The ongoing hypothesis that observed perturbations in mitophagy/autophagy resulting in observed phenotype can be rescued was tested, at least in part, by interventions targeting the mitophagy/autophagy, JAK-STAT pathway, including but not limited to SOCS1 and tofacitinib using a drug repurposing therapy approach. Treatment with a JAK/STAT pan-inhibitor (tofacitinib) partially rescued the phenotype and improved survival of *CLEC16A* KO mice by modulating ER stress, lipolysis, mitophagy and autophagy. However, aberrant, partial phenotypic features remained.

Given the large number of autoimmune, and other disorders correlated with *CLEC16A* loss or dysfunction, it is clear that new treatments and therapeutic agents which help ameliorate the effects of malfunctioning *CLEC16A*, and reduce associated symptoms, are urgently needed.

Summary of the Invention

In accordance with one example of the present disclosure, a method for ameliorating at least one *CLEC16A*-associated symptom in a subject in need thereof, comprising administering an effective amount of at least one mitophagy enhancer, wherein said at least one symptom is selected from robust autoimmune inflammatory responses, severe weight loss, severe neurological symptoms, neuroinflammation, progressive neurodegeneration resembling spinocerebellar ataxia, and fat loss is described. Also described herein are methods for treating a CLEC16A-associated disorder in a subject in need thereof, comprising administering an effective amount of at least one mitophagy enhancer. In certain examples, the CLEC16A-associated disorder is selected from an autoimmune disorder, a lipodystrophic disorder, and a neurodegenerative disorder.

In certain examples of the invention, the at least one mitophagy enhancer enhances the clearance of mitochondria. Exemplary mitophagy enhancers are probucol, quercetin, or acipimox. In certain examples, the methods further comprise administering one or more agents selected from a JAK-STAT inhibitor, an ER stress modulator, and a SOCS1 inhibitor. Exemplary JAK-STAT inhibitors are selected from tofacitinib, ruxolitinib, baricitinib, peficitinib, decernotiniba, filgotinib, solcitinibb, itacitinib, SHR0302, upadacitinib, and PF-04965842. Exemplary ER stress modulators are selected from Rapamycin, 4-phenylbutyric acid (4-PBA), trimethylamine N-oxide dehydrate (TMAO), dimethyl sulfoxide (DMSO), tauroursodeoxycholic acid (TUDCA), AMPK-activated protein kinase, 5′-aminoimidazole-4-carboxymide-1-β-d-

ribofuranoside (AICAR), Glucagon-Like Peptide-1 (GLP-1), DPP4 inhibitors, and n-acetylcysteine (NAC). In certain examples, the methods further comprise administration of a PPARγ inhibitor.

In certain examples, the methods described herein rescue spleen atrophy and/or improves the organ weight ratio of Thymus, inguinal white adipose tissue (iWAT), and/or gonal white adipose tissue (gWAT) when compared to an untreated control. In certain examplesthe treatment delays CLEC16A-associated symptom progression when compared to an untreated control.

Also described herein are methods for treating CLEC16A-associated degeneration of the thymus, comprising administration of a mitophagy enhancer, thereby altering the weight ratio in thymus and ameliorating symptoms associated with degeneration of the thymus. Methods for treating CLEC16A-associated degeneration of spleen, comprising administration of a mitophagy enhancer, thereby altering the weight ratio in spleen, providing therapeutic benefit, and ameliorating symptoms associated with degeneration of the spleen, are also described herein.

In another examplesof the invention, methods for treating CLEC16A-associated degeneration of iWAT, comprising administration of a mitophagy enhancer, thereby altering the weight ratio in iWAT and ameliorating symptoms associated with degeneration of the iWAT are described. Also described herein are methods for treating CLEC16A-associated degeneration of gWAT, comprising administration of a mitophagy enhancer, thereby altering the weight ratio in gWAT and ameliorating symptoms associated with degeneration of the gWAT.

Also described herein are methods for treating *CLEC16A*-associated symptoms in a subject in need thereof, the method comprising, a) diagnosing the subject with a CLEC16A-associated disorder, and b) administering an effective amount of a mitophagy enhancer.

In one aspect, the present disclosure refers to use of at least one mitophagy enhancer in the manufacture of a medicament for ameliorating at least one CLEC16A-associated symptom in a subject in need thereof, wherein said at least one symptom is selected from robust autoimmune inflammatory responses, severe weight loss, severe neurological symptoms, neuroinflammation, progressive neurodegeneration resembling spinocerebellar ataxia, and fat loss.

In another aspect, the present disclosure refers to use of at least one mitophagy enhancer in the manufacture of a medicament for treating a CLEC16A-associated disorder in a subject in need thereof.

In yet another aspect, the present disclosure refers to use of a mitophagy enhancer in the manufacture of a medicament for treating CLEC16A-associated degeneration of the thymus or spleen, wherein the medicament alters the weight ratio in thymus or spleen, and ameliorates symptoms associated with degeneration of the thymus or degeneration of the spleen.

