**Creativity & Innovation**

We discovered a novel galectin-1 inhibitor, LLS2, a pharmaceutically active heterocyclic compound **(patent application No.: 62/318,085)**. LLS2 can efficiently kill the cancer cells. Its target protein is galectin-1 which is a 14 kDa lectin, one of a galectin family with an affinity for β-galactosides participated in variety of cellular process including cell proliferation, apoptosis, cell cycle, and angiogenesis. High expression of galectin-1 is directly implicated in the process of tumorigenesis. Galectin-1 is involved in cancer progression and also associated with a poor prognosis in prostate cancer, lung cancer and ovarian cancer. Intracellular galectin-1 binds to oncogenic H-Ras and activates pERK signaling pathway, resulting in cell transformation. Furthermore, galectin-1 was reported to mediate cell migration through AKT pathway in clear cell renal cell carcinoma. In prostate cancer, AKT and ERK signaling pathways were reported to act additively in cell culture and synergistically in vivo to promote androgen independence. Given the fact that galectin-1 stabled membrane-associated GTP-Ras (activated form), which is a upstream regulator of ERK and AKT signaling pathways. Taken together, galectin-1 shows an excellent therapeutic target for prostate cancer treatment.

**Evidence Base & Effectiveness**

Anti-galectin-1 therapeutic strategies represent an exciting avenue for cancer treatment. We discovered a novel galectin-1 inhibitor, LLS2. We have demonstrated that binding of LLS2 to galectin-1 decreased membrane-associated H-, K-Ras and contributed to the suppression of RAS/MAPK pathway, an important ongenic pathway. We have also found that LLS2 synergizes the anticancer effects of paclitaxel (PTX), both in vitro, and in vivo cancer model. Molecular modeling studies suggest that LLS2 binds to the interface between the dimeric galectin-1 subunit, and is within 6 Å from the β-galactoside binding pocket. Those data has been submitted to publish and filed for patent application **(patent application No.: 62/318,085)**. LLS30, a new class of small molecule targeting galectin-1 that has been demonstrated in our laboratory that they are highly active in prostate cancer xenograft models, particularly when given in conjunction with docetaxel, a first line treatment for CRPC patients. *In vivo* study, LLS30 suppressed tumor growth alone and can potentiate the anti-tumor effects of docetaxel leading to the complete tumor regression in mice with implanted prostate cancer xenograft. No apparent side effects have been observed with such treatment. Most important, LLS30 can enhance response to androgen deprivation therapy.

**Value to public**

Prostate cancer is the most frequently diagnosed cancer in North America. Surgery and radiation are the main treatments for prostate cancer patients. For recurrence or metastatic diseases, hormone therapy will be used for patients. Hormone therapy for prostate cancer is also known as androgen deprivation therapy. Prostate cancer cannot grow without androgens. Hormone therapy decreases the amount of androgens in a man's body and can slow the growth of the cancer and even shrink the tumor. However, poor prognosis was observed when prostate cancers are no longer responding to hormones decrease. That is castration resistant prostate cancer (CRPC). Both abiraterone and enzalutamide are Food and Drug Administration-approved for the treatment of CRPC. Unfortunately, when prostate cancer becomes resistant to one drug, the subsequent response rate to the other drug is 20% or less. Therefore, there is clearly an unmet need to address this resistance.

**Usability**

Unlike many chemotherapeutic agents that are non-specific and associate with many toxic side effects, LLS30 kills tumor cells by targeting galectin-1, which is overexpressed in CRPC tumors. Besides, Androgen receptor (AR) activation is critical in promoting prostate cancer cells to androgen-independent prostate cancer, and LLS30 markedly reduces AR signaling, LLS30 may enhance response to androgen deprivation therapy by preventing or delaying the development of androgen-independent prostate cancer.

**Functional Product**

We propose to conduct a clinical trial to determine the efficacy and toxicity of combination therapy with LLS30 and Hormone therapy. This will greatly speed the development of viable treatment strategies to overcome resistance to hormone therapy.