Award ID:
RP150640

Project Title:
Drug Conjugates of anti-LGR5 Antibodies as Novel Therapeutics for Destroying Cancer Stem Cells

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
The University of Texas Health Science Center at Houston

Lay Summary:

Research has shown that within several different malignant tumors types there exists a subpopulation of cancer cells that behave like normal stem cells. These cancer stem-like cells (CSCs) can renew themselves and sustain the cancer, much like normal stem cells repopulate and maintain our organs and tissues. CSCs can drive tumor growth, metastasis, and resistance to anti-cancer therapies. Since CSCs are often not entirely eliminated by conventional treatments, they can regenerate the tumor and potentially metastasize, leading to a decline in patient survival. Thus it is essential to develop a new generation of therapies that can target and destroy CSCs. The LGR5 receptor resides at low levels on the surface of normal stem cells yet is highly expressed in colon, liver, and ovarian cancers and CSCs of many other solid tumors. We propose to develop an innovative anti-LGR5 antibody-drug conjugate (ADC) that will locate and kill CSCs similar to a guided missile. This ADC will incorporate a chemical toxin that is only released once it enters target cells with high levels of LGR5, like CSCs. Our previous studies have shown that LGR5 is continuously and rapidly internalized into the cell, making it an exceptional transit for fast and specific delivery of ADCs into CSCs. A series of anti-LGR5 ADCs will be generated using two functionally different antibodies and two distinct chemical linkers to incorporate the toxin. We will test the ability of the ADCs to precisely bind and destroy LGR5-positive cancer cells. Based on these results, a lead ADC will be selected for evaluation of anti-tumor effects in a xenograft tumor mouse model. This project will provide preclinical proof-of-concept for the feasibility of the future development of an anti-LGR5 ADC. A CSC-targeted ADC could be a breakthrough treatment to eradicate residual tumors and metastasis, and more importantly, prolong overall quality of life and survival for a large number of cancer patients.