DF/HCC

SCIENTIFIC PRESENTATIONS

SUMMER 2021

YES for CURE

Young Empowered Scientists for ContinUed Research Engagement

CURE

Continuing Umbrella of Research Experiences

Dana-Farber/Harvard Cancer Center
Continuing Umbrella of Research Experiences (CURE)

Launched in 2002, the Continuing Umbrella of Research Experiences (CURE) Program at Dana-Farber/Harvard Cancer Center (DF/HCC) was an important building block in research training initiatives. Under the direction of the DF/HCC Initiative to Eliminate Cancer Disparities (IECD), this inaugural program set the stage to provide underrepresented minority high school and college students with a stimulating and rewarding hands-on research experience that encourages students to pursue education and training in the biomedical sciences and careers in basic, clinical, nursing, and population science cancer research. In 2017 our student training initiatives were expanded to include two NIH funded grants:
Summer Program to Advance Research Careers (SPARC) and Young Empowered Scientists for ContinUed Research Engagement (Yes for CURE).

Dana-Farber/Harvard Cancer Center
Initiative to Eliminate Cancer Disparities

The Initiative to Eliminate Cancer Disparities (IECD) is a center-wide initiative that reflects the high level of commitment of the Cancer Center to addressing cancer disparities and health inequities through its research, education and training, and community engagement activities. The goal of the initiative is to integrate this theme throughout all aspects of the organization by facilitating an intentional and dedicated focus on the reduction/elimination of cancer disparities.

The IECD focuses on four key areas:

- Community engagement and education
- Reducing barriers to care
- Facilitating minority participation in clinical trials
- Fostering diversity in cancer researchers

For more information about the IECD and our student training programs, contact:

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CURE (Summer Only) Virtual Scientific Presentations

Tuesday, August 3, 2021
11:00 AM - 12:30 PM

Wednesday, August 4, 2021
11:00 AM - 12:30 PM

Thursday, August 5, 2021
11:00 AM - 12:30 PM

YES for CURE Virtual Poster Sessions

Tuesday, August 3, 2021
2:00 PM - 2:50 PM
3:10 PM - 4:00 PM

Wednesday, August 4, 2021
2:00 PM - 2:50 PM
3:10 PM - 4:00 PM

Thursday, August 5, 2021
2:00 PM - 2:50 PM
3:10 PM - 4:00 PM

Table of Contents

YES for CURE

CURE Summer Only

Precision Medicine and the Human Protein Interactome Network

Bryan Abreu

Principal Investigator: David Hill, PhD

Scientific Advisor: Anupama Yadav, PhD

Dana-Farber Cancer Institute

Precision medicine is an approach to disease treatment and prevention that takes into account an individual's variability in genes, environment, and lifestyles to make sure that everyone gets customized treatment according to their genetic and environmental background. In order to gain a holistic, mechanistic understanding of cellular physiology, it is necessary to model cellular systems as networks of interacting proteins, identify disease-associated processes, and predict the outcomes of those variations. Genetic variants are often not predictive of the phenotypic outcome. They can manifest to different extents, and sometimes the presence of a disease-associated mutation may not even result in the manifestation of the disease, a phenomenon called incomplete penetrance. This is being observed more and more for example in cystic fibrosis, mutations that cause the disease in one individual could have no effect on another individual's health. Sometimes, even if the mutation is penetrant, it results in different disease presentations. For example, in Huntington's Disease a 40+ CAG nucleotide repeat causes disease in most individuals but the age of onset and disease severity varies. Improving the accuracy of predicted clinical manifestations of genetic variants has become one of the largest challenges presented to scientists in the area of precision medicine. The observed commonality of incomplete prevalence suggests a model of genotype-phenotype relationships that challenges the previously accepted linear model. At the root of these ''non-linear" relationships is complex interactions between genetic and epigenetic factors that is mediated by interactions between regulatory DNA sites, non-coding RNA, and proteins in cells which constitute the cellular 'interactome'. Understanding these interactomes in people consists of many different methods which will be described in this short article. If the networks of proteins interacting can help us more clearly identify the outcome of a DNA mutation further down the road we will be able to have more personalized therapies for many diseases including cancer and even help with their prevention.

The role of epigenetic silencing machinery on tumor cell-intrinsic antigen processing and presentation in glioblastoma

Vanessa Ajtum-Ruiz

Principal Investigators: J. Ricardo McFaline-Figueroa MD, PhD; Jean Zhao, PhD

Dana-Farber Cancer Institute

Glioblastoma (GBM) is a highly aggressive tumor of the brain that is unresponsive to single-agent immune checkpoint inhibitors (ICIs). GBM downregulates expression of cell surface major histocompatibility complex class 1 (MHC) and other antigen processing and presentation machinery (APM), a process previously implicated in immune evasion in other cancer types. We tested the hypothesis that genetic or pharmacologic inhibition of epigenetic modifiers previously implicated in cancer immune evasion can upregulate MHC class 1 and APM and confer sensitivity to ICIs. Indeed, we find that inhibition of EZH2, the catalytic subunit of the polycomb repressor complex 2 or of its binding partner DNA methyltransferase (DNMT) increases expression of MHC class 1 subunits in patient-derived glioblastoma cell lines. We also began to evaluate the effect of DNMT inhibition in combination with ICIs on the glioblastoma tumor microenvironment in a mouse model of GBM. This work suggests that inhibition of EZH2 or DNMT may be a useful adjunct to immune checkpoint inhibitors in the treatment of GBM which should be the topic of further studies.

New Therapy for Pediatric Brain Tumors

Chidinma Amogu

Principal Investigator: Bakhos Tannous, PhD

Scientific Advisor: Jian Teng, PhD

Massachusetts General Hospital

Research into new therapies for pediatric brain tumors is important and needed. Despite brain tumors representing a small amount of all childhood cancers, they are much harder to treat and do not have cures. For example, diffuse intrinsic pontine glioma (DIPG) is a rare, high grade and highly aggressive brain tumor without a cure. The rate of survival hasn't increased for DIPG, however, and has remained at a median survival rate of up to 1 year from diagnosis for both pediatric and adult diagnosis for the past 40 years. When it comes to working with therapeutics and the brain, there has always been a challenge when it comes to treating tumors and whether they bypass the blood brain barrier (BBB). The Tannous Lab specializes in experimental therapeutics for malignant brain tumors and was involved in bringing forward the technique of using Mefloquine to target cancer cells. Mefloquine has antifungal properties and is able to penetrate the brain and functionally target brain tumors. There have been many advances in immunotherapy which include CAR-T therapy, immune checkpoint blockade, and vaccine therapy, but these advances still require additional research and modification to work well on brain tumors. An urgent demand for new therapies for pediatric brain tumors has emerged and differences between pediatric and adult tumors need to be taken into account, as young bodies and brains are still growing and developing and are quite different from that of an adult. We hypothesize that when given the right resources and support, compounds such as obtusaquinone and mefloquine that have cancer cell killing properties, can be enhanced when paired with other therapeutics. So, the focal point should be on amplifying known knowledge to better optimize and use new therapies.

How do BRCA1 and its associated proteins RHAMM and RUNX3 control DNA repair?

Saraina Antoine

Principal Investigator: David Livingston, MD

Scientific Advisors: Vladimir Botchkarev, PhD; Natalie Williams, BS

Dana-Farber Cancer Institute

BRCA1 is a DNA repair protein and a tumor suppressor. People with BRCA1 mutations are predisposed to breast cancer. How BRCA1 and its associated proteins communicate to repair DNA damage and suppress breast cancer is not completely understood. Our lab recently discovered that BRCA1 controls the abundance of the DNA repair protein RUNX3. The goal of my project was to understand how BRCA1 and RUNX3 communicate to control DNA repair and possibly prevent cancer. Our group also recently identified the protein RHAMM as a regulator of BRCA1. Because BRCA1 regulates RUNX3, it was my hypothesis that RHAMM can regulate RUNX3 via BRCA1. This is important to study because discovering a new BRCA1-centric tumor suppressor pathway could lead to future cancer therapies for patients. To address this hypothesis, we used molecular cloning, cell culture, immunofluorescence microscopy, and western blotting. We discovered that RHAMM controls BRCA1 functions after DNA damage. We also have collected new evidence that BRCA1 is important for RUNX3-mediated DNA interstrand cross-link repair. We are currently testing whether RHAMM talks to RUNX3 via BRCA1. In summary, my summer project has revealed new insights into how BRCA1 and its associated proteins RUNX3 and RHAMM are involved in the DNA damage response. These discoveries have the potential to benefit the development of future cancer therapies for patients.

Global Disparities of Traumatic Brain Injury

Cleidi Argueta-Flores

Principal Investigator: Jaime Hart, PhD

Dana-Farber Cancer Institute

Throughout the last decade, traumatic brain injuries (TBI) have become an increasingly overwhelming global burden, and there is growing evidence of disparities in incidence. The epidemiology of TBI emphasizes the health disparities that exist worldwide, with an excess burden of TBI in low-income or developing countries. The purpose of this review is to explore the epidemiology of TBI in these developing countries. This narrative review was conducted with searches in PubMed and Google Scholar. Keywords and phrases included “Traumatic Brain Injury in developing countries”, “Epidemiology of TBI”, “Neurotrauma” and “TBI in low-income countries”. Papers that met our search criteria were read in depth to extract key findings and suggestions for improvement. Eight articles met our inclusion criteria, and were read to extract key risk factors and suggestions for improvement for TBI treatment. Leading causes, rates of TBI, and treatment accessibility were influenced by several factors including political and geographical differences, common modes of transportation, and most commonly lack of access or resources to diagnose and treat injury. Road traffic injuries appeared to be the leading cause of TBI in these countries, and there were few facilities with the capability to treat TBI. Suggestions to improve TBI outcomes included increasing training and the number of facilities to treat TBI. However, it was clear that there are major gaps in the current literature on the causes of TBI in low and middle income countries, and more research is needed to derive country-specific recommendations and solutions to reduce TBI incidence and improve outcomes of TBI victims.

The clinical factors of Sickle cell disease patients that correlate with their ocular complications

Zina Asante

Principal Investigator: Natasha Archer, MD

Scientific Advisors: Omar Halawa; Efren Gonzalez, MD; Reed Jenkins; Patel Nimesh

Boston Children’s Hospital

Sickle cell disease (SCD) is an inherited blood disorder — a result of a point mutation — that causes the healthy, round red blood cells to form a shriveled sickle shape. That change in shape causes the cells to be unable to carry enough oxygen and become viscous in consistency. Complications include retinopathy, retinal detachment, and even vitreous hemorrhages among many others. If left untreated the patient could go blind. Though a wide array of complications have been identified, it is still unknown whether sickle cell disease in itself is the cause of the manifestation of ocular complications or if it is a combination of the disease and unknown clinical factors. Our goal is to identify clinical factors that correlate with ocular complications in SCD patients, along with determining how many of those patients go to their regular eye screening. Methods will entail screening patient information in the database at Boston Children’s Hospital. The research will allow the medical community and SCD patients to determine which clinical factors are related to and causing different ocular complications to optimize care plans.

Vertical Integration: hospital-physician consolidation of oncology practices is associated with increased spending and a potential decrease in the quality of care

Noha Awais

Principal Investigator: Nancy L. Keating, MD, MPH

Dana-Farber Cancer Institute

There has been an increasing trend in small independent oncology practices forming complex affiliations with large hospital systems. These affiliations are usually the direct result of changes in ownership and evolve through vertical integration of hospitals and practices. Vertical integration involves the consolidation of physician practices by hospital systems by means of partial or full ownership. A growing body of research suggests that vertical integration is associated with anti-competitiveness and increased medical spending. While vertical integration might potentially increase efficiency and improve the quality of care, adequate research has not been done to confirm these predictions. The purpose of this systematic review is to use research papers that compare the quality of care in integrated and non-integrated physician practices (including oncology practices, when possible) in order to conclude whether vertical integration has had a negative or positive impact on quality. The papers used were from 2013 to 2021, and supplementary data from our current research--such as ownership changes data--will be used to establish a firm conclusion. The team will characterize changes in ownership among oncology practices since 2010. They then will leverage these changes to deduce if ownership changes affect the quality of care, diffusion of new therapies, utilization, and outcomes, as well as overall health spending. The research will also study how vertical integration affects vulnerable communities that already endure health disparities.

