CMB PhD School Seminars 2022-2023

19th September 2023, 2:00 p.m.

Aula 1, Via Belmeloro 6

Online meeting on Teams

on this link

"Making sense from nonsense: pathophysiological implications and therapeutic approaches"

Mirko Pinotti, PhD

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The 40-minutes scientific talk by Prof. Pinotti will be followed by a 20-minutes "Meet the speaker" Q&A session with the PhD students

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Abstract

Nonsense mutations, by introducing premature termination codons (PTCs) and leading to the synthesis of truncated proteins and/or nonsense mediated mRNA decay, are a relevant cause of genetic disease.

However, nonsense triplets might, albeit at low frequency, undergo a recoding process named ribosome readthrough, which insert specific amino acids, or subset(s) of, depending on the stop codon. This could account for residual expression of full-length (FL) protein in patients and have pathophysiological implications.

Many efforts have been also made to develop readthrough-inducers for therapeutic purposes.

In this view, the dissection of the molecular determinants shaping the outcome of either spontaneous of induced readthrough, namely nucleotide and protein contexts as well as their interplay and impact on protein structure/function, is crucial to identify responsive PTCs resulting in functional FL proteins.

The deficiency of coagulation factor VIII or IX (Hemophilia A or B) represent ideal models to address these issues since nonsense mutations are relatively frequent and even low expression levels might influence the clinical phenotype.

Through the characterization of a large panel of HA/HB-causing mutations we dissected the determinants shaping the outcome of functional readthrough, with the protein context having the pivotal role. This led to classify nonsense mutations and explain a differential association with the development of inhibitory antibodies following replacement therapy, one of the most serious complication. Moreover, the mechanistic findings with readthrough-inducers defined readthrough-favorable features useful to achieve rescue profiles compatible with therapeutic thresholds.

Data help interpreting the variable efficiency of readthrough-inducers in patients for different genetic disorders, and assessing the potential translatability of readthrough into a personalized and mutation-specific, and thus patient-oriented, therapeutic strategy

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