

Bando a Cascata PARTENARIATO ESTESO “Health Extended ALLiance for Innovative Therapies, Advanced Lab-research, and Integrated Approaches of Precision Medicine” - HEAL ITALIA SPOKE N.5 “Next-Gen Therapeutics”

Predictive Research On Personalized Healthcare through Experimental Characterization of Yielding GLYCOprotein Rare Ailments and Responsive Endoplasmic reticulum modulation for therapeutic handling

PROPHECY-GlycoRARE

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Abstract

This project aims to establish an Artificial Intelligence (AI)-based therapeutic strategy for a broad spectrum of congenital rare diseases caused by missense mutations in glycoprotein-coding genes. These mutations typically impair protein folding without abolishing function, resulting in their retention within the endoplasmic reticulum (ER) by UDP-glucose:glycoprotein glucosyltransferase (UGGT), the central enzyme in the ER folding quality control (ERQC) system, ultimately leading to disease.

Recent findings have identified UGGT as a novel drug target, supporting the concept of ER folding quality control modulation therapy (ERQC-MT). Currently, no reliable methods exist to predict the responsiveness of missense mutants to such therapy, nor are selective UGGT inhibitors available. To address these gaps, the proposed work will integrate: (i) AI and molecular dynamics (MD) simulations to evaluate mutant responsiveness; (ii) in silico screening of modulators targeting UGGT:client protein-protein interactions (PPIs); (iii) in vitro, and (iv) in cellula assays to validate computational predictions.

A proof-of-concept study will investigate UGGT interactions with mutant forms of lysosomal α -Galactosidase (α -Gal), implicated in Anderson-Fabry Disease (AFD). This AI-based approach is expected to establish ERQC-MT as a viable, personalized therapeutic strategy for AFD and other related conditions. Furthermore, the methodology will provide a framework to assess patient eligibility and facilitate pharmaceutical industry engagement.