Inherited Genetic Similarities Between Humans and Canines With a Specific Focus on BRCA1/2 Genes: A Review of Literature

Serenity Beaumont

Principal Investigator: Kevin S. Hughes, MD, FACS

Scientific Advisor: Kanhua Yin, MD, MPH

Massachusetts General Hospital

Canine malignancies have been established as comparative models for human cancers due to factors including their similar spontaneous tumor development, risk factor exposure, and response to therapies, which suggests similarities in genetic mechanisms that cause cancer in both species. However, inherited genetic similarity between these two species, specifically surrounding cancer, is an area of research that requires elucidation. The inquiry this cross-species cancer genetics analysis will address is if humans and canines share inherited genetic pathogenic variants that induce cancer development. The objective of this research was to identify high penetrance germline pathogenic variants in susceptibility genes that increase cancer risk and mortality in canines and humans, and to consolidate a list of these genes. Using PubMed as a search platform and employing a search term to generate articles including the words “canine,” “cancer(s),” and “genetic(s),” several genes associated with histiocytic sarcoma, osteosarcoma, and breast cancer were identified: BRCA1, BRCA2, STK11, CDKN2A, and CDKN2B. Upon further analysis of canine mammary tumors, BRCA1 and BRCA2 were identified as the most important genes related to inheritance predisposition to breast cancer in female canines and humans. These genes are highly conserved in both species. Preventive measures, such as an ovariohysterectomy (spay) before the physiological demonstration of BRCA1/2 mutations may help to decrease the cancer risks in canine pathogenic variant carriers. Performing genetic testing on canines may be a powerful way to advance our understanding of hereditary cancers and in developing preventative therapies for humans and companion animals alike.

Targeting Neuropilin-2 in Oral Cancer to Inhibit Tumor Growth and Progression

Zuva Chihwai

Principal Investigator: Diane R. Bielenberg, PhD

Scientific Advisors: Sausan Alfaris, DDS; Yao Gao, MD, PhD; Dakshnapriya Balasubbramanian, PhD

Boston Children's Hospital

Oral squamous cell carcinoma (OSCC) is the most malignant tumor of the oral cavity and affects 54,000 people in the United States each year. OSCC often presents as an innocuous-looking white plaque on the tongue that is frequently overlooked by the patient and by dental hygienists focused on teeth. At diagnosis, 2/3 of patients already have advanced disease that has spread to regional lymph nodes. Late-stage OSCC patients have poor outcomes with a 5-year survival rate under 50%, therefore novel treatment options are urgently needed. An ideal biologic therapy for OSCC may be one that targets multiple cell types within the tumor microenvironment. Our laboratory has found one receptor, Neuropilin-2 (NRP2), that is common to OSCC tumor cells, tumor-associated blood and lymphatic endothelium, and tumor-infiltrating immune cells (T cells). NRP2 binds several growth factors and signals through co-receptors to stimulate growth and migration. We hypothesize that NRP2 expression in these cells is crucial for oral cancer progression. The contribution of NRP2 in each cell type toward oral cancer malignancy will be tested using mutant mice strains and syngeneic OSCC isografts implanted in the tongue. In preliminary experiments, oral cancer growth will be compared in Nrp2-deficient mice and wildtype littermates to test the role of Nrp2 in the host (versus the tumor cells). My specific project focused on expanding the Nrp2 mutant mice cohorts by breeding, genotyping, and preparing mice for the oral cancer studies. Mice were weened at 3 weeks of age and separated by sex. The presence of green fluorescent protein (GFP) was confirmed microscopically, and genomic DNA was isolated from small ear biopsies. PCR analysis using several different primer pairs was used to distinguish the Nrp2 mutant (knockout) mice from Nrp2 heterozygous or wildtype mice. Going forward, these mice will be implanted with murine OSCC cells called WT3, which express Nrp2, and analyzed for tumorigenicity. Isolated tumors will be analyzed histologically for microvessel density and immune cell infiltration. The additional mice generated during this project will add to the statistical power of the overall dataset. Further preclinical studies will be needed to elucidate the necessity of Nrp2 toward oral cancer progression or the efficacy of NRP2-targeting drugs.

Quantifying brain abnormalities in survivors of pediatric brain tumors

Alexandra DaCruz

Principal Investigator: Yangming Ou, PhD

Boston Children's Hospital

Brain tumors are common tumors in the pediatric population and cranial radiation therapy is needed to control the long-term disease in children. Most pediatric patients have a combination of treatments such as chemotherapy, radiation therapy, cranial irradiation, etc. Pediatric brain tumor (PBT) survivors increase each year. However, among the survivors, many develop neurocognitive impairment during recovery. These neurocognitive outcomes affect their academic performance such as verbal problems, memory loss, and complex decision making. Therefore, improving the survivors' neurocognitive outcomes is a crucial need. By conducting this research, we are aiming to improve pediatric brain tumor treatment and outcomes. Evaluating brain abnormalities in survivors of pediatric brain tumors includes reviews and reports on pediatric brain tumor survivors' neurocognitive outcomes, some contributing factors to survivor outcomes, and what could be done differently for a better outcome. There are four risk factors: patient demographics, clinical tumor characteristics, treatment, and MRI. Out of the four, MRI characteristics with neurocognitive outcomes are the least understood. To better understand and predict neurocognitive outcomes, the lab developed an MRI machine that learns and has a selection algorithm that can find subsets of MRI variables that predict outcomes. This algorithm will be used to predict neurocognitive function in normal developing brains between 8 and 22 years of age. With this technique they expect to find age, sex, and alternations of key brain regions underlying neurocognitive pathways to co-decide outcomes. Additionally, in order to quantify brain abnormalities in survivors of pediatric brain tumors and predict neurocognitive outcomes, we would use additional data that has already been collected to understand the mechanisms of neurocognitive outcomes in survivors of ependymoma and medulloblastoma, two common pediatric brain tumor types affecting children ages three to eight. Using this approach, the lab would be able to successfully predict and demonstrate that, jointly using tumor, treatment, demographics, and MRI outperforms each single risk factor in explaining outcomes of individual survivors. This research is impactful and aims to improve PBT treatment and outcome.

Racial/ethnic and geographic disparities in liver cancer incidence and mortality within the U.S.

Tiffany Dang

Principal Investigator: Lorelei A. Mucci, ScD

Scientific Advisors: Bailey Vaselkiv, MPH; Kate Kutzer, BS

Dana-Farber Cancer Institute

Introduction: Hepatocellular Carcinoma (HCC), the most common form of primary liver cancer, is the third leading cause of cancer-related deaths worldwide and sixth within the United States. Despite the advancements in surveillance guidelines and curative therapies for liver cancer, perplexing racial/ethnic and geographic disparities within HCC continue to persist. API, Black, and Hispanic individuals have a higher rate of liver cancer mortality in comparison to their white counterparts. Due to scarce data available in public databases, there is an inadequate assessment of HCC risk factors in vulnerable racial populations.

Methods: We conducted an ecologic study via the Surveillance, Epidemiology, and End Results (SEER) and GLOBOCAN databases in order to analyze patterns in liver cancer incidence and mortality by race/ethnicity and geography. We extracted statistics on the prevalence of three established risk factors: Hepatitis B and C infection and obesity. We calculated ecologic correlation coefficients to assess the relative contribution of these factors in explaining racial and geographic disparities.

Results: The geographic disparities observed in liver cancer incidence between states is sparsely correlated with the prevalence of acute hepatitis B and C infections, whereas the mortality rates showed slight correlation with acute hepatitis B and obesity prevalence. For the racial disparities observed in liver cancer, none of the established risk factors had any significant correlation with mortality or incidence rates.

Conclusion: There is not a strong association between these risk factors and the racial/geographic disparities within liver cancer. Further analysis of chronic hepatitis prevalence and additional risk factors may be needed in explaining these discrepancies.

The role of adaptor protein AP2A2 in VEGFR2 internalization and VEGF-induced migration

Nyah Ebanks

Principal Investigator: Patricia D'Amore, PhD, MBA

Schepens Eye Research Institute of Massachusetts Eye and Ear

VEGF is a key mediator of angiogenesis, the formation of new blood cells, and is essential for cancer development and growth. Upon binding to its primary receptor vascular endothelial growth factor receptor 2 (VEGFR2), VEGFR2 will be activated and internalized for sustained downstream signaling. There are adaptor protein (AP) complexes that mediate intracellular membrane trafficking, but only adaptor protein complex 2 (AP2A2) is expressed on the plasma membrane which is also where VEGFR2 is found. AP2A2 is the subunit alpha of the AP2 adaptor complex that mediates clathrin-dependent endocytosis of membrane proteins. A previous study suggests that AP2 is involved in VEGFR2 clathrin-mediated internalization, whereas the specific role of AP2A2 in VEGF induced angiogenesis is unclear. The aim of this study is to understand the role AP2A2 plays in VEGFR2 internalization and VEGF-induced endothelial cell migration. VEGFR2 internalization is determined by biotinylation assays with or without siAP2A2 knockdown. The cell surface level of VEGFR2 following VEGF stimulation is examined by Western blots, with non-stimulated cells as the control. Migration assays were used to determine the functional role of AP2A2 in VEGF-induced migration. The prevention of VEGFR2 internalization and VEGF-induced endothelial cell migration could negatively regulate tumor angiogenesis and have the potential to be a promising therapeutic strategy.

Reduction of Inflammation Through Activation of PROKR2-Cre Marked Sensory Neurons Triggered by Stretching

Hashem El-Saudi

Principal Investigator: Qiufu Ma, PhD

Scientific Advisors: Shen-Bin Liu, PhD; Lu Qi, PhD

Dana-Farber Cancer Institute

Medical treatment of chronic inflammation has proven to be difficult but alternate methods such as stretching and acupuncture have been used to treat inflammation for thousands of years and have been proven successful. However, the scientific basis on how these alternate methods are able to reduce inflammation is still poorly understood. It is not known if stretching can activate certain sensory neurons which innervate the joint ligament that can act to reduce inflammation. In this study, we hypothesized that a group of sensory neurons marked by Prokr2-Cre can be activated through stretching in order to create anti-inflammatory pathways. This hypothesis is built upon two observations. One is that when activated via acupuncture, this group of sensory neurons has been shown to reduce systemic inflammation by driving the vagal adrenal anti-inflammatory axis. Second, this group of sensory neurons has an innervation to the joint ligament and fascia tissue. To test our hypothesis, we will first build a stretch-induced reduction of inflammation model in mice. Next, we will test if stretching will indeed activate the Prokr2-Cre marked sensory neuron. Third, we will determine if stretch induced reduction of inflammation is dependent on Prokr2-Cre-marked sensory neurons, meaning that in mice with the ablation of these neurons anti-inflammatory effects should be abolished. If our results show that Prokr2-Cre-marked sensory neurons are indeed necessary for the anti-inflammatory effect triggered by stretching, we will for the first time provide a neuroanatomical basis for how stretching may work to control inflammation. We will also discuss the implications if ablation of Prokr2-Cre-marked sensory neurons does not have an impact on stretch-induced anti-inflammatory effects.

