CLAIMS

1. A method of cardiomyocyte transplantation, the method comprising:

administering *in vitro*-differentiated cardiomyocytes or cardiac progenitor cells to a graft site in cardiac tissue of a recipient in need thereof; and

administering a calcineurin inhibitor and an inhibitor of CD80 and/or CD86 signaling to the recipient.

2. The method of claim 1, wherein the *in vitro*-differentiated cardiomyocytes are allogeneic to the recipient.

3. The method of claim 1, wherein the *in vitro*-differentiated cardiomyocytes are autologous to the recipient.

4. The method of claim 1, 2, or 3 wherein the calcineurin inhibitor is selected from the group consisting of: tacrolimus, cyclosporine, voclosporin, and pimecrolimus.

5. The method of any one of claims 1-4, wherein the inhibitor of CD80 and/or CD86 comprises an extracellular domain fragment of CTLA4.

6. The method of claim 5, wherein the extracellular domain fragment of CTLA4 is fused to a heterologous polypeptide.

7. The method of claim 6, wherein the heterologous polypeptide increases the serum half-life of the inhibitor of CD80 and/or CD86.

8. The method of claim 6 or claim 7, wherein the heterologous polypeptide comprises an IgG Fc domain polypeptide.

9. The method of claim 5, wherein the extracellular domain fragment of CTLA4 is conjugated with polyethylene glycol (PEG).

10. The method of any one of claims 1-9, wherein the inhibitor of CD80 and/or CD86 signaling comprises abatacept or belatacept.

11. The method of claim 10, wherein abatacept is administered at a dose between 5 mg/kg and 20 mg/kg via intravenous or subcutaneous administration.

12. The method of any one of claims 1-11, wherein the inhibitor of CD80 and/or CD86 signaling is (i) administered every 2 weeks or every 3 weeks,

(ii) administered every 12-16 days,

(iii) administered every 10-18 days, or

(iv) administered by subcutaneous, oral or intravenous administration.

13. The method of any one of claims 1-12, wherein the calcineurin inhibitor comprises tacrolimus or an immunosuppressive derivative thereof.

14. The method of claim 13, wherein tacrolimus is administered to achieve a serum or plasma concentration of 5-20 ng/ml.

15. The method of claim 13 or 14, wherein the tacrolimus is administered via a continuous infusion, every 2 hours, every 4 hours, every 6 hours, every 8 hours, every 10 hours, every 12 hours, ever 14 hours, every 16 hours, every 18 hours, every 20 hours, every 22 hours, or daily.

16. The method of any one of claims 1-15 wherein the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling are each administered subcutaneously or intravenously or a combination thereof.

17. The method of any one of claims 1-16, wherein immune rejection of the administered cardiomyocytes is reduced relative to rejection of cardiomyocytes administered without the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling.

18. The method of any one of claims 1-17, wherein the need for steroid immunosuppression to suppress immune rejection of the transplanted cardiomyocytes is reduced relative to the need for steroid immunosuppression when cardiomyocytes are transplanted without administering the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling.

19. The method of any one of claims 1-18, wherein CD3+ T cell or CD20+ B cell infiltration into the graft site is reduced relative to infiltration occurring in the absence of administering the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling.

20. The method of claim 19, wherein CD3+ T cell or CD20+ B cell infiltration into the graft site is reduced at 8 weeks post-administration of the cardiomyocytes.

21. The method of claim 19, wherein CD3+ T cell or CD20+ B cell infiltration into the graft site remains reduced at 16 weeks post-administration of the cardiomyocytes.

22. A method of reducing immune rejection of transplanted, *in vitro*-differentiated cardiomyocytes in a recipient, the method comprising administering a calcineurin inhibitor and an inhibitor of CD80 and/or CD86 signaling to the recipient.

23. The method of claim 22, wherein the *in vitro*-differentiated cardiomyocytes are allogeneic to the recipient.

24. The method of claim 22, wherein the *in vitro*-differentiated cardiomyocytes are autologous to the recipient.

25. The method of claim 22, 23, or 24 wherein the calcineurin inhibitor is selected from the group consisting of: tacrolimus, cyclosporine, voclosporin, and pimecrolimus.

