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Towards understanding Pseudomonas aeruginosa susceptibility in Cystic Fibrosis by immune cell phenotyping

Cystic Fibrosis (CF) is the most common lethal recessive genetic disease in western countries. It is caused by mutations of the CFTR gene which is carried by approximately 1 in 30 individuals. Patients suffer from chronic pulmonary infections reducing median life expectancy to 35 years. The dominant microorganism associated with reduced pulmonary function in CF is Pseudomonas aeruginosa (Pa). Large variations between patients are observed in bacterial susceptibility and disease progression by yet still unknown mechanisms. More insight into the inflammatory mechanisms in CF patients that associate with bacterial infection is required to improve therapy and life expectancy of people with CF.

CFTR is expressed in multiple tissues and its association with chronic infection likely results from CFTR-dependent mechanisms. It has long been recognized that lack of CFTR function results in disturbed ion transport at epithelial surfaces leading to thick mucus and impaired mucociliary clearance in the lungs. Mucociliary clearance defects (such as in primary ciliary dyskinesia) have been associated with increased bacterial colonization, but at significantly lower levels as observed in CF (approximately 80% of CF versus 15 % in PCD beyond 30 years of age are chronically colonized with Pa). We recently found that monocytes and lymphocytes also express CFTR suggesting that lack of CFTR function in these cells may further contribute to bacterial accumulation and aberrant inflammation. In agreement with this hypothesis, we observed that lack of CFTR function in monocytes from peripheral blood significantly limits binding, phagocytosis and killing of Pa. This indicates that immune cells obtained from peripheral blood are altered by CFTR deficiency, which may be critical for Pa colonization of the lungs. However, immunological determinants that play a role in Pa colonization in CF are still poorly defined.

We **hypothesize** that human variation in cell surface receptor expression of peripheral blood immune cells associates with Pa colonization in CF patients. This hypothesis will be addressed by an unbiased comparison of cell surface expression levels of various peripheral blood cells (monocytes, lymphocytes, granulocytes) between CF patient groups who are extensively monitored at our clinical centre and display the most extreme phenotype between Pa acquisition.

We **aim** to establish associations between peripheral blood cell phenotype and Pseudomonas colonization in CF. Twenty CF patients between age 14 and 18 that display an extreme difference in Pseudomonas acquisition will be analyzed.

This proposal is an initial step that aims to understand Pa acquisition in CF patients by studying immune cell parameters. Follow up studies should focus on biomarker potential of identified markers that associate with Pa acquisition and unraveling underlying mechanism for such associations to design novel therapeutic strategies to enhance Pa clearance by the immune system. Our clinical center treats approximately 400 CF patients and we have strong collaborations with other clinical centers world wide allowing the inclusion of sufficient patient samples to more clearly define novel biomarkers that associate with predisposition to Pa acquisition. We are also generating a unique longitudinal clinical data set (lung parameters, microbiome status, and peripheral blood cell numbers) in newborn CF patients in which the predictive value of novel biomarkers can be assessed.

In summary, Pa infection is highly is variable between CF patients, but tightly associated with lung function and life expectancy. We propose that surface receptors on immune cells play an important role in Pa clearance. An unbiased analysis of a large panel of surface markers on peripheral blood immune cells of CF patients highly susceptible or insusceptible to Pa acquisition will likely determine relevant immunological pathways involved in Pa clearance. These data can lead to novel predictive markers for Pa acquisition, and the design of therapeutic interventions to limit Pa colonization.