In another aspect, the present disclosure refers to use of a mitophagy enhancer in the manufacture of a medicament for treating CLEC16A-associated degeneration of inguinal white adipose tissue (iWAT), wherein the medicament alters the weight ratio in iWAT and ameliorates symptoms associated with degeneration of the iWAT.

In yet another aspect, the present disclosure refers to use of a mitophagy enhancer in the manufacture of a medicament for treating CLEC16A-associated degeneration of gonal white adipose tissue gWAT, wherein the medicament alters the weight ratio in gWAT and ameliorates symptoms associated with degeneration of the gWAT.

In a further aspect, the present disclosure refers to use of a mitophagy enhancer in the manufacture of a medicament for treating *CLEC16A*-associated symptoms in a subject in need thereof, wherein the subject had been diagnosed with a CLEC16A-associated disorder, and wherein the medicament is to be administered in an effective amount of a mitophagy enhancer.

Brief Description of the Drawings

Figure 1. Body weight in control ± probucol and *CLEC16A* KO ± probucol mice fed with standard chow.

Figures 2A-2L. Organ weight/body weight ratios for control ± probucol and KO ± probucol groups.

What is claimed is:

1. Use of at least one mitophagy enhancer in the manufacture of a medicament for ameliorating at least one *CLEC16A*-associated symptom in a subject in need thereof, wherein said at least one symptom is selected from robust autoimmune inflammatory responses, severe weight loss, severe neurological symptoms, neuroinflammation, progressive neurodegeneration resembling spinocerebellar ataxia, and fat loss.

2. Use of at least one mitophagy enhancer in the manufacture of a medicament for treating a CLEC16A-associated disorder in a subject in need thereof.

3. The use of any one of the preceding claims, wherein the at least one mitophagy enhancer enhances the clearance of mitochondria.

4. The use of any one of the preceding claims, wherein the mitophagy enhancer is selected from probucol, quercetin, or acipimox.

5. The use of any one of the preceding claims, wherein the mitophagy enhancer is probucol.

6. Use of at least one mitophagy enhancer in the manufacture of a medicament for treating CLEC16A-associated degeneration of the thymus or degeneration of the spleen, wherein the medicament alters the weight ratio in thymus or spleen, and ameliorates symptoms associated with degeneration of the thymus or degeneration of the spleen.

7. Use of a mitophagy enhancer in the manufacture of a medicament for treating CLEC16A-associated degeneration of inguinal white adipose tissue (iWAT), wherein the medicament alters the weight ratio in iWAT and ameliorates symptoms associated with degeneration of the iWAT.

8. Use of a mitophagy enhancer in the manufacture of a medicament for treating CLEC16A-associated degeneration of gonal white adipose tissue gWAT, wherein the medicament alters the weight ratio in gWAT and ameliorates symptoms associated with degeneration of the gWAT.

9. The use of anyone of the preceding claims, wherein the medicament is administered in combination with a PPARγ inhibitor.

10. Use of a mitophagy enhancer in the manufacture of a medicament for treating *CLEC16A*-associated symptoms in a subject in need thereof, wherein the subject had been diagnosed with a CLEC16A-associated disorder, and wherein the medicament is to be administered in an effective amount of a mitophagy enhancer.

11. The use of any one of the preceding claims, wherein the CLEC16A-associated disorder is selected from an autoimmune disorder, a lipodystrophic disorder, and a neurodegenerative disorder.

12. The use of any one of claims 7-12, wherein the at least one mitophagy enhancer enhances the clearance of mitochondria.

13. The use of any one of claims 7-13, wherein the mitophagy enhancer is selected from probucol, quercetin, or acipimox.

14. The use of any one of claims 7-14, wherein the mitophagy enhancer is probucol.

15. The use of any one of the preceding claims, wherein the medicament is to be administered in combination with one or more agents selected from a JAK-STAT inhibitor, an ER stress modulator, and a SOCS1 inhibitor.

16. The use of claim 16, wherein

a) the agent is a JAK-STAT inhibitor selected from tofacitinib, ruxolitinib, baricitinib, peficitinib, decernotiniba, filgotinib, solcitinibb, itacitinib, SHR0302, upadacitinib, and PF-04965842,

b) the agent is an ER stress modulator selected from Rapamycin, 4-phenylbutyric acid (4-PBA), trimethylamine N-oxide dehydrate (TMAO), dimethyl sulfoxide (DMSO), tauroursodeoxycholic acid (TUDCA), AMPK-activated protein kinase, 5′-aminoimidazole-4-carboxymide-1-β-d-ribofuranoside (AICAR), Glucagon-Like Peptide-1 (GLP-1), DPP4 inhibitors, and N-acetylcysteine (NAC).

17. The use of claim 17 or 18 wherein the agent is tofacitinib.

18. The use of any one of the preceding claims, wherein the medicament rescues spleen atrophy and/or improves the organ weight ratio of Thymus, inguinal white adipose tissue (iWAT), and/or gonal white adipose tissue (gWAT) when compared to an untreated control.

19. The use of any one of the preceding claims, wherein the medicament delays CLEC16A-associated symptom progression when compared to an untreated control.