DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

42° Cycle

Project proposal for a PhD scholarship

Secondary research line

Title of the research: Cellular and molecular basis of the neurodegenerative dementia FENIB

Supervisor: Maria Elena Miranda Banos
mariaelena.mirandabanos@uniroma1.it
https://corsidilaurea.uniroma1.it/it/users/mariaelenamirandabanosuniroma1it

Summary

Familial encephalopathy with neuroserpin inclusion bodies (FENIB) is a rare neurodegenerative disorder of genetic origin caused by point mutations in neuroserpin, which lead to the formation of neuroserpin polymers within the endoplasmic reticulum of neurons. Neuroserpin polymers induce neuronal toxicity and death through mechanisms incompletely understood, and the structural basis of polymer formation are still unknown. Our recent work has uncovered two novel mutations in neuroserpin that cause FENIB, which have been characterised in cellular models in terms of polymer formation and its correlation with the clinical phenotype of the corresponding FENIB patients. We now propose to create an *in vitro* human neuronal model of FENIB by differentiation of neural progenitor cells overexpressing wild type and polymerogenic variants of neuroserpin, which will be used to further investigate the neuronal mechanisms of toxicity. Our studies in mouse neurons support the involvement of oxidative stress and mitochondrial alterations, but studies in human neurons are needed to confirm these mechanisms in FENIB and to discover novel pathways involved in it. We also aim to define the polymerisation mechanism of two different neuroserpin variants through structural studies in collaboration with Prof. Lomas and Dr. Irving at University College London (UK). With this project, we expect to understand the differences with regards to polymerisation propensity and neuronal toxicity for different variants of neuroserpin and their correlation with the associated clinical phenotypes.

Pertinent publications of the proponent (last 5 years)

Ronzoni R, Aldobiyan I, Miranda E, Heyer-Chauhan N, Elliston EL, Pérez J, Fra A, Irving JA, Lomas DA (2025). Susceptibility of alpha-1 antitrypsin deficiency variants to polymer-blocking therapy. JCI Insight 10(15):e194354

Miranda E, Galliciotti G (2025). Editing out the polymers: Toward a gene therapy for FENIB. Molecular Therapy Nucleic Acids 36(2):102518

Giustini A, Maiocchi A, Serangeli I, Pedrini M, Quintiliani A, Sabato V, Bonato F, Seneci P, Lupo G, Passarella D, Miranda E (2025). An Inducible Neural Stem Progenitor Cell Model for Testing Therapeutic Interventions Against Neurodegeneration FENIB. Drug Development Research 86(1):e70041

Serangeli I, Diamanti T, De Jaco A, Miranda E (2024). Role of mitochondria-endoplasmic reticulum contacts in neurodegenerative, neurodevelopmental and neuropsychiatric conditions. European Journal of Neuroscience 60(5):5040-5068

Denardo A, Ben Khlifa E, Bignotti M, Giuliani R, D'Acunto E, Miranda E, Irving JA, Fra A (2023). Probing of the reactive center loop region of alpha-1-antitrypsin by mutagenesis predicst new type-2 dysfunctional variants. Cellular and Molecular Life Sciences 81:6

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 (2022). Polymeric neuroserpin causes mitochondrial alterations and activates NFkB but not the UPR in a neuronal model of neurodegeneration FENIB. Cellular and Molecular Life Sciences 79:437

Miranda E and Galliciotti G (2022). Editorial: Elucidating the pathological mechanisms of neurodegeneration in the lethal serpinopathy FENIB. Neural Regeneration Research 17:1733

Vapore V, Mazzaglia C, Sibilia D, Del Vecchio M, Fruhmann G, Valenti M, Miranda E, Rinaldi T, Winderickx J, Mazzoni C (2021). Neuroserpin inclusion bodies in a FENIB yeast model. Microorganims 9:1498

Nuñez A, Belmonte I, Miranda E, Barrecheguren M, Farago G, Loeb E, Pons M, Rodriguez-Frias F, Gabriel-Medina P, Rodriguez E, Genescà J, Miravitlles M, Esquinas C (2021). Association between circulating alpha-1 antitrypsin polymers and lung and liver disease. Respiratory Research 22:244

D'Acunto E, Fra A, Visentin C, Manno M, Ricagno S, Galliciotti G, Miranda E (2021). Neuroserpin: structure, function, physiology and pathology. Cellular and Molecular Life Sciences 78:6409

Ronzoni R, Ferrarotti I, D'Acunto E, Balderacchi AM, Ottaviani S, Lomas DA, Irving JA, Miranda E, Fra AM (2021). The importance of N186 in the alpha-1-antitrypsin shutter region is revealed by the novel Bologna deficiency variant. International Journal of Molecular Sciences 22:5668

Ingwersen T, Linnenberg C, D'Acunto E, Temori S, Paolucci I, Wasilewski D, Mohammadi B, Kirchmair J, Glen RC, Miranda E, Glatzel M, Galliciotti G (2021). G392E neuroserpin causing dementia FENIB is secreted from cells but is not synaptotoxic. Scientific Reports 11:8766

Higgins NR, Greenslade JE, Wu JJ, Miranda E, Galliciotti G, Monteiro MJ (2021). Serpin neuropathology in the P497S UBQNL2 mouse model of ALS/FTD. Brain Pathology 29:e12948

Ronzoni R, Heyer-Chauhan N, Fra A, Pearce AC, Rüdiger M, Miranda E, Irving JA, Lomas DA (2021). The molecular species responsible for alpha-1 antitrypsin deficiency are suppressed by a small molecular chaperone. The FEBS Journal, 288:2222-2237