Dr. Timothy Wang

Barrett's esophagus is an increasingly prevalent, preneoplastic disorder that results primarily from gastroduodenal reflux of acid and bile. The applicant group, which includes established investigators from Columbia University, the University of Pennsylvania, and the Mayo Clinic, propose a multidisciplinary, multicenter, translational research program to study the origins and pathogenesis of the disorder. The team, many of whom have collaborated in the past, will focus on the role of chronic inflammation and bile acids in the upregulation of established and novel stem cell markers, and possible ways to target these progenitor cells. The proposal builds on extensive basic science findings, the development of novel transgenic (L2-IL-1beta) and surgical models of BE/esophageal adenocarcinoma, and preliminary analyses of human BE tissues. The groups will bring to the network a very large BE patient population, experienced Barrett's clinical investigators, and bench researchers with extensive experience with stem cells and inflammatory models of GI cancer. Three projects are proposed. Project 1 will focus on the role of Notch signaling in models of Barrett's esophagus, and will determine the effects of Notch inhibition or Notch activation on progression to dysplasia. Project 2 will seek to characterize the cell of origin in Barrett's esophagus in our mouse models. We will use constituitive and inducible mouse models of Cre expression to lineage trace active and quiescent progenitors that are upregulated in our model and in human BE. Additionally, we will carry out a pilot clinical trial using an antagonist of a G-protein coupled receptor expressed on progenitor cells upregulated in BE. Finally, Project 3 will aim to identify novel biomarkers and gene signatures in BE, correlating data sets from animal and human models, clarifying the importance of non-goblet cell columnar epithelium and changes in the gastric cardia. We will also assemble a cohort of patients undergoing radiofrequency ablation, identifying biomarkers of response to therapy and using successfully ablated patients as a novel human model to study the development of BE. Overall, these studies aim to elucidate the earliest stages and cell types that contribute to BE pathogenesis in order to better stratify risk and develop preventive therapies.
