273 Pep42: Therapeutic peptides and their use for huntington's disease

Asset Overview

Product Type	Peptide
Indication	CNS Diseases
Current Stage	Discovery
Target(MoA)	Mutant huntingtin protein
Brief Description	The invention relates to novel therapeutic compounds for use against Huntington's disease. More specifically, the invention relates to an isolated peptide which is less than 100 amino acids in size and which comprises: a first sequence having at least 80% identity with sequence AASSG (SEQ ID No 1), or a second sequence having at least 80% identity with sequence XAGXDXXTEXPXS (SEQ ID No 2), in which X denotes any amino acid. The present invention also relates to the use of an isolated peptide, which is less than 200 amino acids in size and which comprises the above-mentioned sequence(s), as a drug.
Organization	French National Centre for Scientific Research (CNRS)

Differentiation

□ **Huntington's disease (HD) and polyQ-hHtt defects**

- HD is caused by the abnormal expansion of the polyglutamine tract in the human Huntingtin protein (polyQ-hHtt). This mutation behaves dominantly, huntingtin loss of function also contributes to HD pathogenesis
- The wild-type Huntingtin plays a protective role with respect to polyQ-hHtt induced defects

□ **Peptide 42 (Pep42) as Inhibitor of polyQ-hHtt aggregation**

- Pep42 is part of the endogenous Huntingtin protein and lies within a region rich in proteolytic sites that plays a critical role in the pathogenesis process
- Using a Drosophila model of HD, we tested the protective properties of this peptide on aggregation, as well as on different polyQ-hHtt induced neuronal phenotypes: eye degeneration (an indicator of cell death), impairment of vesicular axonal trafficking, and physiological behaviors such as larval locomotion and adult survival

□ **Advantages of Pep42**

- Pep42, a 23 aa-long hHtt peptide, plays a protective role with respect to polyQ-hHtt aggregation as well as cellular and behavioral dysfunctions induced by polyQ-hHtt in vivo
- Pep42 has a protective effect that is specific to polyQ-hHtt induced toxicity