Mitochondrial Dysfunction in Myelodysplastic Syndromes

Mali Glemaud-Thesee

Principal Investigator: Laurie H. Glimcher, MD

Scientific Advisors: Shrestha Ghosh, PhD; Mahesh Raundhal, PhD

Dana-Farber Cancer Institute

Myelodysplastic syndromes are a group of clonal hematologic disorders characterized by peripheral blood cytopenia, ineffective hematopoiesis and bone marrow failure. Mitochondrial dysfunction is often associated with MDS. Despite the great advancements in the understanding of the role of mitochondrial dysfunction in myelodysplastic syndromes (MDSs), the root cause of these abnormalities in the mitochondria of MDS cells is still poorly understood. By conducting this research experiment, we hope to assess if the deletion of RPS14 or APC genes, both known to play a role in MDS pathogenesis, leads to mitochondrial dysfunction. Successfully finding the genes responsible for mitochondrial abnormalities in MDS will open a doorway that could further allow us to link these dysfunctions with specific MDS subtypes. With the use of the Mitotracker, Mitosox and TMRE assays coupled with flow cytometry, we will label and identify mitochondrial function in erythroid progenitor cells. We will be using erythroid progenitor cells for this experiment because it is widely known that a majority of MDS patients also suffer anemia. Using CRISPR/Cas9 gene editing, we will knockdown RPS14 and APC genes in TF-1 cells. After confirming successful gene editing via quantitative polymerase chain reaction analysis, mitochondrial function will be measured by flow cytometry. Once the experiment has been conducted, we hope to draw a correlation between the deletions of the genes and mitochondrial functioning in the erythroid progenitor cells. If there is correlation between one of the deletions of the genes and mitochondrial abnormality, this will answer our research question of what causes mitochondrial dysfunction in MDS and will pave paths to further test whether deletion of other genes implicated in MDS similarly lead to mitochondrial dysfunction. This will further aid in the diagnostic/prognostic process of linking mitochondrial dysfunction with MDS subtypes.

Marijuana and Smartphone Apps: A Content Analysis

Gabriela Gonzalez

Principal Investigator: Bettina B. Hoeppner, PhD, MS

Scientific Advisor: Kaitlyn Siegel

Massachusetts General Hospital

With the popularity of smartphones on the rise, apps have become the latest way of promoting knowledge and resources by many industries—including those related to marijuana. Whether it is to promote use or cessation, there are more marijuana related apps than people realize, but there is hardly any information on them. A content analysis conducted by Ramo et al. (2015) on apps that existed in 2014 indicated that while there were numerous apps that promote use, those that pertain to cessation were underrepresented. Since then, several societal changes and upheavals have occurred, including increasing marijuana legalization by different states within the United States and the worldwide COVID-19 pandemic. These upheavals may well have impacted how marijuana is addressed in smartphone apps. To this end we conducted a qualitative study on the top 15 apps in the Apple App Store that appeared using the keywords “marijuana” and “cannabis.” The identified apps were then coded for the absence/presence of the features highlighted by Ramo et al. (2015). Two independent raters rated each app. Discrepant ratings were reviewed and resolved by consensus. The results from the final consensus-rated descriptors will be transferred to a table where the results of both this study and the previous 2014 study can be compared. The findings from this content analysis will not only provide insight on the type of marijuana content being promoted in the Apple App Store, but also how much the content of these apps have changed in 7 years.

The pieces of the puzzle to the Early Detection of Hepatocellular Carcinoma

Ashley Guardado

Principal Investigator: Nabihah Tayob, PhD

Dana-Farber Cancer Institute

Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Hepatocellular carcinoma is an advanced liver cancer that has a low rate of survival and is not treatable for all patients because it is often diagnosed too late. Thus, biomarkers are important for detecting hepatocellular carcinoma early. Our research question is: What biomarkers might be useful for the early detection of hepatocellular carcinoma? To answer this question, we are using data from the HALT-C trial, where demographic information has been collected on 287 randomized patients. In this trial connections are made between the patient’s background and their social lives to their diagnosis of liver disease or hepatocellular carcinoma. The data that was collected from the HALT-C trial was analyzed to find the possible effectiveness and performance of biomarkers. Analysis is still ongoing, but the goal is to assess if biomarkers could help detect HCC earlier to improve patient outcomes such as survival. Hepatocellular carcinoma is not an easily treatable cancer, particularly when diagnosed in later stages, therefore biomarkers can be helpful if they are used to detect cancer early.

Resistance to toxicity of chemotherapeutic drugs on cancer cells

Sami Haily

Principal Investigator: Stephanie Mohr, PhD

Scientific Advisors: Raghuvir Viswanatha, PhD; Matthew Butnaru, PhD

Dana-Farber Cancer Institute; Harvard Medical School

Cancer is the second-leading cause of death in the United States. To combat this, there is a need to develop new drug treatments, especially in situations where cancer cells develop resistance to current drug treatments. We used CRISPR-Cas9 to conduct a screen to identify genes involved in cancer drug resistance in Drosophila cells. In our screen, our goal was to identify genes involved in resistance to doxorubicin treatment, a chemotherapy drug used in cancer treatment. Potential candidates will be genes that are highly enriched in cells treated with doxorubicin compared to control cells. TOP2 was found in our screen as having the highest resistance to doxorubicin treatment. Future studies will be needed to follow up on the role of TOP2 and other genes that could be involved in doxorubicin resistance. Data from our screen and follow-up studies can potentially help with developing new treatments for doxorubicin resistant cells.

Is Flow Cytometry Effective for Capturing Rare Immune Checkpoint Markers?

Priscila Haro

Principal Investigator: Jerome Ritz, MD

Scientific Advisors: Carol Reynolds, PhD; Max Halpern, BA

Dana-Farber Cancer Institute

Immunotherapy has dominated research in recent years because of its distinctive approach to specifically recognize cancer cells. In fact, the primary treatment option for hematological malignancies has been used in combination with chemotherapy and immunotherapy due to recent advances which has beneficial implications for patients. That being said, immunotherapy can only do so much unless we analyze the patient's biomarkers in order to better understand how each patient's specific cancer will respond to their immune system. Flow cytometry, a technique used to measure cell size, shape, internal (granularity) complexity, and cell lineage, is essential in this line of inquiry because it allows for the identification of cell types in blood samples. This tool is essential for moderating the changes of a patient's immune system at a cellular level which can then illuminate patterns through the course of their treatment. By capturing high-definition snapshots of their cellular makeup, specifically rarer immune markers/checkpoints, it can increase an understanding of the mechanisms of the patient's immune response and development in use of immunotherapy. Ultimately, using tools like flow cytometry can help pin down rare immune checkpoint markers and can help us put together the pieces of the puzzle we call blood cancer.

The correlation of salmonella and colon cancer in the US and higher poverty states

Yelena Hernandez Bonilla

Principal Investigator: Jaime E. Hart, ScD

Dana-Farber Cancer Institute

Colon cancer is the third most commonly diagnosed cancer and fourth leading cause of cancer death in the United States. Many risk factors for colon cancer are known, however the role of food borne illness is only just emerging. Additionally, a large number of studies have shown disparities in colon cancer incidence by race/ethnicity and other measures of socioeconomic status. The goal of our study was to look at correlations between rates of foodborne illnesses and cancer, and to see if these correlations differed by income. Our hypothesis was that areas with higher rates of Salmonella infections would have higher rates of colon cancer incidence, as an emerging literature has shown this to be a risk factor. To date, there is no published research on this relationship that incorporates information on socioeconomic status, so our research aims to fill this gap. We obtained data from the Centers for Disease Control (CDC) on statewide rates of salmonella infections and colon cancer incidents. Socioeconomic status data were obtained from the US Census. In 2018, there were 37 new colon cancers diagnosed per 100,000 people. There were 16.7 Salmonella infections per 100,000 people. In simple linear regression models, there was an association between Salmonella infections and incidence of colon cancer, which was stronger in higher-poverty states. In conclusion, foodborne illnesses may be an emerging risk factor for colon cancer, and the disparities in these infections may explain some of the observed disparities in colon cancer risk.

Utilizing Exercise as a Rehabilitative Measure to Counter Cardiotoxicities in Cancer Patients Undergoing Chemotherapy: A Literature Review

Chaimaa Hossaini

Principal Investigator: Christina Dieli-Conwright PhD, MPH

Scientific Advisors: Mary K. Norris; Rebekah Wilson PhD; Dong-Woo Kang PhD

Dana-Farber Cancer Institute

Chemotherapies treat cancer patients by attacking rapidly dividing cells. Specific therapies, such as anthracyclines, have been shown to harm the cardiovascular system and often reduce efficacy when treating cancer patients. These issues are often referred to as cardiotoxicities, which is when cardiac muscle is damaged. Known deficiencies of the current research are the lack of human-based clinical trials, the lack of integrating the influence of race and ethnicity of the patients on patient outcomes, and whether cancer patients with no past cardiological concerns are treated to the same extent as patients with pre-existing cardiological conditions. Many studies have shown that exercise has improved the quality of life of patients undergoing chemotherapy that developed cardiotoxicities. Using data extraction from other research on the topic at hand, the review discusses the different types of potential cardiotoxicities that a patient may encounter, how these cardiotoxicities affect not only the cardiovascular system but can also contribute to the increased chance of the development of other comorbidities and how exercise is a potential rehabilitative solution to address those issues. Understanding how these cardiotoxicities come to be and to use a cost-effective solution such as exercise can aid a plethora of populations that may not have the ability to access proper healthcare and assess other underlying conditions such as diabetes and other comorbidities.

Exploring Combinatorial Strategies in Advanced Prostate Cancer

Osasenaga Idahor

Principal Investigator: Himisha Beltran, MD

Scientific Advisor: Varadha Balaji Venkadakrishnan, PhD

Dana-Farber Cancer Institute

Prostate cancer is the second leading cause of male cancer death in the United States. The majority of these deaths are attributable to the development of therapy resistance. While hormonal therapies targeting the androgen receptor (AR) are initially effective for the majority of patients with metastatic prostate cancer, we and others have defined a subset of treatment-resistant prostate cancers that undergo lineage plasticity and resist AR-directed therapy. This manifests clinically as a histologic transformation from an AR-driven prostate adenocarcinoma to an AR-negative small-cell/neuroendocrine prostate cancer (NEPC). NEPC represents up to 15-20% of late-stage prostate cancer and is associated with poor prognosis. Our lab identified epigenetic factors as important mediators of lineage plasticity and the development of NEPC. Some of these factors may be exploited as therapeutic targets. However, we found that single-agent targeting of epigenetic regulator(s) yielded only a modest effect in reducing NEPC cell viability and reversing lineage plasticity. Combinatorial targeting of epigenetic regulators remains unexplored in NEPC but show marked effects in other cancers.

Assessing Social Support Aspects of Digital Health Apps for Black or African American Breast Cancer Survivors

Phedjina Jean

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Surviving cancer is a tremendous achievement. A strong support system may play an important role in the cancer survivorship and prevention processes.
The purpose of this study is to examine the extent to which commercially available smartphone applications (apps) for the promotion of physical activity provide social support for Black/African American (BAA) breast cancer survivors and at-risk relatives. We aim to evaluate the existence of mHealth apps that have been designed to promote better health and physical activities for African/Black breast cancer survivors and the Black/African American population. A larger study found 76 apps in the Google and Apple Stores that were designed to promote physical activity or reduce sedentary time for either breast cancer survivors or the general population. An assessment tool was developed to analyze the content of the apps, which included questions about social networking and social support aspects, mainly focusing on ways individuals can interact with one another, such as group calls, group activities, and small interactive group events taking place near them. The analyses of the apps are currently in process. Smartphone apps may provide a place that allows people who have similar life journeys and milestones to connect and potentially encourage each other to engage in healthy behaviors to improve survivorship and prevention.

