SAA - SEATTLE

2020 GRANT AMOUNT: $450,000

GRANT RECIPIENT: Meghan Flanagan, MD, MPH

PROJECT: Association of HSD3B1 (1245C) genotype with recurrence among post-menopausal women with estrogen receptor-positive, HER2-negative breast cancer.

Project Details: Endocrine (antiestrogen) therapy reduces the risk of recurrence and improves mortality among women with hormone-receptor positive breast cancer. However, approximately one-quarter of women are inherently resistant or develop resistance to endocrine therapy. A similar process occurs in prostate cancer with resistance to androgen deprivation therapy. One putative mechanism for this is a germline variant in HSD3B1, which codes for an enzyme that catalyzes the rate-limiting step in the conversion of adrenal androgen precursors to dihydrotestosterone. This results in androgen receptor activation leading to worse progression- free survival. We hypothesize that in women with postmenopausal estrogen-receptor positive breast cancer, this mutation may lead to endocrine therapy resistance and higher rates of recurrence and/or progression. We propose to evaluate associations between HSD3B1 (1245C) variant and recurrence among women with early stage (operable) post-menopausal ER+ HER2- breast cancer. Ultimately, this research may allow us to identify women with innate endocrine resistance, and develop novel therapeutics and treatment strategies.

GRANT RECIPIENT: Dr. Jordan Gauthier

PROJECT: Factors associated with failure of CD19 CAR-T cells in diffuse large B cell lymphoma

Project Details: We have reported high response rates in patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) treated on our clinical trials with autologous CD19 specific chimeric antigen receptor (CAR)-modified T (CD19 CAR-T) cells, manufactured in collaboration with the Seattle Cancer Care Alliance Cellular Therapy Laboratory.1-6 CD19 CAR-T cell therapies have created a paradigm shift in DLBCL management; yet, responses are not complete or not durable in most patients, and many responders will subsequently relapse and die from their disease. In this proposal, we will investigate two factors potentially critical to failure of CD19 CAR-T cell therapy for DLBCL: a) T cell dysfunction, impeding the generation of functional CAR-T cells during manufacturing; b) the suppressive tumor microenvironment (TME). Our aims are: i) to determine if evidence of T cell exhaustion in the leukapheresis product prior to treatment is associated with failure to achieve CR after CD19 CAR-T cell therapy for DLBCL; ii) to determine if transcriptional evidence of T cell exhaustion in the DLBCL TME before treatment associates with failure to achieve CR after CD19 CAR-T cell therapy. Our studies will better characterize T cell dysfunction and the TME as core mechanisms of failure of CD19 CAR-T cells, and identify potential targets to improve outcomes of CAR-T cell therapy for DLBCL.

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GRANT RECIPIENT: Sita Kugel, PHD

PROJECT: Exploring novel functions of HMGA2 in pancreatic cancer

Project Details: Pancreatic Ductal Adenocarcinoma (PDA) is an extremely lethal disease which is likely to become the second leading cause of cancer-related deaths by 2030. Over the last several decades, researchers have come to the conclusion that PDA tumors are genetically very similar both between patients and also within the same patient when comparing the primary tumor to a metastasis. However, we know that pancreatic cancer is much more complex given that patients respond very differently to chemotherapy. In an effort to understand these differences, researchers have more recently been characterizing the transcriptional profiles of PDA tumors. This work led to the discovery that there are two distinct transcriptional subtypes of pancreatic cancer: classical/pancreatic progenitor and quasi-mesenchymal (QM)/basal/squamous. The QM PDA subtype is more aggressive and has the worst overall survival. Understanding what defines each subtype, their susceptibilities and mechanisms of resistance will help to identify new targeted therapies or combination therapies and lead to more treatment options for this devastating disease. Our lab has discovered that the QM PDA subtype expresses high levels of high-mobility group (HMG) protein A2 (HMGA2) and has evolved mechanisms to dramatically increase protein translation over the classical PDA subtype raising the intriguing possibility that the aberrant activation of HMGA2 increases protein translation and may be one mechanism by which PDA attains the highly aggressive QM phenotype. Here, we propose specific aims to elucidate the role of HMGA2 in regulating pre-tRNA transcription in QM PDA and to determine the potential role of HMGA2 in tRNA processing.

