

Patients with sickle cell disease experience a 400 fold increased risk of severe pneumococcal infection. This risk is not shared by other encapsulated pathogens or by other anemias suggesting that there is a potentially causal relationship between severity of pneumococcal disease and the SS phenotype. This application seeks to investigate two aspects of pneumococcal infection in sickle cell disease. First we will take advantage of the presence in this SS Center of a program in pneumococcal pathogenesis and expertise in creating an SS transplant mouse model. These two programs will cooperate to characterize which step in pneumococcal invasion differs between wild type and SS mice. The steps of colonization and invasion will be dissected at the molecular level and intervention with specific receptor antagonists will be tested. We will further determine the level of protection from pneumococcal disease afforded by progressive hematologic correction by transplantation.

Second we will build on a strong history of this Center's study of the colonization of SS patients with antibiotic resistant pneumococci. The introduction of the new seven-valent conjugate pneumococcal vaccine into the SS population has not been studied. We will determine its effect on nasopharyngeal carriage with specific reference to antibiotic susceptibility and shifts away from vaccine serotypes. Further we will measure the prevalence of a new property of antibiotic tolerance emerging in clinical isolates. Tolerance prevents antibiotic killing of pneumococci and may adversely affect the outcome of infection. Spread of this property may have implications for the efficacy of continued penicillin prophylaxis in this at risk population.