CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP120214

Project Title:
Clinical Translation of Therapeutic siRNA in Solid Malignancies

Award Mechanism:
Individual Investigator

Principal Investigator:
Coleman, Robert L

Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Ovarian cancer remains the deadliest of all gynecologic malignancies. More than 75% of women diagnosed with the disease have advanced stage, for which, the majority develop recurrence. Tragically, recurrent disease is rarely (<1%) cured despite surgical and pharmacological interventions (including biologically-targeted agents), which is driving the need for innovative and novel therapeutic approaches. RNA interference (RNAi) is a normal regulatory process by which individual cells control the functionality of genes by producing short RNA fragments (siRNA) which, when bound, can cause gene repression or degradation. We have developed a systemically deliverable siRNA therapeutic (Epharna™), which takes advantage of this process. Our target, EphA2, is a gene that is overexpressed in several cancers, including ovarian, uterine and pancreatic, is associated with a poor prognosis, is generally absent from normal adult tissues, and when silenced leads to tumor regression in animal models. With guidance from the U.S. FDA, we designed and completed formal toxicology evaluation of Epharna™ in two vertebrate animal models. No adverse toxicity was observed in either model, clearing the way for human investigation. We propose a phase I clinical trial to evaluate the ability of Epharna™ to hit its target (EphA2) in tumor tissue, and do so safely. We will be evaluating how Epharna™ is distributed throughout the body and its effects on circulating biomarkers and imaging. Our novel Phase I clinical trial is guided by a unique efficacy/toxicity statistical algorithm (EffTox™), which considers siRNA getting into tumor tissues, along with, any toxicity observed at each dose level, and will maximize the number of patients treated at potentially effective doses. Successful administration of this type of therapy will open the door to a new class of therapeutics, particularly of those genes which are difficult to target. Importantly, the scope could extend beyond oncology.