DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

40° Cycle

Project proposal for a PhD scholarship

Main research line/secondary research line

Title of the research:
Targeting endoplasmic reticulum (ER) stress and the «gut-brain axis» in model systems for Autism Spectrum Disorders: the potential therapeutical role of Glucocorticoids

Supervisor:
Antonella De Jaco
antonella.dejaco@uniroma1.it

Summary (max 500 words)

Autism Spectrum Disorders (ASDs) are neurodevelopmental conditions frequently accompanied by gastrointestinal (GI) disorders such as Crohn's disease and ulcerative colitis. These comorbidities suggest a strong link between the brain and the gut. One of the best-characterized monogenic models of ASD is the Neuroligin3 (NLGN3) R451C mouse, which presents behavioral-like manifestations, neurotransmission alterations and GI symptoms as reported for ASD patients.
We have shown that both *in vitro* and *in vivo*, the R451C mutation leads to NLGN3 misfolding and endoplasmic reticulum (ER) retention, with consequent ER stress and activation of the Unfolded Protein Response (UPR).
In the Enteric Nervous System (ENS), NLGN3 expression has been reported at the messenger level and we aim to assess protein levels in WT and the R451C NLGN3 mice and whether ER stress can disrupt gut function and microbiota. We have shown selective Glucocorticoids (GCs), Dexamethasone (DEX) and Prednisone (PRED), rescue NLGN3 cellular trafficking and reduce ER stress *in vitro*. We propose to evaluate the therapeutic effects of DEX and PRED *in vivo* in the NLGN3 R451C mouse model, assessing effects on ER stress, microbiota composition, GI motility, and inflammation, which represent a challenging clinical need since gut symptoms are often underestimated in ASD patients.

Pertinent Publications of the proponent (last 5 years)

- Serangeli I, Diamanti T, **De Jaco A**, Miranda E. Role of mitochondria-endoplasmic reticulum contacts in neurodegenerative, neurodevelopmental and neuropsychiatric conditions. ***Eur J Neurosci.* 2024 Sep;60(5):5040-5068.** doi: 10.1111/ejn.16485. Epub 2024 Aug 5. Erratum in: Eur J Neurosci. 2024 Sep 20. doi: 10.1111/ejn.16544. PMID: 39099373 (*co-senior author).
- Diamanti T., Trobiani L, Mautone L, Serafini F, Gioia R, Ferrucci L, Lauro C, Bianch S, Perfetto C, Guglielmo S, Sollazzo R, Giorda E, Setini A, Ragozzino D, Miranda E, Comoletti D, Di Angelantonio S, Cacci E, **De Jaco A.** Glucocorticoids rescue cell surface trafficking of R451C Neuroligin3 and enhance synapse formation. ***Traffic* 2024; 25(1):e12930.**
- Gioia R, Seri T, Diamanti T, Fimmanò S, Vitale M, Ahlenius H, Kokaia Z, Tirone F, Micheli L, Biagioni S, Lupo G, Rinaldi A, **De Jaco A**, Cacci E. Adult hippocampal

neurogenesis and social behavioural deficits in the R451C Neuroligin3 mouse model of autism are reverted by the antidepressant fluoxetine.
***J Neurochem.* 2023**;165(3):318-333.

