or more plasma membrane calcium channel inhibitors.

17. The composition for use according to any one of claims 1 or 6-16, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to any one of claim 2 or 6-16, the gap junction inhibitor for use according to any one of claims 3 or 6-16, or the methods according to any one of claims 4-16, further comprising one or more calcium chelators.

18. The composition for use according to claim 16 or 17, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to claim 16 or 17, the gap junction inhibitor for use according to claim 16 or 17, or the methods according to claim 16 or 17, wherein the plasma membrane calcium channel inhibitor is selected from one or more of amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, cilnidipine, clevidipine, efonidipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, pranidipine,

fendiline, gallopamil, verapamil, diltiazem, mibefradil, bepridil, flunarizine, fluspirilene, fendiline, gabapentin and pregabalin;

preferably wherein the plasma membrane calcium channel inhibitor is selected from one or more of arandipine, clevidipine, efonidipine, felodipine, isradipine, lercanidipine, manidipine, nifedipine, nimodipine, nitrendipine, gallopamil, verapamil, diltiazem, mibefradil, fluspirilene, gabapentin or pregabalin.

19. The composition for use according to any one of claims 17-18, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to any one of claims 17-18, the gap junction inhibitor for use according to any one of claims 17-18, or the methods according to any one of claims 17-18, wherein the calcium chelator is selected from one or more of EDTA (Ethylenedioxy-diethylene-dinitrilo-tetraacetic acid); EGTA (Ethylene glycol-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid); DTPA (diethylenetriaminepentaacetic acid); HEDTA (N-(2-Hydroxyethyl)ethylenediamine-N, N',N'-triacetic acid Trisodium salt); NTA (Nitrilotriacetic acid); BAPTA ((1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid)); BAPTA AM (2-[N-[2-(acetyloxymethoxy)-2-oxoethyl]-2-[2-[2-[bis[2-(acetyloxymethoxy)-2-oxoethyl]amino]phenoxy]ethoxy]anilino]acetic acid acetyloxymethyl ester); citric acid; TPEN (N,N,N',N'-Tetrakis(2-pyridylmethyl)ethylenediamine); sodium citrate; and DMSA (dimercapto succinic acid);

preferably wherein the calcium chelator is one or more of DTPA, BAPTA AM, sodium citrate, and citric acid.

20. The composition for use according to any one of claims 1 or 6-19, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to any one of claims 1 or 6-19, the gap junction inhibitor for use according to any one of claims 1 or 6-19, or the methods according to any one of claims 4-19, wherein the tissue damage is a selection of one, more or all of the group consisting of: burns, multiple organ dysfunction syndrome, organ failure, surgical trauma, bedsores, chemical burns, radiation burn, gangrene, alopecia, solar erythema, acute tubular necrosis, ulcers, physical injury, mechanical trauma, heat injury, cold injury, chilblain, trench foot, frostbite, avascular necrosis, pressure injury, and skin graft failure.

21. The composition for use according to any one of claims 1 or 6-20, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to any one of claims 1 or 6-20, the gap junction inhibitor for use according to any one of claims 1 or 6-20, or the methods according to any one of claims 4-20, wherein the tissue is one or more tissues selected from the group comprising or consisting of: epithelial tissue, connective tissue, muscle tissue, and neuronal tissue;

preferably wherein the tissue is one or more tissues selected from the group comprising or consisting of: epithelial tissue, connective tissue, and muscle tissue.

22. The composition for use according to any one of claims 1 or 6-20, the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor for use according to any one of claims 1 or 6-20, the gap junction inhibitor for use according to any one of claims 1 or 6-20, or the methods according to any one of claims 4-20, wherein the organ damage is in a neuronal organ or in an organ that is part of the central nervous system (CNS).

23. A food preservative comprising one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and one or more gap junction inhibitors;

optionally wherein the food preservative further comprises one or more plasma membrane calcium channel inhibitors and/or one more calcium chelators.

24. A food product comprising a food preservative according to claim 23.

25. A method of storing a food product, the method comprising contacting a food product with a food preservative according to claim 23 to store the food product.

26. A method of preserving a live tissue or organ, the method comprising culturing or storing the tissue or organ in a culture media comprising one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and one or more gap junction inhibitors to preserve the tissue or organ;

optionally wherein the culture media further comprises one or more plasma membrane calcium channel inhibitors and/or one or more calcium chelators.