Understanding DNA damage during EMT in cancer

Donald Johnston

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Scientific Advisor: Jacob Matson PhD

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Epithelial to Mesenchymal Transition (EMT) is the process by which epithelial cells show a mesenchymal phenotype for wound healing and other development processes. EMT also affects cancer in that this process allows metastasis, where cells move around the body leading to a metastatic growth. This is really important because the majority of cancer deaths are from cancer metastasis. The research that we are doing is looking at DNA damage during the EMT process in combination with TGF-B, which is important to jump start the process of EMT. My question is how does targeting the EMT pathway specifically impact DNA damage and is the damage pathway specific? We induced EMT specifically with an engineered cell line and measured the response to DNA damage with western blots. We expect to see higher amounts of DNA damage when ATR inhibitor is added to cells during EMT. These findings are important in that it will help how we can better target cells with DNA damage during EMT. Also, these findings could help us better treat cancer cells so that metastasis is less likely to occur, or to allow metastatic cells that have already spread to be killed.

Association of Prostate Cancer Risk Variants with Gene Expression in Stroma

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Approximately 240,000 men are diagnosed with prostate cancer and 34,000 die from it each year in the United States. Other than the epithelial tumor, the predominant cells in the stroma consist of fibroblasts and myofibroblasts. The stroma tissue will change during malignancy and promote growth of the disease along with metastasis. There are few risk factors known today for prostate cancer, but there are several inherited genetic variants found to be associated with risk of prostate cancer. Thus, there is a need to find what gene(s) are associated with those prostate cancer risk variants. The prostate cancer genetic risk variants and prostate tissue stromal expression (measured by RNA-sequencing) were available from prostate cancer cases in the Health Professionals Follow-up Study and Physicians' Health Study. After excluding samples of poor data quality of gene expression, we included 181 samples that consisted of 116 stromal tumor tissue samples and 65 stromal normal tissue samples. We selected 7 SNPs (single nucleotide polymorphism, rs10993994, rs7127900, rs2292884, rs5945619, rs7629490, rs12653946 and rs77559646). We used a linear model to test the association between each SNP and expression of the local gene using the R package Matrix eQTL. $P < 0.05$ was considered statistically significant. In stroma adjacent to tumor, rs7629490 was significantly associated with VGLL3 ($P = 0.02$); rs12653946 was significantly associated with IRX4 ($P = 0.02$); rs77559646 was significantly associated with CAPN10 ($P = 0.05$). For stroma distant from the tumor, rs2292884 was significantly associated with RAB17 ($P = 0.007$), COPS8 ($P = 0.02$), and ILKAP ($P = 0.02$), respectively; rs12653946 was significantly associated with SLC12A7 ($P = 0.003$. In conclusion, we observed some previously reported associations but also novel associations which may suggest genes that contribute to prostate cancer risk within the stromal tissue.

Differentiation lineage of cholangiocarcinoma associates with distinct oncogenic alteration and genetic dependency

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Cholangiocarcinoma (CCA) is an aggressive type of biliary tract cancer that is often detected in its late stages, leading to non-beneficial treatment outcomes and poor survival rates. CCA is divided into subtypes: ICCA, pCCA, and dCCA based on their anatomical locations which harbor distinct differentiation lineages. CCA can be promoted by various types of genetic alterations, including IDH1/2 mutations and loss of CDKN2A. Studies have shown that specific genetic alterations can be associated with certain CCA subtypes and lineages. For example, hot-spot mutations in IDH genes are commonly found in Intrahepatic cholangiocarcinoma (ICCA) associated with a lineage of liver hepatocytes. The focus of this research is to analyze linkage of ductal cell lineage in CCA often with the loss of CDKN2A to specific genetic dependencies that may suggest useful drug sensitivity of the tumor. By using the cancer dependency map from the Broad Institute, we will analyze the correlation between CDKN2A deletion and its collaterally affected genes that result in synthetic lethality. This will help us better understand the mechanisms behind CCA tumorigenesis and form the foundation for new treatment methods.

Misinformation Surrounding Diet, Nutrition, and Cancer Risk

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The American Cancer Society states that, “eating a healthy diet may greatly reduce a person’s lifetime risk of developing cancer” (2020). While this is a known and greatly studied concept surrounding diet and cancer risk, the specifics of what constitutes a “healthy diet” is much more debated and often contains a multitude of misinformation, especially when looking at the public’s perception toward diet. By looking at exposures such as red meat, curcumin, and aspartame, we see a wide variety in how diet and nutrition can affect cancer risk and how studies themselves contradict one another. The clarity among certain exposures is important to dissect because they often have disproportionate impacts among different socioeconomic classes, racial divisions, or specific communities (2009). If this disparity does exist, eliminating the inaccuracies could help all people, of all different communities gain more clarity into what they are eating and how it will affect their health.

Quantifying Accelerated Aging in Pediatric Brain Tumor Survivors

Soomin Lee

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Cancer and its treatment regimens have been linked to accelerated aging in survivors. However, while there has been an increase in studies focusing on this association, there has been no substantial data for pediatric survivors specifically, especially with the rising biomarker ΔBrainAGE, which quantifies the discrepancy between MRI-predicted age and actual chronological age. In order to quantify the accelerated aging in pediatric brain tumor survivors, the lab is conducting a study featuring T1-weighted brain MRIs from pediatric patients in order to develop a brain age predictor for children ages 0-22 years. This would quantify normal and disease/treatment-related aging in pediatric brain tumor survivors. We developed a report analyzing and summarizing results found in research articles on premature aging in cancer survivors. All of the evidence in these papers suggests that the cancer development and treatments cause accelerated aging in survivors, and highlights the importance of examining this consequence in less studied populations like children. While most of these studies were observational and qualitative in nature, some major open questions are: to what extent do survivors of pediatric brain tumors undergo abnormal aging, how their abnormal aging is related to treatment, demographics, and other factors, and whether quantifying such abnormal aging can serve as a biomarker to predict future neurocognitive outcomes early on. By establishing ΔBrainAGE as a quantitative biomarker to predict a cancer survivor's outcomes, the potential age predictor can identify survivors at high risk for abnormal neurocognitive developments and aging due to certain treatments. These high risk patients are perfect target patients for ongoing and future therapeutic trials that aim to further optimize tumor care for not just cures but improved quality of life after cure. This novel study and technique will be able to follow patients to optimize current and future cancer treatments and post-treatment life in order to improve neurocognitive outcomes in cancer survivors and potentially other diseases, as well.

The Effect of Bone Marrow Transplants on Patients Diagnosed with Acute Myeloid Leukemia

Maajda Louaddi

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Acute Myeloid Leukemia (AML) is a cancer within the blood and bone marrow. Chemotherapy is first used to kill these rapidly dividing cancerous cells. Following chemotherapy that will eradicate all of the cancerous and non-cancerous cells in the bone marrow, a bone marrow transplant (BMT) may be used. Different factors can impact outcomes for these patients and can be evaluated for risk of poor outcomes. One of the poor outcomes is graft-versus-host disease (GVHD), a condition in which the donor cells attack healthy cells. The following factors will be evaluated in this study: age; sex; body mass index (BMI), blood glucose, which can impact immune cell function; neutrophils, one of the key immune cells that fight harmful microorganisms; and acute GVHD (AGVHD). The study question was: how does a BMT affect the cells and health of patients diagnosed with AML? We used descriptive statistics and correlation analysis on a data set of 24 patients with AML who received a BMT. Findings included that large neutrophil counts correlated with a decreased risk of AGVHD, as well as a lower risk of cancer relapse. Higher levels of maximum glucose tended to have a great risk of relapsing. BMI was not associated with AGVHD or relapse in this patient group. Observing the different effects of a variety of measurements can lead to better care and outcomes for AML patients who received a BMT.

Geo Mapping to Facilitate Minority Recruitment in Clinical Trials for PAD Screening

Lainie Louis-Jame

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Peripheral artery disease (PAD) is a manifestation of atherosclerosis affecting arteries in the lower limbs. However, the classic symptom of PAD, intermittent claudication is absent in the majority of patients, leading to many patients staying undiagnosed. As a result of this, advanced PAD becomes more common, leading to around 150,000 Americans to undergo limb amputation for PAD annually and this burden falls disproportionately on minority communities, especially in Black and Hispanic communities. Knowing this, recruiting minority participants disproportionately affected by PAD in clinical trials aimed at the disease can both help decrease the population prevalence of advanced PAD and dismantle health disparities. While there are interventions in place to educate and promote screening for conditions such as PAD, these interventions have not been adequately tested among disadvantaged minorities who are ideal participants for screening interventions. Realizing this, the Area Deprivation Index (ADI) is a tool for ranking neighborhoods by the socioeconomic disadvantage in a region of interest. The ADI has been researched and deemed a beneficial tool in assessing neighborhood socioeconomic disadvantage and has been correlated with the health of a community. The purpose of this project was to find the potential applications of the Area Deprivation Index in a clinical trial of PAD screening in minority populations. Participants in the trial will be recruited through several methods targeting high-risk minority groups. We created a 'geomap' of the ADI to identify recruitment areas for the trial. The state of Massachusetts was first geo-mapped to highlight areas where the most disadvantaged minorities (high ADI) lived and additional layers were added to the map to indicate other locations (Optum Care Outpatient Clinics, and Federally Qualified Health Centers) from which participants will be enrolled. Finally, the PAD screening centers were mapped to ensure proximity to recruitment areas. By doing this, we hope to achieve our recruitment goals in this minority-only clinical trial by lowering barriers to participation.

Demographics of Patients from the MGH Chelsea Testing Site by Risk Factors and Trends by Risk Factors During the Pandemic

Segovia Lucas

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Obesity and smoking are both risk factors for severe COVID-19 and cancer. Much of the pandemic research thus far looks at social determinants across the country, and often underserved communities are overlooked due to their COVID-19 statistics being combined with affluent cities. This body of work focuses specifically on an underserved community in Chelsea, MA and its social determinants. Chelsea, MA is a majority Latino community and is disproportionately affected by obesity, having lower percentages of the population finishing high school and obtaining a bachelor's degree than the rest of Massachusetts. I used MGH Chelsea data and census data and conducted a literature review for background to understand what health disparities Chelsea and other underserved communities face. Patients in underserved communities were at higher risk for facing many of these social determinants of health, such as not obtaining a bachelor's degree, English not being a first language, and being on public insurance. Communities like Chelsea are more likely to have higher rates of COVID-19 and experience a greater amount of illness due to their complex medical landscape. Many of these social determinants identified during COVID-19 also contribute to long-term risks for cardiovascular disease and cancer development. The findings of this literature review highlights the need for more public health interventions in underserved communities post-COVID-19.

Cytokine Induced Memory-Like Natural Killer Cells for the Treatment of Myeloid Leukemia

Alba Martini

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Cell-based cancer immunotherapy has successfully utilized the engineered chimeric antigen receptor (CAR) Natural Killer cells and T cells in novel treatments against hematologic malignancies. Compared to CAR-T cells, the CAR-NK cells present with the advantages of shorter production time, minimal Severe Cytokine Release Syndrome (SCRS), and reduced risk for graft-versus-host disease from allogeneic donors. NK cells can be cytokine-activated with Interleukin (IL)-12, IL-15 and IL-18 to induce memory-like functions and enhanced response to target acute myeloid leukemia (AML) tumor cells in vitro. NK cells were purified with CD3-CD56+, activated with IL-12, IL-15 and IL-18 and washed to generate cytokine induced memory-like (CIML)- NK cells. CIML-NK cells showed an enhanced expression of Interferon (IFN)-γ that is crucial in the anti-tumor response. This new approach has shown promising potential in integrating CIML-NK cells in future immunotherapies in treating liquid and solid tumors.

The importance of exercise oncology

Paola Meadows-Muriel

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Exercise oncology is a growing field that in recent years has made great progress in cancer treatment. Although there are many published works about the importance of exercise, there is a lack of research on the biological mechanisms involved that make exercise effective for cancer patients. More studies must be conducted to be able to identify useful ways to prescribe exercise, interpret what components of the immune system can be exploited, and identify other helpful biomarkers. To solve this problem, we looked at many articles about the impact of exercise in cancer patients of diverse backgrounds and extracted data from them to gather all the knowledge we can that is known about exercise oncology. From here we can determine the most effective exercises and can begin identifying what specifically is happening within the body when you combine exercise and immunotherapies.