26. The method of any one of claims 22-25, wherein the inhibitor of CD80 and/or CD86 comprises an extracellular domain fragment of CTLA4.

27. The method of claim 26, wherein the extracellular domain fragment of CTLA4 is fused to a heterologous polypeptide.

28. The method of claim 27, wherein the heterologous polypeptide increases the serum half-life of the inhibitor of CD80 and/or CD86.

29. The method of claim 27 or claim 28, wherein the heterologous polypeptide comprises an IgG Fc domain polypeptide.

30. The method of claim 26, wherein the extracellular domain fragment of CTLA4 is conjugated with polyethylene glycol (PEG).

31. The method of any one of claims 22-30, wherein the inhibitor of CD80 and/or CD86 signaling comprises abatacept or belatacept.

32. The method of claim 31, wherein abatacept is administered at a dose between 5 mg/kg and 20 mg/kg via intravenous or subcutaneous administration.

33. The method of any one of claims 22-32, wherein the inhibitor of CD80 and/or CD86 signaling is (i) administered every 2 weeks or every 3 weeks,

(ii) administered every 12-16 days,

(iii) administered every 10-18 days, and/or

(iv) administered by subcutaneous, oral or intravenous administration.

34. The method of any one of claims 22-33, wherein the calcineurin inhibitor comprises tacrolimus or an immunosuppressive derivative thereof.

35. The method of claim 34, wherein tacrolimus is administered to achieve a serum or plasma concentration of 5-20 ng/ml.

36. The method of claim 34 or 35, wherein the tacrolimus is administered via a continuous infusion, every 2 hours, every 4 hours, every 6 hours, every 8 hours, every 10 hours, every 12 hours, ever 14 hours, every 16 hours, every 18 hours, every 20 hours, every 22 hours, or daily.

37. The method of any one of claims 22-36 wherein the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling are each administered subcutaneously or intravenously or a combination thereof.

38. The method of any one of claims 22-37, wherein immune rejection of the administered cardiomyocytes is reduced relative to rejection of cardiomyocytes administered without the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling.

39. The method of any one of claims 22-38, wherein the need for steroid immunosuppression to suppress immune rejection of the transplanted cardiomyocytes is reduced relative to the need for steroid immunosuppression when cardiomyocytes are transplanted without administering the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling.

40. The method of any one of claims 22-39, wherein CD3+ T cell or CD20+ B cell infiltration into the graft site is reduced relative to infiltration occurring in the absence of administering the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling.

41. The method of claim 40, wherein CD3+ T cell or CD20+ B cell infiltration into the graft site is reduced at 8 weeks post-administration of the cardiomyocytes.

42. The method of claim 40, wherein CD3+ T cell or CD20+ B cell infiltration into the graft site remains reduced at 16 weeks post-administration of the cardiomyocytes.

43. A method of treating a cardiovascular disease or disorder, the method comprising:

administering *in vitro*-differentiated cardiomyocytes to a graft site in cardiac tissue of a subject in need thereof, and

administering a calcineurin inhibitor and an inhibitor of CD80 and/or CD86 signaling to the subject.

44. The method of claim 43, wherein the cardiovascular disease or disorder comprises tachyarrhythmias, bradyarrhhythmias, cardiomyopathy, congenital defects, and muscular dystrophy-associated cardiomyopathy.

45. The method of claim 44, wherein the congenital defects comprise septal defects or hypoplastic syndroms.

46. The method of claim 44, wherein the muscular-dystrophy associated cardiomyopathy comprises cardiomyopathy associated with Duchenne's muscular dystrophy (DMD).

47. The method of claim 43, wherein the *in vitro*-differentiated cardiomyocytes are allogeneic to the recipient.

48. The method of claim 43, wherein the *in vitro*-differentiated cardiomyocytes are autologous to the recipient.

49. The method of claim 43, 44, or 45 wherein the calcineurin inhibitor is selected from the group consisting of: tacrolimus, cyclosporine, voclosporin, and pimecrolimus.

50. The method of any one of claims 43-48, wherein the inhibitor of CD80 and/or CD86 comprises an extracellular domain fragment of CTLA4.

