Refining the bioactivity of P42, a hit therapeutic peptide, and developing a combined therapeutic peptide approach for treating Huntington’s Disease.

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Title of project or programme

Refining the bioactivity of P42, a hit therapeutic peptide, and developing a combined therapeutic peptide approach for treating Huntington’s Disease.

Source of funding information

ANR

Total sum awarded (Euro)

€ 297,887

Start date of award

01/11/2014

Total duration of award in years

5

Keywords
Research Abstract

Huntington’s Disease (HD) is caused by the genomic expansion of glutamine-encoding CAG triplet repeats in the coding region of the IT15 locus in the human genome, which encodes the Huntingtin (hHtt) protein. It is now generally accepted that hHtt protein toxicity originates from

protein misfolding and aggregation. Misfolded/aggregated hHtt triggers deleterious events in neurons, which can result in neuronal dysfunction and cell death. In 2013, F. Maschat's team identified a 23 aa peptide, P42, that possesses the ability to 1) reduce protein aggregation of the HD disease protein, mutant Huntingtin (polyQ-hHtt), 2) rescue HD neuronal phenotypes including axonal transport and locomotor defects, and 3) extend mean survival time of HD transgenic flies in vivo. Consistent protective effects were also observed in HD transgenic mice. In addition to protein toxicity, it has been reported that mutant polyQ disease mRNA transcripts also contribute to neurotoxicity in polyQ degeneration, including HD. E. Chan's team reported the role of RNA toxicity in HD pathogenesis, and developed a 13 aa CAG-RNA toxicity peptidylic inhibitor, P3, which possesses the activity to suppress 1) pre-45s rRNA transcription defects, 2) nucleolar stress induction and 3) neurodegeneration caused by CAG-RNA toxicity in vivo. Since both expanded polyQ-hHtt protein and hHtt CAG-RNA contribute to HD pathogenesis, a therapeutic strategy that simultaneously targets both of these toxic species would be ideal for treating HD. Our aim in the proposed work are (1) to optimize the bioactivities of peptidylic inhibitors using peptide engineering techniques; (2) to develop efficient peptide delivery systems to co-deliver the RNA and protein peptidylic inhibitors to the brain of HD disease mouse model; and (3) to optimize the therapeutic effect of RNA and protein toxicity co-treatment in HD mouse model. In the long run, our work will open up new therapeutic options for HD.

Further information available at:

Types:
Investments < €500k

Member States:
France

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A