“Novel lamin-binding ligands for the treatment of triple negative breast cancer”

Xiangshu Xiao, Ph.D., Associate Professor, Physiology & Pharmacology, Knight Cancer Institute

The goal of this project is to develop small molecule modulators of nuclear lamins as potential therapeutics for triple negative breast cancer. TNBC is subtype of breast cancer lacking expression of estrogen receptor (ER), progesterone receptor (PR) or human epidermal growth factor receptor 2 (HER2). Although targeted therapies exist for ER and HER2-positive breast cancer patients, the only available systemic therapies for TNBC are the conventional cytotoxic chemotherapies that lack sufficient efficacy and safety. Therefore, there is an urgent need to develop novel nontoxic TNBC therapies that are more efficacious and safer. We recently developed a novel class of compounds that have demonstrated selective toxicity in TNBC cells over normal human cells. The prototype of this class of compounds is called lamin-binding ligand 1 (LBL1). Further mechanistic investigations of LBL1 showed that it directly binds to nuclear lamins leading to inhibition of DNA double-strand break (DSB) repair. While LBL1 shows in vitro promise as a novel therapy for TNBC, it does not possess appropriate drug-like properties to achieve pharmacologically relevant concentrations in vivo. In this application, we will take an integrated medicinal chemistry and pharmacology approach to identify an appropriate drug candidate for further preclinical and clinical evaluation.