CLAIMS:

1. A therapeutic polynucleotide comprising sequences encoding a S100 calcium binding protein A~~(S100A)~~ (S100A) polypeptide, a stromal cell derived factor 1 (SDF1) polypeptide, and a vascular endothelial growth factor (VEGF) polypeptide, wherein ~~at least two of~~ the S100A polypeptide, the SDF1 polypeptide, and the VEGF polypeptide are connected by one or more in vivo cleavable linkers, and wherein upon administration and expression of said therapeutic polynucleotide in a subject, said one or more in vivo cleavable linkers can be cleaved to release a free functional form of the at least two polypeptides connected by said one or more in vivo cleavable linkers.

2. The therapeutic polynucleotide of claim 1, wherein said SDF1 polypeptide is selected from the group consisting of SDF-1α and SDF-1β.

3. The therapeutic polynucleotide of claim 1, wherein said VEGF polypeptide is selected from the group consisting of VEGF121, VEGF121b, VEGF145, VEGF165, VEGF165b, VEGF189, VEGF191, and VEGF206.

4. The therapeutic polynucleotide of any one of claims 1 to 3, wherein said ~~S100Apolypeptide~~ S100A polypeptide comprises a sequence as shown in SEQ ID NO: 104; said ~~SDF1polypeptide~~ SDF1 polypeptide comprises a sequence as shown in SEQ ID NO: 102; and said VEGF polypeptide comprises a sequence as shown in SEQ ID NO: 106.

5. The therapeutic polynucleotide of claim 1, wherein said one or more in vivo cleavable linkers encode a sequence that mediates a ribosome skipping translational effect.

6. The therapeutic polynucleotide of claim 1, wherein said one or more in vivo cleavable linkers are selected from the group consisting of a RAKR linker, a fp2a linker, a p2a linker, a GSG-p2a linker, and a fmdv linker, or any combination thereof.

7. The therapeutic polynucleotide of claim 1, wherein said one or more in vivo cleavable linkers comprise a sequence as shown in SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, or SEQ ID NO: 40.

8. The therapeutic polynucleotide ~~polypeptide~~ of claim 6, wherein said one or more in vivo cleavable linkers further comprise a sequence selected from the group consisting of APVKQ (SEQ ID NO: 42), GPVKQ (SEQ ID NO: 43), VPVKQ (SEQ ID NO: 44), IPVKQ (SEQ ID NO: 45),

MPVKQ (SEQ ID NO: 46), APIKQ (SEQ ID NO: 47), GPIKQ (SEQ ID NO: 48), VPIKQ (SEQ ID NO: 49), IPIKQ (SEQ ID NO: 50), MPIKQ (SEQ ID NO: 51), APAKQ (SEQ ID NO: 52), GPAKQ (SEQ ID NO: 53), VPAKQ (SEQ ID NO: 54), IPAKQ (SEQ ID NO: 55), MPAKQ (SEQ ID NO: 56), APVRQ (SEQ ID NO: 57), GPVRQ (SEQ ID NO: 58), VPVRQ (SEQ ID NO: 59), IPVRQ (SEQ ID NO: 60), MPVRQ (SEQ ID NO: 61), APIRQ (SEQ ID NO: 62), GPIRQ (SEQ ID NO: 63), VPIRQ (SEQ ID NO: 64), IPIRQ (SEQ ID NO: 65), MPIRQ (SEQ ID NO: 66), APARQ (SEQ ID NO: 67), GPARQ (SEQ ID NO: 68), VPARQ (SEQ ID NO: 69), IPARQ (SEQ ID NO: 70), MPARQ (SEQ ID NO: 71), APVKN (SEQ ID NO: 72), GPVKN (SEQ ID NO: 73), VPVKN (SEQ ID NO: 74), IPVKN (SEQ ID NO: 75), MPVKN (SEQ ID NO: 76), APIKN (SEQ ID NO: 77), GPIKN (SEQ ID NO: 78), VPIKN (SEQ ID NO: 79), IPIKN (SEQ ID NO: 80), MPIKN (SEQ ID NO: 81), APAKN (SEQ ID NO: 82), GPAKN (SEQ ID NO: 83), VPAKN (SEQ ID NO: 84), IPAKN (SEQ ID NO: 85), IVIPAKN (SEQ ID NO: 86), APVRN (SEQ ID NO: 87), GPVRN (SEQ ID NO: 88), VPVRN (SEQ ID NO: 89), IPVRN (SEQ ID NO: 90), IVIPVRN (SEQ ID NO: 91), APIRN (SEQ ID NO: 92), GPIRN (SEQ ID NO: 93), VPIRN (SEQ ID NO: 94), IPIRN (SEQ ID NO: 95), MPIRN (SEQ ID NO: 96), APARN (SEQ ID NO: 97), GPARN (SEQ ID NO: 98), VPARN (SEQ ID NO: 99), IPARN (SEQ ID NO: 100) or MPARN (SEQ ID NO: 101).

