

Dr. Daniel Freedberg

This proposal details a comprehensive four year training program to expand my clinical and translational research related to loss of gastrointestinal colonization resistance and the subsequent development of multidrug resistant (MDR) bacterial infections in the intensive care unit (ICU), as well as extensive didactic and laboratory-based training in biostatistics and microbiome analysis and methodology. The central hypothesis of this research proposal is that antibiotic resistance in the ICU is a problem of the human gastrointestinal microbiome, and that loss of gastrointestinal colonization resistance within the microbiome leads to antibiotic-resistant infections in at-risk patients. Although colonization resistance cannot be directly measured *in vivo*, it can be assessed through surrogate markers: loss of normal fecal biodiversity, domination by multidrug-resistant organisms (MDROs), and a rise in the total burden of antibiotic resistance genes within the gastrointestinal microbiome. The overall goal of the research is to identify the clinical and gut microbiome-related factors that contribute to loss of colonization resistance in order to facilitate strategies to prevent gut-derived MDR infections in the ICU. To accomplish this, I will perform a prospective cohort study in ICU patients with collection of samples and clinical data at the time of ICU admission and 72 hours later. Using the samples and data collected, I will then determine (1) the clinical exposures that lead to loss of gastrointestinal colonization resistance in the ICU; (2) the specific bacterial taxa that *preserve* gastrointestinal colonization resistance in the ICU; and (3) the impact of antibiotics on the total burden of gastrointestinal antibiotic resistance in the ICU. The results of this research will delineate the key risk factors for loss of colonization resistance, and will form the foundation for future multicenter trials for the prevention of MDR infections in the ICU and in other at-risk settings. Through the proposed complementary career development plan, I will gain additional training in advanced statistical analysis, and the laboratory-based and didactic training in the analysis of the microbiome necessary in order to develop a long-term research program to understand the relationship between the gut microbiome and MDR or other opportunistic infections. Throughout this research and these career development activities, I will be mentored by a team led by Dr. Timothy Wang, an internationally recognized scientist and expert in how gastrointestinal microorganisms can cause human disease. I am committed to a career as an independent investigator in patient oriented research and have constructed my training plan to provide the knowledge and skills needed to make substantial contributions to identifying and modifying the risk factors for gut-derived infections.