Fondazione per la Ricerca
sulla Fibrosi Cistica - Onlus
italian cystic fibrosis research foundation

XIX CONVENTION OF INVESTIGATORS IN CYSTIC FIBROSIS

25 – 26 novembre 2021

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TOWARD THE DEVELOPMENT OF TAILORED THERAPIES FOR INSENSITIVE CF GATING MUTATIONS

CODICE PROGETTO: FFC#3/2021

Partner: **Gergely L. Lukacs** (McGill University, Montreal - Canada)
Adozione: Delegazione FFC Ricerca di Imola e Romagna

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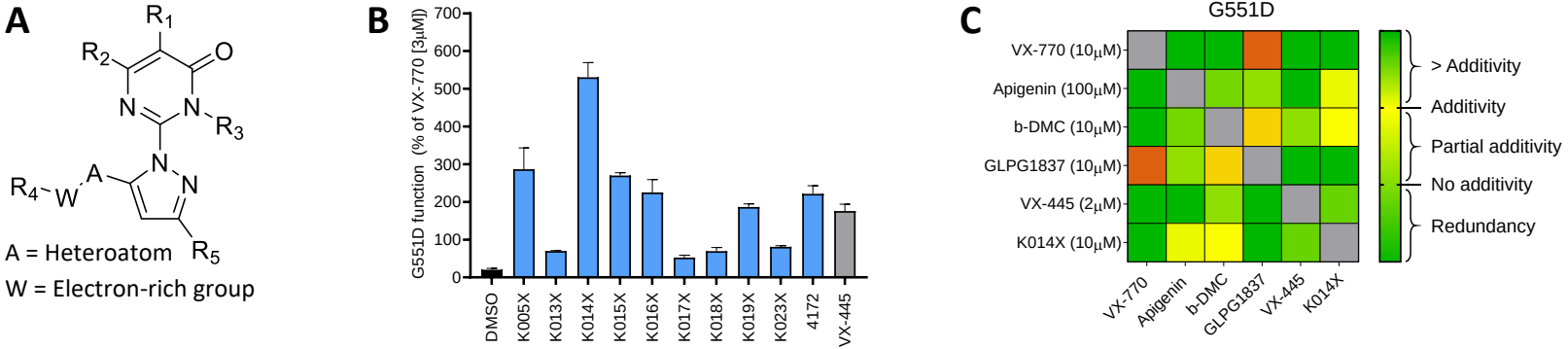
OBIETTIVI SCHEMATICI DEL PROGETTO

Identification of novel modulators that, either alone or in combination, can treat gating-deficient CFTR variants, particularly focusing on mutations characterized by low responsiveness to current modulators.

DATI PRELIMINARI

Identification of novel pyrazole-pyrimidinone derivatives able to significantly improve the G551D-CFTR function.



A) General structure of the derivatives. **B)** Screening of the compounds for G551D-CFTR potentiator effect in CFBE41o- cells. The YFP quenching kinetics was determined in response to extracellular iodide addition in the presence of forskolin (10 µM), IBMX (250 µM), cpt-cAMP (250 µM), after the acute addition of the indicated compounds (10µM) or VX-445 (2µM, saturating concentration); results are expressed as the percentage of positive control (VX-770, 3µM). **C)** Heat map reporting the combinatorial profiling of compounds pairs effect (halide-sensitive YFP quenching kinetics) on G551D function (CFBE41o- cells) in comparison to their theoretical additivities.

COME QUESTO PROGETTO CONTRIBUISCE ALL'AVANZAMENTO DELLA RICERCA SULLA FIBROSI CISTICA

We expected to pave the way for the development of novel polypharmacology that will allow more effective therapy for a CF patient population carrying (ultra-)rare CFTR gating mutations that are poorly responsive to currently approved drugs.