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**Title:** Mechanism and Prevention of the Late Onset Irinotecan-Induced Gastrointestinal Toxicity

Chemotherapy – induced gastrointestinal dysfunction is a common occurrence associated with many classes of chemotherapeutic agents. Gastrointestinal toxicity includes mucositis, diarrhea, constipation, etc. and can often be a dose-limiting complication, induce cessation of treatment and could be life threatening in cancer patients. Irinotecan is a pro-drug for first line treatment for metastatic colorectal cancer. The active metabolite of irinotecan, SN-38, induces apoptosis and causes severe late-onset diarrhea. However, treatment options for the late-onset diarrhea are limited and remain a challenge. The main treatment is loperamide, a peripherally acting mu-opioid agonist that inhibits gastrointestinal motility. In spite of high doses, loperamide is only effective in mild to moderate diarrhea, while many patients progress to severe diarrhea (grades 3 and 4). We hypothesize that irinotecan-induced mucosal inflammation drives an enhanced cholinergic-mediated secretion resulting in severe diarrhea. We will investigate the role of prototoxin, Lynx1, in modulating cholinergic excitation through nicotinic acetylcholine receptors and test whether improving epithelial barrier function mitigates irinotecan-induced inflammation and diarrhea. We will achieve barrier integrity by activation of the master cytoprotective transcription factor, Nrf2, by sulforaphane, a broccoli phytochemical. The successful completion of these studies will provide proof-of-concept for treating and preventing chemotherapy-induced diarrhea by natural and dietary means