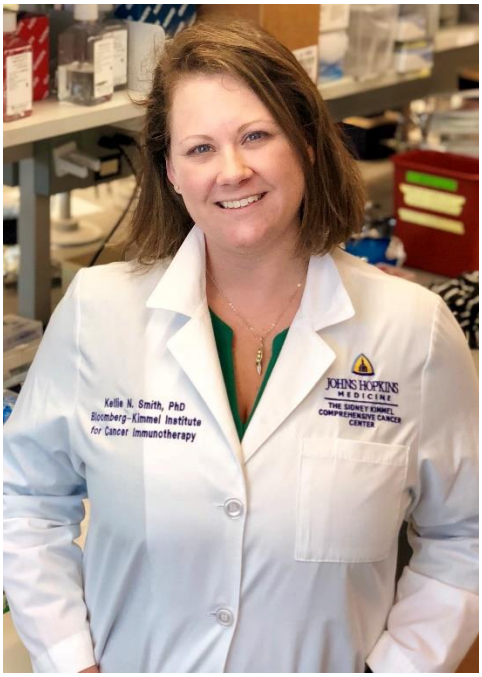
Biographic and Research Information for Swim Across America Baltimore Grants

As Director of the Swim Across America Lab at the Johns Hopkins Kimmel Cancer Center, **William G. Nelson, M.D., Ph.D.**, convened a committee of senior cancer investigators to solicit, review and select promising cancer research projects at the Kimmel Cancer Center through a rigorously competitive peer-reviewed grant process.

Central to the selection of the projects through this process has been our focus on funding high impact science and novel research across all cancer types that, through proof of principle, can lead to clinical trials and innovative therapies for cancer patients. This is true, "bench to bedside medicine" or translational research for which the Johns Hopkins Kimmel Cancer Center has traditionally excelled at conducting.

Launching their studies in 2023 are:



Kellie Smith, Ph.D., is Associate Professor of Oncology at the Kimmel Cancer Center. Dr. Smith graduated from Stevenson University with a B.S. in Biology and Chemistry, and completed medical school at the University of Pittsburgh. She earned her Ph.D. at the Johns Hopkins School of Medicine and joined the faculty thereafter. As a faculty member, Smith's work focuses on the immunological mechanisms that are associated with intratumoral mutational density, neoantigen recognition by T cells, and a clinical response to anti-PD-1 immunotherapy in multiple tumor histologies. Of relevance to her research funded by Swim Across America, she and her colleagues have made promising findings in a subset of non-small cell lung cancer and colorectal cancer patients who achieved disease stabilization following PD-1 blockade despite having low tumor mutational burden.

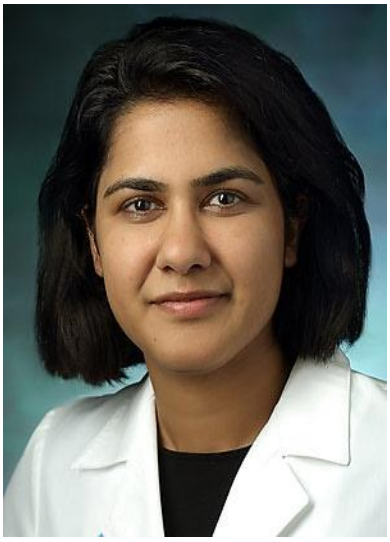
Dr. Smith's SAA Funded Study: A 2019 SAA grantee, Dr. Smith's past research project used a laboratory test called MANAFEST, for *Mutation Associated NeoAntigen Functional Expansion*

of Specific T cells, which she designed, to identify cancer-specific proteins that can be recognized by immune cells called T cells. For her recently approved SAA grant, Dr. Smith proposes to develop a next-generation MANAFEST platform and test its implementation in patients with lung cancer. The expectation is that developing this new platform provides a more streamlined approach that will increase the throughput of tumor-reactive TCR discovery and, ultimately, therapeutic development. She will also develop a user-friendly, publicly-available graphical user interface (GUI) for bioinformatic identification of antigen-specific TCRs. While the biospecimens used in this study are from lung cancer patients, if successful, this assay will have broad applicability to all tumor types for which antigen-specific TCRs can be studied. Not only is this essential for academic and scientific discovery, but such an assay will significantly enhance the speed with which TCR-based therapeutics are developed and clinically implemented.