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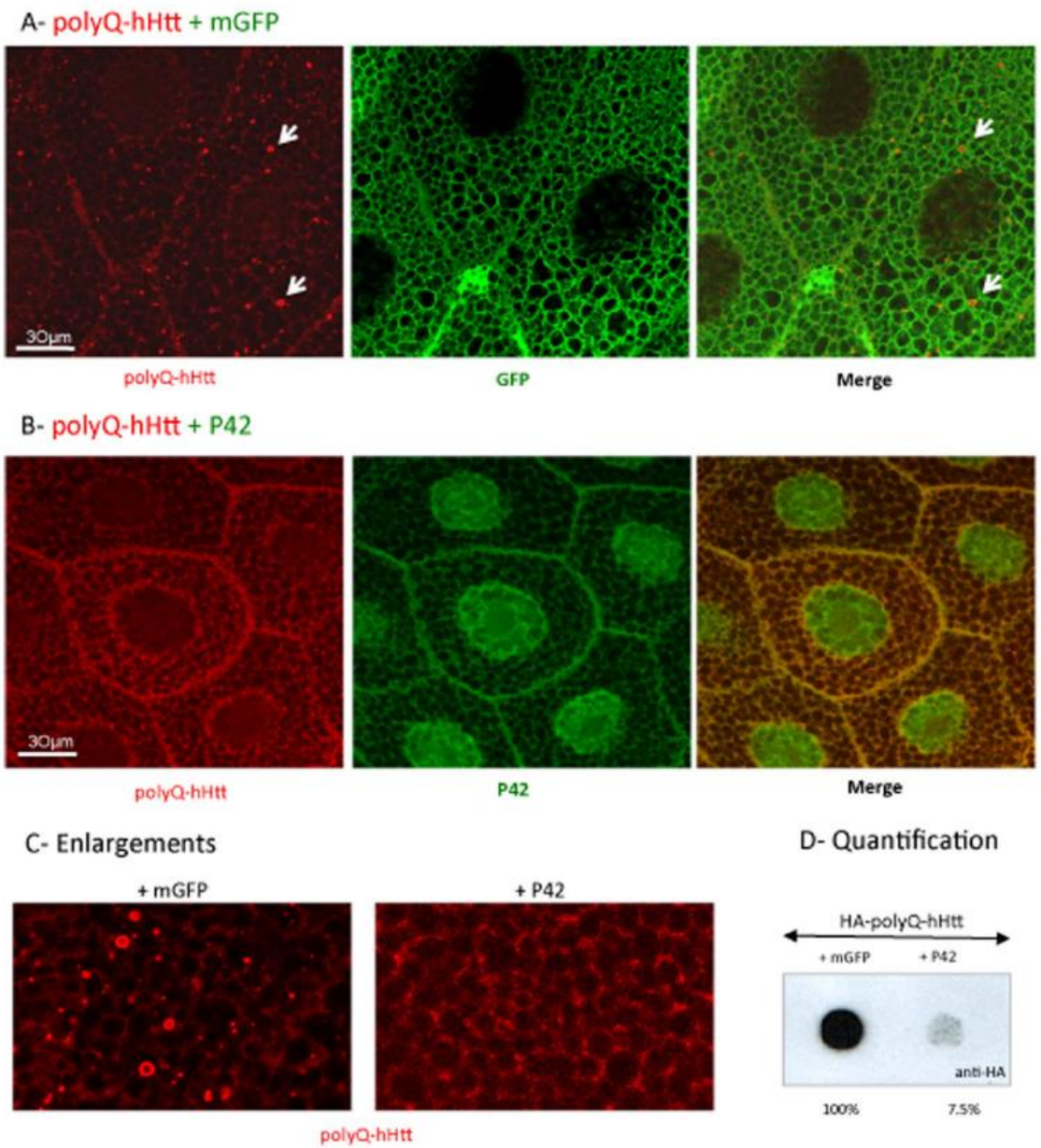
Key Data

Pep42 reduces aggregate formation of polyQ-hHtt in salivary glands



A–C: Anti-HA detection (in red) of HA-138Q-hHtt171aa expressed in salivary glands of MS1096-Gal4, UAS-HA-138Q-hHtt171aa/+ larva, in the presence of either A- one copy of a membrane-associated GFP neutral transgene (UAS-mGFP) (in green) or B- one copy of P42 (UAS-GFP-P42) (in green). Focal plan is at the level of the nuclei. Merged images are shown as indicated. A high magnification zoom from another focal plane is shown in C (HA staining only). D- Quantification of aggregation by dotblot filtration assay performed on two independent sets of experiments; the percentage of aggregates formed in presence of P42 was determined with respect to the control (+mGFP) set up at 100%.