This research is helpful in that it has numerous future applications, demonstrating that exercise can play a large role in changing our biological mechanism. From these applications, we can then exploit and utilize exercise and immunotherapies to stop the spread of cancer. This could not only lead to less intense and aggressive cancers but can also improve the quality of life in cancer patients. Exercise can combat tumor growth and slow the progression of the cancer but can also potentially be a form of cancer prevention.

Breast Cancer Predisposition in Middle Eastern Patients

Hirlary Mendez Pena

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Despite best efforts to narrow down major genetic factors that may predispose one to develop breast cancer, studies and data are mainly limited to mainly European ancestry. However, this leaves populations from non-European ancestry at a disadvantage, since there can be differences in genetic makeup across individuals from geographically diverse areas and different racial and ethnic ancestry. Thus, there may be additional genes that influence susceptibility of developing breast cancer. In our attempts to expand data to study breast cancer predisposition in non-European ancestry patients, we were able to acquire a sample of 240 breast cancer patient genetic information from individuals of Middle Eastern descent. Using coding language R, we plan to narrow down genes which may be a factor in breast cancer susceptibility in these patients. We plan to compare the data we obtain to genes identified in datasets of European ancestry. This work has the potential to identify new targets to investigate predisposition to breast cancer.

The Role of Platelet Angiopoietin-1 in Endothelial Cell Activation

Andrea Mines

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Brigham and Women's Hospital

Metastasis, the spread of cancer cells from the primary tumor to surrounding tissues and to distant organs, is responsible for approximately 90% of all cancer deaths. Targeting this hallmark of cancer is a crucial aspect of advancing the current treatments for cancer. Platelets are an integral part of hemostasis and the subsequent wound healing process and have granules which store a plethora of angiogenic regulators. Angiogenesis is the development of blood vessels, triggered by the release of proangiogenic regulators following platelet activation. Platelets have the potential to be effective targets for anti-metastasis therapies by controlling expression and release of these pro-angiogenic factors, such as Angiopoietin-1 (Ang-1). Previous studies have investigated the role and potential of Ang-1 as a target for anti-cancer therapy. I further this investigation by studying the interaction and activation of tumor cells with endothelial cells, an essential stage of angiogenesis and thus metastasis. I perform cell adhesion assays between SVEC 4-10 and MET1-GFP cells under conditions with varying levels of Ang-1. Flow Cytometry is also used to detect the activation of SVEC 4-10 by MET1-GFP cells under these same conditions. Further, I can relate these findings to platelets as a target for treating cancer metastasis as they provide insight into the mechanism by which platelets release Ang-1 into the surrounding blood.

Micronucleus Development and Transcription in Osteosarcoma and Retinal Pigment Epithelial Cells

Hawa Ndiaye

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Micronuclei are small nuclear bodies that contain chromosomes and chromosome fragments outside of the primary nucleus. Since the micronuclei have an unstable nuclear envelope, they rupture and expose their DNA content to the cytoplasm. When the micronucleus ruptures, it disrupts transcription in Retinal Pigment Epithelial Cells. When a cell goes through mitosis, the micronuclear chromosomes could be incorporated into the primary nuclei. As a result, micronuclei may affect transcription in the primary nucleus as well. But could we see the same outcome in human bone osteosarcoma cells (U2OS)? We used nocodazole to arrest cells and induce micronuclei formation. We then tested if transcription in the micronucleus is defective and if reincorporated chromosomes would corrupt transcription in the primary nucleus in U2OS cells. This was done through the method of immunofluorescence of gammaH2AX, MDC1, and 53BP1 that were used to monitor DNA damage in the micronucleus and primary nucleus. MDC1 protein tracked incorporation of micronuclei to the primary nucleus. When studying micronuclei, it was important to also understand if ruptured micronuclei lose their transcription machinery. We tracked the nucleus' ability to transcribe through immunofluorescence against two antigens, RNAPolIIs5 and H3K27ac. As a result, we evaluated transcription in micronuclei before and after their incorporation into the primary nucleus. This research expands the knowledge of how micronuclei function and strengthens the understanding of how they might contribute to tumorigenesis.

Is flow cytometry effective for capturing rare immune checkpoint markers on CAR-T cells?

Abigaelle Norbrun

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The latest advances in immunotherapy are centered around the novel Chimeric Antigen Receptor T cell (CAR-T cell) therapy in combination with flow cytometry assays to capture distinct features of cells. This new immunotherapy was initially discovered many decades ago and is now seeing a resurgence in cancer research and clinical treatment protocols. The use of CAR-T cell therapy is most prominent in hematopoietic and B-cell malignancies as a way to facilitate and improve the immune system's response in fighting tumor cells. By extracting blood samples from patients and harvesting their T-cells, Chimeric Antigen Receptors (CARs) are engineered using a retrovirus that introduces new genetic information to identify tumorous cells. In order to best understand the distinct features of each patient's cells, samples are analyzed using flow cytometry assays that measure cell size, shape, granularity, and assess lineage. The effectiveness of flow cytometry is most apparent when comparing and analyzing the specific immune checkpoints that are found on cancer cells. Using various lasers at different wavelengths, cell surface markers are shown when light is emitted by the fluorescent monoclonal antibodies used in flow cytometry. The combination of CAR-T cell therapy and flow cytometry will continue to discover and identify more cell surface markers for the benefit of immunotherapy. Considering the surge of CAR-T cell therapy, there are some adverse effects that include cytotoxicity and anaphylaxis. Nonetheless, its bright future lies ahead in redefining cell surface markers and treating solid tumors as well.

Splenic irradiation uses pre-hematopoietic stem cell transplant for patients with myelofibrosis

Roxana Portillo

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Massachusetts General Hospital

Myelofibrosis (MF) is a hematologic neoplasm in which excessive scar tissue forms in the bone marrow, preventing the process of hematopoiesis from occurring. Patients suffering from MF often show signs of splenomegaly. Hematopoietic stem cell transplantation (HSCT) is the only curative treatment for MF. However, massive splenomegaly is considered to be a factor in determining the effectiveness of this treatment in patients as it may lead to delayed engraftment or cause graft failure overall. Splenic irradiation (SI) is a procedure that is done pre-transplantation in order to shrink the spleen pre-HSCT in the hopes of improving engraftment. The use of a procedure, either a splenectomy or SI, that assists in reducing the spleen size in patients with MF pre-transplantation is currently a debated topic. In this study, we performed a retrospective chart review of 48 patients that underwent HSCT at Massachusetts General Hospital between 2011-2021. All of the patients were diagnosed with a form of MF and were observed for a median of 4 years following their initial transplant. We compared the outcome of the transplanted patients who received splenic irradiation pre-transplant to those who did not. We hypothesized that patients that underwent SI had improved engraftment rates post-transplant without complications, a shorter hospitalization, and a reduced chance of death post-transplant.

Understanding nutrition and its impact on pediatric brain tumor survivors

Bertha Posada Villanueva

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Dana-Farber Cancer Institute

Nutrition is an important component of how people take care of their bodies. The emphasis on nutrition is set from an early age to further develop in the adult stages of life. Data has shown that nutrition affects the survivorship of pediatric brain tumor patients. However, the data has only demonstrated an improvement of nutritional aspects for a short period. Long-term research is needed to develop the correlation and findings further. Survivorship is novel research due to the medical advances and treatments that have increased the survival rates. Despite the increase, survivors are prone to long-term chronic illnesses because of therapy and nutrition. Researching this topic is vital because it also extends to the continuum of care and the need to see the impact nutrition has on pediatric brain tumor survivors. This body of work uses three articles about nutrition, cancer, and how they both are connected between different studies. It also uses knowledge from observing clinical sessions. Furthermore, it establishes nutritional deficit and physical activity as an impact on survivorship. Nutrition has to be monitored from the beginning of treatment to potentially decrease the risks of long-term chronic illness.

Is there a solution to the low survival rates in GIST surgery patients?

Camilla Quintana

Principal Investigator: Jiping Wang, MD, PhD

Scientific Advisor: Mark Fairweather, MD

Dana-Farber Cancer Institute

Surgery in gastrointestinal stromal tumors (GIST) has evolved into a recurring battle to improve the survival rate of patients. With varying sizes, surgeons have spent decades trying to find the ultimate surgery that is the most non-invasive, promises and shows progression free survival, and completely extracts the tumor. The research I am conducting consists of shadowing and observing how these surgeons at Brigham and Women's Hospital / Dana-Farber Cancer Institute approach the problem of survival in surgery in GIST. Although several doctors from across the globe have attempted to solve progression free and overall survival in GIST patients, this ongoing investigation stems from two of the most dangerous GISTs which are large and metastatic. I tackled the issue of understanding survival in GIST by reading and annotating scientific papers and analyzing clinical data. From my research, I learned that in a case that dealt with figuring out if laparoscopic surgery for large gastric GIST was feasible, it was concluded that laparoscopic surgery would be a good alternative to open surgery for GISTs larger than 5cm when performed by a skillful surgeon who is very familiar with neoplastic characteristics of GIST. However, one case that dealt with tackling surgery of residual disease following molecular-targeted therapy with Imatinib in advanced/metastatic GIST concluded that the studies presented did not encourage surgery of residual disease. The impact of my research furthers my understanding of diseases that are not advocated. The work to improve survival rates in GIST patients is constantly a work in progress.

Evaluating the Safety and Efficacy of COVID-19 Vaccination in Patients with Lung Cancer

Julia Rivera

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Primary Ovarian Insufficiency (POI) is the deterioration of proper ovarian function Multiple FDA-approved vaccines have been developed against the COVID-19 virus, which has impacted the lives of individuals worldwide. The vaccines were proven safe and effective in individuals with limited medical comorbidities, but it is still unknown if cancer patients experience different rates of seroconversion due to their disease or clinical treatment. Therefore, we sought to analyze the effectiveness of COVID-19 vaccination in cancer patients treated at the Massachusetts General Hospital Cancer Center, with a specific focus on lung cancer patients and the effect of their cancer treatment on vaccine efficacy. In this study of 50 patients with lung cancer who underwent COVID-19 vaccination, 62% harbored targetable oncogenes (such as EGFR, ALK, ROS1, RET, KRAS, BRAF) and 66% were current or former smokers. 70% were diagnosed with stage IV disease and the remaining 30% had stage I-III disease. Within this cohort, the most common side effect from vaccination was pain in the injected arm, occurring in 44% (22/50) and 34% (17/50) of patients following their first and final doses of vaccine, respectively. Notably, 38% (19/50) and 26% (13/50) of patients experienced no side effects from the vaccine following their first and final doses, respectively. These data support the overall safety of the COVID-19 vaccine across a heterogeneous group of lung cancer patients. Our ongoing analysis will explore the relationship between anti-cancer treatment (chemotherapy, radiation, and surgery), vaccine side effects, and the effectiveness of each type of COVID-19 vaccine in terms of seroconversion rates.

Crystallography and Its Use in Creating a Better Drug for Lung Cancer

Jhasmer Santana

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Scientific Advisor: Tyler S. Beyett, PhD

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Lung cancer is the second most common cancer with EGFR (epidermal growth factor receptor) mutations being a leading cause. Only some drugs inhibit EGFR enough, and have low enough toxicity to be considered selective, which is how well a drug affects a certain protein. Although there are many drugs to combat this, there are some cancers that are drug resistant. Poziotinib is a drug in human trials that works for some resistant cancers but has high inhibition of wild-type EGFR, an undesirable outcome. This lack of mutant selectivity is important, because if a drug such as poziotinib were given to a patient, it can do more harm to the patient as it has a higher toxicity level than a selective drug targeting mutant EGFR. In order to study drugs like poziotinib, the protein has to be purified. Using purified EGFR protein, we performed inhibition assays to look into the selectivity of poziotinib and other inhibitors for wild-type and mutant proteins. We also crystallized the purified protein to get a crystal structure of the protein and how it binds to the drug. Improving selectivity can make poziotinib more effective and improve the quality of life for the patient by allowing drugs to be used at dosages that do not inhibit wild-type protein. This work is helpful because it may show ways to modify poziotinib to better inhibit the EGFR mutation without all of its serious side effects from inhibiting wild-type EGFR.