Christopher Douville, Ph.D., is Assistant Professor of Oncology at the Kimmel Cancer Center. Dr. Douville received a B.S.E. in Chemical Engineering at the University of Michigan. A former swimmer for the University of Michigan, Dr. Douville was an Honorable Mention All-American and a Big Ten Distinguished Scholar-Athlete. He came to Johns Hopkins where he received his Ph.D. in Biomedical Engineering, and continued his post-doctoral studies in Oncology. He has worked in the Ludwig Lab alongside cancer research luminaries Drs. Bert Vogelstein, Ken Kinzler and Nickolas Papadopoulos. He is a former Sidney Kimmel Chief Research Fellow and a Benjamin Baker Scholar. His work focuses on the use of machine learning and next generation sequencing to develop improved computational algorithms and molecular diagnostics to detect cancers and to develop the best possible treatment options for patients.

Dr. Douville's SAA Funded Study: Dr. Douville specializes in designing algorithms for the detection of cancer from various next generation sequencing assays. One of his own developments is called RealSeqS, for *Repetitive Element Aneuploidy Sequencing System*. His Swim Across America project aims to use RealSeqS to develop novel molecular diagnostics to reliably classify bile duct strictures, leading to correct treatment options for cholangiocarcinoma and pancreatic ductal carcinoma patients. Biliary tree cholangiocarcinoma and pancreatic ductal carcinoma are highly aggressive cancers – both which are commonly diagnosed via endoscopic bile duct brushings. There is a critical need to develop novel molecular diagnostics to reliably classify bile duct strictures. This project will assess the ability of the (RealSeqS) to identify specific chromosome alterations that indicate the presence of cancer and also apply and evaluate performance in endoscopic brushings of the biliary tree. The outcome of this project is to develop a molecular diagnostic based on aneuploidy for the reliable classification of lesions of the bile duct.

Continuing their studies this year are several 2022 grantees:

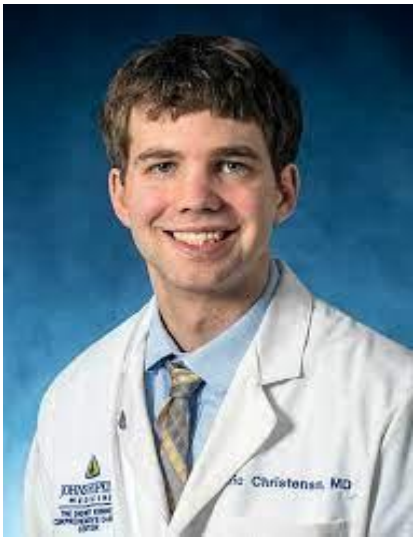


Tania Jain, M.B.B.S., is Assistant Professor of Oncology at the Hopkins Kimmel Cancer Center. Dr. Jain received her MBBS degree in Medicine from the Government Medical College, in Patiala, Punjab, India. She then attended Wayne State University/ Detroit Medical Center, in Detroit, Michigan for her Residency in Internal Medicine and served as Chief Resident there. Dr. Jain next attended the Mayo School of Graduate Medical Education in Phoenix, Arizona for her Fellowship in Hematology/Oncology and served as Chief Fellow there. After serving an additional Fellowship in Stem Cell Transplantation and Cellular Therapy at Memorial Sloan Kettering Cancer Center in New York, Dr. Jain joined the faculty at Johns Hopkins. Dr. Jain's training and research are focused on understanding nuances of disease pathogenesis and factors affecting outcomes in patients with myeloproliferative neoplasms treated with various therapies including transplantation. Her goals are to develop strategies to optimize outcomes following blood or marrow transplantation in myeloproliferative neoplasms, which remains the only potential curative treatment for this life-threatening hematological malignancy.

Dr. Jain's SAA Funded Study: Patients suffering from clonal chronic myeloid malignancies have a median survival of under 2 years in high-risk disease. Bone Marrow Transplant (BMT) is the only potential cure. With the availability of post-transplantation cyclophosphamide (PTCy) and non-myeloablative conditioning, BMT has now expanded to older patients and those who do not have a matched donor. However, over half of these patients will relapse which remains the major impediment to successful outcomes. The goal of our study is to define the molecular signature of residual clones responsible for relapse and develop a personalized approach to identify patients at high-risk of disease recurrence. If successful, this will allow us to implement maintenance strategies aimed at prevention of relapse following BMT.