- Diamanti T, Prete R, Battista N, Corsetti A, **De Jaco A**. Exposure to Antibiotics and Neurodevelopmental Disorders: Could Probiotics Modulate the Gut-Brain Axis?
***Antibiotics* (Basel) 2022;11(12):1767.**
- Bonsi P, **De Jaco A**, Gubellini P. Editorial to the special issue: The neurobiology of synaptic dysfunction in brain disorders.
***Neurobiol Dis.* 2023 Jan; 176:105968.**
- Elisa Maria Turco, Angela Maria Giada Giovenale, Laura Sireno, Martina Mazzoni, Alessandra Cammareri, Caterina Marchioretti, Laura Goracci, Alessandra Di Veroli, Elena Marchesan, Daniel D'Andrea, Antonella Falconieri, Barbara Torres, Laura Bernardini, Maria Chiara Magnifico, Alessio Paone, Serena Rinaldo, Matteo Della Monica, Stefano D'Arrigo, Diana Postorivo, Anna Maria Nardone, Giuseppe Zampino, Roberta Onesimo, Chiara Leoni, Federico Caicci, Domenico Raimondo, Elena Binda, Laura Trobiani, **Antonella De Jaco**, Ada Maria Tata, Daniela Ferrari, Francesca Cutruzzolà, Gianluigi Mazzoccoli, Elena Ziviani, Maria Pennuto, Angelo Luigi Vescovi and Jessica Rosati.
Retinoic acid-induced 1 gene haploinsufficiency alters lipid metabolism and causes autophagy defects in Smith-Magenis syndrome.
***Cell Death Dis* 2022; 13: 981.** DOI: 10.1038/s41419-022-05410-7.
- Bonsi P, **De Jaco A***, Fasano L, Gubellini P. Postsynaptic autism spectrum disorder genes and synaptic dysfunction.
***Neurobiol Dis.* 2022**; 162:105564. *first co-author
- D'Acunto E, Gianfrancesco L, Serangeli I, D'Orsi M, Sabato V, Guadagno NA, Bhosale G, Caristi S, Failla AV, **De Jaco A**, Cacci E, Duchen MR, Lupo G, Galliciotti G, Miranda E. Polymerogenic neuroserpin causes mitochondrial alterations and activates NFκB but not the UPR in a neuronal model of neurodegeneration FENIB.
***Cell Mol Life Sci.* 2022**; 79:437.
- 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.
***Neurosci Biobehav Rev.* 2020**; 119:37-51 (*co-corresponding author).
- Salome Azoulay-Ginsburg S; Trobiani L; Setini A; Favaloro FL; Giorda E; Jacobs A; Hauschner H; Levy L; Cestra G; **De Jaco A***; Gruzman A. The lipophilic 4-phenylbutyric acid derivative prevents aggregation and retention of misfolded proteins.
***Chemistry.* 2020; 26(8):1834-1845** (*co-corresponding author)

REFERENCES (for the above section DESCRIPTION OF THE RESEARCH)

Information on the financial sustainability of the proposal (research funds, student financial coverage):

2024 ERA4HEALTHNUTRIBRAIN-090: component of the Italian unit (PI Prof. Gaetani, Sapienza University) of the Partnership Fostering a European Research Area for Health (ERA4Health) (GA N° 101095426 of the EU Horizon Europe Research and Innovation Programme). Starting date of the project: April 2025

2024 Sapienza-Rome Technopole per l'internazionalizzazione della ricerca-Linea di finanziamento 1 "Creazione di network internazionali" (FP7 del rome technopole) PI: Silvana Gaetani (20,000 euro).

2024 Sapienza Ateneo Funding: PI of the project Antonella De Jaco (Dept. Biology and Biotechnology, Sapienza University of Rome). Title: Rescue strategies for a monogenic form of ASD expressing the mutant protein R451C Neuroligin3 (9000 euro)

Collaborations of the supervisor with national and international laboratories, relevant for this research project
This project will be in collaboration with:

NATIONAL
For this project we are starting a collaboration with two research groups experts in stress related pathologies and pathologies with gastro-intestinal dysfunctions:
-Michele Sallese, Miriam Di Mattia, Mirko Pesce
University of Chieti-Pescara
-Loris Riccardo Lopetuso
Digestive Disease Center CeMAD- Fondazione Policlinico Universitario "A. Gemelli"

INTERNATIONAL
Davide Comoletti, Victoria University, Wellington (New Zealand)
The long-lasting collaboration with the lab of Prof. Comoletti allows the interaction between our research groups. The role in this project will be focused on understanding the alternative partners of Neuroligin3 in the enteric nervous system.