

CLAIMS

We claim:

1. A gene-integrating composition, comprising:
a gene therapy construct comprising, from 5' to 3', a polynucleotide sequence encoding (a) a 5' homology arm, (b) a 2A coding sequence encoding a 2A peptide, wherein the 2A coding sequence has or comprises the nucleotide sequence SEQ ID NO: 2, (c) a therapeutic payload, and (d) a 3' homology arm, wherein the gene therapy construct integrates at an endogenous albumin target site such that the albumin locus is transcribed to produce albumin-2A and the therapeutic payload as separate proteins;
wherein the 2A peptide serves as a surrogate for the expression of the therapeutic payload.
2. The gene-integrating composition according to claim 1, wherein:
(i) the 5' homology arm is 1.3 Kb in length or 1 Kb in length and;
(ii) the 3' homology arm is 1.4 Kb, 1 Kb, or 750 bp in length.
3. The gene-integrating composition according to claim 1 or 2, wherein the therapeutic payload of the gene therapy construct encodes phenylalanine hydroxylase (PAH), glucose-6-phosphatase catalytic subunit (G6PC), propionyl-CoA carboxylase, subunit alpha (PCCA), ATP binding cassette subfamily B member 11 (ABCB11), ornithine carbamoyltransferase (OTC), UDP glucuronosyltransferase family 1 member A1 (UGT1A1), Acid alpha-glucosidase (GAA), Lysosomal acid glucosylceramidase (GBA), Frataxin (FTX), Factor IX (F9), or alpha-1-antitrypsin (SERPINA1).
4. The gene-integrating composition according to any one of claims 1-3, wherein the therapeutic payload of the gene therapy construct encodes a peptide expressed intracellularly.
5. The gene-integrating composition according to any one of claims 1-3, wherein the therapeutic payload of the gene therapy construct encodes a peptide secreted extracellularly.
6. The gene-integrating composition according to any one of claims 1-5, wherein the therapeutic payload of the gene therapy construct encodes a peptide that has cell-intrinsic or cell-extrinsic activity that promotes a biological process to treat a medical condition.

7. The gene-integrating composition according to any one of claims 1-6, wherein the therapeutic payload of the gene therapy construct encodes a peptide that is normally expressed in liver cells.
8. The gene-integrating composition according to any one of claims 1-7, wherein the therapeutic payload of the gene therapy construct encodes a peptide that is ectopically expressed in liver cells.
9. The gene-integrating composition according to any one of claims 1-8, wherein integration of the gene therapy construct at the endogenous albumin target site does not significantly disrupt expression of the albumin encoded at the target site.
10. The gene-integrating composition according to any one of claims 1-9, wherein the gene therapy construct comprises an AAV vector.