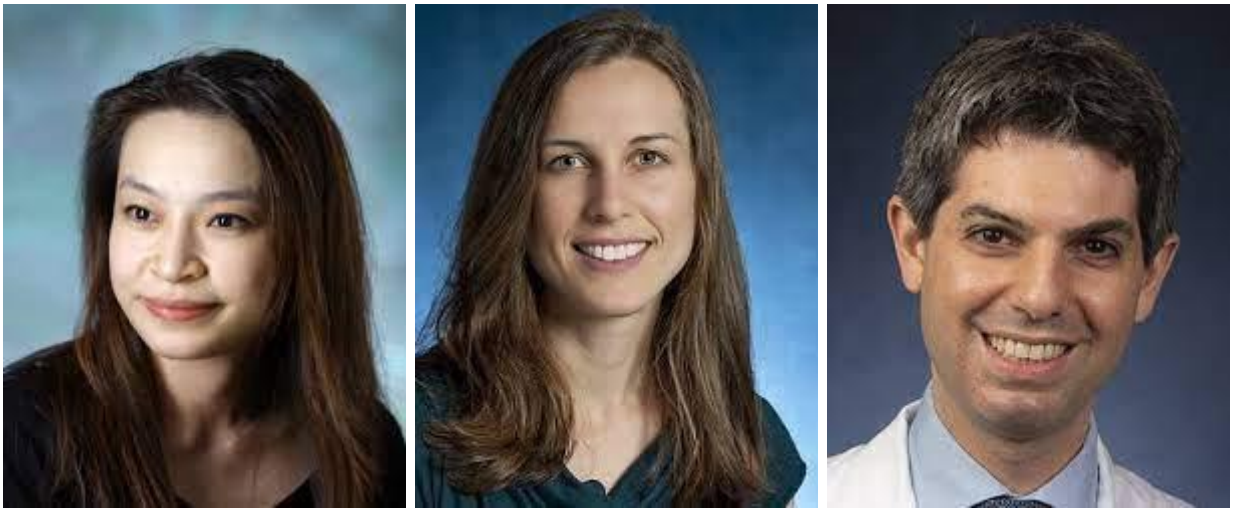
Suman Paul, M.B.B.S., Ph.D., Assistant Professor of Oncology at the Kimmel Cancer Center. Dr. Paul received his MBBS degree in Medicine and Surgery from the University of Calcutta, Kolkata Medical College, in Kolkata, West Bengal, India. He then attended the Uniformed Services University, Bethesda, Maryland where he received his PhD. in Microbiology and Immunology. Dr. Paul's residency was at the University of Toledo in Toledo, Ohio and served as Chief Medical Resident there. He came to Johns Hopkins for his Fellowship in Oncology and joined the faculty thereafter. Dr. Paul's research focuses on developing targeted therapies for the treatment of T cell leukemias and lymphomas. Patients with T cell cancers have few treatment options and a poor prognosis. Developing T cell cancer is challenging, as the therapies have to preserve the normal T cells that maintain a functioning immune system. My research goal is to continue developing novel therapies for ultimate application in human T cell cancer patients through early phase clinical trials.

Dr. Paul's SAA Funded Study: T cell leukemias and lymphomas, collectively known as T cell cancers, affect ~100,000 patients worldwide each year. Most T cell cancers are treated with chemotherapies and have a modest 5-year survival of between 7% and 38%. Thus, there is a critical need to develop novel therapies targeting T cell cancers to improve patient outcomes. Developing new therapies against T cell cancers is challenging as the therapies will have to kill the T cell cancers while preserving the healthy T cells that are required for our immune system. The goal of this study is to generate a type of immunotherapy using antibodies that specifically kill the T cell cancers and not the healthy T cells. This immunotherapy may provide additional treatment options and improve outcomes in patients suffering from T cell cancers.



Eric Christenson, M.D., Ph.D., is an Instructor in Medical Oncology at the Hopkins Kimmel Cancer Center. Dr. Christenson earned a B.S. in Biology at Villanova University in Villanova, Pennsylvania, and attended medical school at Drexel University in Philadelphia. He came to Johns Hopkins for his Residency in Internal Medicine and a post-doctoral fellowship in Medical Oncology. Dr. Christenson has a strong clinical and research focus on improving the care of patients with rectal adenocarcinoma. One of the biggest unmet needs in rectal cancer is determining the optimal management of patients with locally advanced disease that undergo total neoadjuvant treatment. In approximately 30% of these patients, a complete clinical response is achieved with chemotherapy and radiation alone, creating a debate over whether these patients should proceed with surgery or transition to a surveillance paradigm. Evidence shows that clinical evaluation alone is an imperfect method of risk stratifying patients, and leads to both false positives, causing unneeded treatment, and false negatives, where patients pursue observation only to later suffer a recurrence. To address this dilemma I hope to develop novel biomarker-driven strategies to differentiate and improve the care of these two groups.

