

double strand break in the absence of an externally supplied repair template (*e.g.* “donor” or “transgene”) is commonly used for the inactivation of the targeted gene via mutations (insertions and/or deletions known as “indels”) introduced by the cellular NHEJ pathway. For instance, U.S. Patent Publication 20110082093 discloses specific zinc finger proteins targeted to Htt and U.S. Patent Publication No. 20130253040 relates to DNA-binding proteins that modulate expression of an HD allele such as Htt. U.S. Publication No. 20150335708 relates to methods of modifying medium spiny neurons.

[0011] However, there remains a need for methods for the diagnosis, study, treatment and/or prevention of Huntington’s Disease, including for modalities that exhibit widespread delivery to the brain.

SUMMARY

[0012] In one aspect, the present disclosure refers to a non-naturally occurring zinc finger protein that binds to a huntingtin (Htt) gene, the zinc finger protein comprising 5 zinc finger domains ordered F1 to F5, wherein the zinc finger domains comprise the recognition helix regions sequences ordered as shown in a single row of Table 1. In another aspect, the present disclosure refers to a fusion protein comprising a zinc finger protein as described herein and a functional domain, wherein the functional domain is a transcriptional repression domain or a nuclease domain. In another aspect, the present disclosure refers to a polynucleotide encoding one or more zinc finger proteins as described herein. In another aspect, the present disclosure refers to a polynucleotide encoding one or more fusion proteins as described herein. In another aspect, there is provided an AAV vector comprising the polynucleotide as described herein. In another aspect, the present disclosure refers to a host cell comprising one or more zinc finger proteins, one or more fusion proteins, a polynucleotide and/or an AAV vector as described herein. In another aspect, the present disclosure refers to a composition comprising one or more polynucleotides as described herein and/or one or more AAV vectors as described herein. In another aspect, the present disclosure refers to a pharmaceutical composition comprising one or more polynucleotides also described herein and/or one or more AAV vectors also described herein. In another aspect, the present disclosure refers to an *in vitro* method of modifying expression of a huntingtin (Htt) gene in a cell, the

method comprising administering to the cell one or more polynucleotides, one or more AAV vectors and/or one or more pharmaceutical compositions as described herein. In yet another aspect, the present disclosure refers the use of a composition in the manufacture of a medicament for treating and/or preventing Huntington's Disease

5 (HD) in a subject in need thereof, the composition comprising one or more polynucleotides, one or more AAV vectors and/or one or more pharmaceutical compositions as described herein.

CLAIMS

What is claimed is:

- 5 1. A non-naturally occurring zinc finger protein that binds to a huntingtin (Htt) gene, the zinc finger protein comprising 5 zinc finger domains ordered F1 to F5, wherein the zinc finger domains comprise the recognition helix regions sequences ordered as shown in a single row of Table 1.
- 10 2. A fusion protein comprising a zinc finger protein of claim 1 and a functional domain, wherein the functional domain is a transcriptional repression domain or a nuclease domain.
3. A polynucleotide encoding one or more zinc finger proteins of claim 1.
- 15 4. A polynucleotide encoding one or more fusion proteins of claim 2.
5. An AAV vector comprising the polynucleotide of claim 3.
- 20 6. An AAV vector comprising the polynucleotide of claim 4.
7. A host cell comprising one or more zinc finger proteins of claim 1, one or more fusion proteins of claim 2, a polynucleotide of claim 3 or claim 4 and/or an AAV vector of claim 5 or claim 6.
- 25 8. A composition comprising one or more polynucleotides according to claim 3 and/or one or more AAV vectors according to claim 5.
9. A pharmaceutical composition comprising one or more polynucleotides
- 30 according to claim 4 and/or one or more AAV vectors according to claim 6.
10. An *in vitro* method of modifying expression of a huntingtin (Htt) gene in a cell, the method comprising administering to the cell one or more polynucleotides

according to claim 4, one or more AAV vectors according to claim 6 and/or one or more pharmaceutical compositions according to claim 9.

11. The *in vitro* method of claim 10, wherein the Htt gene comprises at least
5 wild-type and/or one mutant allele.

12. The *in vitro* method of any claim 10 or claim 11, wherein the fusion protein comprises a repression domain and expression of the Htt gene is repressed.

10 13. The *in vitro* method of any of claims 10 to 12, wherein the cell is a neuronal cell.

14. The polynucleotide according to claim 4, the AAV vector according to claim 6 and/or the pharmaceutical composition according to claim 9 for use in
15 therapy.

15. Use of a composition in the manufacture of a medicament for treating and/or preventing Huntington's Disease (HD) in a subject in need thereof, the composition comprising one or more polynucleotides according to claim 4, one or
20 more AAV vectors according to claim 6 and/or one or more pharmaceutical compositions according to claim 9.