

### C3 / Padres Pedal the Cause 2020

“Microbe-Associated Colorectal Cancer (M.A.C.S)”

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### SCIENTIFIC ABSTRACT

Although inflammation driven by microbes is believed to be a key contributor to the initiation and progression of colorectal polyps to cancers (CRCs), how that happens, and which microbes are capable remain unknown. Here, a disease map of colon polyps was built by querying human transcriptomic datasets using unbiased computational approaches. It revealed that suppression of the metabolic master-regulator, AMPK $\alpha$ 2 (PRKAA2) and its ability to orchestrate a specialized polarity pathway are one of the earliest steps in adenoma initiation, whereas an IL8- predominant proinflammatory signature, leakiness, and Wnt-driven EMT/stemness are late events during adenoma initiation and progression. These events were recapitulated when mouse and human enteroid monolayers were infected with anaerobic, CRC-associated bacteria *Fusobacterium nucleatum* (FN). Analyses of transcriptomic datasets from time-lapse models of polyp-to-CRC and colitis-to-CRC progression showed that the unique set of late events imply higher risk of progression to CRCs, spurring the name MACS (Microbe-associated CRC-signature). It is hypothesized that: loss of epithelial polarity is an early event in CRC initiation and that activation of the specialized polarity pathway with AMPK-agonists is a promising strategy for CRC chemoprevention, and that the MACS program could help identify which host epithelium is at risk for infection-inflammation-driven CRC progression and which microbes carry the highest potential to fuel such progression. This multi-PD/PI proposal will use the powerful synergy of the expertise of three PIs to test both hypotheses through 3 Aims: (1) Model infection-inflammation-driven polyp- to-CRC progression using normal and genetically predisposed human organoids in co-culture with cancer-associated microbes and patient-derived fecal slurry; (2) Determine the prognostic impact of the MACS via the development of a 'polyp-print', i.e., an IHC-panel of high ranking genes within MACS that can identify mucosa at greatest risk for infection-inflammation-driven polyp-to-CRC progression. Ultimately, understanding of the human microbiome's relationship with cancer and its precursor lesions could transform immune-modulating therapies.

## **LAY ABSTRACT**

This proposal revolves around the discovery, characterization, disease modeling and harnessing the diagnostic and therapeutic potential of a novel tumor suppressive pathway in the gut that normally protects the gut barrier from the luminal microbes but is lost during the initiation of colon cancers. The combined synergy of several transdisciplinary approaches is used to reveal when and how the microbes may alter host cell properties to ultimately fuel cancer initiation. The proposal also promises to deliver a therapeutic target/therapy for protecting the gut from these cancer-causing microbes and halt the formation and progression of colon polyps and to validate a novel set of markers for predicting which polyps in the colons are at highest risk for progressing to colon cancers.