Understanding the role of RB in the cellular response to DNA damage reagents

Mariam Sirage

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Scientific Advisors: Camille Cushman; Hembly Riveras

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Introduction: The retinoblastoma (RB) protein is a cell cycle regulator that controls cell entry into S phase. In non-cycling cells, RB is bound to the E2F2 transcription factor, which represses early cell cycle gene expression. RB dissociates from E2F2 when it is hyperphosphorylated by cyclin D, cyclin E, and the accompanying cyclin-dependent kinases (CDKs), which are upregulated and activated by high growth factor levels. RB release of E2F2 leads to transactivation of cell cycle genes required for DNA replication and S phase entry. Many cancers have mutated RB and the functional status of cell cycle regulators like RB can contribute to chemotherapy treatment outcomes. What role does the RB protein play in response to DNA damage-causing chemotherapy drugs? We hypothesize that RB loss confers resistance to DNA damaging agents through transcriptional activation of DNA replication and repair machinery.

Methods: Using the CRISPR-Cas9 system, we aim to knock out the RB protein in non-small lung cancer A549 cells, which express the wild-type RB1 gene. To this end, we first designed two distinct guide RNAs that target the RB1 gene. Using restriction enzyme cloning, we cloned these guide RNAs into plasmids that contained the necessary Cas9 scaffold sequence and a promoter. We then validated these plasmids via sequencing. Following that, we performed golden gate assembly cloning to generate a multiguide plasmid that contains the two guide RNAs against RB, two non-targeting guide RNAs, and a ds-RED reporter gene. The reporter protein will help us by allowing us to see which cells received the final vector. We will then assess the efficiency of the RB1 knockout by immunoblot.

Results: We expect that introduction of the RB1 multiguide vector will lead to the expression and production of the RFP reporter. Future experiments will focus on validating whether expression of the RB1 targeting guide RNAs will lead to knockout of the RB1 gene.

Conclusion: Given the important role of the cell cycle in cancer development, cell cycle regulation is a critical area of cancer research. RB is a key cell cycle regulator commonly mutated in cancer. Furthering our understanding of the RB protein and its role in cancer responses to DNA damaging agents allows us to create more effective target therapies.

APC mutation with colorectal cancer

Zion St. Fort

Principal Investigator: Danielle Braun, PhD

Scientific Advisor: Theo Huang, PhD

Dana-Farber Cancer Institute

Mutations in the APC gene seem to be apparent in cases involving colorectal cancer. This work reviews the literature to study an association between the APC mutation and colorectal cancer. Knowing this information can help prevention of colorectal cancer because it can lead to more screenings and possibly earlier detection of the cancer. The research question at hand is, what is the risk of getting colorectal cancer if you have a mutated APC gene? To begin to address this question, a review was conducted through a Google Scholar search with keywords: hereditary colorectal cancer, and APC mutation in colorectal cancer. Articles that were published within the years 2000 and 2021 were reviewed. A study conducted by Preisler et al. (2021) shows that there were different proliferation rates in different mutated APC germlines. It shows that the tumors resulting from APC mutation in colorectal cancer tumors are not a straight line and need to be handled accordingly. With an APC mutation, colorectal cancer tumors can start developing at 10 years old and become very severe by the age of 40 based on Lynch et al (2003). APC mutations can also trigger Familial adenomatous polyposis (FAP), which can develop into colorectal cancer. It is important to conduct research on the association between APC mutations and colorectal cancer because the APC mutations in colorectal cancer tumors are prevalent according to Fodde et al (2002) and finding a way to prevent the APC from mutating may help lower the amount of colorectal cancer patients.

REGENERATE: Racial/ethnic Equity in GENetic Education, Risk Assessment, and TEsting

Reem Sulieman

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Approximately 7-10% of pancreatic ductal adenocarcinoma (PDAC) cases are due to a deleterious germline variant. The five year survival rate for patients diagnosed with PDAC is only 10%. However, early detection of PDAC through genetic education and testing can identify these variants and lead to PDAC cancer surveillance, early cancer detection, and interception. Previous research has evaluated the efficacy of traditional cascade genetic testing, but no studies have yet been conducted on remote methods for genetic education and testing among patients at risk for hereditary PDAC addressing low genetic testing uptake. GENetic Education, Risk Assessment, and TEsting (GENERATE), the parent study for Racial/ethnic Equity in GENetic Education, Risk Assessment, and TEsting (REGENERATE), has found that online genetic education and testing is an effective alternative to traditional cascade genetic testing. However, despite Black and Latino/a/x populations having disproportionately higher PDAC incidence and mortality rates as well as lower survival outcomes, the majority of study participants self-identified as White/Caucasian (n=577; 97%). REGENERATE seeks to address the low enrollment of Black and Latino/a/x individuals in the GENERATE study by utilizing information gathered from community stakeholders and designing REGENERATE to be linguistically appropriate and culturally sensitive. The goal is that through appropriate genetic education, testing, and early screening interventions, there will be cancer interception of PDAC cases across Black populations, resulting in a decrease in PDAC incidence and mortality, and an increase in survival outcomes among Black and Latino/a/x groups.

The Impacts of the Social Determinants of Health on Patients Treated With Radiation Oncology

Prionti Talukdar

Principal Investigator: Helen Shih, MD

Scientific Advisor: Audrey Aitelli

Dana-Farber Cancer Institute

Social Determinants of Health (SDOH) not only can determine one's overall health but may also impact one's healthcare treatment in terms of one's access to proper care, treatment, and other variables which may impact one's treatment in the future. The SDOH takes into account where we reside, learn, work, and grow and variables such as one's financial state or education. Dr. Shih's lab will perform 100 patient interviews in order to understand different variables in relation to the Social Determinants of Health on patients who receive radiation therapy for all kinds of cancers. Exclusion criteria consists of those under the age 18, prisoners or inmates, non-English speakers, and those who are unable to consent. Data will be collected through interviews using a survey which asks about SDOH variables directly and EPIC medical records to understand the patient's treatment. Data will be recorded and analyzed to determine common response variables, and to encourage discussion around methods of care for those who are disproportionately affected by SDOH. Out of the 35 patients who have been surveyed, results indicate that most people (24 patients) are able to see or talk to people that they care about five or more days a week. This study is ongoing and will be important for understanding how to improve radiation therapy treatment for patients.

An Insight into Health Disparities, Prostate Cancer, and Genomics.

Kevin Tesorero Lopez

Principal Investigator: Lorelei A. Mucci, MPH, ScD

Scientific Advisors: J. Bailey Vaselkiv, MPH; Katherine Kutzer

Dana-Farber Cancer Institute

Background. Prostate cancer is the most commonly diagnosed cancer among men in the United States, and the second leading cause of cancer death in men. The observed connections between social factors and health disparities are displayed clearly when analyzing the overall demographic statistics. Non-Hispanic Black men have a 76% higher risk of being diagnosed with prostate cancer and 2.2 times higher risk of death than non-Hispanic white men. Despite this, marginalized communities are underrepresented in prostate cancer genomic studies. When conducting genomic studies of prostate cancer, tumors utilized vastly originated from European/European-descent males, with racial/ethnic minority males being underrepresented; this further exacerbates health disparities pertaining to prostate cancer.

Objective. The objectives of this study are to explore publicly available genomic datasets on prostate cancer, estimate the percent of underrepresented racial groups in these studies, and if possible, to show the prevalence of the top mutations across racial and ethnic groups.

Higher representation of racial/ethnic minorities in genomic studies of prostate cancer could allow for further examination of racial/ethnic specific mutations. A conglomerate of socioeconomic conditions alongside rare and understudied genetic mutations, such as BRCA2 in African American males, are linked to the higher mortality rates of prostate cancer in racial/ethnic populations. The data from the observed studies suggests that the current methods of conducting genomic studies are negatively impacted by social factors, necessitating a more inclusive and widened approach to prostate cancer genomic research.

The Impact of Race/ Ethnicity and Molecular Subtype of Tumors on Breast Cancer Survival

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Scientific Advisor: Paulette Chandler MD, MPH

Massachusetts General Hospital

Breast cancer is the most widely diagnosed cancer and has the second highest mortality rate for women. African American women have been reported to have the highest breast cancer mortality rates among the United States. Molecular subtypes are involved with diagnosing different forms of breast cancer. The different subtypes also have different incidence and mortality rates based on race. Prevalence of the subtype also differs based on race. It is important to examine the relationship between molecular subtype and race/ethnicity because it can help eliminate health disparities in the field by identifying trends between race and breast cancer morality. The purpose of this body of work is to create a systematic review and meta-analysis to examine the role subtypes play. First, two independent researchers conducted a literature search using PubMED with some qualifications being articles published from January 1, 2000 through May 31, 2021 and studies that are U.S based. These final documents will include data comparing survival according to race and molecular subtype, as well as the hazard ratio for risk of death in black vs white patients. Molecular subtypes will be defined as ER only, ER and PR or ER/PR/HER2, or PAM50 subtypes. From there the information will be put into statistical software to generate a pool and estimate the impact of race on survival based on subtype. The conclusion of the study will show the relationship between race and breast cancer survival according to subtype, which can contribute to elimination of health disparities.

Quality of Life & Patient Perceptions of Ovarian Cancer Treatment in the US

Handel Ulysse

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Scientific Advisor: Marilyn Hammer, PhD, DC, RN, FAAN

The Phyllis F. Cantor Center for Research in Nursing and Patient Care Services
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Ovarian cancer is an ongoing issue for women diagnosed in the US. It is the deadliest of all gynecological cancers. Therefore, the goal of this project was to answer the following question: How does ovarian cancer directly impact women physically, functionally, emotionally, and how does this affect the perception of their illness concerning the care being provided? We used conventional content analysis to analyze patient interviews and descriptive statistics to summarize quality of life (QoL) scores as measured by the Functional Assessment for Cancer Therapy - General (FACT-G). In interviews, participants reported that pain may affect them functionally, emotionally, or physically. The degree to which participants reported being able to cope with this pain relied on their perception of their illness and the quality of care they received during their treatment. The mean FACT-G total score among interview participants was 82.77 (range 39.3-104). Patients with low FACT-G scores generally wanted more clarity in terms of what to expect. They desired to be heard and guided through their treatment process more thoroughly by their provider. The implications that this research provides are that ovarian cancer patients' perception of well-being is subjective to the individual experience. Thus, client sensitivity must be a priority for every health professional. Patients will otherwise be unable to cope with cancer to the best of their ability.

A look at pediatric brain tumor survivorship

Nayeli Villa

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Boston Children's Hospital

Several cancer treatments in recent and past years have proven extremely effective in aiding those affected by cancer. In pediatric brain tumor treatment specifically, however, there has been evidence of decreased cognitive function after recovery. There are several factors as to why the research in this area is insufficient, one being the inability to properly quantify or measure the cognitive dysfunction as it may be minimal in some survivors who may be able to live their lives as any other person. Others include the inability to properly track and monitor the states of these survivors. By conducting this research we look to be able to predict future brain abnormalities in order to reduce the adverse effects of the treatment. In order to reach our goals, the lab developed an MRI machine learning and feature selection algorithm. As a part of the method, the lab chose to use a larger sample size than in some previous studies. Using the developed algorithm, the lab predicted neurocognitive function in normal developing brains between 8 and 22 years of age. In past research for this field there have been instances of single-risk factor research showing insufficient or limited data. The algorithm included four different risk factors rather than one, the factors being patient demographics, clinical tumor characteristics, treatment, and MRI, to try to improve the efficacy of predicting these neurocognitive outcomes. Using this study and these methods the lab will be able to predict the outcomes of neurocognitive dysfunction and minimize the adverse effects.