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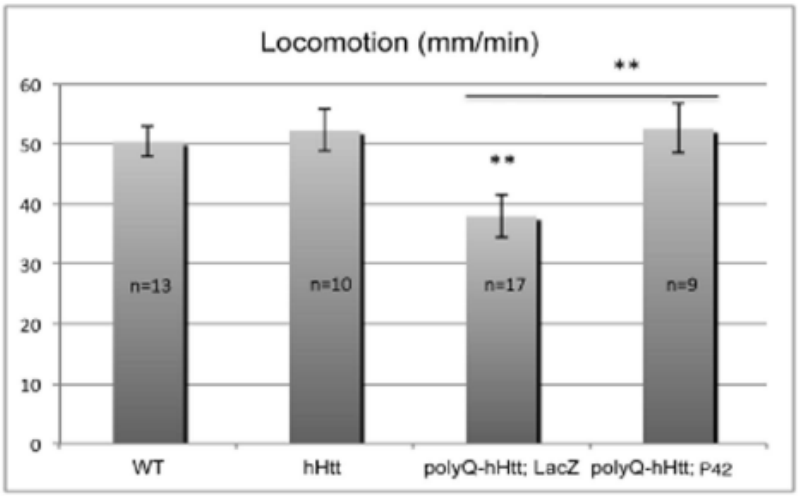
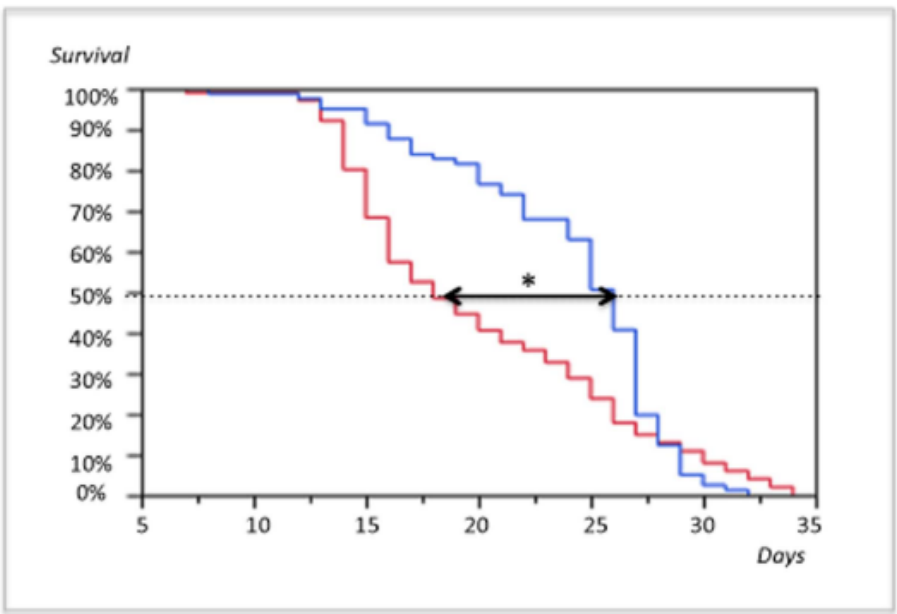
Pep42 rescues physiological behaviors induced by polyQ-hHtt

A- Larval locomotion



B- Adult fly lifespan



A- Larval locomotion was examined during 2 min in four different genetic backgrounds: Mean values are calculated on (n = 9 to 17), as indicated. Compared to the WT control, the presence of 128Q-hHtt548aa reduced larval locomotion, whereas P42 rescued the locomotion defect. B- Analysis of adult lifespan for UAS-128Q-hHtt548aa; elav-Gal4/UAS-LacZ (polyQ-hHtt; LacZ in blue) and UAS-128Q-hHtt548aa; elav-Gal4/UAS-P42 (polyQ-hHtt; P42 in red) flies are shown. The number of flies that survived from each cohort was evaluated once per day.

