

What is claimed:

1. Use of a therapeutically effective amount of an agent comprising ~~a Bel2-associated anthanogene 3 (BAG3) protein or active variant thereof, or~~ an expression vector expressing a BAG3 protein or biologically active variant-fragment thereof, in the preparation of a medicament for the treatment of ~~cardiac disease-heart failure~~ in a patient, wherein the patient has been identified as having at least one BAG3 genetic variant as compared to a control BAG3 nucleic acid sequence, wherein ~~detection of certain said~~ genetic ~~variants are~~variant is predictive of whether an increase in BAG3 levels is therapeutic for the patient, and wherein ~~the agent modulates expression or amount of BAG3 molecules, proteins or peptides thereof in a target cell or tissue, as compared to a normal control~~ said genetic variant comprises a 3 nucleotide insertion that adds an alanine at position 160 (p.Ala160dup, 10:121429647 A/AGCG; rs139438727) or a single nucleotide variant (SNV) in-frame insertion comprising: p.Pro63Ala (10:121429369 C/G; rs133031999); p.His83Gln (10:151331972; rs151331972); Ala479Val (10:121436502 C/T, rs34656239) or combinations thereof.
2. The use of claim 1, wherein the presence of the genetic variant negatively influences the outcome of patients with non-ischemic or ischemic dilated cardiomyopathy.
3. ~~—— The use of claim 2, wherein the genetic variant is a nucleotide variant (NV) in frame insertion, in frame deletions, truncation, substitutions or combinations thereof.~~
4. ~~—— The use of claim 3, wherein the in frame insertion encodes for an amino acid.~~
5. ~~—— The use of claim 3, wherein the in frame insertion encodes for a nonpolar amino acid.~~
6. ~~—— The use of claim 3, wherein the in frame insertion comprises a 3 nucleotide insertion that adds an alanine at position 160 (p.Ala160dup, 10:121429647 A/AGCG; rs139438727).~~
7. ~~—— The use of claim 2, wherein the genetic variant is a single nucleotide variant (SNV) in-frame insertion, in frame deletions, truncation, substitutions or combinations thereof.~~

~~83.~~ The use of claim ~~41~~, wherein the ~~SNVs comprise genetic variant comprises a combination of:~~ p.Pro63Ala (10:121429369 C/G; rs133031999); ~~p.His83Gln (10:151331972; rs151331972); and~~ Pro380Ser (10:121436204 C/T; rs144692954); ~~Ala479Val (10:121436502 C/T, rs34656239) or combinations thereof.~~

~~9.~~ ~~The use of claim 1, wherein the agent comprises an expression vector expressing a BAG3 protein or active variant thereof, or combinations of all thereof.~~

~~104.~~ The use of claim ~~91~~, wherein the expression vector comprises a viral vector, cardiotropic vector, plasmid, or a yeast vector.

~~115.~~ The use of claim ~~104~~, wherein a cardiotropic vector comprises an adenovirus vector, an adeno-associated virus vector (AAV), a coxsackie virus vector, cytomegalovirus vector, Epstein-Barr virus vector, parvovirus vector, or hepatitis virus vectors.

~~126.~~ The use of claim ~~111~~, wherein the expression vector is a cardiotropic pseudotyped viral vector.

~~13.~~ ~~The use of claim 1, wherein the agent comprises a BAG3 protein or active variant thereof.~~

~~14.~~ ~~The use of claim 1, wherein the cardiac disease is heart failure.~~

~~157.~~ Use of a therapeutically effective amount of an agent comprising a Bcl2-associated anthanogene 3 (BAG3) protein or biologically active variant fragment thereof, or an expression vector expressing a BAG3 protein or biologically active variant fragment thereof, in the preparation of a medicament for the treatment of ~~cardiac disease~~heart failure in a patient, wherein the patient has at least one BAG3 nucleotide genetic variant (NV) in-frame insertion as compared to a control BAG3 nucleic acid sequence, wherein the medicament is to be administered to the patient and wherein ~~the agent modulates expression or amount of BAG3 molecules, proteins or peptides thereof in a target cell or tissue~~ said genetic variant comprises a 3 nucleotide insertion that adds an alanine at position 160 (p.Alala160dup, 10:121429647 A/AGCG; rs139438727) or a single nucleotide variant (SNV) in-frame insertion comprising: p.Pro63Ala

(10:121429369 C/G; rs133031999); p.His83Gln (10:151331972; rs151331972); Ala479Val (10:121436502 C/T, rs34656239) or combinations thereof.

~~16. The use of claim 15, wherein the in-frame insertion encodes for an amino acid.~~

~~17. The use of claim 15, wherein the in-frame insertion encodes for a nonpolar amino acid.~~

~~18. The use of claim 15, wherein the in-frame insertion comprises a 3 nucleotide insertion that adds an alanine at position 160 (p.Ala160dup, 10:121429647 A/AGCG; rs139438727) genetic variant comprises a combination of: p.Pro63Ala (10:121429369 C/G; rs133031999); and Pro380Ser (10:121436204 C/T; rs144692954).~~

~~19. A method of identifying a heart disease failure patient having a worse prognosis, comprising: screening a patient sample for the presence of a Bcl2-associated anthanogene 3 (BAG3) nucleotide variant (NV) in-frame insertion as compared to a control BAG3 nucleic acid sequence, wherein the in-frame insertion comprises a 3 nucleotide insertion that adds an alanine at position 160 (p.Ala160dup, 10:121429647 A/AGCG; rs139438727) and wherein detection of the BAG3 nucleotide variant (NV) in-frame insertion identifies the heart disease failure patient as having a worse prognosis.~~

