Pre-Cancer States and Drivers of Cell Transformation in the Gastrointestinal Tract

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Scientific Abstract:

Cancers in the gut are typically preceded by a distinct pre-neoplastic metaplasia→dysplasia cascade. Genomic studies have solidified the role of predisposing host genetic factors that favor cell transformation, but such insights are yet to be integrated with environmental factors unique to each gut segment or translated into markers that can objectively assess/track cancer risk and therapeutics that mitigate the same. In this **multi-PD/PI** proposal, a **transdisciplinary team** of investigators seek to unravel the fundamental cell and molecular mechanisms underlying normal→metaplasia→adenoCa progression in the esophagus (**Project #1**), stomach (**Project #2**) and the colon (**Project #3**) by leveraging two **unique technological assets** provided by **two CORE components** within the UC San Diego Institute for Network Medicine: The _first_ is an AI-enabled creation of computational **maps of the cellular continuum states built using transcriptomic datasets** from human samples; these are created and validated at the Center for Precision Computational Systems Network. The _second_ is an adult stem-cell derived organoid-based disease modeling approach that includes map-informed additional dimensions (organoids, acid/bile, microbes, immune and stromal cells); these are created and validated by the HUMANOID™ CoRE. Leveraging the two assets, **preliminary work** has formally defined with gene signatures pre-neoplastic states in the three segments of the gut and identified drivers of cell transformation, exposed basis for racial disparity, provided guidance for precision disease modeling and most importantly, exposed high-value targets to reset the network and halt cell transformation. Studies proposed in 3 projects seek to systematically validate these findings in human pre-clinical disease models. Computational tools, datasets, models, biomarkers (gene signatures) and therapeutic will be rapidly released and are expected to spur new discoveries geared to prevent GI cancers.

Lay Abstract:

Cancers that begin in epithelial cells may have a precancerous state before they turn into cancer. This is particularly true in both the upper and lower parts of our gastrointestinal (GI) tract. What pre-cancer states allow is a chance to intervene, i.e., prevent cancer and not just treat our way out of it. The primary positive outcome of cancer screening is the reduction of cancer by detecting and treating cases of pre-cancer before they progress to cancer. In 2019, the American cancer Society estimated that if people changed their lifestyle and followed cancer screening guidelines, the challenge goal of reducing cancer death rates in the United States 40% by 2035 could be achieved. Achieving this goal could lead to 1.3 million fewer cancer deaths from 2020 to 2035. Although we have known of such pre-cancer states, there are **two urgent and unmet needs**: **(i)** incomplete knowledge of what drives pre-cancer to cancer progression in each environment; such knowhow would spur the development of biomarkers to define, measure and track the 'risk' of such progression; (ii) inability to therapeutically intervene; such interventions will allow us to 'act' during surveillance. This proposal uses an off-the-beaten path

transdisciplinary approach to fulfil these two needs. Findings are expected to spur the development of biomarkers for risk assessment and therapeutics to mitigate risk in the **short term** and enable patients for judicious use of cancer screening programs, which is expected to translate to cancer prevention in the long term.