

Title: Novel Pharmacokinetics Treatments of CF Lung Pa Infection

PI: Goverdhan Sachdev, Ph.D.

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Abstract

Cystic Fibrosis (CF) is the most common genetic disease of Caucasians and *Pseudomonas aeruginosa* (Pa) infection in these patients is a leading cause of morbidity and mortality. The molecular mechanisms by which Pa preferentially attaches and preferentially colonizes the lungs of CF patients are mostly unknown. Pathogenesis is initiated in part, by interactions of Pa with the O-glycans in airway mucins in the lungs of CF patients. In our preliminary studies to explore the nature of the airway mucin glycans recognized by a mucoid Pa strain 8830, we showed it binds to glycoconjugates expressing the sialyl-Le-x structure and not to related glycans (Glycoconjugate J. 2007). This has led us to hypothesize that the higher density of highly sialylated and fucosylated glycans (Glycobiology 2005), especially of sialyl-Le-x epitopes, observed in airway CF mucins promotes *P. aeruginosa* adherence to CF airway mucins through saccharide-specific surface adhesins with subsequent lung colonization. To explore the basis of this interaction, we developed new methods (Nature Methods, 2005) to attach glycans containing the sialyl-Le-x structure to affinity gel and have used this approach to purify Pa surface adhesins (12, 46, 48 kDa). We have identified and characterized the 12 kDa surface adhesin. Therefore, the specific aims of this proposal are to: 1) characterize the two other 46 and 48 kDa sialyl-Le-x-specific surface adhesins from *P. aeruginosa* by proteomic analyses and prepare recombinant forms of the three major adhesins for further characterization; 2) create isogenic strains of *P. aeruginosa* with 12kDa or other 46kDa and 48kDa sialyl-Le-x specific adhesins genetically inactivated and other with this inactivation restored by gene complementation using a cloned, expressed copy of the gene, and 3) determine the inhibition of the binding of *P. aeruginosa* to the CF airway mucin by soluble synthetic multivalent neoglycoconjugates of sialyl-Le-x and human albumin and polylysine peptides. Development of glycomimetic inhibitors will open additional pharmacological approaches to prevent the binding of Pa to airway mucins of CF patients and airway epithelial cells. In view of the growing problems of bacterial resistance to conventional antibiotics, such synthetic conjugates may provide added therapeutic and/or prophylactic options to clinicians and their patients. These studies will lead to the understanding of the molecular mechanism of colonization of Pa in the lungs of CF patients and could lead to new pharmacological therapeutics for treatment of Pa lung infection in CF and limit lung damage and thus prolong the lives of CF patients.