PROJECT

Supervisor:	Alessandra Bragonzi
Title:	Gut-Lung axis in Cystic Fibrosis: pathophysiological basis for diagnostic and therapeutic approaches
Curriculum:	Basic and Applied Immunology and Oncology
Link to the personal page of the University or relevant hospital site website:	https://research.hsr.it/en/divisions/immunology-transplantation-and-infectious-diseases/infections-and-cystic-fibrosis/alessandra-bragonzi.html

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Cystic Fibrosis (CF) is a multi-organ genetic disease. The lung of patients with CF (pwCF) is where fatal complications occur and account for the majority of CF-related morbidities. Chronic obstructive lung disease evolves from early onset mucus plugging, neutrophilic inflammation, and bacterial infection. While much research has focused on the lung, fundamental questions on CF pathogenesis are still unanswered. The picture remains unclear regarding the initial airway inflammation and infection, which develop unpredictably, and the incomplete efficacy of CFTR-modulator therapies in managing chronic disease.

This knowledge gap may stem from a lack of studies investigating the role of distal organs beyond the lung. As well as respiratory complications, gastrointestinal manifestations are clinically significant in pwCF, emerging before pulmonary disease and influencing long-term outcomes. Emerging data connect gut microbiology and immunology to respiratory outcomes, but the mechanisms of gut-lung cross-talk in CF are largely unexplored. It's unclear whether pathological events in the CF lung and gut are distinct or linked to the direct translocation of bacteria and/or microbial products within the host.

Rationale and hypothesis

This project builds on the concept of multi-organ crosstalk, explored through new CF mouse model in previous work of the lab. CF mouse model shows a breakdown of gut barrier integrity with overgrowth of enteric bacteria and shared lung-gut microbiota. GI *P. aeruginosa* colonization serves as a reservoir for CF-related pathogens, acting as a source of infection for distal organs like the lung and liver. Preliminary data in pwCF reveal enteric bacteria in the lung

and identical *P. aeruginosa* strains in fecal and sputum samples, highlighting gut-lung crosstalk and its potential clinical relevance.

Objectives and specific aims

We aim to determine the mechanisms of gut-lung crosstalk in the newly established genetically diverse Collaborative Cross CC037 mice with the ΔF508/ΔF508 mutation in the *Cftr* gene of P. aeruginosa infection by investigating the microbiological and immunological mechanisms of this opportunistic bacteria in the GI tract, including different bacterial phenotype, the nature of this interaction (asymptomatic carriage or infection) and the risk of transmission through fecal shedding. Data in murine models will be complemented with those collected from pwCF to determine whether sputum and feces harbor genetically identical bacterial strains using microbiological culture and sequencing techniques.

Expected outcomes

We anticipate gaining insights into whether intestinal infection and microbial products are sources of infection and inflammation, continuing to impact the lung. These efforts are anticipated to offer crucial insights into the influence of extrapulmonary manifestations on lung pathology and generate novel hypotheses for gut-targeted diagnostic approaches.

Skills that the student should acquire (max. 600 characters including spaces):

Throughout this project, the PhD student will acquire technical skills in mouse handling, microbiological, and immunological assays such as bacterial culture, flow cytometry and immunohistochemistry. Functional and genomic analysis will be implemented. He/she will also establish new mouse models of gut infection and will work in close collaboration with the clinical team for the collection and management of bacterial strains from pwCF. The student will develop critical thinking, problem-solving abilities, and project management skills. Additionally, he/she will enhance oral communication and scientific writing skills, crucial for presenting findings effectively. He/she will also develop the capacity to share projects with various stakeholders, including the patient community.

References (max. 15)

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