UC San Diego
MOORES CANCER CENTER

2021 Jawsome Shark Tank – Multidisciplinary Pilot Project Program

Targeting the NRF2-EZH2-stimulated metabolic switch in human PDAC

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Scientific Abstract:

Despite relatively advanced understanding of pancreatic ductal adenocarcinoma (PDAC) etiology and pathogenesis, therapeutic approaches to this highly lethal malignancy are limited and have barely improved in the past 20 years. Cancer initiating *KRAS* mutations generate pancreatic intraepithelial neoplasia 1 (PanIN1) lesions that remain quiescent in most individuals, but in response to stress and tissue injury they start proliferating and progress to invasive PDAC through unknown mechanisms. **Our study is based on an innovative ex vivo system in which precursor PanIN1 lesions can be converted to malignant PDAC.** With this system we have identified that PanIN1 lesions harboring oncogenic *KRAS* mutations progress to invasive PDAC upon encountering environmental challenges that activate the NRF2 transcription factor, which in turn induces the epigenetic regulator EZH2. The NRF2-EZH2 module triggers a metabolic reprogramming cascade, which sustains elevated cell proliferation and bypasses stroma-imposed nutritional restriction. Thus, compounds that inhibit either NRF2-induced EZH2 expression or critical lipid metabolizing enzymes downstream of the NRF2- EZH2 module should interfere with PanIN1 to PDAC progression, providing novel options for **PDAC prevention, early interception and treatment**.
Three **Specific Aims** will be pursued:

1. Test the hypothesis that NRF2-EZH2 stimulated lipid metabolism and induction of macropinocytosis initiating proteins are required for human PDAC development and progression.
2. Identify druggable transcriptional targets downstream of the NRF2-EZH2 module in human PDAC.
3. Evaluate the effect of inhibitors of lipid uptake/metabolism and macropinocytosis initiating proteins as monotherapy or in combination with other drugs on human PDAC PDX growth and survival.

Lay Abstract:

Pancreatic ductal adenocarcinoma (PDAC), has an extremely poor prognosis, as it is difficult to detect at early stages. Treatment options are few and have barely advanced in the past 30 years. **It is therefore essential to identify more effective treatments for this deadly disease, but even more effort should be placed on detection, prevention, and early interception.** Well-established risk factors increase the chance of pancreatic cancer because of tissue damage and imbalance between the production and elimination of free radicals (oxidative stress). Although the majority of diagnosed PDACs have somatic mutations in the *KRAS* oncogene, such mutations generate premalignant lesions, pancreatic

intraepithelial neoplasia (PanIN1), most of which never become cancerous, unless they experience further stress and challenges. Improved understanding of the mechanisms that lead to PDAC establishment can be gained from a **novel experimental system we established in which oxidative stress converts preneoplastic PanIN1 lesions to malignant progenitors under well controlled in-vitro conditions.** Using this system, we have identified two proteins, NRF2 and EZH2, that collaborate to reprogram the metabolism of preneoplastic cells and endow them with malignant features that are supported through enhanced energy generation. We will test whether molecules that inhibit the activity of these metabolic regulators can block malignant conversion either alone or in combination with gemcitabine, the main drug used to treat PDAC. Cancer cells rapidly develop resistance to anti-cancer drugs, but they should find it harder to resist treatments that will cut off their energy supply lines and starve them to death.