51. The method of claim 49, wherein the extracellular domain fragment of CTLA4 is fused to a heterologous polypeptide.

52. The method of claim 50, wherein the heterologous polypeptide increases the serum half-life of the inhibitor of CD80 and/or CD86.

53. The method of claim 51 or claim 52, wherein the heterologous polypeptide comprises an IgG Fc domain polypeptide.

54. The method of claim 50, wherein the extracellular domain fragment of CTLA4 is conjugated with polyethylene glycol (PEG).

55. The method of any one of claims 43-54, wherein the inhibitor of CD80 and/or CD86 signaling comprises abatacept or belatacept.

56. The method of claim 55, wherein abatacept is administered at a dose between 5 mg/kg and 20 mg/kg via intravenous or subcutaneous administration.

57. The method of any one of claims 43-56, wherein the inhibitor of CD80 and/or CD86 signaling is (i) administered every 2 weeks or every 3 weeks,

(ii) administered every 12-16 days,

(iii) administered every 10-18 days, and/or

(iv) administered by subcutaneous, oral or intravenous administration.

58. The method of any one of claims 43-57, wherein the calcineurin inhibitor comprises tacrolimus or an immunosuppressive derivative thereof.

59. The method of claim 58, wherein tacrolimus is administered to achieve a serum or plasma concentration of 5-20 ng/ml.

60. The method of claim 58 or 59, wherein the tacrolimus is administered via a continuous infusion, every 2 hours, every 4 hours, every 6 hours, every 8 hours, every 10 hours, every 12 hours, ever 14 hours, every 16 hours, every 18 hours, every 20 hours, every 22 hours, or daily.

61. The method of any one of claims 43-60 wherein the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling are each administered subcutaneously or intravenously or a combination thereof.

62. The method of any one of claims 43-61, wherein immune rejection of the administered cardiomyocytes is reduced relative to rejection of cardiomyocytes administered without the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling.

63. The method of any one of claims 43-62, wherein the need for steroid immunosuppression to suppress immune rejection of the transplanted cardiomyocytes is reduced relative to the need for steroid immunosuppression when cardiomyocytes are transplanted without administering the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling.

64. The method of any one of claims 43-63, wherein CD3+ T cell or CD20+ B cell infiltration into the graft site is reduced relative to infiltration occurring in the absence of administering the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling.

65. The method of claim 64, wherein CD3+ T cell or CD20+ B cell infiltration into the graft site is reduced at 8 weeks post-administration of the cardiomyocytes.

66. The method of claim 65, wherein CD3+ T cell or CD20+ B cell infiltration into the graft site remains reduced at 16 weeks post-administration of the cardiomyocytes.

67. Use of a calcineurin inhibitor in combination with an inhibitor of CD80 and/or CD86 signaling for the treatment or prevention of immune-mediated rejection of a cardiac graft.

68. The use according to claim 67, comprising any of the features of claims 22-42.

69. Use of *in vitro*-differentiated cardiomyocytes or cardiac progenitor cells for cardiomyocyte transplantation, the use comprising:

in vitro-differentiated cardiomyocytes or cardiac progenitor cells to be administered to a graft site in cardiac tissue of a recipient in need thereof, and

a calcineurin inhibitor and an inhibitor of CD80 and/or CD86 signaling that is to be administered to the recipient.

70. The use according to claim 69, comprising any of the features of claims 2-42.

71. Use of *in vitro*-differentiated cardiomyocytes for treating a cardiovascular disease or disorder, the use comprising:

in vitro-differentiated cardiomyocytes to a graft site in cardiac tissue to be administered to a subject in need thereof, and

a calcineurin inhibitor and an inhibitor of CD80 and/or CD86 signaling to be administered to the subject

72. The use according to claim 71, comprising any of the features of claims 44-66.

CLAIMS

1. Use of *in vitro*-differentiated cardiomyocytes or cardiac progenitor cells in the manufacture of a medicament for cardiomyocyte transplantation, in which the medicament comprising *in vitro*-differentiated cardiomyocytes or cardiac progenitor cells is to be administered to a graft site in cardiac tissue of a recipient in need thereof; and in which the medicament is to be administered to the recipient with a calcineurin inhibitor and an inhibitor of CD80 and/or CD86 signaling.