Dr. Christenson's SAA Funded Study: Colorectal cancer is the second leading cause of cancer-related death in the United States each year with rectal cancer accounting for approximately 30% of new diagnoses. Novel strategies that can identify patients at highest risk of recurrence could improve patient outcomes for this population. Cell-free DNA (cfDNA) is an emerging technology to detect the presence of tumor-specific genetic alterations shed into the bloodstream by residual cancer cells. This approach has shown high positive predictive value in identifying a subset of patients at extremely high risk for relapse of rectal cancer, and can allow for some patients to undergo a surveillance program instead of further treatment. This study will assess value of tumor infiltrating lymphocytes in predicting responsiveness of locally advanced rectal cancer to neoadjuvant treatment in a retrospective cohort, and determine independent and additive value of cfDNA and tumor-infiltrating lymphocytes in predicting treatment outcomes in locally advanced rectal cancer.



Dung Le, M.D., Katherine Bever, M.D., and Mark Yarchoan, M.D.

Dung Le, M.D., is Professor of Oncology at the Hopkins Kimmel Cancer Center. Dr. Le received her undergraduate degree at Yale University. She then came to Johns Hopkins for Medical School, Residency and Fellowship, and joined the faculty thereafter. Her research focus is on novel therapies for patients with gastrointestinal malignancies. Dr. Le is a past SAA grant recipient. Monies from SAA Baltimore have funded her groundbreaking research in immunotherapies. In a report of a proof-of-principle study of patients with colon and other cancers for whom standard therapies failed, Dr. Le and colleagues found that mistakes in so-called mismatch repair genes, first identified by Johns Hopkins and other scientists two decades ago, may accurately predict who will respond to certain immunotherapy drugs known as PD-1 inhibitors. Results of the trial with pembrolizumab, marketed as Keytruda, was published by the New England Journal of Medicine on June 25, 2015. On May 23, 2017 the U.S. Food and Drug Administration granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This was the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated. This achievement was named as a Scientific Breakthrough of the Year in 2017.

Katherine Bever, M.D., is Assistant Professor of Oncology at Johns Hopkins. She earned her undergraduate degree in Biophysics from Johns Hopkins University and her medical degree from the University of Maryland School of Medicine. She completed her residency at the Boston University School of Medicine and her fellowship in Medical Oncology at Johns Hopkins. She joined the Johns Hopkins faculty in 2015. Dr. Bever's research focus is on advanced gastrointestinal malignancies. She is a past SAA grant recipient. Her 2018-2019 grant allowed her to study a rare type of aggressive cancer known as high grade neuroendocrine carcinoma or small cell carcinoma, with the goal of identifying targets for novel therapies to serve as a basis for future clinical trials in these patients.

Mark Yarchoan, M.D. is Assistant Professor of Oncology and the Director of the Liver and Biliary Cancer Multidisciplinary Clinic at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.
Dr. Yarchoan received his B.A., cum laude, in Neuroscience from Amherst College in Amherst, Massachusetts and his M.D. from the Perelman School of Medicine at the University of Pennsylvania in Philadelphia. He completed an internship and residency at the Hospital of the University of Pennsylvania and came to Johns Hopkins for his Fellowship in Medical Oncology, joining the faculty thereafter. Dr. Yarchoan's clincal and research interests focus on cancers of the liver and biliary tract.

Drs. Le, Bever, and Yarchoan's SAA Funded Study – Immunotherapy has recently become established as standard first-line therapy in Hepatocellular carcinoma (HCC). Similar to the experience of immunotherapy in other tumor types, only a fraction of patients with HCC will respond, and among the subset who respond, secondary resistance is commonly observed after approximately one year. Little is known about the mechanisms of immune resistance in HCC, however it is anticipated that tumor heterogeneity and clonal evolution may result in the outgrowth of resistant clones. The use of ctDNA can be used to deconvolute mutations into distinct clusters, and predict the clonal fraction of each cluster over time, thereby identifying mutations that contribute to immune resistance. Our overarching hypothesis is that serial monitoring of immunotherapy treatment response with tumor-uninformed ctDNA can predict clinical benefit and also identify genomic mechanisms of secondary immune resistance in HCC.