

C3 / Padres Pedal the Cause 2018

“Epigenetic Profiling of Endometrial Cancer”

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SCIENTIFIC ABSTRACT

Endometrial cancer (EC) is the fourth most common cancer in women. Early stage disease can be effectively managed with surgery, followed by adjuvant radiotherapy and/or chemotherapy as necessary. However, effective therapies are lacking for women with advanced disease; the median survival among patients with metastatic or recurrent endometrial cancer is < 1 year [1]. As such, there is a critical need for targeted therapies. Activating mutations in PIK3CA are common, and co-occur with loss-of-function mutations in PTEN in Type I endometrioid and TP53 in Type II serous-like EC. However, these driver events are not associated with actionable targets. Thus, alternative methods are necessary to identify molecular targets and pathways that are key dependencies in EC. We hypothesize that epigenetic profiling can be used to classify ECs and to identify subtype-specific cancer dependencies. We will perform super-enhancer and DNA accessibility profiling on 20 EC samples from UCSD Moore's Cancer Center to define molecular subtypes that have shared regulatory circuitry. We will further identify genes associated with high enhancer activity ('super-enhancers') that we propose will have essential function in specific EC subtypes. These studies will provide a novel classification system that could be used in determining diagnosis or prognosis and will identify targets that could be leveraged for the development of targeted therapies.

LAY ABSTRACT

Endometrial Cancer is the fourth most common cancer in women and the most commonly diagnosed gynecologic cancer, and is rising in both incidence and mortality. While the prognosis for patient with early stage EC is quite good, those presenting with advanced stage or recurrent disease have a more guarded prognosis. Treatment often involves surgery to remove the uterus and other affected organs. Radiation and/or chemotherapy are sometimes required to help improve outcomes. Despite advances in surgical management and therapeutics, the 5-year survival for patients with advanced stage or recurrent disease approaches 50% and represents a significant unmet clinical need. In an effort to improve outcomes, researchers are looking to leverage knowledge of genetic events caused by mutations in the DNA sequence that promote or “drive” EC. This approach is limited, however, by the effectiveness of targeted therapies for each “driver” event. Indeed, many genetic drivers are non-targetable. Alternatively, we hypothesize that the epigenetic signature of EC will reveal many more genes with potential “driver” activity based not on genetic mutation, but modifications at regulatory

sequences affecting gene expression. Our approach is to profile 20 EC samples from patients treated at the Moores Cancer Center, UC San Diego using next-generation sequencing methods. These data will be used to classify ECs into subtypes and to identify genes on which each subtype depends. Our goal is to develop a classification system based on epigenetic features that will improve diagnosis and help identify novel treatment strategies for EC.