DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

41st CYCLE
Project proposal for a Sapienza PhD scholarship

Title: Rescue strategies for a monogenic form of ASD expressing the mutant protein R451C Neuroligin3

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Summary

Autism Spectrum Disorders (ASDs) are neurodevelopmental syndromes, characterized by social deficits and a strong genetic background. In the last decades, the synaptic signaling has been identified as one of the recurrent affected pathways. Indeed, several ASD-risk genes are involved in the functioning of the synapse however the molecular mechanisms are scarcely investigated and no therapies act on rescuing impaired signaling. Neuroligin3 is a post-synaptic cell adhesion molecule interacting with a presynaptic partner of the Neurexin family. The mutation R451C in Neuroligin3 has been reported in ASD-children and we have shown it affects folding and cell surface trafficking of the protein impairing the correct communication between neurons.
We have shown insoluble dexamethasone improves exposure of R451C NLGN3 to the cell membrane in two cellular model systems in vitro. We propose to characterize the effect of a soluble form of dexamethasone on neuronal properties and ER stress in neural stem cells expressing R451C NLGN3 endogenously and the mechanism of action of the compound in vitro.
Finally, we will test the efficacy of Dex in vivo in improving social behaviours in a monogenic mouse model of ASD expressing the human R451C mutation in the endogenous gene.

Pertinent Publications of the proponent (last 5 years)

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*co-senior author

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Trobiani L, Meringolo M, Diamanti T, Bourne Y, Marchot P, Martella G, Dini L, Pisani A, **De Jaco A***, Bonsi P. The neuroligins and the synaptic pathway in Autism Spectrum Disorder.
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*co-corresponding author

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Chemistry. **2020**; 26(8):1834-1845.
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