Fred Hutch Cancer Center

SWIM ACROSS AMERICA
MAKING WAVES TO FIGHT CANCER

Swim Across America — Seattle

2022 Impact Report

March 2023

Since 2009, Swim Across America has contributed more than $4.9 million for clinical research at Fred Hutchinson Cancer Center (formerly Seattle Cancer Care Alliance). Funds raised by the event, and the intrepid swimmers who bring it life, enable early-career investigators to pursue groundbreaking research. Investigators who received funding in 2019 and 2020 continue to build on research made possible by Swim Across America to advance understanding of breast cancer, lymphoma, pancreatic cancer, and sarcoma. We are delighted to provide an update on how the projects you've supported have advanced.

Dr. Meghan Flanagan

Meghan R. Flanagan, MD, MPH | Breast Cancer

Physician and affiliate investigator, Fred Hutch; assistant professor of Surgery, UW Medicine

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

Background: Anti-estrogen endocrine therapy decreases deaths, and reduces the risk of recurrence, among individuals with hormone-receptor positive breast cancer. However, approximately one-quarter of patients are inherently resistant or develop resistance to endocrine therapy. Ultimately, this research may allow us to identify people with innate endocrine resistance and develop novel therapeutics and treatment strategies.

Progress statement 2021: Swim Across America helped our team evaluate whether an association exists between a specific gene mutation (HSD3B1, which is involved in hormone biosynthesis) and breast cancer outcomes. Using an extensive collection of clinical and pathologic data about patients, their tumors, treatments, and recurrence rates, we demonstrated that patients with two mutations in the HSD3B1 gene had higher rates of distant metastatic recurrence compared to people who did not have these mutations.

2022 update: In July, we published findings from research supported by Swim Across America in the Annals of Surgical Oncology. Based on these results, our team received funding to study whether inheriting two copies of the HSD3B1 variant of interest — which occurs in 10% to 15% of patients with estrogen-receptor-positive, post-menopausal breast cancer — decreases the effectiveness of anti-estrogen medications, which are used universally in this population. Our results could indicate the need for alternative treatment strategies for these patients. Enrollment has begun for this 60-patient study and we expect to begin generating preliminary data within the next few months.

Fred Hutchinson Cancer Center is an independent, nonprofit organization that also serves as the cancer program for UW Medicine. This unique relationship allows for enhanced care coordination with one of the world's leading integrated health systems while accelerating the latest scientific breakthroughs in cancer and other life-threatening diseases.

Fred Hutch is proud to raise funds that fuel the adult oncology program on behalf of both Fred Hutch and UW Medicine.

UW Medicine

Jordan Gauthier, MD, MsC | Lymphoma


Dr. Jordan Gauthier

Physician and assistant professor, Fred Hutch and UW Medicine

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

Background: We are investigating two factors — T-cell dysfunction during manufacturing and the suppressive tumor microenvironment — that may play a critical role in the failure of CD19-targeting chimeric antigen receptor (CAR) T-cell therapy for people with diffuse large B-cell lymphoma (DLBCL). We are working to better characterize T-cell dysfunction and the tumor microenvironment as core mechanisms of failure of CD19 CAR T cells and identify potential targets to improve outcomes of CAR T-cell therapy for patients with DLBCL.

Progress statement 2021: The Swim Across America grant allowed us to explore two parallel questions. First, to understand whether exhausted T cells are associated with treatment failure after CAR T-cell therapy for patients with DLBCL, we analyzed blood samples from 34 patients treated on a clinical trial. 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. Second, to determine if an exhausted gene signature in T cells from lymphoma tumors is associated with treatment failure, we analyzed pre-treatment tumor biopsies from 17 patients receiving CAR T-cell therapy. In patients who had a complete response to CAR T-cell therapy, we found that T-cell-associated genes were overexpressed compared to patients not in complete response after treatment. Our results suggest that tumors more susceptible to T-cell infiltration might respond better to CAR T-cell therapy.

2022 update: Funds from Swim Across America supported the development of two cutting-edge tools that will help us better understand why CAR T-cell therapy does not work in some patients. We are now able to specifically study how CAR T cells "talk" to other cells inside lymphoma tumors. Identifying why CAR T cells fail will have a dramatic impact on designing the next generations of CAR T-cell therapies.

Dr. Sita Kugel

Sita Kugel, PhD | Pancreatic Cancer

Assistant professor, Fred Hutch

Project: Exploring novel functions of HMGA2 in pancreatic cancer

Background: Pancreatic ductal adenocarcinoma (PDA) is an extremely lethal disease with an overall five-year survival rate of 12%. 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 subtype is more aggressive and leads to the worst overall survival. Our laboratory has been focused on understanding the mechanisms that drive each subtype with the aim of identifying therapeutic vulnerabilities that may be exploited in the clinic.

Progress statement 2021: Within an already challenging malignancy, certain transcriptional subtypes of pancreatic ductal adenocarcinoma are especially lethal. Funding from Swim Across America is helping us understand what defines each subtype, as well as their susceptibilities and mechanisms of resistance, to help to identify potential new treatment options for this devastating disease.

2022 update: With Swim Across America funding, our team has recreated the classical and QM subtypes in the lab and managed to explore the differences between the two, including how they acquire resistance to first-line therapies. Our work will lay the groundwork for more targeted treatments for PDAs that can also account for their respective escape mechanisms, thereby improving outcomes.

John K. Lee, MD, PhD | Sarcoma

Physician and assistant professor, Fred Hutch and UW Medicine

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

Background: Approximately 200 adolescents and young adults in the U.S. are diagnosed each year with Ewing sarcoma, a cancer of the soft tissue and bone. When Ewing sarcoma spreads, patients face a very grim prognosis, as no available treatments eradicate the disease. If successful, our studies will help lay the groundwork for the development and clinical translation of a first-in-field CAR T-cell immunotherapy for Ewing sarcoma that targets the protein STEAP1.

Dr. John K. Lee

Progress statement 2021: We used the Swim Across America funding to evaluate whether a novel CAR T-cell therapy targeting the protein STEAP1 could be an effective strategy to treat patients with 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 rational to translate STEAP1 CAR T-cell therapy into clinical trials for Ewing sarcoma.

2022 update: We are pleased to report that STEAP1 CAR T cell therapy has shown highly promising activity in multiple preclinical models of Ewing sarcoma, and we have licensed the technology to a company for clinical development.

Jonathan Sham, MD, MBEE | Pancreatic Cancer

Physician and assistant professor, Fred Hutch and UW Medicine; attending surgeon, UW Medicine

Project: Novel drug-eluting biopolymer to reduce pancreatic fistula and improve outcomes after pancreatic surgery

Background: Pancreatectomy, or removal of the pancreas, 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(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.

Progress statement 2021: Swim Across America is advancing our work to improve outcomes after pancreatic surgery. Your support is enabling a trailblazing collaboration between surgeons and bioengineers to develop novel ways to stop leaks after pancreas surgery and help patients live 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 experiments.

2022 update: Our work continues to be enhanced by support from Swim Across America. Through your support, we have expanded our team and published on our groundbreaking research, including our development of a preclinical model for studying POPF. We continue to move this work closer to impacting patients with pancreatic cancer.

Dr. Jonathan Sham

Andrea Larson, Associate Director, Peer-to-Peer and Patient Family Fundraising
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