

Swim Across America Seattle 2021 Impact Report

To date, Swim Across America has contributed close to \$4.6 million for clinical research at SCCA. Starting in 2019, funds raised from the event have gone to support breakthrough research by young investigators at SCCA. In 2021, six grants were awarded to researchers focused on: lymphoma, sarcoma, breast, pancreatic and urological cancer research. Below, the grant recipients share progress statements on their research over the last year.



Dr. Meghan Flanagan

Research focus:
Breast cancer

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

Background: 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. Ultimately, this research may allow us to identify women with innate endocrine resistance and develop novel therapeutics and treatment strategies.

Progress Statement: The SAA funds were used to evaluate whether an association exists between a mutation in a gene (HSD3B1, involved in hormone biosynthesis) and breast cancer outcomes.

Using extensively collected clinical and pathologic data about patient demographics, tumor and treatment data and recurrence rates, we were able to show that women with two mutations in the HSD3B1 gene had higher rates of distant metastatic recurrence compared to those women who did not have this mutation. Future studies will be forthcoming to determine how this mutation may decrease the effectiveness of anti-estrogen medications that are used universally in post-menopausal ER+ breast cancer. This mutation is found in up to 15 percent of ER+ post-menopausal breast cancer patients, and if shown to decrease the effectiveness of anti-estrogen medications, there would be potential indications for alternative treatment strategies in these patients.



Dr. Sita Kugel

Research focus:
Pancreatic cancer

Project title: Exploring novel functions of HMGA2 in pancreatic cancer

Background: Pancreatic Ductal Adenocarcinoma (PDA) is an extremely lethal disease with a 5-year

survival rate of less than 10%. Recent work has led to the discovery that PDA can be subdivided into two principal subtypes based on transcriptional signatures: classical

and quasi-mesenchymal (QM). The QM PDA subtype is more aggressive and has the worst overall survival. Our laboratory has been focused on understanding of the mechanisms that drive each subtype in hopes of identifying therapeutic vulnerabilities that may be exploited in the clinic.

Progress Statement: Within an already challenging malignancy, there are transcriptional subtypes of pancreatic ductal adenocarcinoma that are especially lethal. Understanding what defines each subtype, as well as 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.



Dr. Jonathan Sham

Research focus:
Pancreatic cancer

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

Background:

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. The use of a biopolymer, poly(Nisopropylacrylamide) (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.

Progress Statement: Swim Across America is advancing our work to improve outcomes after pancreatic surgery. Their support is enabling a trailblazing collaboration between surgeons and bioengineers to develop novel ways to stop leaks after pancreas surgery and make patients live happier, healthier and longer lives. Polymer synthesis is moving forward, and two teams are working on creating and testing polymers with different characteristics for use in our animal experiments.



Dr. Jordan Gauthier

Research focus: CAR T-cell therapy

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

Background: We are investigating 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 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.

Progress Statement: The Swim Across America grant allowed us to explore the two following aims.

Aim 1: To determine whether exhausted T cells are associated with treatment failure after CAR T-cell therapy

for diffuse large B-cell lymphoma (DLBCL). We analyzed blood samples from 34 DLBCL patients treated on a clinical trial of CAR T-cell therapy. While we did not confirm an association between exhausted T cells and treatment failure, we found that a higher proportion of terminally differentiated T cells may have an adverse impact on the outcomes of CAR T-cell therapy.

Aim 2: To determine if an exhausted gene signature in T cells from lymphoma tumors is associated with treatment failure, we analyzed pre-treatment tumor biopsies obtained from 17 patients receiving CAR T-cell therapy. In biopsies from patients in complete response after CAR T-cell therapy, we found that T cell-associated genes were overexpressed compared to patients not in complete response after treatment. This suggests that tumors more permissive to T cell infiltration might respond better to CAR T-cell therapy. So far, we have not confirmed that an exhausted gene signature is associated with treatment failure. The SAA grant has been used to design and optimize novel assays that will allow us to further address this aim in the future.





Dr. John Lee

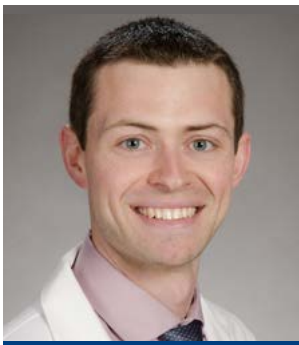
Research focus: *Sarcoma*

Project title: **Development of STEAP1 chimeric antigen receptor T-cell therapy for Ewing sarcoma**

Background: 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. 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.

Progress Statement: We applied the Swim Across America grant to evaluate whether a novel chimeric antigen receptor (CAR) T cell therapy targeting the protein STEAP1 could be an effective strategy to treat Ewing sarcoma. Our results indicate that human Ewing sarcoma tumor models commonly express STEAP1 and are susceptible to killing by STEAP1 CAR T cells. In related studies, we have also determined that STEAP1 CAR T cell therapy appears safe in a novel mouse model that we engineered to express human STEAP1. Together, these findings provide the rationale to translate STEAP1 CAR T cell therapy into clinical trials for Ewing sarcoma in the near future.



Dr. Adam Gadzinski

Research focus: *Urological cancer*

Project title: **Interstate Telehealth to improve access to urological cancer care among rural patients**

Background: 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 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.

Progress Statement: Our SAA grant has been used to support our telemedicine research efforts to assess the quality of telemedicine visits for cancer patients from rural areas and the Pacific Northwest states. We have demonstrated that telemedicine visits save cancer patients and their families a significant amount of time and money that would have been spent traveling to doctor appointments. We also found that patients are very satisfied with receiving cancer care remotely via telemedicine, especially during the COVID-19 pandemic.

