RETROGRADE CORONARY VENOUS OR SINUS ADMINISTRATION OF THERAPEUTICS

INTRODUCTION

[0001] Recent studies have shown that functional mutations in cardiac genes can result in the development of a dilated cardiomyopathy (DCM). While gene therapy has successfully ameliorated disease in non-cardiac familial conditions, attempts to correct gene expression in DCM have not been successful – raising the question of whether the heart can be successfully transduced using a viral vector.

SUMMARY

[0002] Mutations in the BCL2-Associated Athanogene 3 (*BAG3)* gene have been associated with development of familial DCM, and patients may be able to be treated by cardiac transduction of wild type (WT) BAG3. In order to assess the efficacy of different routes of delivery to heart an antegrade delivery and retrograde delivery were studied in a large animal model.

[0003] Using a recombinant adeno-associated virus (rAAV) vector and selective catheterization of the left coronary artery for antegrade and distal to the great cardiac vein for retrograde delivery of a recombinant adeno-associated virus, serotype 2/9 (AAV2 ITR, AAV9 capsid; rAAV2/9)–BAG3 gene to Yucatan minipigs. Subsequent vector gene transduction was measured in various regions of the heart after administration of the rAAV vector.

[0004] In accordance with the disclosure, there are provided methods of delivering a therapeutic to the heart. In one example, a method includes administering a therapeutic to a subject via retrograde coronary venous or sinus delivery thereby delivering the therapeutic to the heart.

[0005] In another example, a method includes administering a therapeutic to a subject via retrograde coronary venous or sinus delivery, without occluding the left main coronary artery or without occluding antegrade flow, thereby delivering the therapeutic to the heart.

[0006] In another example, a method includes administering a therapeutic to a subject via retrograde coronary venous or sinus delivery, with occluding the left main coronary artery or with occluding antegrade flow, thereby delivering the therapeutic to the heart.

[0007] In certain examples, the therapeutic is delivered to the heart by a catheter positioned proximal to the coronary sinus and distal to the great cardiac vein.

[0008] In certain examples, the therapeutic is delivered to the heart by a catheter positioned in or occluding the coronary sinus and distal to the origin of the great cardiac vein or the great cardiac vein.

[0009] In certain examples, the protein comprises BCL2-Associated Athanogene 3 (BAG3).

[0010] In certain examples, the nucleic acid comprises an expression vector.

[0011] In certain examples, the expression vector comprises a viral vector, eukaryotic or yeast vector.

[0012] In certain examples, the viral vector comprises an adeno-associated virus (AAV) vector, adenovirus vector, lentiviral vector or retroviral vector.

[0013] In certain examples, the AAV vector comprises a capsid or inverted terminal repeat from any one of the following AAV serotypes: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 or AAV12.

[0014] In certain examples, the expression vector comprises a promoter functional in heart.

[0015] In certain examples, the promoter is cardiac specific.

[0016] In certain examples, the expression vector comprises a promoter functional in heart and a BAG3 polynucleotide or cDNA sequence.

[0017] In certain examples, the subject is human.

[0018] In certain examples, the subject or human is suffering from heart failure.

[0019] In certain examples, the subject or human is suffering from heart failure with reduced ejection fraction.

[0020] In certain examples, the subject or human is suffering from heart failure with preserved ejection fraction.

[0021] In certain examples, the subject or human is suffering from familial dilated cardiomyopathy.

[0022] In certain examples, the subject or human is suffering from non-familial dilated cardiomyopathy.

[0023] In certain examples, the subject or human is suffering from ischemic heart disease or cardiomyopathy.

[0024] In certain examples, the subject or human is suffering from nonischemic heart disease or cardiomyopathy.

[0025] In certain examples, the subject or human is at risk of ischemia/reperfusion injury.

[0026] In certain examples, the subject or human is scheduled for or is a candidate for a vascular interventional or medical procedure that could be to ischemia/reperfusion injury.

[0027] In certain examples, the vascular interventional or medical procedure comprises a procedure using a catheter, a stent, angioplasty, bypass surgery or coronary artery bypass graft.

[0028] In certain examples, the subject or human is scheduled for or is a candidate for peripheral vascular disease surgery.

[0029] In certain examples, the subject or human has a mutation in their endogenous BAG3 polynucleotide or polypeptide.

[0030] In certain examples, the subject or human has reduced expression or activity of endogenous BAG3 polynucleotide or polypeptide.

[0031] In certain examples, the therapeutic is administered to the subject or human via the great cardiac vein.

[0032] In certain examples, the therapeutic is administered via a catheter positioned proximal but distal to the great cardiac vein.

[0033] In certain examples, the therapeutic is delivered into the great cardiac vein, left azygous or any veins that feed off the coronary sinus.

