PROPHECY-GlycoRARE

Predictive **R**esearch **O**n **P**ersonalized **H**ealthcare through **E**xperimental **C**haracterization of **Y**ielding **GLYCO**protein **R**are **A**ilments and **R**esponsive **E**ndoplasmic reticulum modulation for therapeutic handling

Bando a cascata progetto "Health Extended ALliance for Innovative Therapies, Advanced Lab-research, and Integrated Approaches of Precision Medicine - HEAL ITALIA"
PE_00000019 – CUP H43C22000830006 – Spoke 5 "Next-Gen Therapeutics"

Subject B: Innovative methods for the development of new drugs for precision medicine

Sub-theme B2. Artificial Intelligence approaches for discovery of drugs targeting protein-protein interactions (PPIs)

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Dr G Andreotti

ibf

CNR - Istituto di Biofisica

Consiglio Nazionale delle Ricerche | Dipartimento Scienze Fisiche e Tecnologie della Materia

https://www.ibf.cnr.it/

Dr T Giorgino

Consiglio Nazionale delle Ricerche

IBBA

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Dr M Pellegrini

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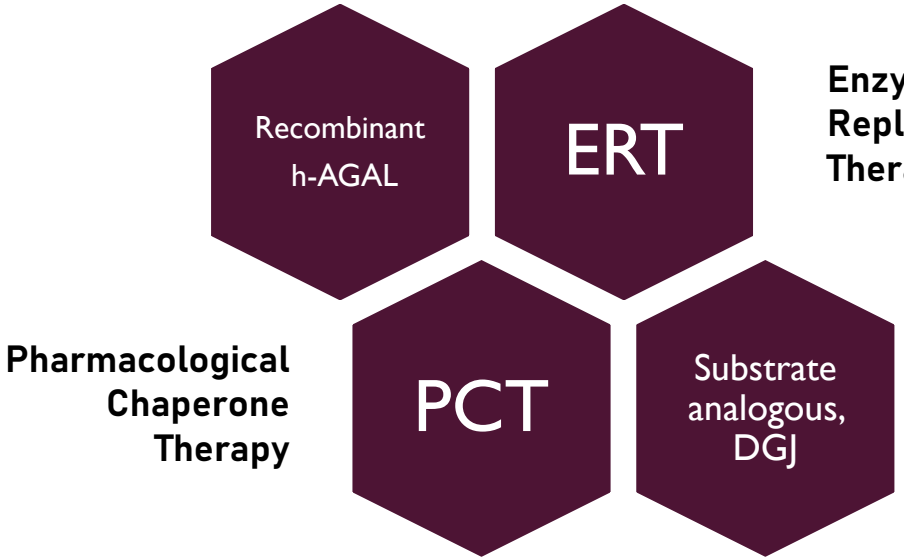
Fabry disease

> 1000 α-GAL mutations
> 400 α-GAL missense mutations

Currently approved therapies

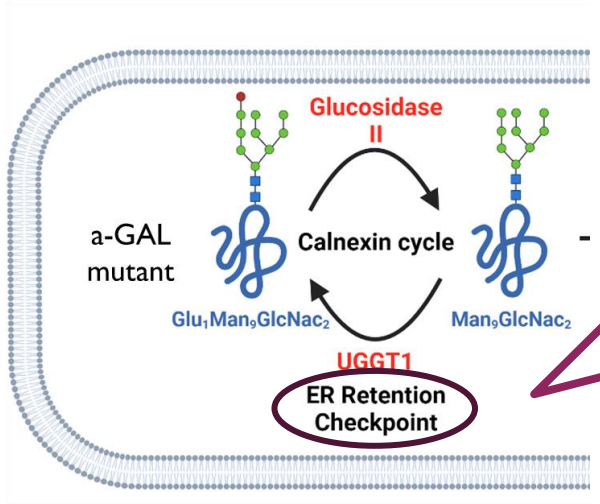


Many limitations!

