

Defining Key Genomic Alterations in the Carcinogenesis of Colitis-associated Cancers

Principal Investigator:

- Rona Yaeger, MD - Memorial Sloan Kettering Cancer Center

Co-Principal Investigators:

- David Kelsen, MD - Memorial Sloan Kettering Cancer Center
- Adam Bass, MD - The Broad Institute of MIT & Harvard

Abstract: While inflammation has been long recognized to contribute to gastrointestinal (GI) cancer development, recent data indicate that tumors emerging in inflamed GI tissues have distinct genomic features. Despite these findings, colitis-associated cancers (CAC), which develop in the setting of inflammatory bowel disease (IBD), are treated the same as sporadic colorectal cancer (CRC), and early detection strategies for CAC merely rely on endoscopic appearance, fail to account for the distinct development of CAC, and do not clearly improve survival. In this proposal, we will characterize the progression of genomic alterations (GA) in CAC, as compared to sporadic CRC and other inflammation-associated GI cancers. We will further functionally interrogate GA specific to CAC. Our preliminary data identified key differences between CAC and sporadic CRC including: (1) near universal *TP53* mutations, commonly missense mutations with neomorphic properties; (2) recurrent alterations in genes not implicated in CRC, such as *IDH1R*¹³² mutations and *FGFR2* fusions; and (3) infrequent *WNT* pathway dysregulation. We will characterize the genomic features of progression of precancerous lesions to invasive CAC. We will functionally interrogate how GA associated with CAC cooperate with inflammation to promote cancer using diverse *in vivo* models. We will further evaluate unique potential therapeutic targets emerging from genomic profiling of CAC by functional validation using an existing panel of patient derived xenografts developed from CAC. Our ultimate goal is to define how GA drive progression to dysplasia and subsequent carcinoma with gastrointestinal inflammation, thus enabling new approaches for early detection and therapy.