Dr. Timothy Wang

OVERALL PROJECT SUMMARY

Barrett's esophagus is an increasingly prevalent, preneoplastic disorder resulting from acid/bile reflux and chronic inflammation at the GE junction. This application is a renewal of a long-standing multicenter, translational research program from Columbia University, the University of Pennsylvania and the Mayo Clinic. The team, which has been highly productive, will now focus on the role of microbiota and the tumor microenvironment in the development and progression of Barrett's esophagus and esophageal adenocarcinoma. The group has added additional collaborative sites at MIT, the Dana Farber Cancer Institute and Munich Technical University, and will utilize heavily a new Microbiome and Metabolomics Core at Penn-CHOP. Thus, the team comprises broad and unique expertise in mouse models, genomics, microbiology and clinical research. The application is built around the hypothesis that the inflammation-dependent tumor microenvironment, modulated by the GE junction microbiome, is critical for early progression of esophageal carcinogenesis. The proposal will utilize both the novel transgenic (L2-IL-1β) and innovative 3D organoid models, along with a cross-sectional study of 100 BE patients. Project 1 will study the role of microbiota and myeloid cells in the L2-IL-1β mouse model of Barrett's esophagus. This project will incorporate germ-free housing, antibiotic eradication, colonization with defined flora, myeloid cell ablation and correlative human studies. Project 2 is focused on the characterization of microenvironment drivers in BE, and will include FACS/IHC analysis of CAFs and immune cells (MDSCs/Tregs) in BE patients, along with 3D organoids in culture. The role of IL-6 in response to epithelial TP53 mutations and immune cell activation will be defined. Finally, Project 3 will seek to identify novel biomarkers and gene signatures related to the microbiome and microenvironment. The study will analyze bile acids, a product of microbes, and minimally invasive tests such as saliva/breath test/tethered capsule sponge to analyze microbes to develop screening/surveillance strategies. Overall, these projects will advance the science of the microbiome and microenvironment in BE that will hopefully lead to translational applications.