ERT:
- does not reach the CNS
- anti-drug antibody response
- elevated costs

PCT:
- effective for some AGAL mutants only
- the approved PC (DGJ or Migalastat) is an inhibitor, and a discontinuous dosage regimen is required

HYPOTESIS



UDP-Glucose Glucosyl Transferase (UGGT) is the checkpoint of the ER glycoprotein folding quality control!

Test if UGGT induces ER retention of α-Gal mutants

If so, modulation of UGGT:α-Gal mutant interaction could help α-Gal to reach the lysosomes!

OUR STEPS

The objectives of our proposal are

i) to **identify** novel negative modulators of the α-Gal mutant client PPIs, by using Machine Learning and MD;

ii) to **predict** which α-Gal missense mutants carry residual activity (and thus to aid clinicians to stratify patients and to select candidates for PCT and or ERQC-MT), by cutting-edge Machine Learning models;

iii) to **validate** *in vitro* and *in cellula* the PPI modulation activity of the identified compounds, and the responsiveness of α-Gal mutants identified for PCT and/or ERQC-MT of Fabry disease.

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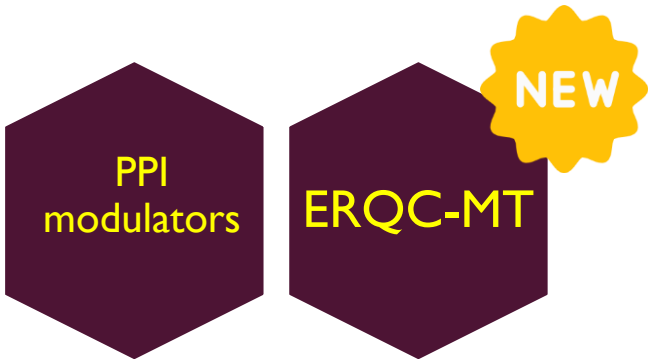
OUR GOALS

1. **Discovery of novel PPIs drug candidates targeting α-Gal mutants for precision medicine in Fabry Disease**

2. **This is a seminal project. Indeed it is possible to foreseen applications to more other different protein targets**

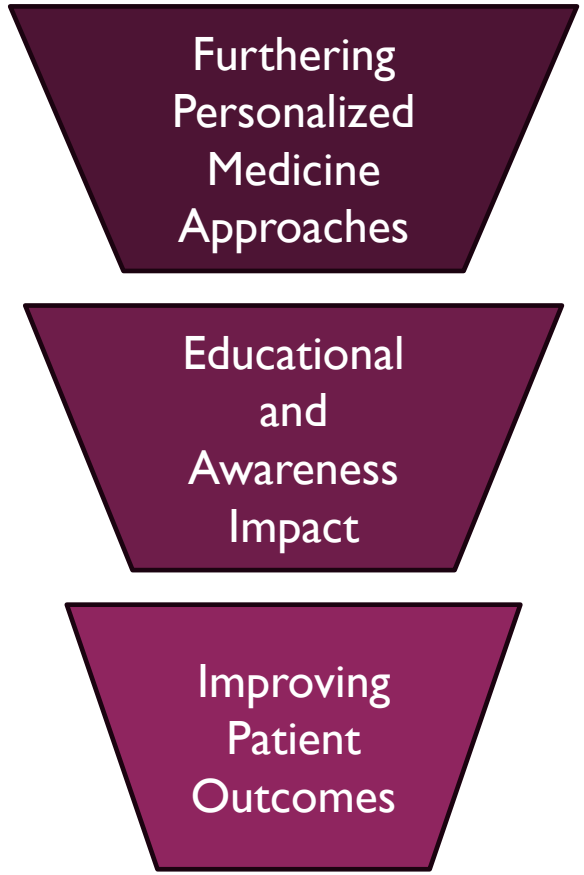
Endoplasmic Reticulum Quality Control Modulation Therapy



OUR MAIN AREAS OF EXPERTISE

Cell biology
Structural biology
Biochemistry
Computational biology
Bioinformatics
Mass spectrometry
NMR spectroscopy
Molecular dynamics
Virtual screening
Training of Machine Learning classification models
Immunoblot
Enzymatic assays
Immunofluorescence
Cellular Thermal Shift Assay

IMPACT



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