Dr. Angela Gomez-Simmonds

PROJECT ABSTRACT:
Rationale: Resistance to broad-spectrum carbapenem antibiotics has spread rapidly among *Enterobacteriaceae* since the early 1990s, posing an escalating threat to medical care. While *Klebsiella pneumoniae* comprise the majority of CRE in the United States, recent evidence suggests that CRE are rapidly diversifying. This reflects the ability of carbapenem resistance genes to spread to between different strains of *Enterobacteriaceae* via mobile genetic elements, particularly plasmids. Despite their important infection control implications, the mechanisms by which these plasmids spread have not been fully elucidated. **Candidate:** As an infectious diseases clinician with a masters' degree in biostatistics, Dr. Angela Gomez-Simmonds' previous publications characterize the clinical and molecular epidemiology of CRE. Formal training in advanced bioinformatics and genomic epidemiology will be critical for the completion of the proposed research and the advancement of her career. With primary mentor Dr. Anne-Catrin Uhlemann, she has assembled a multidisciplinary advisory team of experts to guide her training and research progress. Dr. Gomez-Simmonds' long-term goal is to become an NIH-funded independent researcher using next-generation sequencing to understand links between the bacterial evolution, resistance mechanisms, and clinical epidemiology of multidrug-resistant Gram-negative nosocomial pathogens. **Environment:** The Uhlemann laboratory at Columbia University Medical Center (CUMC) has the microbiology and sequencing tools necessary to carry out the proposed research, as well as a large retrospective collection of CRE clinical isolates from diverse sites to perform genomic studies. CUMC has a strong track record of supporting the career development of young physician-scientists. **Approach:** *We hypothesize that horizontal transfer of plasmids encoding bla_{KPC}, the dominant carbapenem resistance gene in the United States, is an important contributor to the spread of CRE within hospitals*. To overcome limitations in previous genomics studies using traditional sequencing platforms such as Illumina, we will perform long-range plasmid sequencing. Plasmid-mediated transmission of bla_{KPC} will be characterized through three aims. In Aim 1 we will systematically assess the contribution of horizontal transfer to the spread of CRE in a large retrospective collection of CRE isolates collected between 2009-2016. In Aim 2 we will perform a case-control-control study to assess unique clinical risk factors associated with horizontal transfer versus clonal spread; a third control group will consist of CRE-negative patients. In Aim 3 we will determine whether hospital environmental surfaces such as sink drains are reservoirs for bla_{KPC}-harboring plasmids. Phylogenetic analyses will be used to assess links between plasmid sequences from clinical and environmental CRE and published genomes. In addition to elucidating the role of plasmids in the diversification and spread of CRE, this research may contribute to the integration of long-range sequencing in effective infection surveillance and control protocols to account for plasmid-mediation CRE transmission.