

As additionally disclosed herein, *inter alia*, it has now been discovered that BAG3 interacts directly with the mitochondrial import receptor subunit TOM22, and the Ca²⁺ uniporter, mitochondrial metabolism and the generation of the mitochondrial membrane potential respectively.

As additionally disclosed herein, *inter alia*, it has now been discovered that decreased BAG3 results in an increase in poly (ADP-ribose) polymerase 1 (PARP1). Such an increase in PARP1 can result in an increase in alpha-synuclein and a worsening of Parkinson's symptoms. Accordingly, BAG3 can be used or formulated to reduce, inhibit or decrease PARP1.

In accordance with the disclosure, BAG3 can be used or formulated to modulate TNF signaling. In particular examples, BAG3 can be used or formulated to reduce, inhibit or decrease TNF signaling.

In accordance with the disclosure, BAG3 can be used or formulated to modulate inflammation. In particular examples, BAG3 can be used or formulated to reduce, inhibit, decrease or treat inflammation.

In accordance with the disclosure, BAG3 can be used or formulated to modulate an inflammatory response. In particular examples, BAG3 can be used or formulated to reduce, inhibit, decrease or treat an inflammatory response.

The inflammation or inflammatory response can be systemic, regionally or locally, such as in an organ or tissue. In particular examples, nonlimiting examples of inflammation or inflammatory response that BAG3 can be used or formulated to reduce, inhibit, decrease or treat occur in the pulmonary system, lung, cardiovascular system, central nervous system, bone, skeletal joints, skeletal muscle, gastrointestinal system, stomach, small intestine, large intestine, liver, kidney and pancreas.

In particular examples, nonlimiting examples of inflammation or inflammatory response that BAG3 can be used or formulated to reduce, inhibit, decrease or treat include chronic inflammatory

disease, chronic inflammatory demyelinating polyneuropathy, primary immune thrombocytopenia, geriatric anorexia, gut inflammation, inflammatory bowel disease, ulcerative colitis, Crohn's disease, lupus, rheumatoid arthritis, chronic myocarditis, chronic myocarditis after Covid 19 infection, psoriasis, psoriatic arthritis and ankylosing spondylitis.

In accordance with the disclosure, BAG3 can be used or formulated to modulate PARP1 levels, expression or activity. In particular examples, BAG3 can be used or formulated to reduce, inhibit, or decrease PARP1 levels, expression or activity. In particular examples, BAG3 can be used or formulated to reduce, inhibit, decrease or stabilize amounts of alpha-synuclein. In particular examples, BAG3 can be used or formulated to reduce, inhibit, decrease or decrease worsening or severity one or more symptoms of Parkinson's disease.

In particular examples, a BAG3 encoding nucleic acid comprises an expression vector expressing a BAG3 protein or active BAG3 peptide thereof.

In particular examples, an expression vector comprises a promoter, the promoter comprising an inducible promoter, a constitutive promoter, bicistronic promoter, tissue specific promoter or cardiac specific promoter.

In particular examples, an expression vector comprises a viral vector, cardiotropic vector, plasmid, or a yeast vector.

In particular examples, a viral or 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.

In particular examples, an AAV vector comprises a capsid protein having 90% or more sequence identity to any of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7m AAV8, AAV9, AAV10, AAV11 or AAV12.

In particular examples, an expression vector is a pseudotyped viral vector.

In particular examples, the inflammation or inflammatory response is induced or increased by a cytokine.

In particular examples, a cytokine comprises tumor necrosis factor (TNF).

In particular examples, a patient expresses lower than normal levels of BAG3 in a tissue or organ or does not detectably express or produce functional BAG3.

In particular examples, the inflammation or inflammatory response occurs in the pulmonary system, lung, cardiovascular system, central nervous system, bone, skeletal joints, skeletal muscle, gastrointestinal system, stomach, small intestine, large intestine, liver, kidney or pancreas.

In particular examples, an expression vector further comprises a promoter, the promoter optionally comprising an inducible promoter, a constitutive promoter, bicistronic promoter or tissue specific promoter.

In particular examples, a promoter confers expression in the pulmonary system, lung, cardiovascular system, central nervous system, bone, skeletal joints, skeletal muscle, gastrointestinal system, stomach, small intestine, large intestine, liver, kidney or pancreas.

In particular examples, an expression vector further comprises an AAV inverted terminal repeat (ITR).

In particular examples, an expression vector further comprises a polyadenylation sequence and/or stop codon.

In particular examples, a patient or subject is human.

In particular examples, a patient, subject or human has a mutation in their endogenous BAG3 polynucleotide or polypeptide.

In particular examples, a patient, subject or human has reduced expression or activity of endogenous BAG3 polynucleotide or polypeptide.

In particular examples, a viral vector is administered or formulated at a dose from about 0.1×10^{12} vector genomes (vg)/weight of the patient in kilograms (vg/kg) to about 1.0×10^{14} vg/kg.

In particular examples, a viral vector is administered or formulated at a dose from about 1.0×10^{12} vg/kg to about 0.5×10^{14} vg/kg.

In particular examples, a viral vector is administered or formulated at a dose from about 3.0×10^{12} vg/kg to about 1.0×10^{13} vg/kg.

In particular examples, a viral vector is administered or formulated at a dose from about 3.0×10^{12} vg/kg to about 9.0×10^{12} vg/kg.

In particular examples, a viral vector is administered or formulated at a dose from about 3.0×10^{12} vg/kg to about 8.0×10^{12} vg/kg.

In particular examples, a viral vector is administered or formulated at a dose from about 3.0×10^{12} vg/kg to about 5.0×10^{12} vg/kg.

