



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170245

Project Title:
Discovery of antibody-drug conjugates targeting a receptor broadly expressed in solid tumors

Award Mechanism:
Bridging the Gap: Early Translational Research Awards

Principal Investigator:
Liu, Qingyun

Entity:
The University of Texas Health Science Center at Houston

Lay Summary:

Antibody-drug conjugates (ADCs) are monoclonal antibodies (mAbs) that are covalently linked to cell-killing drugs and have emerged as a major modality in anti-cancer treatment. This approach combines high specificity of mAbs against their antigen targets with highly potent cytotoxic drugs, resulting in "armed" mAbs that deliver the payload (drug) to tumor cells with enriched levels of the antibody target. As antibody engineering and linker-payload optimization are becoming more and more mature, the discovery and development of new ADCs is increasingly dependent on the identification and validation new targets that are suitable to this approach. LGR4 is a seven transmembrane domain receptor with highly upregulated expression in all major types of solid tumors, including colorectal, liver, lung, and ovarian cancers. Notably, this receptor is rapidly internalized into intracellular vesicles in a constitutive fashion. The highly upregulated expression of LGR4 in tumor cells and its robust internalization makes it a strong target for ADC development. We have demonstrated that ADCs targeting LGR4 have excellent potency and efficacy in inhibiting the growth of cancer cells with high expression of the target. In this application, we seek funding to further the research and development efforts to create multiple ADC candidates targeting LGR4 for clinical development. Specifically, we will improve the characteristics of the antibodies and evaluate various linker-drug designs followed by testing the candidates in animal models of cancer. The final goal is to create two preclinical candidates with excellent safety and efficacy that are ready for future development as therapeutic leads. The work may lead to the launching of a novel target therapy that will have major impact on care of a large population of patient with currently intractable cancers.