SCAF/16 01 - Targeting the Intestinal Stem Cell Niche through Energy and Metabolism Signalling, via mTOR, for Colorectal Cancer Chemoprevention

Colorectal cancer (CRC), a common cause of cancer death, is largely preventable. CRC risk factors including diabetes, obesity, and metabolic syndrome, highlight strong links with metabolism and diet. The key metabolic regulator mTOR modulates the intestinal stem cell response to nutrients to maintain homeostasis. mTOR is progressively abnormal in CRC. Hence, there is powerful rationale to capitalise on known preventive agents to realign deranged metabolism and recalibrate mutation and transformation vulnerable stem cells. Robust data indicates that aspirin and metformin greatly reduce CRC risk. I previously showed that aspirin activates AMPK (negative mTOR regulator) and inhibits mTOR in CRC cells and mouse and patient intestine(*3*). My data also showed that 33% of patients on aspirin develop CRC(*2*). Hence, the absence of biomarkers of resistance prevent their use as mainstream chemopreventives. Here, I present new compelling data that aspirin inhibits protein translation in CRC, alters epithelial-mesenchymal transition (EMT), decreases critical stem cell markers (Lgr5) and rescues the APC-associated (Wnt) cystic phenotype in human FAP colorectal organoids, inducing a wild-type (budding) phenotype. I will test the hypothesis that aspirin and metformin recalibrate aberrant stem cell metabolism, driven by excessive nutrients, to prevent pre-neoplastic phenotypes. I will identify markers of resistance in patients to define susceptible populations.