

## THE ROLE OF ANAEROBIC BACTERIAL INFECTION IN CYSTIC FIBROSIS

Cystic fibrosis lung disease reflects a failure of innate lung defense mechanisms against chronic bacterial infection. Recently, it has become apparent that the CF airway lumen is filled with adherent mucus that is relatively hypoxic. The present proposal tests the hypothesis that the hypoxic environment of the CF airways promotes infection by obligate anaerobes as mixed infections that are pathogenic for the CF lung. Accordingly, a consortium of investigators from Northern Ireland (Stuart Elborn), the Irish Republic (Gerald McElvaney), and the U.S. (Richard Boucher) have explored this hypothesis and produced the following preliminary data: 1) anaerobes are present in the CF lung, as revealed by rigorous culture and molecular diagnostic techniques; 2) the anaerobes detected in CF lung do not reflect oral contamination; and 3) the high density (equal to *Pseudomonas*), and changes with acute exacerbation support the notion that anaerobic bacteria are pathogenic in the CF lung. The consortium will test three hypotheses that relate to the role of anaerobes in the pathogenesis of CF lung disease: 1) Specific Aim 1 will test whether there are anaerobes in the CF but not normal lung, that anaerobes and *P. aeruginosa* are acquired over similar time intervals, and that anaerobes are pathogens and not innocent bystanders. 2) Specific Aim 2 will test the hypothesis that anaerobes identified in the clinical study are pathogenic, investigating the molecular mechanisms underlying anaerobe growth and pathogenesis in vitro. 3) Specific Aim 3 will test the hypothesis that a complex environment is required in the diseased mouse lung in vivo to support anaerobic growth/infection, and that anaerobes are pathogenic if growth is established in the lung. The long-term goals of this project are to test the hypothesis that anaerobes are pathogenic in the CF lung, identify when they produce this pathogenic effect, and identify the mechanisms mediating pathogenesis. The outcome of these studies will be critical in designing strategies to improve therapy of CF lung disease, focused on such key issues as: should anaerobes be treated at all, and if so, treated in young patients prior to or after *Ps. aeruginosa* acquisition? This study will generate a bank of clinical isolates of anaerobes from CF patients that will serve for testing antimicrobial sensitivities and selecting antibiotics for future antibiotic trials to clinically test the role of anaerobes in the pathogenesis of CF lung disease.

This proposal is designed to test the hypothesis that obligate anaerobic bacteria are pathogens in the CF lung. If so, this observation would raise the possibility that they are pathogens in other major airways diseases, e.g., chronic bronchitis. Such observations might change the way physicians approach antibiotic therapy of patients with airways disease.