[0034] In certain examples, the therapeutic is administered via infusion for a time up to about 20 minutes.

[0035] In certain examples, the therapeutic is administered at a rate of about 1 ml per minute to 5 ml per minute.

[0036] In certain examples, the therapeutic is administered at a rate of about 1 ml per minute.

[0037] In certain examples, the therapeutic is administered in a volume from about 10 ml to about 100 mL.

[0038] In certain examples, the therapeutic is administered in a volume from about 20 ml to about 75 mL.

[0039] In certain examples, the therapeutic is administered in a volume from about 30 ml to about 60 mL.

[0040] In certain examples, the therapeutic is administered in a volume from about 40 ml to about 50 mL.

[0041] In certain examples, the therapeutic is delivered to and/or expressed in one or more of anterior left ventricle, anterior lateral left ventricle, inferior left ventricle, inferior lateral ventricle, septum or right ventricle.

[0042] In certain examples, the therapeutic is expressed throughout the heart.

[0043] In certain examples, the therapeutic reduces one or more symptoms of a cardiac disease.

[0044] In certain examples, the therapeutic improves cardiac function or cardiac contractility.

[0045] In certain examples, the therapeutic increases left ventricle ejection fraction.

[0046] In certain examples, a therapeutic, such as a viral vector is administered or used.

[0047] In certain examples, a viral vector is administered or used at a dose from about $1x10^{11}$ vg/kg to about $1.0x10^{14}$ vg/kg.

[0048] In certain examples, a viral vector is administered at a dose from about $1.0x10^{12}$ vg/kg to about $0.5x10^{14}$ vg/kg.

[0049] In certain examples, a viral vector is administered at a dose from about $3.0x10^{12}$ vg/kg to about $1.0x10^{13}$ vg/kg.

[0050] In certain examples, a viral vector is administered at a dose from about $3.0x10^{12}$ vg/kg to about $9.0x10^{12}$ vg/kg.

[0051] In certain examples, a viral vector is administered at a dose from about $3.0x10^{12}$ vg/kg to about $8.0x10^{12}$ vg/kg.

[0052] In certain examples, a viral vector is administered at a dose from about $3.0x10^{12}$ vg/kg to about $5.0x10^{12}$ vg/kg.

[0052a] In one aspect, the present disclosure provides use of a therapeutic comprising an expression vector comprising a nucleic acid encoding a BCL2-Associated Anthanogene 3 (BAG3) protein in the manufacture of a medicament for treating a subject suffering from heart

failure, wherein the medicament is to be delivered to the heart of a subject via retrograde coronary venous or sinus delivery, without occluding the left main coronary artery or without occluding antegrade flow.

DESCRIPTION OF THE DRAWINGS

[0053] Figure 1A shows coronary retrograde administration.

[0054] Figure 1B shows coronary antegrade administration.

[0055] Figure 1C shows retrograde coronary sinus administration.

CLAIMS

1. Use of a therapeutic comprising an expression vector comprising a nucleic acid encoding a BCL2-Associated Anthanogene 3 (BAG3) protein in the manufacture of a medicament for treating a subject suffering from heart failure, wherein the medicament is to be delivered to the heart of a subject via retrograde coronary venous or sinus delivery, without occluding the left main coronary artery or without occluding antegrade flow.
2. The use of claim 1, wherein the expression vector comprises a viral vector, eukaryotic or yeast vector.
3. The use of claim 2, wherein the viral vector comprises an adeno-associated virus (AAV) vector, adenovirus vector, lentiviral vector or retroviral vector.
4. The use of claim 3, wherein the AAV vector comprises a capsid or inverted terminal repeat from any one of the following AAV serotypes: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 or AAV12.
5. The use of claim 1, wherein the expression vector comprises a promoter functional in heart.
6. The use of claim 5, wherein the promoter is cardiac specific.
7. The use of claim 1, wherein the expression vector comprises a promoter functional in heart and a BAG3 polynucleotide or cDNA sequence.
8. The use of any of claims 1 – 7 wherein the subject is human.
9. The use of any one of claims 1 – 8, wherein the subject or human is suffering from heart failure with reduced ejection fraction or heart failure with preserved ejection fraction.
10. The use of any one of claims 1 – 9, wherein the subject or human is suffering from familial dilated cardiomyopathy.
11. The use of any one of claims 1 – 9, wherein the subject or human is suffering from non-familial dilated cardiomyopathy.
12. The use of any one of claims 1 – 9, wherein the subject or human is suffering from ischemic heart disease or cardiomyopathy.
13. The use of any one of claims 1 – 9, wherein the subject or human is suffering from nonischemic heart disease or cardiomyopathy.
14. The use of any one of claims 1 – 9, wherein the subject or human is at risk of ischemia/reperfusion injury.