2. Use according to Claim 1, in which the *in vitro*-differentiated cardiomyocytes are allogeneic to the recipient or autologous to the recipient.

3. Use according to Claim 1, in which the calcineurin inhibitor is selected from the group consisting of: tacrolimus, cyclosporine, voclosporin, and pimecrolimus.

4. Use according to Claim 1, in which the inhibitor of CD80 and/or CD86 comprises an extracellular domain fragment of CTLA4.

5. Use according to Claim 1, in which the extracellular domain fragment of CTLA4 is fused to a heterologous polypeptide and/or conjugated with polyethylene glycol (PEG).

6. Use according to Claim 5, in which the heterologous polypeptide increases the serum half-life of the inhibitor of CD80 and/or CD86, or in which the heterologous polypeptide comprises an IgG Fc domain polypeptide.

7. Use according to Claim 1, in which the inhibitor of CD80 and/or CD86 signaling comprises abatacept or belatacept.

8. Use according to Claim 7 in which abatacept is to be administered at a dose between 5 mg/kg and 20 mg/kg via intravenous or subcutaneous administration.

9. Use according to Claim 1, in which the inhibitor of CD80 and/or CD86 signaling is to be:

(i) administered every 2 weeks or every 3 weeks;

(ii) administered every 12-16 days;

(iii) administered every 10-18 days; or

(iv) administered by subcutaneous, oral or intravenous administration.

10. Use according to Claim 1, in which the calcineurin inhibitor comprises tacrolimus or an immunosuppressive derivative thereof.

11. Use according to Claim 10, in which tacrolimus is to be:

administered to achieve a serum or plasma concentration of 5-20 ng/ml; or

administered via a continuous infusion, every 2 hours, every 4 hours, every 6 hours, every 8 hours, every 10 hours, every 12 hours, ever 14 hours, every 16 hours, every 18 hours, every 20 hours, every 22 hours, or daily.

12. Use according to Claim 1, in which the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling are each to be administered subcutaneously or intravenously or a combination thereof.

13. Use according to Claim 1, in which the administering the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling results in any one or more of the following:

reduced immune rejection of the administered cardiomyocytes relative to rejection of cardiomyocytes administered without the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling;

reduced need for steroid immunosuppression to suppress immune rejection of the transplanted cardiomyocytes relative to the need for steroid immunosuppression when cardiomyocytes are transplanted without administering the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling;

reduced CD3+ T cell and/or CD20+ B cell infiltration into the graft site relative to infiltration occurring in the absence of administering the calcineurin inhibitor and the inhibitor of CD80 and/or CD86 signaling;

reduced CD3+ T cell or CD20+ B cell infiltration into the graft site at 8 weeks post-administration of the cardiomyocytes; and

reduced CD3+ T cell or CD20+ B cell infiltration into the graft site at 16 weeks post-administration of the cardiomyocytes.

14. Use according to Claim 1, in which the recipient subject has any one or more of the following:

a cardiovascular disease or disorder, in which the cardiovascular disease or disorder comprises tachyarrhythmias, bradyarrhythmias, cardiomyopathy, congenital defects, and muscular dystrophy-associated cardiomyopathy;

a congenital defect, in which the congenital defect comprises a septal defect or a hypoplastic syndrome; and

muscular-dystrophy associated cardiomyopathy comprises cardiomyopathy associated with Duchenne's muscular dystrophy (DMD).

15. Use of a calcineurin inhibitor in combination with an inhibitor of CD80 and/or CD86 signaling for the treatment or prevention of immune-mediated rejection of a cardiac graft or for treating a cardiac disease or disorder.

16. Use according to Claim 15, comprising any of the features of Claims 1 to 14.

17. Use of a calcineurin inhibitor in combination with an inhibitor of CD80 and/or CD86 signaling for the treatment or prevention of a cardiac disease or disorder.

18. Use according to Claim 17, comprising any of the features of Claims 1 to 14.