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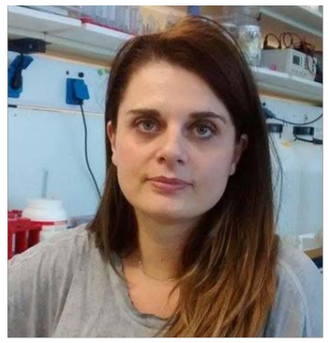
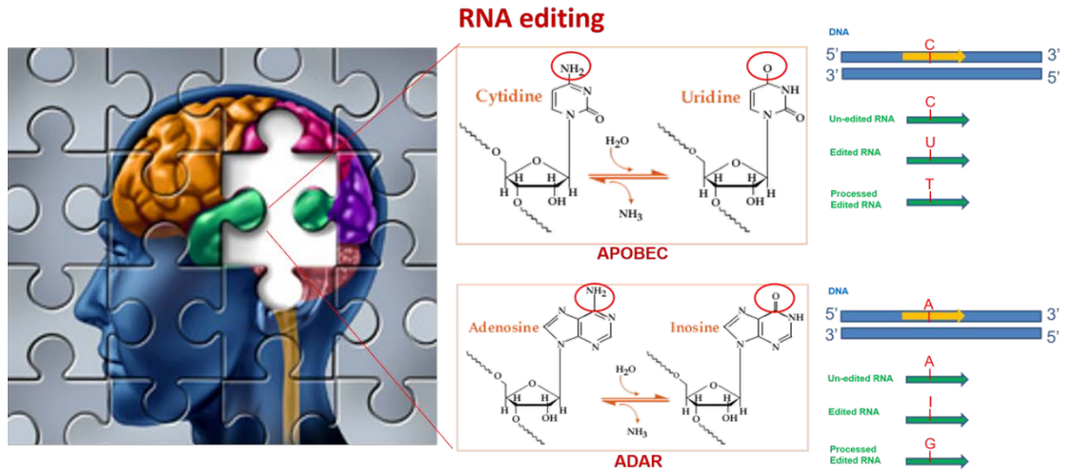
Hellenic Foundation for Research & Innovation

Description of the funded research project

2nd Call for H.F.R.I. Research Projects to Support Post-Doctoral Researchers





Title of the research project: Identification of novel, differentially edited RNA molecules involved in neurodegenerative disorders pathogenesis

Principal Investigator: Eirini Kanata-Tsiami

Reader-friendly title: RNAeditNDs

Scientific Area: Life Sciences

Institution and Country: Aristotle University of Thessaloniki, Greece

Host Institution: Aristotle University of Thessaloniki

Collaborating Institution(s): German Center For Neurodegenerative Diseases (DZNE)

Project webpage (if applicable):

Budget: 180,000 Euros

Duration: 36 months

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Research Project Synopsis

The funded project aims at the identification of RNA editing events commonly occurring in neurodegenerative disorders (NDs), the experimental verification and the functional study of selected differentially edited molecular targets possibly involved in NDs pathogenesis. Our working hypothesis is that similar editing patterns across different NDs with common clinicopathological features indicate driver molecules in common pathogenetic mechanisms indicative of proteostasis perturbations. For the implementation of this project we will perform *in silico* integrative analyses to select the most potent RNA editing events commonly occurring in Alzheimer's disease (AD) and in sporadic Amyotrophic Lateral Sclerosis (sALS) and predict their potential functional effects on proteostasis related mechanisms. Biological material from AD and sALS patients and from corresponding healthy control samples will be utilized to provide experimental verification of selected targets. Subsequent *in vitro* functional analyses will be performed utilizing cell lines to investigate the selected targets' contribution in molecular mechanisms associated with NDs pathogenesis.

Project originality

The originality of the funded project refers to the identification and experimental verification of non-genetic regulatory mechanisms at the RNA level affected by RNA editing, that commonly occur in Neurodegenerative Disorders (NDs), specifically in AD and sALS, and could explain the pathogenesis of sporadic ND cases, utilizing integrative and functional prediction bioinformatics analysis tools and state-of the-art experimental methodologies.

RNA editing entails the deamination of Adenosines or Cytidines on RNA molecules through the catalytic action of ADAR and APOBEC enzyme family members respectively, resulting in RNA:DNA differences (RDDs), and is emerging as a significant contributor in NDs, providing a new promising research area in disease pathogenesis. Global RNA editing alterations have been recently associated with NDs including autism, epilepsy and prion diseases, the latter contributed by our research team. Distinct NDs display commonalities in clinicopathological manifestation and in their majority (90%) occur as sporadic cases, suggesting common non-genetic effectors in underlying disease pathogenesis mechanisms. The funded project *focuses on the contribution of RNA editing in the delineation of disease mechanisms related to RNA regulation*. Thus, the novelty of the study relies on the *investigation of common patterns of epigenetic alterations referring to RNA editing among NDs, aiming at the identification and functional characterization of common driver pathogenetic events*.

Expected results & Research Project Impact

Focusing on the study of common RNA editing alterations in AD and sALS, we anticipate to identify *novel, disease-associated molecules undergoing differential editing*, and address the challenge of *deciphering their role as driver events in molecular mechanisms underlying neurodegeneration.* The outcomes of the project are expected to establish future potential for the delineation of pathogenetic mechanisms in a wide range of disorders, including other NDs and neoplastic diseases. Identification of common, driver epigenetic events referring to RNA editing, will provide a better understanding of common pathogentic mechanisms in NDs and aid the elucidation of sporadic NDs pathogenetic processes by indicating novel targets with diagnostic and therapeutic potential. Differential ND diagnosis is challenging and entails extensive studies aiming at the identification of disease-specific biomarkers that will enable early and accurate disease diagnosis. Identification of disease-specifc RNA editing modifications is expected to provide new tools in NDs differential diagnosis and boost the production of multiplex analytical platforms consisting of selected biomarkers to aid accurate ND diagnosis. In this regard, extensions of the approach proposed here to disease specific RNA editing alterations is expected to find applications in NDs diagnostics. Further, delineation of underlying pathogenetic mechanisms details is expected to provide novel targets for therapeutic interventions. Thus, we anticipate to acquire results that will have a *significant impact on both basic and applied research fields in NDs.*

The importance of this funding

The H.F.R.I. funding allows me to conduct innovative and competitive research in the Neurosciences field, the main field of my research interests. Coverage of expenses for specialised reagents and consumables, which represent a significant proportion of the project budget, is important for the implementation of the project. Of special significance is the coverage of salaries, as it promotes my financial livelihood and allows the employment of the most appropriate personnel as part of the research team, thus ensuring efficient research implementation. However, the most important benefit this funding offers me is the opportunity, to design, manage and implement a research project, for the first time, within the research field of my interest, in Greece. This will promote my organization and management skills and contribute to the establishment of a robust collaborating network, providing me with valuable experiences that will enhance my personal and scientific development.

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COMMUNICATION

185 Syggrou Ave. & 2 Sardeon St. 2
171 21, N. Smyrni, Greece
+30 210 64 12 410, 420
communication@elidek.gr
www.elidek.gr