

We claim:

1. A ~~rodent non-human animal or non-human animal genome~~ 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 and all or part of the extracellular domain~~ is encoded by a segment of the endogenous *Asgr1* locus that has been deleted and replaced with an orthologous human *ASGR1* sequence, ~~and~~

wherein the ~~non-human animal 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 non-human animal or non-human animal genome~~ of claim 1, wherein the extracellular domain ~~further~~ comprises ~~a coiled-coil domain and~~ a C-type lectin domain, and ~~all or part of 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 non-human animal or non-human animal genome of claim 2, wherein the C-type lectin domain is a human *ASGR1* C-type lectin domain.~~

~~34. The rodent non-human animal or non-human animal genome of claim 2 or 3, wherein the C-type lectin domain comprises the sequence set forth in SEQ ID NO: 28.~~

~~5. The non-human animal or non-human animal genome of claim 1, wherein the extracellular domain comprises a coiled-coil domain and a C-type lectin domain, and all or part of the coiled-coil domain is encoded by the segment of the endogenous *Asgr1* locus that has been deleted and replaced with an orthologous human *ASGR1* sequence.~~

~~6. The rodent non-human animal or non-human animal genome of claim 5, wherein the coiled-coil domain is a human *ASGR1* coiled-coil domain.~~

~~47. The non-human animal rodent or non-human animal genome of claim 5 or 6 any one of claims 1-3, wherein the coiled-coil domain comprises the sequence set forth in SEQ ID NO: 27.~~

~~58. The non-human animal rodent or non-human animal genome of any one of claims 2-47, wherein all or part of 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.~~

~~9. The non-human animal or non-human animal genome of claim 8, wherein the C-type lectin domain is a human *ASGR1* C-type lectin domain, and the coiled-coil domain is a human *ASGR1* C-type lectin domain.~~

~~610.~~ The ~~rodent non-human animal or non-human animal genome~~ of ~~claim 8 or 9~~ 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.

~~711.~~ The ~~rodent non-human animal or non-human animal genome~~ of any preceding claim, wherein the orthologous human *ASGR1* sequence comprises exons 3-8 of a human *ASGR1* gene.

~~812.~~ The ~~rodent non-human animal or non-human animal genome~~ of claim ~~711~~, wherein the orthologous human *ASGR1* sequence encodes an *ASGR1* protein segment comprising the sequence set forth in SEQ ID NO: 31.

~~913.~~ The ~~rodent non-human animal or non-human animal genome~~ of any one of the preceding claims, wherein all or part of at least a fragment of the cytoplasmic domain is encoded by an endogenous ~~non-human animal~~ *Asgr1* sequence.

~~104.~~ The ~~rodent non-human animal or non-human animal genome~~ of any one of the preceding claims, wherein all or part of at least a fragment of the transmembrane domain is encoded by an endogenous ~~non-human animal~~ *Asgr1* sequence.

~~115.~~ The ~~rodent non-human animal or non-human animal genome~~ of claim ~~913~~ or ~~104~~, wherein ~~all or part of~~ both the cytoplasmic domain and the transmembrane domain are encoded by an endogenous ~~non-human animal~~ *Asgr1* sequence.

~~126.~~ The ~~rodent non-human animal or non-human animal genome~~ of any one of the preceding claims, wherein the ~~rodent non-human animal or non-human animal genome~~ is heterozygous for the genetically modified endogenous *Asgr1* locus.

~~137.~~ The ~~rodent non-human animal or non-human animal genome~~ of any one of claims 1-~~115~~, wherein the ~~rodent non-human animal or non-human animal genome~~ is homozygous for the genetically modified endogenous *Asgr1* locus.

~~18.~~—The ~~non-human animal or non-human animal genome~~ of any preceding claim, wherein the ~~non-human animal is a mammal or the non-human animal genome is a mammalian genome~~.

~~19.~~—The ~~non-human animal or non-human animal genome~~ of claim ~~18~~, wherein the ~~non-human animal is a rodent or the non-human animal genome is a rodent genome~~.

~~1420.~~ The ~~rodent non-human animal or non-human animal genome~~ of any one of the preceding claims ~~19~~, wherein the ~~non-human animal~~ rodent is a rat or mouse ~~or the non-human animal genome is a rat genome or a mouse genome~~.

~~1521.~~ The ~~rodent non-human animal or non-human animal genome~~ of claim ~~2014~~, wherein the ~~non-human animal~~ rodent is a mouse ~~or the non-human animal genome is a mouse genome~~.

~~1622.~~ The ~~rodent non-human animal or non-human animal genome~~ of claim ~~1521~~, wherein ~~all or part of~~ the cytoplasmic domain is encoded by an endogenous mouse *Asgr1* sequence.