15. The use of any one of claims 1 – 14, wherein the subject or human is scheduled for or is a candidate for a vascular interventional or medical procedure that could be to ischemia/reperfusion injury.
16. The use of any one of claims 1 – 14, wherein the medicament is to be delivered to the heart by a catheter positioned proximal to the coronary sinus and distal to the great cardiac vein.
17. The use of any one of claims 1 – 14, wherein the medicament is to be delivered to the heart by a catheter positioned in or occluding the coronary sinus and distal to the origin of the great cardiac vein or the great cardiac vein.
18. The use of claim 17, wherein the vascular interventional or medical procedure comprises a procedure using a catheter, a stent, angioplasty, bypass surgery or coronary artery bypass graft.
19. The use of any one of claims 1 – 17, wherein the subject or human is scheduled for or is a candidate for peripheral vascular disease surgery.
20. The use of any one of claims 1 – 17, wherein the subject or human has a mutation in their endogenous BAG3 polynucleotide or polypeptide.
21. The use of any one of claims 1 – 17, wherein the subject or human has reduced expression or activity of endogenous BAG3 polynucleotide or polypeptide.
22. The use of any one of claims 1 – 21, wherein the medicament is to be administered to the subject or human via the great cardiac vein.
23. The use of any one of claims 1 – 21, wherein the medicament is to be administered via a catheter positioned proximal but distal to the great cardiac vein.
24. The use of any one of claims 1 – 21, wherein the medicament is to be delivered into the great cardiac vein, left azygous or any veins that feed off the coronary sinus.
25. The use of any one of claims 1 – 24, wherein the medicament is to be administered via infusion for a time up to about 20 minutes.
26. The use of any one of claims 1 – 24, wherein the medicament is to be administered at a rate of about 1 ml per minute to 5 ml per minute.
27. The use of any one of claims 1 – 24, wherein the medicament is to be administered at a rate of about 1 ml per minute.

28. The use of any one of claims 1 – 27, wherein the medicament is to be administered in a volume of about 10 ml to about 100 mL.
29. The use of any one of claims 1 – 27, wherein the medicament is to be administered in a volume of about 20 ml to about 75 mL.
30. The use of any one of claims 1 – 27, wherein the medicament is to be administered in a volume of about 30 ml to about 60 mL.
31. The use of any one of claims 1 – 27, wherein the medicament is to be administered in a volume of about 40 ml to about 50 mL.
32. The use of any one of claims 1 – 31, wherein the medicament is to be administered to the subject and is to be delivered to one or more of anterior left ventricle, anterior lateral left ventricle, inferior lateral left ventricle, inferior lateral ventricle, septum or right ventricle, and/or the therapeutic is to be expressed in one or more of anterior left ventricle, anterior lateral left ventricle, inferior lateral left ventricle, inferior lateral ventricle, septum or right ventricle.
33. The use of any one of claims 1 – 31, wherein the therapeutic is expressed throughout the heart.
34. The use of any one of claims 1 – 33, wherein the therapeutic reduces one or more symptoms of a cardiac disease.
35. The use of any one of claims 1 – 34, wherein the therapeutic reduces one or more symptoms of heart failure.
36. The use of any one of claims 1 – 35, wherein the therapeutic improves cardiac function or cardiac contractility.
37. The use of any one of claims 1 – 36, wherein the therapeutic increases left ventricle ejection fraction.
38. The use of any one of claims 1-37, wherein the medicament is to be administered to the subject, the subject thereby receiving the viral vector at a dose from about $1x10^{11}$ vg/kg to about $1.0x10^{14}$ vg/kg.
39. The use of any one of claims 1-37, wherein the medicament is to be administered to the subject, the subject thereby receiving the viral vector at a dose from about $1.0x10^{12}$ vg/kg to about $0.5x10^{14}$ vg/kg.

40. The use of any one of claims 1-37, wherein the medicament is to be administered to the subject, the subject thereby receiving the viral vector at a dose from about $3.0x10^{12}$ vg/kg to about $1.0x10^{13}$ vg/kg.

41. The use of any one of claims 1-37, wherein the medicament is to be administered to the subject, the subject thereby receiving the viral vector at a dose from about $3.0x10^{12}$ vg/kg to about $9.0x10^{12}$ vg/kg.

42. The use of any one of claims 1-37, wherein the medicament is to be administered to the subject, the subject thereby receiving the viral vector at a dose from about $3.0x10^{12}$ vg/kg to about $8.0x10^{12}$ vg/kg.

43. The use of any one of claims 1-37, wherein the medicament is to be administered to the subject, the subject thereby receiving the viral vector at a dose from about $3.0x10^{12}$ vg/kg to about $5.0x10^{12}$ vg/kg.