In one aspect, the disclosure provides use of a BCL2-associated athanogene 3 (BAG3) encoding nucleic acid, BAG3 protein or BAG3 peptide in the manufacture of a medicament for reducing, inhibiting or decreasing aberrant or undesirable inflammation or an inflammatory response in a patient, wherein the patient expresses lower than normal levels of BAG3 in a tissue or organ or does not detectably express or produce functional BAG3, wherein the aberrant or undesirable inflammation or inflammatory response affects the pulmonary system, lung, cardiovascular system, central nervous system, bone, skeletal joints, skeletal muscle, gastrointestinal system, stomach, small intestine, large intestine, liver, kidney or pancreas.

DESCRIPTION OF DRAWINGS

Figures 1A-1B show data indicating that young mice with a deletion of one allele of Bag3 demonstrate a unique proteome that emphasizes alterations in the pathways of apoptosis and cellular metabolism despite the presence of normal LV function and size. **A)** Scatter plots with bar graphs showing results of transthoracic echocardiography of 8 to 10 wk old BAG3^{+/-} and BAG3^{wt} mice including measures of left ventricular (LV) ejection fraction (EF%), LV internal diameter in diastole (LVIDd) and LV internal diameter in systole (LVIDs) both in millimeters (mm). **B)** Levels of BAG3 were diminished by approximately 50% in all BAG3^{+/-} groups

CLAIMS

1. Use of a BCL2-associated athanogene 3 (BAG3) encoding nucleic acid, BAG3 protein or BAG3 peptide in the manufacture of a medicament for reducing, inhibiting or decreasing aberrant or undesirable inflammation or an inflammatory response in a patient, wherein the patient expresses lower than normal levels of BAG3 in a tissue or organ or does not detectably express or produce functional BAG3, wherein the aberrant or undesirable inflammation or inflammatory response affects the pulmonary system, lung, cardiovascular system, central nervous system, bone, skeletal joints, skeletal muscle, gastrointestinal system, stomach, small intestine, large intestine, liver, kidney or pancreas.
2. The use according to claim 1, wherein the aberrant or undesirable inflammation or inflammatory response comprises chronic inflammatory disease, chronic inflammatory demyelinating polyneuropathy, primary immune thrombocytopenia, geriatric anorexia, gut inflammation, inflammatory bowel disease, ulcerative colitis, Crohn's disease, lupus, rheumatoid arthritis, chronic myocarditis, chronic myocarditis after Covid 19 infection, psoriasis, psoriatic arthritis or ankylosing spondylitis.
3. The use according to claim 1 or claim 2, wherein the BAG3 encoding nucleic acid comprises an expression vector expressing a BAG3 protein or active BAG3 peptide thereof.
4. The use according to claim 3, wherein the expression vector comprises a viral vector, a cardiotropic vector, a plasmid, a yeast vector, or a pseudotyped viral vector.
5. The use according to claim 4, wherein the viral or cardiotropic vector comprises an adenovirus vector, an adeno-associated virus vector (AAV), a coxsackie virus vector, a cytomegalovirus vector, an Epstein-Barr virus vector, a parvovirus vector, or a hepatitis virus vector.

6. The use according to claim 5, wherein the AAV vector comprises a capsid protein having 90% or more sequence identity to any of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 or AAV12.
7. The use according to any one of claims 4-6, wherein the expression vector further comprises a promoter, optionally wherein the promoter comprises an inducible promoter, a constitutive promoter, a bicistronic promoter, a tissue specific promoter, or a cardiac specific promoter.
8. The use according to claim 7, wherein the promoter confers expression in the pulmonary system, lung, cardiovascular system, central nervous system, bone, skeletal joints, skeletal muscle, gastrointestinal system, stomach, small intestine, large intestine, liver, kidney or pancreas.
9. The use according to any one of claims 1-8, wherein the expression vector further comprises:
- a. an AAV inverted terminal repeat (ITR); or
 - b. a polyadenylation sequence and/or stop codon.
10. The use according to any one of claims 1-9, wherein the patient is a human.
11. The use according to any one of claims 1-10, wherein the patient has a mutation in their endogenous BAG3 polynucleotide or polypeptide.
12. The use according to any one of claims 1-11, wherein the medicament is to be administered to the patient, wherein the medicament comprises a dose of the viral vector from about 0.1×10^{12} vector genomes (vg)/weight of the patient in kilograms (vg/kg) to about 1.0×10^{14} vg/kg.
13. The use according to any one of claims 1-11, wherein the medicament is to be administered to the patient, wherein the medicament comprises a dose of the viral vector from about 1.0×10^{12} vg/kg to about 0.5×10^{14} vg/kg.

14. The use according to any one of claims 1-11, wherein the medicament is to be administered to the patient, wherein the medicament comprises a dose of the viral vector from about 3.0×10^{12} vg/kg to about 1.0×10^{13} vg/kg.

15. The use according to any one of claims 1-11, wherein the medicament is to be administered to the patient, wherein the medicament comprises a dose of the viral vector from about 3.0×10^{12} vg/kg to about 9.0×10^{12} vg/kg.

16. The use according to any one of claims 1-11, wherein the medicament is to be administered to the patient, wherein the medicament comprises a dose of the viral vector from about 3.0×10^{12} vg/kg to about 8.0×10^{12} vg/kg.

17. The use according to any one of claims 1-11, wherein the medicament is to be administered to the patient, wherein the medicament comprises a dose of the viral vector from about 3.0×10^{12} vg/kg to about 5.0×10^{12} vg/kg.