27. The method of claim 26, wherein the culture media is the University of Wisconsin (UW) solution.

28. A method of engineering a tissue or an organ, the method comprising contacting the organ or tissue with a culture media comprising one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and one or more gap junction inhibitors;

optionally wherein the culture media further comprises one or more plasma membrane calcium channel inhibitors and/or one or more calcium chelators.

29. A method of preserving or culturing blood cells, the method comprising contacting a culture media comprising blood cells with one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and one or more gap junction inhibitors;

optionally wherein the contacting step further comprises contacting the culture media with one or more plasma membrane calcium channel inhibitors and/or one or more calcium chelators.

30. The method of claim 29, wherein the culture media is blood, plasma or serum.

31. A method of preserving blood, DNA or fertility samples, the method comprising contacting the samples with one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and one or more gap junction inhibitors to preserve the samples;

optionally wherein the contacting step further comprises contacting the samples with one or more plasma membrane calcium channel inhibitors and/or one or more calcium chelators.

32. A method of preserving grafts, the method comprising contacting the graft with one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and one or more gap junction inhibitors to preserve the graft;

optionally wherein the contacting step further comprises contacting the graft with one or more plasma membrane calcium channel inhibitors and/or one or more calcium chelators.

33. A method of preserving or culturing cells during cultivation of cells lines in a bioreactor, the method comprising contacting the cells with one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and one or more gap junction inhibitors to preserve or culture the cells;

optionally wherein the contacting step further comprises contacting the cells with one or more plasma membrane calcium channel inhibitors and/or one or more calcium chelators.

34. A method of preserving or growing cell cultures, the method comprising contacting a culture media with one or more endoplasmic/sarcoplasmic reticulum calcium channel inhibitors and one or more gap junction inhibitors to preserve or grow the cell cultures;

optionally wherein the contacting step further comprise contacting the culture media with one or more plasma membrane calcium channel inhibitors and/or one or more calcium chelators.

35. The food preservative according to claim 23, the food product according to claim 24, or the methods according to any one of claims 25-34, wherein the endoplasmic/sarcoplasmic reticulum calcium channel inhibitor, and/or the gap junction inhibitor, and/or the plasma membrane calcium channel inhibitor, and/or the calcium chelator is as recited in any one of claims 6-19.

36. A method of preserving a live tissue or organ, the method comprising culturing or storing the tissue or organ in a culture media comprising one or more calcium chelators to preserve the tissue or organ.

37. The method of claim 36, wherein the culture media is the University of Wisconsin (UW) solution.

38. A method of engineering a tissue or an organ, the method comprising contacting the organ or tissue with a culture media comprising one or more calcium chelators.

39. The methods according to any one of claims 36-38, wherein the culture media comprises a relatively high dose of the one or more calcium chelators, optionally wherein the culture media comprises the calcium chelator in an amount of about four times the dose typically used, optionally wherein the culture media comprises the one or more calcium chelators according to the amounts recited in Aspect A.

40. A composition comprising one or more calpain inhibitors and one or more cathepsin inhibitors for use in a method of treating or preventing (i) necrosis, (ii) tissue damage, (iii) organ damage, or (iv) cell death, in a subject.

41. The composition for use according to claim 40, wherein the one or more calpain inhibitors is selected from one or more members selected from the group comprising or consisting of: a calpastatin, MG101, MG132, vidupiprant, an α-mercaptoacrylate, a 5-azolone, a carboxamide and a α-helical cysteine protease inhibitor.

42. The composition for use according to claim 40 or 41, wherein the one or more cathepsin inhibitors is selected from one or more of dexamethasone, rifampicin, E64, E64d, calpeptin, CA 074, SID26681509, L006235, bafilomycin, aloxistatin, astaxanthin, chloroquine, clofazimine, dec-RVKR, and dexamethasone.

43. A combination comprising dantrolene, or a pharmaceutically acceptable salt or a solvate thereof, and quinine, or a pharmaceutically acceptable salt or a solvate thereof.

44. The combination of claim 43, further comprising one or more additional endoplasmic/sarcoplasmic reticulum calcium channel inhibitors.

