***DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO (38° Ciclo)***

**Title:** Analysis of the effect of CFTR modulators on the innate immune response of people with cystic fibrosis.

**Supervisor:** Paola Del Porto ([paola.delporto@uniroma1.it](mailto:paola.delporto@uniroma1.it))

**Summary** The pulmonary disease represents the main cause of morbidity and mortality in people with Cystic fibrosis (pwCF). In the CF airways the loss of CFTR mediated anion transport in epithelial cells causes air-liquid dehydration and defective mucociliary clearance leading to chronic bacterial infections and inflammation (1). In addition, an impairment in the antimicrobial activity of monocytes/macrophages further contribute to CF chronic infection and inflammation (2). Recently the development of small molecule drugs termed CFTR modulators targeting CFTR itself has revolutionized the treatment of Cystic fibrosis (3). However, at present, the effects of modulator therapy have been mainly evaluated in clinical trials demonstrating improvement in lung function, respiratory symptoms, reduced risk of acute pulmonary exacerbation and weight gain while *in vitro* studies were mainly focused on epithelial cells. Thus, the aim of this project is to analyse *ex vivo* and *in vitro* the effects of CFTR modulators on the innate immune responses of pwCF.

References

1. Elborn, J.S. (2016). Lancet 388: 2519-2531.

2. Leveque M. (2017). J Cyst Fibros. 16: 443-453.

3. Lopez-Pachedo (2019) M. Front Pharmacol 10: 1662

**Pertinent Publications of the proponent (last 5 years)**

1. Blaconà G, R. Raso, S. Castellani, S. Pierandrei, P. Del Porto, G. Ferraguti, F. Ascenzioni, M. Conese, Lucarelli M. Downregulation of epithelial sodium channel (ENaC) activity in cystic fibrosis cells by epigenetic targeting. 2022. Cell Mol Life Sci. 79(5):257. doi:

10.1007/s00018-022-04190-9.

2. Lapa D, P. Del Porto, C. Minosse, G. D'Offizi, A. Antinori, M. R. Capobianchi MR, Visco-Comandini U, McPhee F, Garbuglia AR, Zaccarelli M. 2021. Clinical Relevance of Torque Teno Virus (TTV) in HIV/HCV Coinfected and HCV Monoinfected Patients Treated with Direct-Acting Antiviral Therapy. J Clin Med. 10(10):2092. doi: 10.3390/jcm10102092.

3. Occhicone A., P. Del Porto, N. Danz, P. Munzert, A. Sinibaldi, F. Michelotti. 2021. Enhanced fluorescence detection of Interleukin 10 by Means of 1D Photonic Crystals. *Crystals*. 11: 1517. https://doi.org/10.3390/cryst11121517

4. Pierandrei S., G. Truglio, F. Ceci, P. Del Porto, Bruno SM, Castellani S, Conese M, Ascenzioni F, Lucarelli M. 2021. DNA Methylation Patterns Correlate with the Expression of

*SCNN1A*, *SCNN1B*, and *SCNN1G* (Epithelial Sodium Channel, ENaC) Genes. *Int J Mol*

*Sci*. 22(7):3754. doi: 10.3390/ijms22073754.

5. Sias C., V. Guarrasi, C. Minosse, D. Lapa, F.D. Nonno, M. R. Capobianchi, A. R. Garbuglia, P. Del Porto, P. Paci. 2020 Human Papillomavirus Infections in Cervical Samples

From HIV-Positive Women: Evaluation of the Presence of the Nonavalent HPV Genotypes

and Genetic Diversity. *Front Microbiol*. 11:603657. doi: 10.3389/fmicb.2020.603657.

6. Cavinato L., E. Genise E, F. R. Luly FR, E. G. Di Domenico, P. Del Porto, F. Ascenzioni. 2020. Escaping the Phagocytic Oxidative Burst: The Role of SODB in the Survival of *Pseudomonas aeruginosa* Within Macrophages. *Front Microbiol*. 11:326. doi:

10.3389/fmicb.2020.00326.

7. Luly F.R, M. Lévêque, V. Licursi, G. Cimino, C. Martin-Chouly, N. Théret N, R. Negri, L. Cavinato, F. Ascenzioni, P. Del Porto. 2019. MiR-146a is over-expressed and controls IL-

6 production in cystic fibrosis macrophages. *Sci Rep.* 9(1):16259. doi: 10.1038/s41598-019-

52770-w.

8. Dragotto J, S. Canterini, P. Del Porto, A. Bevilacqua, MT Fiorenza. 2019. The interplay between TGF-β-stimulated TSC22 domain family proteins regulates cell-cycle

dynamics in medulloblastoma cells. *J Cell Physiol*. 234(10):18349-18360. doi:

10.1002/jcp.28468.

9. De Rocco D, B. Pompili, S. Castellani, E. Morini, L. Cavinato, G. Cimino, M.A. Mariggiò, S.Guarnieri, M. Conese, P. Del Porto, F. Ascenzioni. 2018. Assembly and

Functional Analysis of an S/MAR Based Episome with the Cystic Fibrosis Transmembrane

Conductance Regulator Gene. *Int J Mol Sci*. pii: E1220. doi: 10.3390/ijms19041220.

10. Totani L, R. Plebani , A. Piccoli, S. Di Silvestre , P. Lanuti, A. Recchiuti, E. Cianci E, G. Dell'Elba, S. Sacchetti, S. Guarnieri, M.A. Mariggiò, V.C. Mari, M. Anile, F. Venuta, P.

Del Porto, P. Moretti, M. Prioletta, F. Mucilli, M. Marchisio, A. Pandolfi, V. Evangelista, M.

Romano. 2017. Mechanisms of endothelial cell dysfunction in cystic fibrosis. *Biochim*

*Biophys Acta Mol Basis Dis.* 1863(12):3243-3253. doi: 10.1016/j.bbadis.2017.08.011.

11. Plebani R, R. Tripaldi, P. Lanuti, A. Recchiuti, S. Patruno, S. Di Silvestre, P. Simeone, M. Anile, F. Venuta, M. Prioletta, F. Mucilli, P. Del Porto, M. Marchisio, A. Pandolfi, M. Romano. 2017. Establishment and long-term culture of human cystic fibrosis endothelial cells. *Lab Invest*. 97(11):1375-1384. doi: 10.1038/labinvest.2017.74.

12. Gilardini Montani MS, M. Granato, C. Santoni, P. Del Porto, N. Merendino, G. D'Orazi, A. Faggioni, M. Cirone 2017. Histone deacetylase inhibitors VPA and TSA induce apoptosis and autophagy in pancreatic cancer cells. *Cell Oncol* (Dordr). 40(2):167-180. doi:

10.1007/s13402-017-0314-z.

13. Lévêque M, S. Le Trionnaire, P. Del Porto, C. Martin-Chouly. 2017. The impact of impaired macrophage functions in cystic fibrosis disease progression. *J Cyst Fibros*.

16(4):443-453. doi: 10.1016/j.jcf.2016.10.011.