GRANT RECIPIENT: John K. Lee, MD, PHD

PROJECT: Development of STEAP1 chimeric antigen receptor T cell therapy for Ewing sarcoma

Project Details: Ewing sarcoma (ES) is a soft tissue/bone cancer with 200 newly diagnosed adolescents/young adults per year in the United States. Patients with metastatic dissemination face a very grim prognosis as available treatments are unable to eradicate the disease. New therapeutic approaches are needed. Immune therapies are transforming cancer medicine as they can provide enhanced specificity and potency beyond what is achievable with chemotherapy. Chimeric antigen receptor (CAR) T cell therapy is one technology that has produced astounding results in hematologic malignancies and is developing early traction for solid tumors. We have previously developed and validated the activity of a CAR with specificity for the cell surface antigen STEAP1. STEAP1 is highly expressed in ES and prostate cancer while demonstrating limited expression in normal human tissues. In this project, we will characterize the activity of STEAP1 CAR T cells against human ES cell lines with varying levels of STEAP1 expression. Importantly, we will investigate the therapeutic efficacy of STEAP1 CAR T cells in vivo using highly relevant orthotopic and metastatic models of ES. If successful, these studies will help lay the groundwork for the development and clinical translation of a first-in-field STEAP1 CAR T cell immunotherapy for ES.

GRANT RECIPIENT: Jonathan G. Sham, MD

PROJECT: Novel Drug-eluting Biopolymer to Reduce Pancreatic Fistula and Improve Outcomes After Pancreatic Surgery

Project Details: Pancreatectomy is the mainstay of any potentially curative treatment regimen for pancreatic cancer. Despite an overall improvement in the safety of pancreatic surgery over the past several decades, the morbidity of pancreatectomy remains exceedingly high. The most significant complication after pancreatic surgery is postoperative pancreatic fistula (POPF), which occurs in up to 60% of cases. POPF can lead to intra-abdominal infection, uncontrolled hemorrhage, sepsis, and even death. When it occurs, POPF nearly doubles the direct healthcare costs of pancreatectomy and is independently associated with a significant reduction in overall survival. Multiple surgical and pharmacologic interventions to decrease rates of POPF have been studied, unfortunately none have proven effective. We herein propose the development of a novel biocompatible, biodegradable, thermoresponsive polymer containing octreotide-eluting microspheres with the goal of reducing the incidence of POPF and improving patient outcomes after pancreatic surgery. The use of a biopolymer, poly(N-isopropylacrylamide) (PNIPAM), is an innovative method to prevent leakage of pancreatic juice from the cut surface of the gland, while the suspended octreotide-eluting microspheres will simultaneously reduce baseline pancreatic fluid secretion. This novel dual-action approach will be tested in a validated rat model of POPF with the goal of rapid clinical translation and patient benefit.

GRANT RECIPIENT: Adam Gadzinski, MD, MS

PROJECT: Interstate Telehealth to improve access to urological cancer care among rural patients

Project Details: Timely access to urological cancer care is challenging for rural patients who often travel great distances to tertiary centers. This is particularly true for patients residing in the WWAMI (Washington, Wyoming, Alaska, Montana, Idaho) region. We propose implementing an Interstate Telehealth program to improve access to urological cancer care for rural and underserved persons. We will compare patient-centered outcomes and health system outcomes between patients evaluated with Telehealth to those seen at traditional in-person appointments. Patient- centered outcomes will include patient satisfaction, direct healthcare costs, indirect costs (i.e., travel, work absenteeism), and time to treatment initiation. Health system outcomes include time from referral to visit, reimbursement, clinical efficiency of the appointment (e.g., additional consultations, laboratory or radiology studies), and referrals from a geographic area. We hypothesize that Telehealth will provide similar patient satisfaction, reduced costs, and earlier time to treatment. We further hypothesize that implementation of the interstate Telehealth program will decrease referral to visit time and increase clinical efficiency. Lastly, we hypothesize that providing Telehealth appointments will increase the frequency of referrals from rural areas. We anticipate that implementation of our interstate Telehealth program will improve access to urological cancer care for rural and underserved patients throughout the WWAMI region.

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