9. A polypeptide encoded by the therapeutic polynucleotide of any one of claims 1 to 8, wherein said polypeptide comprises said S100A polypeptide, said SDF1 polypeptide, and said VEGF polypeptide, and wherein ~~at least two of~~ said S100A polypeptide, said SDF1 polypeptide and said VEGF polypeptide are connected by said one or more in vivo cleavable linkers.

10. A cell comprising the therapeutic polynucleotide of any one of claims 1 to 8, or the polypeptide of claim 9.

11. An expression vector comprising the therapeutic polynucleotide of any one of claims 1 to 8, wherein said therapeutic polynucleotide is operably linked to a promoter.

12. The expression vector of claim 11, wherein said promotor is a constitutive promoter, a tissue specific promoter, or an inducible promoter.

13. The expression vector of claim 12, wherein said inducible promoter is a small molecule ligand-inducible two polypeptide ecdysone receptor-based gene switch.

14. The expression vector of any one of claims 11 to 13, wherein said expression vector is a cardiac expression vector.

15. A pharmaceutical composition comprising:

the therapeutic polynucleotide of any one of claims 1 to 8, the polypeptide of claim 9, or the expression vector of any one of claims 11 to 14; and,

a pharmaceutically acceptable excipient.

16. A method comprising: contacting at least one cardiac cell with the therapeutic polynucleotide of any one of claims 1 to 8, the polypeptide of claim 9, or the expression vector of any one of claims 11 to 14, wherein the contacting is ex vivo.

17. The method of claim 16, wherein said cardiac cell is a myocardial cell.

18. Use of a therapeutically effective amount of the pharmaceutical composition of claim 15~~26~~ in the manufacture of a medicament for the treatment of a cardiac disease in a subject in need thereof.

19. The use of claim 18, wherein said cardiac disease is cardiomyopathy, vasculogenesis, congestive heart failure, arrhythmia, pericardial disease, aorta disease, Marfan syndrome, or coronary artery disease.

20. The use of claim 18 or 19, wherein said subject is a human subject.

21. Use of a therapeutically effective amount of a composition in the manufacture of a medicament for the treatment of a cardiac disease in a subject in need thereof, wherein the composition comprises a microbubble complex, wherein said microbubble complex comprises a lipid, a gas, and a plasmid comprising the therapeutic polynucleotide of any one of claims 1 to 8,~~;~~ wherein the medicament is to be administered by contacting said microbubble complex with ultrasonic energy sufficient to result in targeted microbubble destruction (UTMD).

22. The use of claim 21, wherein said lipid forms a shell enclosing said gas and said plasmid.

23. The use of any one of claims 18 to 22, wherein said ~~contacting,~~ treatment, or administering is to be via retrograde coronary sinus infusion (RCSI).

24. The polynucleotide of any one of claims 1 to 3, wherein said S100A polypeptide is a S100A1 polypeptide.

~~25. A therapeutic polynucleotide comprising sequences encoding a S100 calcium binding protein A(S100A) polypeptide, a stromal cell derived factor 1 (SDF1) polypeptide, and a vascular~~

endothelial growth factor (VEGF) polypeptide, wherein said S100A polypeptide, said SDF1 polypeptide, and said VEGF polypeptide are connected to each other by one or more in vivo cleavable linkers, and wherein upon administration and expression of said therapeutic polynucleotide in a subject, said one or more in vivo cleavable linkers can be cleaved to release a free functional form of said S100A, said SDF1, and said VEGF polypeptides connected by said one or more in vivo cleavable linkers.

26. A pharmaceutical composition comprising the therapeutic polynucleotide of claim 25.