

CLAIMS

1. A truncated GAA polypeptide, comprising a deletion of at least one amino acid from the N-terminal
5 end of a parent GAA polypeptide, wherein the parent polypeptide corresponds to a precursor form of a
GAA polypeptide devoid of its signal peptide,
wherein said truncated GAA polypeptide has 1 to 75 consecutive amino acids deleted at its N-
terminal end as compared to the parent GAA polypeptide, and
wherein said truncated GAA polypeptide further comprises a signal peptide fused to its N-
10 terminal end.
2. The truncated GAA polypeptide of claim 1, wherein said truncated GAA polypeptide has 1 to 75
consecutive amino acids deleted at its N-terminal end as compared to the parent GAA polypeptide, in
particular 6, 7, 8, 9, 10, 40, 41, 42, 43, 44, 45 or 46 consecutive amino acids deleted at its N-terminal
15 end as compared to a parent GAA polypeptide, even more particularly 8, 42 or 43 consecutive amino
acids truncated at its N-terminal end as compared to a parent GAA polypeptide.
3. The truncated GAA polypeptide of claim 1 or 2, wherein the parent polypeptide is a human GAA
(hGAA), in particular the hGAA having the amino acid sequence shown in SEQ ID NO:1 or in SEQ
20 ID NO:33, in particular in SEQ ID NO:1, or a hGAA which is a functional variant of the hGAA
having the amino acid sequence shown in SEQ ID NO:1 or in SEQ ID NO:33, in particular in SEQ ID
NO:1.
4. The truncated GAA polypeptide of any one of claims 1 to 3, wherein the truncated GAA
25 polypeptide has the amino acid sequence shown in SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO: 34
or SEQ ID NO:35.
5. The truncated GAA polypeptide of any one of claims 1 to 4, wherein said fused signal peptide is
selected in the group consisting of SEQ ID NO:3 to 7, in particular the signal peptide of SEQ ID
30 NO:3.
6. A nucleic acid molecule encoding a truncated GAA polypeptide of any one of claims 1 to 5, said
nucleic acid molecule being in particular a nucleotide sequence optimized to improve the expression
of and/or improve immune tolerance to the truncated GAA polypeptide *in vivo*, such as the nucleic
35 acid sequence shown in SEQ ID NO:12, SEQ ID NO:13 SEQ ID NO:48, SEQ ID NO:49, SEQ ID
NO:50 or SEQ ID NO:51.

7. A nucleic acid construct, comprising the nucleic acid molecule of claim 6, comprising said nucleic acid molecule operably linked to a promoter, in particular a promoter that is a liver-specific promoter preferably selected in the group consisting of the alpha-1 antitrypsin promoter (hAAT), the transthyretin promoter, the albumin promoter and the thyroxine-binding globulin (TBG) promoter, wherein said nucleic acid construct further optionally comprises an intron, in particular an intron selected in the group consisting of a human beta globin b2 (or HBB2) intron, a FIX intron, a chicken beta-globin intron, and a SV40 intron, wherein said intron is optionally a modified intron such as a modified HBB2 intron of SEQ ID NO:17, a modified FIX intron of SEQ ID NO:19, or a modified chicken beta-globin intron of SEQ ID NO:21.
8. The nucleic acid construct of claim 7, comprising, preferably in this order,; an enhancer; an intron; a promoter, in particular a liver-specific promoter; the nucleic acid sequence encoding the GAA protein; and a polyadenylation signal, the construct comprising preferably, in this order: an ApoE control region; a HBB2 intron, in particular a modified HBB2 intron; a hAAT promoter; the nucleic acid sequence encoding the truncated GAA polypeptide; and a bovine growth hormone polyadenylation signal, said nucleic acid construct more particularly comprising the nucleotide sequence of any one of SEQ ID NO:22 to 26.
9. A vector comprising the nucleic acid molecule or the nucleic acid construct according to any one of claims 6 to 8, which is a viral vector, preferably a retroviral vector, such as a lentiviral vector, or an AAV vector.
10. The vector according to claim 9, which is a single-stranded or double-stranded self-complementary AAV vector, preferably an AAV vector with an AAV-derived capsid, such as an AAV1, AAV2, variant AAV2, AAV3, variant AAV3, AAV3B, variant AAV3B, AAV4, AAV5, AAV6, variant AAV6, AAV7, AAV8, AAV9, AAV10 such as AAVcy10 and AAVrh10, AAVrh74, AAVdj, AAV-Anc80, AAV-LK03, AAV2i8, and porcine AAV, such as AAVpo4 and AAVpo6 capsid or with a chimeric capsid.
11. The vector according to claim 10, wherein the AAV vector has an AAV8, AAV9, AAVrh74 or AAV2i8 capsid, in particular an AAV8, AAV9 or AAVrh74 capsid, more particularly an AAV8 capsid.
12. A cell transformed with the nucleic acid molecule of claim 6, the nucleic acid construct of any one of claims 7 to 8 or the vector of any one of claims 9 to 11, wherein the cell is in particular a liver cell or a muscle cell.

13. A pharmaceutical composition, comprising, in a pharmaceutically acceptable carrier, the truncated GAA polypeptide of any one of claims 1 to 5, the nucleic acid molecule of claim 6, the nucleic acid construct of any one of claims 7 to 8, the vector of any one of claims 9 to 11, or the cell according to claim 12.

5

14. The truncated GAA polypeptide of any one of claims 1 to 5, the nucleic acid molecule of claim 6, the nucleic acid construct of any one of claims 7 to 8, the vector of any one of claims 9 to 11, or the cell according to claim 12, for use as a medicament.

- 10 15. The truncated GAA polypeptide of any one of claims 1 to 5, the nucleic acid molecule of claim 6, the nucleic acid construct of any one of claims 7 to 8, the vector of any one of claims 9 to 11, or the cell according to claim 12, for use in a method for treating a glycogen storage disease, such as GSDI (von Gierke's disease), GSDII (Pompe disease), GSDIII (Cori disease), GSDIV, GSDV, GSDVI, GSDVII, GSDVIII and lethal congenital glycogen storage disease of the heart, more particularly
- 15 GSDI, GSDII or GSDIII, even more particularly GSDII and GSDIII, and most particularly GSDII.