***DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO***

***39 CYCLE***

**Project proposal for a Sapienza PhD scholarship**

**Main research line**

**Title: Microbial dynamics in the gut–lung-skin axis during Elexacaftor-Tezacaftor-Ivacaftor therapy in people with cystic fibrosis.**

**Short: MYSTIC**

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**Summary**

Lung disease is the leading cause of morbidity and mortality in people with cystic fibrosis (CF). However, other typical CF manifestations include maldigestion and malabsorption of nutrients, small intestinal bacterial overgrowth, and elevated chloride concentrations in sweat (1-3). In the lungs of people with CF, high mucus production and hyperinflammation provide favorable conditions for chronic colonization with opportunistic pathogens (4-6). Similarly, significant variations in the diversity and composition of the gut microbiota have been reported compared to healthy controls (7,8). Clinical interventions to improve outcomes have been demonstrated to impact lung and gut microbiota. (9-11). Those observations allowed defining the gut–lung axis, linking the state of the gut microbiota to respiratory health outcomes (12,13). Other studies demonstrated that the airway and gut microbiome diversity decreases as the diseases progress over time, becoming dominated by opportunistic pathogens (4). Besides, dysbiosis in the gut microbiome of people with CF has been associated with increased intestinal inflammation, the development of gastrointestinal malignancy, liver cirrhosis, and airway colonization (14-17). The airway and gut microbiota affect local and distant immune responses, providing evidence for a bidirectional link between dysbiosis and the pathophysiology of multiple inflammatory skin diseases (18-21). Indeed, people with CF showed increased rates of atopy, drug hypersensitivity reactions, and cutaneous vasculitis than the general population (22). Thus, the imbalance between the microbial communities may affect the homeostasis of different epithelial districts, suggesting a complex host-wide network that broadens the gut-lung axis by including the skin and potentially other body districts (23).

The advent of cystic fibrosis transmembrane conductance regulator (CFTR) modulators has greatly improved the treatment of people with CF (24-26). The triple combination of elexacaftor, tezacaftor, and ivacaftor (ETI) has demonstrated a real clinical benefit in people with one or two copies of the F508del CFTR allele (27,28). In particular, ETI therapy showed modulatory activity on the sputum microbiome diversity in approximately 75% of treated individuals (29). Furthermore, the increase in microbial alpha diversity after ETI demonstrates that the lung microbiome of people with CF became more complex, reducing the relative abundance of pathogens (29). In addition, the increase in pulmonary and body

mass index (BMI) after ETI treatment suggests that clinically significant improvements outside of lung function can be obtained (28,30). Thus, understanding the changes affecting the airway, gut, and skin microbiota during ETI treatments may help develop novel strategies and therapeutic interventions for improving the activity of the CFTR modulator and the overall live quality of people with CF.

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

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