**Dr. Julian Abrams**

Title: Randomized Placebo-Controlled Trial of a Gastrin Receptor Antagonist in Barrett's Esophagus

The incidence of esophageal adenocarcinoma (EAC) has risen five-fold over the past several decades, yet the prognosis for EAC remains extremely poor. As such, EAC represents a very attractive target for chemoprevention. Barrett's esophagus (BE) is the precursor lesion for EAC, and acid reflux is a major risk factor for both BE and EAC. Virtually all patients with BE, regardless of the presence of reflux, are treated with proton pump inhibitors to suppress the production of gastric acid. However, proton pump inhibitors have not conclusively been shown to reduce the risk of progression to EAC. This may be due to the fact that acid suppression results in increased gastrin production by antral G cells in the stomach, and gastrin has numerous proneoplastic effects on BE tissue, such as increasing cellular proliferation and COX-2 expression and inhibiting apoptosis. We have previously demonstrated in BE patients that high levels of serum gastrin are associated with high grade dysplasia and EAC, and serum gastrin levels are correlated with cellular proliferation in BE. Together, these findings suggest that gastrin may in fact promote the progression of Barrett's esophagus to esophageal adenocarcinoma.

Netazepide is a novel gastrin receptor antagonist that effectively and selectively blocks the effects of gastrin. In experiments with a mouse model of BE and EAC that was developed by our group, treatment with netazepide significantly reduced cellular proliferation and expression of intestinal stem cell markers. We therefore hypothesize that gastrin receptor inhibition may reduce the risk of progression to EAC in Barrett's patients. Building directly on our prior work in this field, we have designed and begun enrollment for a phase II randomized, double-blind, placebo-controlled trial in 16 patients with BE to investigate the effects of netazepide on biomarkers associated with progression to EAC. We are currently requesting additional support to allow for the successful completion of this trial and to achieve the following Specific Aims: 1) To determine whether the gastrin receptor antagonist netazepide reduces cellular proliferation in patients with Barrett's esophagus; and 2) To determine whether netazepide reduces the expression of other markers associated with progression to EAC. In this fashion we hope to demonstrate that treatment of Barrett's esophagus patients with a gastrin receptor antagonist represents a novel and potentially effective strategy to reduce the risk of esophageal adenocarcinoma.