TASK FORCE FOR CYSTIC FIBROSIS EXTENSION

Principal Investigator: Tiziano Bandiera, Istituto Italiano di Tecnologia (IIT), Genova
Partner: Nicoletta Pedemonte, U.O.C. Genetica Medica, Istituto Giannina Gaslini (IGG), Genova
External Collaborator: Luis J.V. Galietta, Telethon Institute for Genetics and Medicine (TIGEM), Pozzuoli (NA)
Participants: IGG – Valeria Tomati, Emanuela Caci, Loretta Ferrera, IIT – Fabio Bertozzi, Francesco Berti, Federico Sorana, Alejandra Rodriguez

Keywords: Cystic fibrosis, CFTR, correctors, preclinical development [doi.org/chfb]

1. Background

The most frequent mutation among patients with cystic fibrosis (CF), F508del, causes defective maturation and early degradation of CFTR protein[1]. The F508del defect can be targeted with compounds known as *correctors*[2]. Proteins carrying F508del and other mutations also show a channel gating defect that can be addressed with another type of compounds called *potentiators*[3]. Currently, there are no F508del-CFTR correctors with adequate efficacy in human. Therefore, new compounds are needed[4].

2. Hypothesis and objectives

The project aims at the selection of a compound to progress to preclinical development, and at starting preclinical development activities. In parallel, activities to identify a backup compound will be conducted.

3. Methods

The compound that will be selected for preclinical development will be tested in a large set of assays to verify first if there is any sign of genetic toxicity and, second, if other molecular targets are hit. A preliminary in vivo toxicity study will also be conducted.

4. Preliminary Results

Among the 500+ compounds synthesized as correctors in the TFCF project, we identified molecules that in primary bronchial epithelial cells from CF patients show rescue of F508del-CFTR activity at nanomolar concentrations. Those compounds have been evaluated more in-depth for their drug-likeness in a number of assays conducted at IGG, IIT, and Contract Research Organizations (CROs). Those studies allowed us to identify 2÷3 compounds as possible candidates for preclinical development.

5. Spin-off for research & clinical purposes

The best compounds identified in the TFCF project represent possible candidates to develop novel drugs for the correction of the CF basic defect.

References

1) Lukacs and Verkman, Trends Mol Med 18:81-91, 2012 https://doi.org/10.1016/j.molmed.2011.10.003 PMid:22138491 PMCid:PMC3643519

2) Okiyoneda et al., Nat Chem Biol 9:444-454, 2013 https://doi.org/10.1038/nchembio.1253 PMid:23666117 PMCid:PMC3840170

3) Yu et al., J Cyst Fibros 11:237-245, 2012 https://doi.org/10.1016/j.jcf.2011.12.005 PMid:22293084

4) Mall and Galietta, J Cyst Fibros 14:561-570, 2015; Li et al., J Cyst Fibros doi: 10.1016/j.jcf.2017.08.013, 2017 https://doi.org/10.1016/j.jcf.2017.08.013