~~20. A method of identifying a patient at risk of heart disease failure, comprising: screening a patient sample for the presence of a Bcl2-associated anthanogene 3 (BAG3) nucleotide variant (NV) in-frame insertion as compared to a control BAG3 nucleic acid sequence, wherein the in-frame insertion comprises a 3 nucleotide insertion that adds an alanine at position 160 (p.Ala160dup, 10:121429647 A/AGCG; rs139438727) and wherein detection of the BAG3 nucleotide variant (NV) in-frame insertion identifies the patient as being at risk of heart disease failure.~~

~~21. The method of claim 19 or 20, wherein the in-frame insertion encodes an amino acid.~~

~~22. The method of claim 19 or 20, wherein the in-frame insertion encodes a nonpolar amino acid.~~

~~23. The method of claim 19 or 20, wherein the in-frame insertion comprises a 3 nucleotide insertion that adds an alanine at position 160 (p.Ala160dup, 10:121429647 A/AGCG; rs139438727).~~

2411. A method of identifying a patient at risk of heart ~~disease~~failure, comprising: screening a patient sample for the presence of a Bcl2-associated anthanogene 3 (BAG3) genetic variant, wherein the BAG3 genetic variant comprises p.Ala160dup (10:121429647 A/AGCG; rs139438727); p.Pro63Ala (10:121429369 C/G; rs133031999); p.His83Gln (10:151331972; rs151331972); ~~Pro380Ser (10:121436204 C/T; rs144692954);~~ Ala479Val (10:121436502 C/T, rs34656239) or combinations thereof.

2512. A kit comprising one or more probes conjugated to a detectable label for identifying BCL2-associated athanogene 3 (BAG3) variants in a biological sample, wherein the BAG3 variants comprise one or more of: p.Ala160dup (10:121429647 A/AGCG; rs139438727); p.Pro63Ala (10:121429369 C/G; rs133031999); p.His83Gln (10:151331972; rs151331972); or Ala479Val (10:121436502 C/T, rs34656239).

2613. The kit of claim 2512, further comprising one or more probes conjugated to a detectable label for identifying a BCL2-associated athanogene 3 (BAG3) variant in a biological sample wherein the BAG3 ~~variants comprise~~variant comprises one or more of: p.Ala160dup (10:121429647 A/AGCG; rs139438727); p.Pro63Ala (10:121429369 C/G; rs133031999); p.His83Gln (10:151331972; rs151331972); ~~Pro380Ser (10:121436204 C/T; rs144692954); or~~ Ala479Val (10:121436502 C/T, rs34656239).

2714. The kit of claim 2512, wherein detection of certain variants are predictive of whether a subject will benefit from a treatment.

2815. Use of a pharmaceutical composition comprising a therapeutically effective amount of at least one agent ~~which modulates expression or amount of a BCL2-associated athanogene 3 (BAG3) molecule~~ comprising a Bcl2-associated anthanogene 3 (BAG3) protein or biologically active fragment thereof, or an expression vector expressing a BAG3 protein or biologically

active fragment thereof in the preparation of a medicament for the treatment of heart failure in a subject at risk of or suffering from heart failure, wherein the subject has at least one BAG3 genetic variant as compared to a control BAG3 nucleic acid sequence, wherein the BAG3 genetic variant is an in-frame insertion comprising a 3 nucleotide insertion that adds an alanine at position 160 (p.Ala160dup, 10:121429647 A/AGCG; rs139438727) or a single nucleotide variant (SNV) in-frame insertion comprising: p.Pro63Ala (10:121429369 C/G; rs133031999); p.His83Gln (10:151331972; rs151331972); Ala479Val (10:121436502 C/T, rs34656239) or combinations thereof, wherein the medicament is to be administered to the subject, and wherein the agent comprises an expression vector encoding a BCL2-associated athanogene 3 (BAG3) molecule.

~~29. — The use of claim 28, wherein the in-frame insertion encodes an amino acid.~~

~~30. — The use of claim 28, wherein the in-frame insertion encodes a nonpolar amino acid.~~

~~31~~16. The use of claim ~~28~~15, wherein the ~~in-frame insertion comprises a 3 nucleotide insertion that adds an alanine at position 160 (p.Ala160dup, 10:121429647 A/AGCG; rs139438727)~~ BAG3 genetic variant comprises a combination of: p.Pro63Ala (10:121429369 C/G; rs133031999); and Pro380Ser (10:121436204 C/T; rs144692954).

~~32. — The use of claim 28, further comprising identifying in a biological sample, variants which are predictive of whether an increase in BAG3 levels is therapeutic for the subject, and, administering to the patient identified as having such a variant, a therapeutically effective amount of an agent wherein the agent modulates expression or amount of BAG3 molecules, proteins or peptides thereof in a target cell or tissue, as compared to a normal control.~~

~~33~~17. The use of any of claims 1 – 8 or the method of any of claims 9 – 11, wherein the genetic variants negatively influence the outcome of patients with non-ischemic or ischemic dilated cardiomyopathy through modulation of the function of BAG3.

18. The method of claim 11, wherein the BAG3 genetic variant comprises a combination of:
p.Pro63Ala (10:121429369 C/G; rs133031999) and Pro380Ser (10:121436204 C/T;
rs144692954).