# Polymeric Drug Delivery Systems and Biofilms in the Lung

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## Overview of Current Investigations

A biofilm is a community of microorganisms embedded in a matrix of polysaccharides and assorted proteins and nucleic acids. Biofilms can form on implanted medical devices leading to life-threatening infections. Biofilms are also found within the lungs of patients with chronic pulmonary infections including patients with cystic fibrosis (CF) and are the major cause of morbidity and mortality in this patient population. The medical treatment of such infections is complicated by the fact that the constituent microorganisms of many biofilms display far more resistance to antimicrobial agents than the same microorganisms growing as free-swimming, planktonic individuals. Consequently, the persistence of microorganisms in biofilm growth mode despite conventional antibiotic therapy poses significant health threats to numerous patient populations. This project specifically addresses the treatment of biofilms that develop in the respiratory tract.

The basic goal of this project is to develop a safe and effective drug delivery system to kill bacteria growing in biofilms in the lung. The delivery system is based upon nebulization, the process of aerosolizing therapeutic agents for delivery by inhalation to the respiratory tract. The treatment strategy is based upon silver-based antimicrobial compounds, in particular, silver carbene complexes (SCCs). Other potential therapeutic agents include silver-efflux inhibitors, anti-quorum sensing drugs, and enzymes that

degrade the extracellular polymeric substances (EPS), or structural components of the biofilm. The research is exploring the efficacy of delivering these agents both in an aqueous solution, as well as in biodegradable polymer nanospheres. Agents delivered to the biofilm in soluble form enter the biofilm through its surface. The nanospheres, on the other hand, penetrate the biofilm through its cracks and pores, and then dissolve and slowly release the therapeutic agents over time.

An interdisciplinary team of engineers, chemists, biologists, applied mathematicians, and a medical doctor are conducting the research. Members of this team synthesize novel silver carbene complexes as candidate antimicrobial agents, fabricate biodegradable polymeric nanospheres that contain silver-based complexes and other agents, perform in vitro and in vivo experiments to determine the efficacy of various compounds and delivery systems for treating biofilms of Pseudomonas aeruginosa, methicillin resistant Staphylococcus aureus (MRSA), and anthrax, and develop comprehensive mathematical models as a predictive tool for discovering effective treatment strategies. The success of the research depends in an essential way on the interplay between experimental work and mathematical modeling.

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