CLAIMS

1. A composition comprising an enzyme associated with a lysosomal storage disease (LSD) and an antigen-binding protein,

wherein the enzyme is selected from the group consisting of α-galactosidase, β-galactosidase, α-glucosidase (GAA), β-glucosidase, saposin-C activator, ceramidase, sphingomyelinase, β-hexosaminidase, GM2 activator, GM3 synthase, arylsulfatase, sphingolipid activator, α-iduronidase, iduronidase-2-sulfatase, heparin N-sulfatase, N-acetyl-α-glucosaminidase, α-glucosamide N-acetyltransferase, N-acetylglucosamine-6-sulfatase, N-acetylgalactosamine-6-sulfate sulfatase, N-acetylgalactosamine-4-sulfatase, β-glucuronidase, hyaluronidase, and lysosomal acid lipase (LAL),

wherein the antigen-binding protein binds an internalization effector, and

wherein the internalization effector is CD63.

2. The composition of claim 1, wherein the enzyme is selected from the group consisting of α-galactosidase (GLA), β-galactosidase (GLB), and α-glucosidase (GAA).

3. The composition of claim 1 or 2, wherein the antigen-binding protein is selected from the group consisting of a receptor-fusion molecule, a trap molecule, a receptor-Fc fusion molecule, an antibody, an Fab fragment, an F(ab')2 fragment, an Fd fragment, an Fv fragment, a single-chain Fv (scFv) molecule, a dAb fragment, an isolated complementarity determining region (CDR), a CDR3 peptide, a constrained FR3-CDR3-FR4 peptide, a domain-specific antibody, a single domain antibody, a domain-deleted antibody, a chimeric antibody, a CDR-grafted antibody, a diabody, a triabody, a tetrabody, a minibody, a nanobody, a monovalent nanobody, a bivalent nanobody, a small modular immunopharmaceutical (SMIP), a camelid antibody (VHH heavy chain homodimeric anibody), and a shark variable IgNAR domain.

4. The composition of any one of claims 1-3, wherein the enzyme is covalently linked to the antigen-binding protein, and optionally wherein:

(i) the antigen-binding protein comprises a half-antibody, the enzyme is covalently linked to an immunoglobulin Fc-domain, and the Fc-domain that is covalently linked to the enzyme associates with the Fc-domain of the antigen-binding protein; or

(ii) the antigen-binding protein comprises an antibody, and the enzyme is covalently linked to the C-terminus of the heavy chain of the antibody.

5. The composition of any one of claims 1-3, wherein the enzyme is not covalently linked to the antigen-binding protein, and optionally wherein:

(i) the antigen-binding protein binds to both the internalization effector and the enzyme; and/or

(ii) the antigen-binding protein is a bispecific antibody that binds the internalization effector and the enzyme.

6. The composition of any one of claims 1-5, wherein the enzyme is GAA or GLA or comprises GAA or GLA activity.

7. The composition of any one of claims 1-6, wherein:

(i) the enzyme is GAA or comprises GAA activity, and the enzyme comprises the amino acid sequence of SEQ ID NO:l; or

(ii) the enzyme is GLA or comprises GLA activity, and the enzyme comprises the amino acid sequence of SEQ ID NO:2.

8. A biotherapeutic complex for use in a method of treating a subject suffering from a lysosomal storage disease (LSD), wherein the method comprises administering to the subject the biotherapeutic complex and wherein the biotherapeutic complex enters a lysosome of a cell of the subject and provides an enzyme activity ("replacement enzyme") that replaces the enzymatic activity that is associated with the LSD ("endogenous enzyme"), wherein the biotherapeutic complex comprises:

(a) the replacement enzyme selected from the group consisting of α-galactosidase, β-galactosidase, α-glucosidase (GAA), β-glucosidase, saposin-C activator, ceramidase, sphingomyelinase, β-hexosaminidase, GM2 activator, GM3 synthase, arylsulfatase, sphingolipid activator, α-iduronidase, iduronidase-2-sulfatase, heparin *N*-sulfatase, *N*-acetyl-α-glucosaminidase, α-glucosamide *N*-acetyltransferase, *N*-acetylglucosamine-6- sulfatase, *N*-acetylgalactosamine-6-sulfate sulfatase, *N*-acetylgalactosamine-4-sulfatase, β-glucuronidase, hyaluronidase, and lysosomal acid lipase (LAL), and

(b) an antigen binding protein that binds an internalization effector, wherein the internalization effector is CD63.

9. The biotherapeutic complex for use according to claim 8, wherein the LSD is:

(i) selected from the group consisting of a sphingolipidosis, a mucopolysaccharidosis, and a glycogen storage disease;

(ii) selected from the group consisting of Fabry disease, Gaucher disease type I, Gaucher disease type II, Gaucher disease type III, Niemann-Pick disease type A, Niemann-Pick disease type BGM1-gangliosidosis, Sandhoff disease, Tay-Sachs disease, GM2-activator deficiency, GM3-gangliosidosis, metachromatic leukodystrophy, sphingolipid-activator deficiency, Scheie disease, Hurler-Sceie disease, Hurler disease, Hunter disease, Sanfilippo A, Sanfilippo B, Sanfilippo C, Sanfilippo D, Morquio syndrome A, Morquio syndrome B, Maroteaux-Lamy disease, Sly disease, MPS IX, and Pompe disease; or

(iii) Fabry disease or Pompe disease.

10. The biotherapeutic complex for use according to claim 8 or 9, wherein:

(i) the replacement enzyme does not induce an immunological reaction in the subject; and/or

(ii) the replacement enzyme is an isozyme.

11. The biotherapeutic complex for use according to claim 10, wherein the replacement enzyme is an isozyme and wherein:

(i) the LSD is Pompe disease, the endogenous enzyme is α-glucosidase (GAA), and the isozyme is selected from the group consisting of acid α-glucosidase (GAA), sucrase-isomaltase (SI), maltase-glucoamylase (MGAM), glucosidase II (GANAB), and neutral α-glucosidase (C GNAC); or

(ii) the LSD is Fabry disease, the endogenous enzyme is α-galactosidase A (GLA), and the isozyme is α-*N*-acetylgalactosaminidase engineered to gain GLA activity.

12. The biotherapeutic complex for use according to claim 10 or 11, wherein the antigen binding protein that binds the internalization effector is an antibody or an antibody fragment.

13. The biotherapeutic complex for use according to any one of claims 8-12, wherein:

(i) the biotherapeutic complex comprises a replacement enzyme and a bispecific antibody that binds the replacement enzyme and an internalization effector, and optionally wherein (a) the biotherapeutic complex comprises GLA and a bispecific antibody that binds GLA and CD63, and the LSD is Fabry disease, or (b) the biotherapeutic complex comprises GAA and a bispecific antibody that binds GAA and CD63, and the LSD is Pompe disease;

(ii) the biotherapeutic complex comprises an enzyme-Fc fusion protein and an anti-internalization effector half-body;

(iii) the biotherapeutic complex comprises the replacement enzyme covalently linked to the C-terminus of the heavy chain of an anti-internalization effector antibody; or

(iv) the biotherapeutic complex comprises the enzyme covalently linked to the N-terminus of the heavy chain of an anti-internalization effector antibody.