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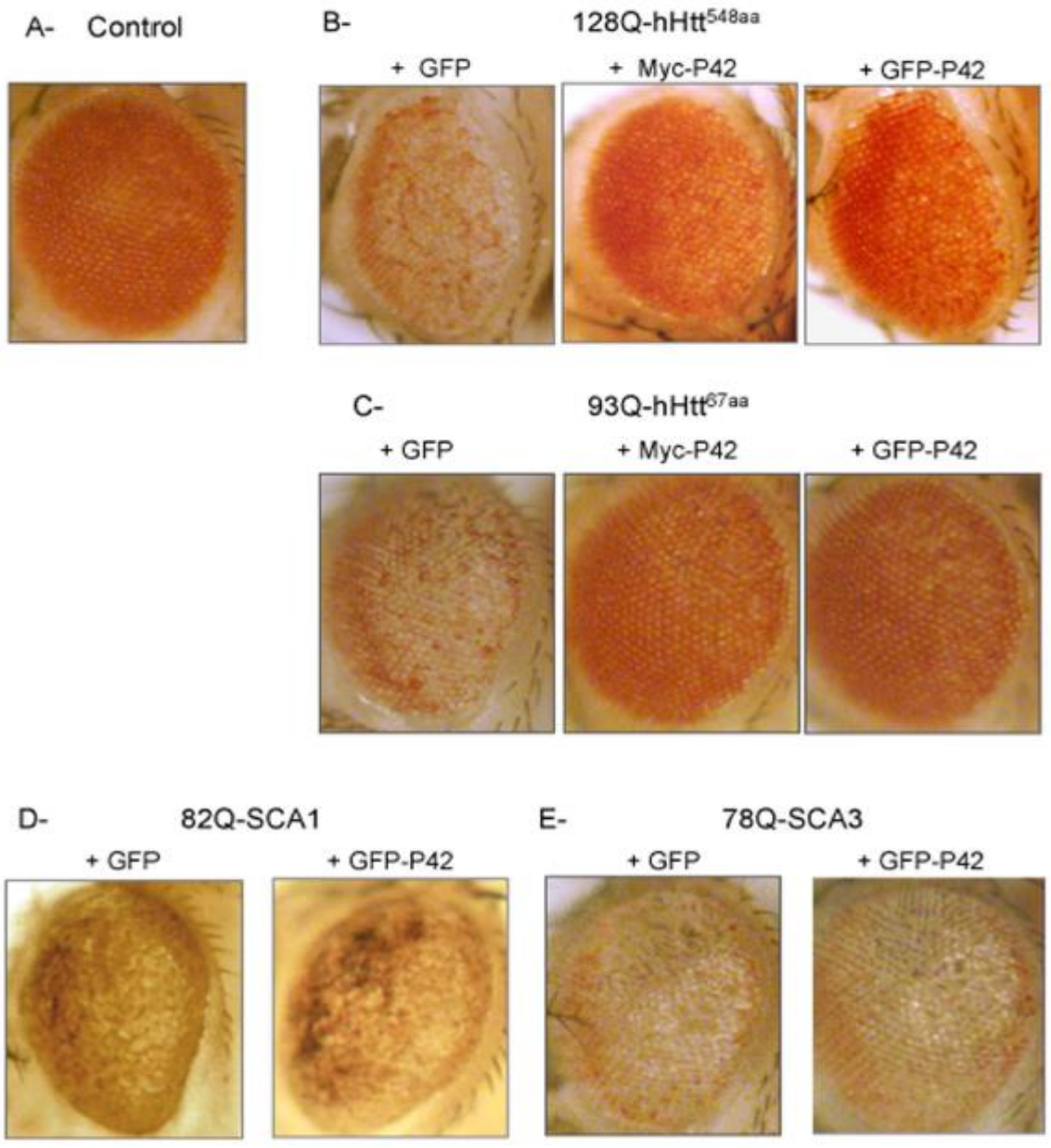
Influence of Pep42 on eye toxicity induced by different polyQ mutant proteins



A- As a control to examine eye toxicity, we used GMR-Gal4/UAS-GFP flies that exhibit normal eyes. Adult eye phenotypes were analyzed in four different genetic backgrounds: B- GMR-Gal4/UAS-128Q-hHtt548aa, C- GMR-Gal4/+; UAS-93Q-hHtt67aa/+, D- GMR-Gal4/+; UAS-82Q-SCA1/+, and E- GMR-Gal4/+; UAS-78Q-SCA3/+, which was tested either in the presence of the UAS-GFP neutral transgene, or in the presence of P42 tagged with Myc or GFP, as indicated.

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Intellectual Property

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Contact Information

Contact Person	Brahim Sennane
Email	Brahim.sennane@cnrsinnovation.fr
URL	http://www.cnrsinnovation.com/catalogue-cnrs/5617-2/?lang=en