Description of Funded Research Projects
1st Call for H.F.R.I. Research Projects to support Post-Doctoral Researchers

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Research Project Title:

Blocking the aggregation promoting ATXN1Q82-MED15 protein-protein interaction

Principal Investigator:
Spyros Petrakis

Popular Title:

Blocking the aggregation promoting ATXN1Q82-MED15 protein-protein interaction

Scientific Field:
Life Sciences

Host Institution:
INAB/CERTH

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Research Project Summary

Spinocerebellar ataxia type-1 (SCA1) is an autosomal dominant and lethal neurodegenerative disorder characterized by progressive movement disorders. It belongs to the group of polyglutamine (polyQ) diseases. It is caused by trinucleotide (CAG) expansions in the coding region of ataxin-1 (ATXN1) gene resulting in polyQ chains in the relevant protein. The mutant protein misfolds into toxic oligomers and forms intranuclear aggregates that cause neurodegeneration in the cerebellum. We have previously shown that the interaction between mutant ATXN1 and MED15 promotes polyQ protein aggregation and proteotoxicity. Therefore, suppressing ATXN1-MED15 protein-protein interaction (PPI) may rescue neurons from cell death.

Here, we aim to identify the exact PPI site between ATXN1 and MED15 and block it with chemical compounds having a similar structure. These compounds may also suppress polyQ protein aggregation and reduce cytotoxicity. To minimize the experimental workload, we are going to use a combination of computational and experimental techniques. First, we aim to predict the ATXN1-MED15 PPI site using a protein-protein docking algorithm. This prediction will be validated in a quantitative cell-based PPI assay. Then, we are going to perform a virtual screening and select chemical compounds that have similar structure to the ATXN1-MED15 PPI site. These compounds will be tested whether they block ATXN1-MED15 PPI in cell-based assays. Finally, hit compounds will be tested whether they suppress MED15-mediated ATXN1Q82 protein aggregation in a novel stem cell model using automated high-content screening. We expect that compounds blocking ATXN1-MED15 PPI would also suppress polyQ protein aggregation in primary human cells. Such compounds would be candidates for the development of novel anti-aggregating drugs in polyQ diseases.

#BrainGain #strongergreece

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Project Impact on Society

Presently, there is no treatment for the neurodegenerative polyQ diseases while the main research effort is focused on large compound screening. Our targeted small-scale screening will focus on a characterized protein aggregation mechanism and may lead to new candidate compounds against polyQ diseases. This methodology may be useful for similar approaches in other neurodegenerative diseases.

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To me, H.F.R.I. funding would mean...

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HFRI funding offers me the opportunity to, set up my research team and expand my network of collaborations. By doing so, I choose to stay in Greece and do research focused on my own interests.

The Principal Investigator,
Spyros Petrakis

Funding

Amount: **180,000 €**

Duration: **36 months**

Foundation: **H.F.R.I.**

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