



BioISI - Biosystems & Integrative Sciences Institute

Understanding the molecular basis of mitochondrial neurological diseases – Studies on aminoacyl-tRNA synthetase disease variants

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Protein Misfolding and Amyloids in Biomedicine Laboratory (<http://folding.fc.ul.pt/>)

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Mitochondrial diseases (MDs) represent the most common group of inherited metabolic diseases. These disorders are clinically and therapeutically very challenging because they can affect any organ, and due to the involvement of both nuclear and mitochondrial genes.

Interestingly, a relatively frequent cause of nuclear MDs are the defects in protein synthesis associated with mutations in mitochondrial aminoacyl-tRNA synthetases (mt-aaRS), which are enzymes responsible for the addition of the corresponding amino acid into the correct tRNA molecules. More than 150 disease mutations on mt-aaRSs have been reported, associated in the vast majority to pathologies of the central nervous system, however the molecular mechanism of disease is yet not fully established.

This project is dedicated to understanding the molecular pathophysiology of mt-aaRS related neurological diseases, with a focus on disease variants of the protein glutamyl-tRNA synthetase (EARS2), as model protein for neurological mitochondrial diseases.

A combination of multiple experimental methods will be applied, in particular we will: i) optimize recombinant protein expression (EARS2-wild-type (WT), and disease-related variants, EARS2-p. Gly110Ser, EARS2-p. Asp349Asn and EARS2-p. Arg489Gln); ii) establish EARS2 variants purification protocols using a combination of chromatographic methodologies; iii) characterize structure, conformation and function of EARS2-WT and variants using circular dichroism (CD), Fourier Transform Infrared Spectroscopy (FTIR) and fluorescence spectroscopy; iv) investigate variants' conformational stability by chemical and thermal denaturation; v) perform preliminary studies for protein detection and analysis in patient-derived fibroblasts (in collaboration with Professor Rita Horvath, Cambridge University).

All resources (materials and instrumentation) required for this project are available at the host laboratory and at BioISI facilities.

Students selected for this project, after thesis registration, are eligible to apply to the BioISI Junior Programme (supporting 8 students with a 6-month scholarship (BII)), being the selection criterium the academic merit of the candidates.

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