

Epithelial ovarian cancer (EOC) is the most common cause of gynecological cancer death. Each year, an estimated 230,000 women are diagnosed with EOC globally, and 150,000 women die of the disease. Ovarian cancer ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system. Ovarian clear cell carcinoma (OCCC), a subtype of ovarian cancer, is the second most common type of ovarian cancer affecting approximately 10-13% of women with ovarian tumors. OCCC is also the predominant histologic type of gynecological malignancy that harbors activating mutations within the telomerase reverse transcriptase (hTERT) promoter, causing its increased expression. The telomerase (hTERT) gene is hyperactive in many cancers and has been identified as a potential target for treatment. Although this led to multiple telomerase-targeting approaches, disappointingly, none have been successful in clinics. To circumvent this concern, our team has applied a genetic approach called synthetic dosage lethality (SDL), to exploit hTERT overexpression to identify potential targets to treat cancer. SDL is a genetic concept, where a normally non-lethal gene inactivation kills cells only in the context of overexpression of another gene like hTERT. My project aims to apply this concept to treat hTERT-overexpressing cancers and specifically, ovarian cancer. Our laboratories have used lentiviral-based, pooled CRISPR/Cas9 and pooled shRNA-screening platforms to systematically query the entire genome and recently identified several SDL partners of hTERT. These potential partners will be validated using a novel CRISPR-based strategy in an in vivo pooled screen, which is already in progress. We also plan to apply these therapies in combination with existing therapies to amplify the efficiency of treatment against cancers. The results will identify new targets exploiting hTERT overexpression and provide preclinical evidence to support the development of novel OCCC therapies.