negatively regulates autophagy via modulation of mTOR activity. How this relates to the autoimmune function is yet to be determined.

In our previous work in type-1 diabetes, the protective *CLEC16A* alleles were associated with higher levels of CLEC16A (formally known as *KIAA0350*). We also recently showed that ubiquitous loss of CLEC16A led to disrupted mitophagy in immune cells.

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 ameliorate the effects of malfunctioning CLEC16A are urgently needed.

Summary

The current disclosure implicates CLEC16A as a critical regulator of lipophagy and endoplastmic reticulum (ER) stress, involving a robust cytokine response that results in a systemic inflammatory response and lipolytic processes responsible for substantive weight loss. As CLEC16A is a major autoimmune gene associated with at least 16 autoimmune diseases, including type-1 diabetes, multiple sclerosis, lupus and inflammatory bowel disease.

In accordance with the present disclosure, a combination therapy for the treatment of at least one autoimmune disorder associated with aberrant CLEC16A function is provided. In one aspect, the present disclosure provides a use of one or more agents in the manufacture of a medicament for treating thymus degeneration or atrophy resulting from loss or reduction of CLEC16A in a subject in need thereof, wherein said one or more agents is selected from a mitophagy suppressor/modulator, an ER suppressor, a JAK2 inhibitor and SOCS1 inhibitor which ameliorates symptoms associated with thymus degeneration or atrophy.

In yet another aspect, the present disclosure provides a use of one or more agents selected from a mitophagy suppressor/modulator, an ER suppressor, a JAK2 inhibitor and SOCS1 inhibitor in the manufacture of a medicament for treating spleen degeneration resulting from loss or reduction of CLEC16A in a subject in need thereof, said agent altering the white red pulp ratio in the spleen and ameliorating symptoms associated with degeneration of the spleen. In a further aspect, the present disclosure provides a use of an agent which inhibits CD163 expression and/or immune cell infiltration and/or acini cell degeneration in the pancreas in the manufacture of a

medicament for treating CLEC16A-associated degeneration of the pancreas, thereby reducing autoimmune symptoms.

In one example a method for treating CLEC16A-associated degeneration of the thymus is provided comprising administration of an agent that modulates expression of one or more of CD163, Bcl-2, Pax-5, V-cam1, CD8 and FoxP3, thereby altering the medulla cortex ratio in thymus and ameliorating symptoms associated with degeneration of the thymus. In another embodiment, a method for treating CLEC16A-associated degeneration of spleen is provided comprising administration of an agent that modulates expression of one or more of CD163, CD68, Bcl-2, CD40, Pax5, Vcam1, CD3, and GzmB, thereby altering the white red pulp ratio in the spleen and ameliorating symptoms associated with degeneration of the spleen. The disclosure also discloses a method for treating CLEC16A-associated degeneration of the pancreas comprising administration of an agent which modulates CD163 expression and/or immune cell infiltration and/or acini cell degeneration in the pancreas, thereby reducing autoimmune symptoms.

As noted above, the disclosure includes a combination the combination therapy that can include at least two of a mitophagy suppressor/modulator, ER suppressor, a JAK2 inhibitor and

What is claimed is:

1. Use of one or more agents in the manufacture of a medicament for treating thymus degeneration or atrophy resulting from loss or reduction of CLEC16A in a subject in need thereof, wherein said one or more agents is selected from a mitophagy suppressor/modulator, an ER suppressor, a JAK2 inhibitor and SOCS1 inhibitor which ameliorates symptoms associated with thymus degeneration or atrophy.

2. The use of claim 1, wherein said one or more agents alter the medulla cortex ratio in thymus.

3. Use of one or more agents selected from a mitophagy suppressor/modulator, an ER suppressor, a JAK2 inhibitor and SOCS1 inhibitor in the manufacture of a medicament for treating spleen degeneration resulting from loss or reduction of CLEC16A in a subject in need thereof, said agent altering the white red pulp ratio in the spleen and ameliorating symptoms associated with degeneration of the spleen.

4. Use of an agent which inhibits CD163 expression and/or immune cell infiltration and/or acini cell degeneration in the pancreas in the manufacture of a medicament for treating CLEC16A-associated degeneration of the pancreas, thereby reducing autoimmune symptoms.

5. The use of any of claims 1 - 4, wherein the loss or reduction of said CLEC16A is associated with an autoimmune disorder selected from type-1 diabetes, multiple sclerosis, primary adrenal insufficiency, Crohn's disease, primary biliary cirrhosis, juvenile idiopathic arthritis, rheumatoid arthritis, and alopecia areata, uveitis, neurodegeneration and lupus.

6. The use of any of claims 1 - 5, wherein said agents are rapamycin and tofacitinib.

7. The use of any of claims 1-5, wherein a nucleic acid from said subject is first assessed for an alteration in a CLEC16a encoding nucleic acid.