Prevention of type 2 diabetes through remotely-administered lifestyle programs: a systematic review

Valaree Villegas

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Dana-Farber Cancer Institute and Brigham and Women's Hospital

The prevalence of type 2 diabetes (T2DM) has dramatically increased within the past few decades. While developing viable treatments is necessary for individuals diagnosed with T2DM, the development of effective interventions is critical in preventing the onset of T2DM. In a landmark RCT, an in-person lifestyle program, the Diabetes Prevention Program (DPP), significantly reduced the risk of T2DM by 58% in comparison to standard drug administration. While the DPP is the recommended intervention for T2DM, the in-person component limits the intervention's reach due to cost, convenience, and participant's willingness to commit. In order to minimize these barriers, future research must consider how those in-person programs can be transitioned to virtual, remote formats while maintaining efficacy. The current, available research on technology-based interventions primarily focuses on how lifestyle changes may result in weight loss. Although weight loss is a target for diabetes prevention, there is little research that identifies how technology-based interventions directly affect the progression of T2DM. Prospective studies should continue to expand this field of research by examining how remotely-administered interventions could prove to be effective in reducing the risk of T2DM in at-risk individuals. This systematic review assessed eight clinical trial articles that investigate the effect of remotely-administered lifestyle interventions on T2DM prevention in comparison to in-person programs.

Role of Mitochondrial Dynamics in the Beneficial Effects of Exercise on Prostate Cancer

Madison Webber

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Scientific Advisor: Benjamin A. Kugler, MS

Dana-Farber Cancer Institute and University of Massachusetts, Boston

Prostate cancer (PCa) is the most diagnosed cancer and second leading cause of death in males. Previous research has shown exercise training is beneficial for chronic illnesses as well as different cancers, including PCa. By understanding the underlying mechanism(s) of how exercise is beneficial for prostate cancer patients, good daily habits can be strongly reinforced for preventative measures and exploited in the medical field for effective treatments. Previous studies have shown dysregulation of mitochondrial dynamics of PCa tumor tissues in comparison to healthy tissues. Exercise training has also been widely reported to rescue mitochondrial dysfunction by improving mitochondrial quality control in many tissues. However, its effects on mitochondrial dynamics in PCa tissues is only minimally explored. Given that mitochondria play important roles in energy metabolism in tumor tissues, it is critical to investigate the role of mitochondria dynamics in the beneficial effects of exercise on reducing PCa development and progression. Delving into the specific processes of mitochondrial dynamics could shine light on discovering novel key pathways and proteins utilized in the reduction of PCa via exercise training.

The association between Lynch Syndrome and breast cancer: a literature review

Feven Woldesenbet

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Scientific Advisors: Theodore Huang, PhD; Stephen Knapp

Dana-Farber Cancer Institute

Lynch syndrome (LS) is an inherited disorder that is caused by pathogenic mutations in DNA mismatch repair (MMR) genes. Carriers of the mutations are predisposed to a higher risk of certain cancers. The possibility that LS may increase breast cancer risk, in particular, has been a topic of debate as different studies present conflicting results. As more recent studies are published, it is important to regularly evaluate the current literature available to understand breast cancer's association with LS. To that end, ten relevant studies were identified and analyzed to determine the relationship, if any, between LS and breast cancer. The data published in each paper were extracted and themes observed among the studies were underscored. Eight out of the ten papers included in this review published evidence showing that a pathogenic mutation in at least one of the MMR genes is associated with breast cancer, and two papers concluded that breast cancer is not associated with LS. These results, however, cannot be used to definitively determine the relationship between breast cancer and LS as there is inconsistent data and study design issues decrease the reliability of some of the studies. This evaluation of the literature, then, provides valuable findings regarding the study design complications that must be overcome to conduct more effective research on LS and breast cancer. It also echoes the calls for larger, more diverse prospective studies with longer periods of follow-up that have been stressed in many of the papers reviewed.

Vitamin C supplementation and the risk of developing COVID-19

Jackey Zhang

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Scientific Advisor: JoAnn E. Manson, MD, DrPH

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The COVID-19 pandemic is characterized by fever, persistent cough, acute respiratory distress syndrome, dysregulation of the immune system, and suppression of the host antiviral response. Older patients are particularly vulnerable to COVID-19 because of the weakening of the immune response with age. While many risk factors have been suggested for the primary prevention of COVID-19, more research is needed. Several dietary supplements such as vitamin C have potential immune-boosting, antiviral, and anti-inflammatory roles. Therefore, we examined whether vitamin C supplementation reduces the risk of developing COVID-19 as well as symptoms related to COVID-19. We examined REDCap survey responses from May 2020 on vitamin C supplement use (including dose) and risk factors from 22,677 older women and men from the VITAL, COSMOS, and WHS cohorts. We identified new COVID-19 outcomes through early 2021 from subsequent REDCap and postal mailings defined by self-report of either a positive test, being told by a healthcare provider that they had COVID-19, or COVID-19 hospitalization. Our analyses will examine the association between vitamin C supplement use, and COVID-19 outcomes and symptoms. Based on completed analyses to date, 4,255 (19%) participants reported vitamin C supplement use. Subjects were more likely to be female and non-white, taking selected over-the-counter medication and other dietary supplements ($p<0.05$) with a slightly greater number of CDC symptoms for COVID-19. The findings from this study will improve public health and clinical messaging on the role of vitamin C as an accessible and affordable dietary supplement for immune function and COVID-19 prevention.

An Urgent Need for Policy Change: The Cancer Susceptibility Mutation R337H with a Founder Effect in South and Southeastern Brazil

Mell Aguiar

Principal Investigator: Danielle Braun, PhD

Scientific Advisor: Theo Huang, PhD

Dana-Farber Cancer Institute

An increase in the incidence of and mortality from breast cancer (BC) has been observed in women between 20 and 49 years in all parts of Brazil, with the South and Southeastern regions experiencing the highest incidence rates. The TP53 gene R337H germline mutation occurs at an unusually high frequency in these regions because of a founder effect and is thought to increase BC risk in women. Despite R337H's elevated prevalence and role in the proliferation of hereditary BC cases in this part of Brazil, there is still widespread disagreement over what constitutes an appropriate manner of identifying carriers, particularly for patients between the ages of 36 and 46. All points considered, establishing region-specific testing criteria for this at-risk group of young, female BC patients is of utmost importance. In this context, the aim of this review was to investigate different testing recommendations for this population and to explore the accessibility of testing. Qualitative analysis revealed that TP53 variant testing could be justified for all female BC patients meeting hereditary breast and ovarian cancer criteria in South Brazil who were diagnosed before the age of 45. But, any such protocol, regardless of efficacy, will not impact the population until major public policies are changed. Genetic testing is not available under Brazil's public healthcare system which covers approximately 75% of the population, and only BC patients diagnosed below the age of 35 are eligible for TP53 mutation testing under the private system which covers the remaining 25% of the population. Based on these findings, it is clear that TP53 variant testing criteria should be adapted to the specifics of South and Southeastern Brazil and that Brazilian healthcare policies must change alongside them for the proper implementation of hereditary BC management in the country.

Therapeutic Effects of Stearoyl CoA Desaturase-5 on in Vivo Mice Models

Aracely Alicea

Principal Investigator: Christian E. Badr, PhD

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Massachusetts General Hospital

Glioblastoma Multiforme (GBM) is an incredibly deadly form of central nervous system cancer that leaves most of its patients with under a year to live after diagnosis. Developing various methods to target GBM and decrease malignancy is essential towards elongating the lives of these patients. Recently, scientists have been able to discover that certain components helping to maintain homeostasis in the endoplasmic reticulum (ER) hold a strong position in benefiting GBM cells to proliferate. One of these components is Stearoyl CoA Desaturase-1 (SCD1), which is an enzyme that catalyzes the conversion of saturated fatty acids to unsaturated fatty acids. By suppressing this enzyme in vivo mice, models have been cured of GBM by 25%-100%. In this experiment, a lesser-understood component of fatty acid metabolism called Stearoyl CoA Desaturase-5 (SCD5) is being studied. Prior to injection, the GBM cells were infected with two different constructs silencing the SCD5 gene. The presence and growth of the tumors was confirmed via bioluminescent imaging and a survival study is underway. The experimental groups with silenced SCD5 genes had lower cellular proliferation as well as a higher survival time with all control mice reaching 100% mortality within five weeks of implantation. Research into identifying target genes relating to fatty acid metabolism could demonstrate therapeutic potential for GBM patients and could prove to be the future of GBM treatment.

Immunosuppressive Role of HLA-G in Human Cancers

Chisom Amadi

Principal Investigator: Robert Manguso, PhD

Scientific Advisor: Sarah Kate Lane-Reticker

The Broad Institute of MIT and Harvard

Immunotherapy is the artificial stimulation of the immune system to treat cancer. Checkpoint inhibitors, in particular, work by blocking the immune system-inhibiting effects of tumor cell surface proteins. Unfortunately, these inhibitors are not effective in every cancer patient, so the identification of other checkpoints that prevent drug efficacy could help scientists to develop more targeted therapies. To discover novel tumor immune checkpoints, our group had performed in vivo CRISPR screens in mice which identified the non-classical MHC molecule Qa-1b/HLA-E to be a strong inhibitor of tumor immunity across multiple different cancer cell lines. This led researchers to study HLA-E (the human homolog for Qa-1b) and begin to hypothesize about the possible coexpressionary effects of HLA-G in HLA-E's exercising of its full immune-inhibitory potential. Past studies suggested that HLA-G may contribute to the inhibitory efficiency of HLA-E, but the lack of an HLA-G homolog in mice has made studying its effects challenging. In addition, HLA-G expression is lost during ex vivo culture of cancer samples. Here, we use lentivirus to overexpress HLA-G in melanoma and lung cancer cell lines to see if there is a correlation between the coexpression of it, and the binding affinity between HLA-E and NKG2A receptors on immune cells. We then measured the strength of NKG2A signaling in T-cells. This research will help scientists identify types of cancers in patients where the tumors are dependent on HLA-E to keep themselves from being killed by the immune system.

Therapeutic Promise of Quinoline Methanol Derivatives Against Diffuse Intrinsic Pontine Gliomas

Catarina Barros

Principal Investigator: Bakhos A. Tannous, PhD

Scientific Advisor: Jian Teng, PhD

Massachusetts General Hospital

Diffuse Intrinsic Pontine Glioma (DIPG) is the most prevalent type of brain cancer in children aged five through ten, in which tumors of glial-cell origin develop in the pons and spread into other tissues. The rarity of DIPG, and the consequent lack of research on the disease has complicated the search for treatments capable of prolonging life for diagnosed children. Cancer cells are known to upregulate autophagy — the process by which cells digest unwanted materials, enabling them to survive and evade cell death even under stressful conditions. Anti-malarial drugs such as chloroquine and mefloquine have proven to be effective autophagy inhibitors in various types of cancer cells. In contribution to Dr. Tannous's Lab initiative to identify compounds from the Walter Reed Army Institute of Research that are effective in the treatment of DIPG, we tested the effectiveness of four stereoisomers of mefloquine in killing DIPG cells isolated from patient tumor tissues. By treating DIPG cells from two different cell lines with varying concentrations of each drug, we were able to evaluate the dose-dependent cell death of tumor cells in culture. Although relative DIPG cell viability decreased as drug concentration increased for all four stereoisomers, compound 193, the 11S, 12R stereoisomer of mefloquine (IC50 ≈ 1x103 in both cell lines), led to the most dramatic decrease in relative cell viability. These results suggest that autophagy inhibition by mefloquine, especially by the 11S, 12R stereoisomer, demonstrates therapeutic promise for the treatment of DIPG.

