A new druggable approach for the early intervention in Alzheimer disease

Moad El Bouatmani[2], Michela Matteoli[1,2], Antonella Borreca[1,2]

1. Institute of Neuroscience (IN-CNR), National Research Council of Italy, Via Follerau, 3 Vedano al Lambro (MB). Italy.

2. IRCCS Humanitas Research Hospital, Laboratory of Pharmacology and Brain Pathology, via Manzoni 56, 20089 Rozzano, Milano, Italy

Background:

Emerging evidence suggests that external agents, such as environmental factors, infections, and lifestyle choices, may play a role in triggering or accelerating the onset of Alzheimer's disease (AD). These external influences can contribute to chronic inflammation, oxidative stress, and other cellular disturbances that initiate or exacerbate the pathological processes in the brain, such as amyloid-β plaque formation and tau hyperphosphorylation. In sporadic AD cases, these external stressors may interact with molecular pathways involved in gene expression regulation.

Methods and Results:

Biochemical identification of RNA Binding protein (RBP) unbalance of in APP/PS1 mice model: FMRP and hnRNPC. We plan to identify new G-quartet molecule mimicking the FMRP-mRNA APP binding aiming to reduce the APP levels and, consequently, the Aβ production. We plan to test these molecules in vitro in hippocampal primary neurons and in vivo mice model: biochemical, molecular and behavioural analysis will be conducted. We specifically aim to act upstream the molecular neurological decline appears.

Conclusions and Significance:

A promising therapeutic approach could involve identifying drugs that mimic the binding of these RNA-binding proteins to the APP messenger, thereby reducing the overproduction of APP and, ultimately, amyloid-β plaque formation. By targeting these upstream processes, such drugs could offer a new avenue for slowing or preventing AD progression in its earliest stages.

Keywords: RNA Binding protein, APP metabolism, early intervention.

References:

Bleuzé L, Triaca V, **Borreca A.** FMRP-Driven Neuropathology in Autistic Spectrum Disorder and Alzheimer's disease: A Losing Game. Front Mol Biosci. 2021 Oct 25;8:699613. doi: 10.3389/fmolb.2021.699613.

Corsetti V*, **Borreca A***, Latina V, Giacovazzo G, Pignataro A, Krashia P, Natale F, Cocco S, Rinaudo M, Malerba F, Florio R, Ciarapica R, Coccurello R, D'Amelio M, Ammassari-Teule M, Grassi C, Calissano P, Amadoro G. Passive immunotherapy for N-truncated tau ameliorates the cognitive deficits in two mouse Alzheimer's disease models. Brain Commun. 2020 Apr 6;2(1):fcaa039. doi: 10.1093/braincomms/fcaa039.

Borreca A, Valeri F, De Luca M, Ernst L, Russo A, Nobili A, Cordella A, Corsetti V, Amadoro G, Mercuri NB, D'Amelio M, Ammassari-Teule M. Transient upregulation of translational efficiency in prodromal and early symptomatic Tg2576 mice contributes to Aβ pathology. Neurobiol Dis. 2020 Jun;139:104787. doi: 10.1016/j.nbd.2020.104787.

Borreca A, Gironi K, Amadoro G, Ammassari-Teule M. Opposite Dysregulation of Fragile-X Mental Retardation Protein and Heteronuclear Ribonucleoprotein C Protein Associates with Enhanced APP Translation in Alzheimer Disease. Mol Neurobiol. 2016 Jul;53(5):3227-3234. doi: 10.1007/s12035-015-9229-8.