UC San Diego
MOORES CANCER CENTER

2023 MCC Cancer Biology and Signaling Pilot Project Award

A small molecule CSC differentiating agent for PDAC and TNBC

Stephanie Fraley, PhD

Scientific Abstract:

Cancer stem cells (CSCs) are directly responsible for recurrence, metastasis, and multidrug resistance of multiple tumor types, including pancreatic ductal adenocarcinoma (PDAC) and triple-negative breast cancer (TNBC). PDAC is one of the most aggressive solid tumors, characterized by a five-year survival rate less than 8%, and its resistance to treatment is conferred by CSCs. TNBC is also highly aggressive, lacks targeted therapy options, and is associated with a higher risk of early metastasis and poorer outcomes than other breast cancer subtypes. These two diseases disproportionately impact people in minority populations. We have identified a small molecule, CR-22, and several highly similar analogs that are potent inducers of CSC differentiation and mesenchymal-to-epithelial transition (MET). Treatment of PDAC and TNBC cell lines and patient-derived organoids with these compounds significantly enhances their susceptibility to chemotherapy. In Aims 1 and 2, we will establish the *in vivo* efficacy of CR-22 to eliminate CSCs in mouse models of PDAC and TNBC by conducting a limiting dilution tumor initiation (LDTI) to measure frequency of CSCs within each population. In Aim 3, we will further assess on-target effects of CR-22 *in vivo* by comparing CSC differentiation status, immune infiltration, and stromal architectures of vehicle and CR22-treated tumors. The successful completion of this pilot study will yield data substantiating the *in vivo* efficacy of a lead compound to eliminate CSCs of TNBC and PDAC. This data will directly address the primary critique from reviewers of a larger grant proposal, thereby enabling us to acquire translational funding.

Lay Abstract:

We have discovered a molecule that blocks the growth of PDAC and TNBC and makes them susceptible to chemotherapy. PDAC is highly aggressive and responds poorly to clinical chemotherapies. Survival for most PDAC patients is measured in months. TNBC is also highly aggressive, lacks targeted therapy options, and is associated with poorer outcomes than other breast cancer subtypes. These features are largely driven by cancer stemness. Cancer stemness is a property that confers cancer cells with the ability to self-renew. This is the direct cause of tumor development and contributes to tumor malignancy by enabling recurrence, metastasis, heterogeneity and multidrug resistance. The molecule we discovered inactivates this tumor aggressiveness by targeting cancer stemness. Previous major clinical efforts focused on inhibiting cancer stemness pathways have failed in patients with PDAC and TNBC tumors. In contrast, our molecule works by overactivating these same signaling pathways, representing a promising new way to treat and inactivate cancer stem cells. In this proposal, we will test the effect of the molecule on stemness in tumors implanted into mice. This will allow us to assess the ability of the molecule to work in a complex living system. If successful, this proposal will enable us to acquire funding for additional drug optimization and subsequent clinical trials. With sufficient follow-

on funding for our studies, the molecule could reach the clinical trial phase within 4 years. We hope this work will lead to a potentially life-saving treatment for PDAC and TNBC cancer patients.