CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP121035

Project Title:
Development and Pre-clinical Testing of Therapeutic MYCN Vaccine

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

The overall goal of project-3 is to develop a safe and effective immunotherapy of neuroblastoma (NB) by targeting MYCN oncogene with a novel type of cancer vaccine. MYCN is a causative oncogene in MYCN-amplified (MYCN-A) NB, the most deadly type of the disease. MYCN represents a nearly ideal target for immunotherapy since it is highly expressed in the malignant neuroblasts, essential for their survival, and not detectable in normal tissues after birth. We recently reported a new type of oral cancer vaccine that uses type-3 secretion system of Salmonella to translocate tumor-associated antigens into the cytosol of antigen-presenting cells. Our new MYCN vaccine carried by an attenuated Salmonella showed potent therapeutic efficacy against tumor transplants derived from a TH-MYCN transgenic mouse. To eliminate the risk of oncogenesis associated with the vaccine-delivered MYCN protein, MYCN transcriptional activity has been irreversibly abrogated via site-directed mutagenesis without affecting vaccine immunogenicity. The anti-tumor efficacy of this MYCN vaccine was further enhanced by a ligand for Natural Killer T (NKT) cells, 7WD8-5 which serves as an adjuvant. Therefore, we hypothesize that a Salmonella-based oral MYCN vaccine can be safe and effective in patients with MYCN-A NB. The vaccine immunogenicity and therapeutic efficacy may further be enhanced by the use of NKT ligand, 7WD8-5 as an adjuvant. The following specific aims will address our hypotheses: 1) to optimize the components of SPI2 vector and generate a GMP grade MYCN vaccine (years 1-2); 2) to evaluate the safety, immunogenicity, and potential anti-tumor efficacy of oral attenuated CVD908-MYCN vaccine in patients with relapsed/refractory NB (years 3-5); 3) to evaluate the mechanistic basis and the therapeutic potential of combined use of MYCN vaccine with the NKT cell ligand, 7WD8-5 as an adjuvant (years 3-5). We will use established murine models of NB that are shared by all projects of the Program. The vaccine will also be evaluated in combination with new therapies that target MYCN proteasomal degradation and MYCN-mediated stem-cell signaling developed in Project-1 and -2, respectively. The vaccine will be manufactured to clinical standards in our GMP facility and tested in a phase-I clinical trial at our clinical care center. The resulting product should be simple to produce, easy to administer and have low toxicity with curative potential for children with MYCN-A NB.