Title: Exploring host:microbiome interaction phenomena through integrated in vitro human gastrointestinal co-culture models

Abstract: The gut microbiome is rapidly emerging as the nexus of human health being linked to both chronic (e.g. PTSD, Alzheimer's) and acute (e.g. diarrhea, fatigue) physiological and disease states, as well as both cognitive and physical performance. The dynamics of the gut microbiome that drives the links to physiological states can be manipulated, in part, through dietary and/or pharmaceutical supplementation, making the gut microbiome an enticing, non-invasive means to modulate Soldier health and performance. However, before realizing this opportunity, there is a need to gain an understanding of the dynamics within the gut microbiome, particularly pertaining to the multitude of cellular and chemical interactions within the host, lumen, and at the host:lumen interface. Here, we aim to create a novel, in vitro, flow-through based host:lumen model by leveraging the current capabilities and expertise of both Tufts University and DEVCOM SC to fill fundamental knowledge gaps at the host:lumen interface, specifically related to mucosal-associated bacteria and the bi-directional fate of small molecules. The flexibility of the host:lumen, integrated gut model will also allow exploration of differential interfacial dynamics as a function of healthy and stressed states. The work herein is an exciting opportunity to derive knowledge unattainable through current capabilities yet critical fundamental understanding as a basis for the gut microbiome as a gateway toward modulating Soldier health and performance.

Specific Objectives: 1) Design and create an integrated host:lumen model to simulate real-time microbial-associated interactions with host tissue; 2) Explore real-time gut-lumen interaction phenomena; and 3) Derive an understanding of host:lumen interfacial genomic and biochemical factors that drive bi-directional transport phenomena of small molecules and the host:lumen feedback loop.

Significance: Gaining deep understanding of host:lumen interaction phenomena in human studies is extremely challenging due to the lack of experimental bandwidth and cohort sizes required to compensate for differences across individual microbiomes while use of animal models has benefits, such as germ-free models for highly controlled studies and more manageable "n", although translation to human outcomes is uncertain. Here, the integrated, in vitro gut model will overcome these challenges by simulating the complexities of both the host and lumen components of the gut microbiome in a cost-effective platform with broad experimental capacity capable of managing multi-variate, well-controlled basic research studies to significantly advance the current state-of-the-art and enable derivation of unprecedented and translatable knowledge regarding host:lumen interfacial dynamics and impacts of acute stressors, relevant to both military and civilian sectors.

Potential Impact: The foundational knowledge gained will advance DEVCOM SC mission to explore and understand the functional, physiological impact of host:lumen interactions as a basis for identification and acceleration of microbiome-based solutions to keep Soldiers within the fight longer, improve recovery and maximize lethality upon exposure to acute operational stress.