~~1723.~~ The ~~rodent non-human animal or non-human animal genome~~ of claim ~~1622~~, wherein the cytoplasmic domain comprises the sequence set forth in SEQ ID NO: 29.

~~1824.~~ The ~~rodent non-human animal or non-human animal genome~~ of claim ~~1521~~, wherein ~~all or part of the~~ transmembrane domain is encoded by an endogenous mouse *Asgr1* sequence.

~~1925.~~ The ~~rodent non-human animal or non-human animal genome~~ of claim ~~1824~~, wherein the transmembrane domain comprises the sequence set forth in SEQ ID NO: 30.

~~206.~~ The ~~rodent non-human animal or non-human animal genome~~ of any one of claims ~~1522-1925~~, wherein ~~all or part of~~ both the cytoplasmic domain and the transmembrane domain are encoded by an endogenous mouse *Asgr1* sequence.

~~217.~~ The ~~rodent non-human animal or non-human animal genome~~ of claim ~~206~~, 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.

~~228.~~ The ~~rodent non-human animal or non-human animal genome~~ of any one of claims ~~1521-217~~, wherein the extracellular domain comprises a coiled-coil domain and a C-type lectin domain, and wherein ~~all or part of~~ 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 ~~all or part of~~ both the cytoplasmic domain and the transmembrane domain are encoded by an endogenous mouse *Asgr1* sequence.

~~29.—The non-human animal or non-human animal genome of any one of claims 21-28, wherein the C-type lectin domain is a human ASGR1 C-type lectin domain, and the coiled-coil domain is a human ASGR1 coiled-coil domain, the cytoplasmic domain is a mouse Asgr1 cytoplasmic domain, and the transmembrane domain is a mouse Asgr1 transmembrane domain.~~

~~2330.~~ The ~~rodent non-human animal or non-human animal genome~~ of claim ~~228 or 29~~, 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.

~~2431.~~ The ~~rodent non-human animal or non-human animal genome~~ of claim ~~3023~~, wherein the modified *Asgr1* protein comprises the sequence set forth in SEQ ID NO: 3.

~~32.—A method of assessing delivery of a therapeutic complex to the liver via human ASGR1-mediated internalization in vivo, comprising:~~

(a) — ~~administering the therapeutic complex to the non-human animal of any one of claims 1-31, wherein the therapeutic complex comprises a therapeutic molecule and an antigen-binding protein or ligand that specifically binds human ASGR1; and~~

(b) — ~~assessing delivery of the therapeutic molecule to the liver of the non-human animal.~~

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.

2633. The use according to method ~~rodent model~~ of claim 3225, wherein the therapeutic molecule is a lysosomal replacement protein or enzyme or a nucleic acid encoding the lysosomal replacement protein or enzyme, and ~~step (b) comprises assessing~~ wherein the presence or activity of the lysosomal replacement protein or enzyme in the liver of the ~~rodent non-human animal~~ is assessed.

2734. The use according to method ~~rodent model~~ of claim 3225, wherein the therapeutic molecule is a nucleic acid encoding the therapeutic secreted protein, and ~~step (b) comprises assessing~~ wherein the serum levels or activity of the therapeutic secreted protein in the ~~rodent non-human animal~~ is assessed.

35. — A method of assessing efficacy of a therapeutic molecule targeting a liver cell surface protein or a soluble protein in the liver for internalization via human ASGR1 *in vivo*, comprising:

(a) — ~~administering the therapeutic molecule to the non-human animal of any one of claims 1-31, 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~~

(b) — ~~assessing cell surface levels or activity of the liver cell surface protein in the liver of the non-human animal or assessing expression or activity of the soluble protein in the liver of the non-human animal.~~

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.

2936. A ~~rodent non-human animal~~ 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,

and ~~all or part of the~~ 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.

307. The ~~rodent non-human animal~~ cell of claim 3296, wherein the ~~rodent non-human animal~~ cell is a hepatocyte.

318. The ~~rodent non-human animal~~ cell of claim 2936, wherein the ~~rodent non-human animal~~ cell is a pluripotent cell.

329. The ~~rodent non-human animal~~ cell of claim 318, wherein the ~~rodent non-human animal~~ cell is an ES cell.

3340. The ~~rodent non-human animal~~ cell of claim 318, wherein the ~~rodent non-human animal~~ cell is a germ cell.

3441. A composition comprising ~~thea~~ ~~rodent non-human animal~~ cell of any one of claims 2936-3340.

3542. A nucleic acid comprising a sequence selected from the group ~~comprising-consisting~~ of SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, ~~SEQ ID NO: 22~~, SEQ ID NO:23, and a combination thereof.

3643. The nucleic acid of claim 3542, comprising a sequence set forth as SEQ ID NO:24.

3744. The nucleic acid of claim 4235 or claim 4336, characterized in that it encodes an amino acid sequence set forth as SEQ ID NO:3.