Community-associated Staphylococcus aureus (CA-SA), such as USA300, the epidemic methicillin-resistant strain in the US, have led to a dramatic increase of skin and soft tissues infections over the past decade. Some of these infections are also invasive and often occur in otherwise healthy individuals. CA-SA appear to posses an enhanced capacity for both transmission and invasion, though we have limited understanding of how they spread and persist in the community. It is likely that strains adapt with minor genetic modifications to their environment and become more ecologically "fit". We have obtained proof of principle of discrete genetic adaptations over time by sequencing closely related USA300 strains, longitudinally collected from the same households. Concurrently, it appears that the originally zoonotic strain ST398 MSSA is emerging in the Northern Manhattan, without any
animal contact. It is now amongst the most prevalent strains of our clinical infectious MSSA isolates, has a remarkable ability to spread from person-to-person, and shows enhanced survival on colonized environmental household surfaces.

The overall goal of this study is to define the mechanisms of transmission and persistence of successful *S. aureus* strains as they adapt to their environmental niches, taking the examples of the well established epidemic USA300 and the evolving zoonotic strain ST398, by using a combined epidemiologic and genetic approach. Specifically, the aims of this proposal are to (1) define the functional impact on *S. aureus* fitness and environmental adaptation of recent genetic changes in USA300, (2) define the reservoirs and modes of transmission of ST398 in Northern Manhattan, and (3) determine how the pig strain ST398 has evolved as a human pathogen. We will first study in vitro fitness, survival and cell adhesion properties of mutations of the sequenced later USA300, that we hypothesized have altered the fitness and survival of these strains. We will then extend our studies to the emerging ST398 to define the basis of its transmission in Northern Manhattan. Based on a cluster-based design we will interview and culture ST398 positive subjects, their contacts and contacts of contacts to determine factors associated with acquisition and spread of ST398. Critically, these studies will provide samples for comparative sequencing and will allow for comparison of human colonizing strains, infectious strains, as well as persisting and non-persisting strains. Sequence differences will be studied on isogenic mutants in functional assays implemented in studies on USA300. We anticipate that this work will lead to the identification of genetic traits accounting for the direct person-to-person transmission of ST398 and that contribute to enhanced fitness and ecological adaptation.