45. The combination of claim 44, wherein the additional endoplasmic/sarcoplasmic reticulum calcium channel inhibitor is a ryanodine receptor antagonist;

optionally wherein the additional ryanodine receptor antagonist is selected from one or more of DHBP dibromide, cis-Ned 19, trans-Ned 19, ryanodine, SKF 86365 hydrochloride, ruthenium red, procaine, and tetracaine;

optionally wherein the additional ryanodine receptor antagonist is ryanodine.

46. The combination of any one of claims 43-45, further comprising one or more additional gap junction inhibitors.

47. The combination of claim 46, wherein the additional gap junction inhibitor is selected from (i) one or more of a fatty acid, a polyamine and a cyclodextrin, optionally wherein the fatty acid contains 13-21 carbons, or (ii) a connexin inhibitor and/or a pannexin inhibitor, preferably a connexin inhibitor, or (iii) one or more of 18α-glycyrrhetinic acid, 18β-glycyrrhetinic acid, carbenoxolone disodium, heptanol, octanol, halothane, oleic acid, oleamide, linoleic acid, arachidonic acid, palmitoleic acid, flufenamic acid, myristic acid, lauric acid, quinidine, dihydroquinidine, mefloquine, meclofenamic acid, probenecid, niflumic acid, flufenamic acid, astaxanthin, and retinoic acid.

48. The combination of any one of claims 43-47, further comprising one or more plasma membrane calcium channel inhibitors.

49. The combination of claim 48, wherein the plasma membrane calcium channel inhibitor is selected from one or more of amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, cilnidipine, clevidipine, efonidipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, pranidipine, fendiline, gallopamil, verapamil, diltiazem, mibefradil, bepridil, flunarizine, fluspirilene, fendiline, gabapentin and pregabalin;

preferably wherein the plasma membrane calcium channel inhibitor is selected from one or more of arandipine, clevidipine, efonidipine, felodipine, isradipine, lercanidipine, manidipine, nifedipine, nimodipine, nitrendipine, gallopamil, verapamil, diltiazem, mibefradil, fluspirilene, gabapentin or pregabalin.

50. The combination of any one of claims 43-49, further comprising one or more calcium chelators.

51. The combination of claim 50, wherein the calcium chelator is selected from one or more of EDTA (Ethylenedioxy-diethylene-dinitrilo-tetraacetic acid); EGTA (Ethylene glycol-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid); DTPA (diethylenetriaminepentaacetic acid); HEDTA (N-(2-Hydroxyethyl)ethylenediamine-N, N',N'-triacetic acid Trisodium salt); NTA (Nitrilotriacetic acid); BAPTA ((1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid)); BAPTA AM (2-[N-[2-(acetyloxymethoxy)-2-oxoethyl]-2-[2-[2-[bis[2-(acetyloxymethoxy)-2-oxoethyl]amino]phenoxy]ethoxy]anilino]acetic acid acetyloxymethyl ester); citric acid; TPEN (N,N,N',N'-Tetrakis(2-pyridylmethyl)ethylenediamine); sodium citrate; and DMSA (dimercapto succinic acid);

preferably wherein the calcium chelator is one or more of DTPA, BAPTA AM, sodium citrate, and citric acid.

52. The combination of dantrolene, or a pharmaceutically acceptable salt or a solvate thereof, and quinine, or a pharmaceutically acceptable salt or a solvate thereof, for use in therapy.

53. Dantrolene, or a pharmaceutically acceptable salt or a solvate thereof, for use in therapy, wherein the dantrolene, or pharmaceutically acceptable salt or solvate thereof, is administered in a combination with quinine, or a pharmaceutically acceptable salt or a solvate thereof.

54. Quinine, or a pharmaceutically acceptable salt or a solvate thereof, for use in therapy, wherein the quinine, or pharmaceutically acceptable salt or solvate thereof, is administered in a combination with dantrolene, or a pharmaceutically acceptable salt or a solvate thereof.

55. The dantrolene and/or the quinine for use according to any one of claims 53-54, wherein the combination is as defined in any one of claims 44-51.

56. The dantrolene and/or the quinine for use according to any one of claims 52-55, wherein the dantrolene, or pharmaceutically acceptable salt or solvate thereof, and quinine, or pharmaceutically acceptable salt or solvate thereof, are administered simultaneously, separately or sequentially.

57. Use of a combination of any one of claims 43-52, or the dantrolene and/or the quinine for use according to any one of claims 53-56, in a method of treating or preventing (i) necrosis, (ii) tissue damage, (iii) organ damage, or (iv) cell death, in a subject.