A PROPOSED CLINICAL ASSAY TO PREDICT 5-FLUOROURACIL EFFICACY AGAINST PANCREATIC DUCTAL ADENOCARCINOMA BY UTILIZING A PRE-OPERATIVE DOSE OF XELODA

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Introduction: 5-Flourouracil (5 FU) is a widely used anti-cancer agent. Nearly 80% of 5 FU is degraded in the liver before it becomes cytotoxic to tumor cells. 5FU in cells is metabolized to fluorinated deoxyuridinemonophosphate (FdUMP) which binds and inhibits thymidylate synthase (TS). The metabolized drug, FdUMP forms a ternary complex with TS which is a distinct hallmark of 5 FU metabolism. The formation of the ternary complex inhibits TS and creates thymidylate depletion in a cancer cell and thus an eventual 'thymineless death.' TS targeting is believed to be an indicator of 5 FU effectiveness, but currently no clinical test to detect this 5 FU-induced TS modification exists.

Methods and Results: We provide the proof of principle work that this 5 FU-induced TS modification can be detected in vivo. The 5 FU-induced TS modification in a mouse colon cancer model was detected 15 minutes and up to 7 days post-treatment (see figure below). We further extended these studies to human tissue. Results show the ability to detect TS expression in human tissue via biopsy and post-operatively. In theory, a pre-operative dose of Xeloda would be a safe, effective delivery of a 5FU based drug to the tumor before tumor tissue resection. Immediately post-op tumor tissue will be used to detect TS modification (see schematic below).

Conclusions: A clinical assay, capable of assessing 5 FU targeting immediately after or before treatment, would provide clinicians with pertinent information to monitor and accordingly adjust 5 FU dosing in individual patients. We propose a small pre-operative dose of Xeloda and an analysis of TS modification as a predictive assay of 5FU effectiveness in pancreatic ductal adenocarinoma patients (see schematic below).

Reference: Cancer Biol Ther 2006 Aug 2;5(8).

Figure. In vivo detection of TS ternary complex formed upon exposure to 5FU based therapy. Theoretical trial based on previous in vivo work.