

We claim:

1. A rodent comprising a genetically modified endogenous *Asgr1* locus encoding a modified Asgr1 protein, wherein the modified Asgr1 protein comprises a cytoplasmic domain, a transmembrane domain, and an extracellular domain,

wherein the extracellular domain comprises a coiled-coil domain that is encoded by a segment of the endogenous *Asgr1* locus that has been deleted and replaced with an orthologous human *ASGR1* sequence,

wherein the rodent expresses the modified Asgr1 protein and a wildtype endogenous Asgr2 protein, and

wherein total cholesterol and triglyceride levels in the rodent are not significantly different than those of a control rodent that expresses a wildtype Asgr1 protein.

2. The rodent of claim 1, wherein the extracellular domain further comprises a C-type lectin domain, and at least a fragment of the C-type lectin domain is encoded by the segment of the endogenous *Asgr1* locus that has been deleted and replaced with an orthologous human *ASGR1* sequence.

3. The rodent of claim 2, wherein the C-type lectin domain comprises the sequence set forth in SEQ ID NO: 28.

4. The rodent of any one of claims 1-3, wherein the coiled-coil domain comprises the sequence set forth in SEQ ID NO: 27.

5. The rodent of any one of claims 2-4, wherein both the coiled-coil domain and the C-type lectin domain are encoded by the segment of the endogenous *Asgr1* locus that has been deleted and replaced with an orthologous human *ASGR1* sequence.

6. The rodent of any one of claims 2-5, wherein the C-type lectin domain comprises the sequence set forth in SEQ ID NO: 28, and the coiled-coil domain comprises the sequence set forth in SEQ ID NO: 27.

7. The rodent of any preceding claim, wherein the orthologous human *ASGR1* sequence comprises exons 3-8 of a human *ASGR1* gene.

8. The rodent of claim 7, wherein the orthologous human *ASGR1* sequence encodes an ASGR1 protein segment comprising the sequence set forth in SEQ ID NO: 31.

9. The rodent of any one of the preceding claims, wherein at least a fragment of the cytoplasmic domain is encoded by an endogenous *Asgr1* sequence.

10. The rodent of any one of the preceding claims, wherein at least a fragment of the transmembrane domain is encoded by an endogenous *Asgr1* sequence.

11. The rodent of claim 9 or 10, wherein both the cytoplasmic domain and the transmembrane domain are encoded by an endogenous *Asgr1* sequence.
12. The rodent of any one of the preceding claims, wherein the rodent is heterozygous for the genetically modified endogenous *Asgr1* locus.
13. The rodent of any one of claims 1-11, wherein the rodent is homozygous for the genetically modified endogenous *Asgr1* locus.
14. The rodent of any one of the preceding claims, wherein the rodent is a rat or mouse.
15. The rodent of claim 14, wherein the rodent is a mouse.
16. The rodent of claim 15, wherein the cytoplasmic domain is encoded by an endogenous mouse *Asgr1* sequence.
17. The rodent of claim 16, wherein the cytoplasmic domain comprises the sequence set forth in SEQ ID NO: 29.
18. The rodent of claim 15, wherein the transmembrane domain is encoded by an endogenous mouse *Asgr1* sequence.
19. The rodent of claim 18, wherein the transmembrane domain comprises the sequence set forth in SEQ ID NO: 30.
20. The rodent of any one of claims 15-19, wherein both the cytoplasmic domain and the transmembrane domain are encoded by an endogenous mouse *Asgr1* sequence.
21. The rodent of claim 20, wherein the cytoplasmic domain comprises the sequence set forth in SEQ ID NO: 29, and the transmembrane domain comprises the sequence set forth in SEQ ID NO: 30.
22. The rodent of any one of claims 15-21, wherein the extracellular domain comprises a coiled-coil domain and a C-type lectin domain, and wherein both the coiled-coil domain and the C-type lectin domain are encoded by the segment of the endogenous *Asgr1* locus that has been deleted and replaced with an orthologous human *ASGR1* sequence, and both the cytoplasmic domain and the transmembrane domain are encoded by an endogenous mouse *Asgr1* sequence.
23. The rodent of claim 22, wherein the C-type lectin domain comprises the sequence set forth in SEQ ID NO: 28, the coiled-coil domain comprises the sequence set forth in SEQ ID NO: 27, the cytoplasmic domain comprises the sequence set forth in SEQ ID NO: 29, and the transmembrane domain comprises the sequence set forth in SEQ ID NO: 30.
24. The rodent of claim 23, wherein the modified *Asgr1* protein comprises the sequence set forth in SEQ ID NO: 3.

25. Use of a therapeutic complex in the manufacture of a medicament for treating a lysosomal storage disease in a subject in need thereof,

wherein the therapeutic complex is to be delivered to a liver of the subject via human ASGR1 mediated internalization;

wherein the subject is the rodent of any one of claims 1 – 24;

wherein the therapeutic complex comprises a therapeutic molecule and antigen-binding protein or ligand that specifically binds human ASGR1; and

wherein the therapeutic complex is to be administered to the rodent to assess delivery of the therapeutic complex to the liver of the rodent.

26. The use according to claim 25, wherein the therapeutic molecule is a lysosomal replacement protein or enzyme or a nucleic acid encoding the lysosomal replacement protein or enzyme, and wherein the presence or activity of the lysosomal replacement protein or enzyme in the liver of the rodent is assessed.

27. The use according to claim 25, wherein the therapeutic molecule is a nucleic acid encoding the therapeutic secreted protein, and wherein the serum levels or activity of the therapeutic secreted protein in the rodent is assessed.

28. Use of a therapeutic molecule in the manufacture of a medicament for treating a lysosomal storage disease in a subject in need thereof,

wherein the therapeutic molecule is to be delivered to a liver of the subject targeting a liver cell surface protein or a soluble protein for internalization via human ASGR1;

wherein the subject is the rodent of any one of claims 1 – 24;

wherein the therapeutic molecule comprises a bispecific antigen-binding protein that specifically binds the liver cell surface protein or the soluble protein, and specifically binds human ASGR1, and

wherein the therapeutic molecule is to be administered to the rodent to assess: (i) cell surface levels or activity of the liver cell surface protein, or (ii) expression or activity of the soluble protein, in the liver of the rodent.

29. A rodent cell comprising:

(i) a wildtype endogenous *Asgr2* gene encoding a wildtype endogenous Asgr2 protein, and

(ii) a genetically modified endogenous *Asgr1* locus encoding a modified Asgr1 protein,

wherein the modified *Asgr1* protein comprises a cytoplasmic domain, a transmembrane domain, and an extracellular domain,

wherein the extracellular domain comprises a coiled-coiled domain that is encoded by a segment of the endogenous *Asgr1* locus that has been deleted and replaced with an orthologous human *ASGR1* sequence.

30. The rodent cell of claim 29, wherein the rodent cell is a hepatocyte.
31. The rodent cell of claim 29, wherein the rodent cell is a pluripotent cell.
32. The rodent cell of claim 31, wherein the rodent cell is an ES cell.
33. The rodent cell of claim 31, wherein the rodent cell is a germ cell.
34. A composition comprising the rodent cell of any one of claims 29-33.
35. A nucleic acid comprising a sequence selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO:23, and a combination thereof.
36. The nucleic acid of claim 35, comprising a sequence set forth as SEQ ID NO:24.
37. The nucleic acid of claim 35 or claim 36, characterized in that it encodes an amino acid sequence set forth as SEQ ID NO:3.