Dr. Julian Abrams

PROJECT TITLE:
Use of a gastrin-receptor antagonist for chemoprevention in patients with Barrett's esophagus

SYNOPSIS OF PROPOSAL: (use only space provided below; minimum 11 point font)

Barrett's esophagus (BE) is the primary precursor lesion for the development of esophageal adenocarcinoma (EAC), and the incidence of this malignancy continues to rise at an alarming rate in western countries. Given the strong association between acid reflux symptoms, BE and subsequent EAC, gastric acid suppression with proton pump inhibitors (PPIs) is recommended for all BE patients in the hopes of reducing the risk of progression to EAC. However, this acid suppression can result in marked physiologic increases in gastrin production. Gastrin has been shown *in vitro* and *in vivo* to have many pro-neoplastic properties. In BE cells, gastrin selectively binds to the cholecystokinin-2 receptor (CCK2R), which in turn promotes cellular proliferation, inhibits apoptosis, and results in loss of cell-cell adhesion. We have previously demonstrated that elevated serum gastrin is associated with a history of high grade dysplasia and adenocarcinoma in patients with BE. As such, the obvious question is raised: does gastrin *promote* neoplastic progression in BE? We propose a multi-disciplinary approach to assess the potential utility of a gastrin-receptor (CCK2R) antagonist for the chemoprevention of EAC. YF476 is a selective CCK2R antagonist, and trials in healthy subjects have demonstrated that the drug is safe and well-tolerated. We therefore propose to conduct a randomized placebo-controlled trial of YF476 in patients with non-dysplastic Barrett's esophagus. Our hypothesis is that treatment with YF476 in patients with BE will result in a significant reduction in tissue expression of Ki67, a marker of cellular proliferation. We will also assess the effects of YF476 on the expression of other biomarkers potentially associated with the development of EAC. Additionally, we will perform decision analyses to determine the ranges of cost and efficacy for YF476 to be cost-effective for the chemoprevention of EAC. We will evaluate strategies of various combinations of YF476, PPIs, and endoscopic surveillance to determine the most cost-effective means of preventing EAC. It is anticipated that the results of these multidisciplinary studies will then merge and lead to a larger, multi-center trial with histological endpoints to investigate YF476 as a chemopreventive agent in patients with BE.