Survivin-2B Regulation Using Alternative Splicing

Gabriel Benavidez

Principal Investigator: Edward Benz, MD

Scientific Advisor: Shu-Ching Huang, PhD

Dana-Farber Cancer Institute

Survivin is important in the progression of certain cancers through the inhibition of apoptosis. Certain isoforms of Survivin upregulate (Survivin-2B) or downregulate (Survivin-WT) apoptosis in cancers. These different isoforms of Survivin are expressed through alternative splicing in RNA. Alternative splicing of RNA can be influenced through mutations in splicing factors or alterations in splicing factor regulation. Our study aims to find which splicing factors up or downregulate pro-apoptotic Survivin-2B. Identifying which splicing factor has a role in upregulation or downregulation could close in on potential therapies for cancer. My project is focused on Survivin and what effect different splicing factors have on the expression of Survivin WT or Survivin-2B Isoforms. I will be looking at which splicing factors have an up or downregulation of expression of the two isoforms. In order to identify those splicing factors, HeLa cells were co-transfected with a Survivin Minigene and each splicing factor. RT-PCR was used to amplify spliced products which were analyzed on an acrylamide fragmentation gel. Splicing factors hnRNPK andSF1B increased the Survivin-2B isoform. Splicing factors RBM16, SFRS15, Sma68, CUGBP2, and SRp20 reduced Survivin-2B expression. In conclusion, the results portray that individual splicing factors can up or downregulate Survivin isoforms. In order to conclude if the splicing factors were expressed in the transfected cells, further study will take place. It is also notable to add that multiple splicing factors can also affect the splicing of an exon.

Developmental and Genetic Determinants of Relapse in B-Cell Acute Lymphoblastic Leukemia

Mia Blennau

Principal Investigator: Mark A. Murakami, MD

Scientific Advisor: Hyun Hwan (Phillip) An

Dana-Farber Cancer Institute

Although therapeutic advances have improved outcomes in acute lymphoblastic leukemia (ALL) among children, adults continue to experience high rates of relapse even after achieving complete remissions, resulting in a poor prognosis. Efforts to improve outcomes through incorporation of therapeutic agents targeting oncogenic mutations largely have failed due in part to non-genetic, phenotypic inter-tumor heterogeneity. Accumulating evidence has demonstrated that, unlike its myeloid counterpart, ALL is a developmentally plastic disease without a fixed clonal hierarchy. Moreover, developmental stage and other transcriptional cell states are increasingly recognized as critical factors influencing the cellular fitness effect of oncogenic mutations. This may partly explain the underwhelming results of genotype-informed therapy agnostic of cellular context. Indeed, we have previously demonstrated a strict divergence in oncogenic mutation patterns at relapse, despite mutational heterogeneity in remission, that was explained by B-cell differentiation state among primary human BCR-ABL-rearranged ALLs. In this study we retrospectively defined an institutional cohort of relapsed adult B-ALL patients to define the strength of association between genetic and immunophenotypic shifts across all molecular subtypes of B-ALL common prevalent among adults. We sought to answer the question: Are the spectra of treatment-emergent, clonally dominant oncogenic mutations observed at the time of progression in acute lymphoblastic leukemia restricted by leukemia developmental stage across multiple cytogenetic subtypes? First, we obtained clinical annotation and linked leukemia mutational profiling data from adult patients who relapsed after first line therapy for B-ALL through the Dana-Farber Hematologic Malignancy Data Repository (HMDR). Next, we manually abstracted immunophenotypic patient tumor immunophenotype data to identify the prevalence and nature of immunophenotypic shifts within individual patient leukemias. We then interrogated our combined data set for recurrent associations between mutations in oncogenic signaling pathways and B-cell differentiation state derived from clinical immunophenotyping. To validate promising findings from this medical record review, we retrieved samples of blood and bone marrow from the Dana-Farber Cancer Institute Pasquarello Tissue Bank. To confirm associations through a high-resolution approach, we isolated B-ALL cells and performed single-cell gene expression profiling (single-cell RNA sequencing) to reveal the differentiation and biological state distributions of leukemic and non-leukemic cells. We found that there are crucial genotype-phenotype associations present in B-ALL patients that permit a more sophisticated understanding of the cellular fitness effects of key oncogenic mutations. This knowledge potentially can be used to more accurately risk stratify patients receiving first line therapy for B-ALL and inform the development of novel therapeutic approaches targeting only those mutationally dysregulated pathways with the potential to drive relapse within a given phenotypic cell state. Ultimately, we intend to explore how this biological paradigm can bring the field closer to realizing the promise of precision medicine in leukemia.

Advanced Molecular Detection – COVID

Jonathan Bonilla

Principal Investigator: Latrice G. Landry, PhD, MS, MMSc

Dana-Farber Cancer Institute

Under the supervision of Dr. Latrice G. Landry, this research project will evaluate the landscape of COVID-19 molecular precision medicine research and support molecular and genetic science to combat this infectious disease. Throughout the world there are over 193 million cases and over 4 million deaths from the COVID-19 pandemic. One of the challenges of the COVID-19 pandemic is our lack of diversity in research. As we enter halfway into our second year of the pandemic, more studies are coming out noting certain populations have yet to receive the vaccine or antibody testing and increasing the number of COVID-19 vaccinated individuals is a public health concern. Our goal is to generate a database to conduct a landscape analysis to evaluate COVID-19 vaccine distribution. We will 1) extract literature using key terms in a precision medicine database, 2) carefully curate abstracts in a database, 3) name and identify database features while coding and cleaning the database, and 4) lastly, we will use geo-spatial and other visual analyses of the data. Understanding how well we are handling researching all populations and distributions in COVID-19 molecular research will benefit progression towards combating this disease.

Understanding Familial Hypercholesteremia's Genetic Variants to Improve Testing and Diagnosis

Rhonique Brown

Principal Investigator: Latrice Landry, PhD, MS, MMSc

Dana-Farber Cancer Institute

Familial Hypercholesterolemia affects around 1.3 million people in the US. Despite the disease being life-threatening, only a small fraction is aware they have it. It is essential that Familial Hypercholesterolemia be treated early on as individuals who are affected by it possess a higher risk of heart attacks and heart disease; therefore, it is important physicians can determine adequate preemptive strategies and manage the effects timely. However, due to poor public knowledge, failure to acknowledge a genetic component to the disease and the varying, often covert symptoms patients may show, the condition goes largely undiagnosed. As Familial Hypercholesterolemia can be traced to inheritable mutations in several genes, it is critical in the endeavor to increase diagnosis that the US establish a national screening for Familial Hypercholesterolemia as a form of preventive care. Researchers are confronted with the issue of equity when it concerns genetic testing. There is a disproportionate amount of information on genetic variation among different ethnic groups. A first-step solution to this challenge is conducting landscape analyses that would allow for an evaluation on the extent of equity in the Familial Hypercholesterolemia genetic field. By combing through the gnoMAD Database and calculating the allele frequency of Familial Hypercholesterolemia causing genes in various races/ethnic groups, it can be determined where equity falls short. Through this process, it could be determined that there is an equity issue in genetic information for various groups. Future research may be able to account for this issue and further advance equity in genetic testing.

Double-Strand Break Repair in Relation to Drug Resistance in Glioblastoma Multiforme Cells

Nery Matias Calmo

Principal Investigator: Zachary Nagel, PhD

Scientific Advisor: Daniel J. Laverty, PhD

Harvard T.H. Chan School of Public Health

Glioblastoma multiforme (GBM) is an aggressive brain cancer with poor patient prognosis and limited treatment options. Frontline therapies include ionizing radiation and drugs such as temozolomide (TMZ), which kill GBM cells by damaging DNA. Although many patients initially respond to treatment, relapse is a common problem, especially due to changes in DNA repair efficiency. Changes in mismatch repair and methylguanine methyltransferase efficiency are clinically important TMZ-resistance mechanisms. We hypothesized that additional DNA repair pathways such as homologous recombination (HR) and microhomology-mediated end joining (MMEJ) may be important for TMZ resistance in patients. This is especially interesting because MMEJ inhibitors, such as the antibiotic novobiocin (NVB) have recently been reported.

To study DNA repair pathways involved in TMZ resistance and find vulnerabilities in GBM cells, we created plasmid-based fluorescence reporter assays to study MMEJ (blue fluorescent protein) and HR (mCherry). We amplified the plasmids in E. coli, introduced double-stranded DNA breaks, and tested the reporter plasmids in GBM cell lines, U251 and U87. We also determined concentration ranges for TMZ and NVB in GBM cell lines and tested a TMZ-NVB combination therapy to determine if NVB increases TMZ toxicity in GBM cells.

Together, these studies will demonstrate different approaches to uncovering potential drug targets and treatment conditions to evade relapse and increase survival rates in GBM patients.

Validating Recurrent Enhancer Amplification in Glioma with Enhancer Knock-In

Jaime Chow

Principal Investigator: Rameen Beroukhim MD, PhD

Scientific Advisors: Frank Dubois, MD; Alexander Crane

Dana-Farber Cancer Institute

Profiling of high-grade brain tumors of 179 children in our group revealed recurring amplifications that are hypothesized to activate the oncogene MYC and contribute to tumor growth. This question is new as these recurring amplifications were discovered by our group and are unknown to other researchers. To test this hypothesis, we need to create a model recapitulating these alterations in tumor cell lines. Additionally, few labs are capable of recreating amplifications in cell lines with current technologies. We are going to use CRISPR-Cas9 induced knock-in to recapitulate the recurring variant we see in tumors in cell line models. With this technology, constructive edits are made to the genome of cells by targeted insertions through homology directed repair (HDR) from a repair template supplied with the CRISPR reagents. We so far have validated necessary experimental steps including single cell cloning, lipid-based transfection, and Ribonucleoprotein complexes and expect to optimize the use of electroporation. The final model of the recurring cancer variant can be used to establish pharmacologic ways to target this potential driver. Additionally, we establish the method of constructive genome editing for creating models for other variants in brain cancer, hopefully helping the community of researchers working on this devastating disease to create working targeted therapies.

The Nurses' Health Studies and its Substantiality for Metabolomic Profiles in Breast Cancer Research

Gabriella Forchion

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Breast cancer continues to be one of the major chronic diseases for women and continued studies are actively searching for potential treatments and adaptable measures that can be adopted into one's lifestyle for preventative rectifications. The Nurses' Health Studies have been powerful agents in the medical and scientific fields as they offer invaluable information into women's health and the lifestyle factors that impact their risk of developing the disease. Modern studies are modifying traditional techniques to include metabolomics and understand the biochemical processes that may be contributors to the risk of developing breast cancer. However, a lack of in-depth metabolomic studies on breast cancer leaves room for conversation on what is pertinent to the risk of developing breast carcinogenesis. The purpose of this study was to determine any correlations in metabolomics data that could be used to further breast cancer prevention and treatment studies. By completing a thorough literature review of scientific journals on breast cancer and metabolomics and by conducting a correlation analysis that incorporates metabolomics information from the Nurses' Health Studies, potential metabolites have been identified as risk factors of developing breast cancer. Within this paper, I will explain the impact of the Nurses' Health Studies and metabolomic profiles that may be indicative of breast cancer risk. 2- methyl-butyryl carnitine has been identified as a prospective metabolite of continued consideration when researching ER+ breast cancer. The Nurses' Health Studies, metabolomic profiles, and breast cancer intersectionalities are prime areas of study for the evolution of breast cancer prevention and treatment.

A Standard Quality Assurance Protocol for High-Resolution Magic Angle Spinning MRS of Human Blood Serum

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In recent years, high-resolution magic angle spinning (HRMAS) proton magnetic resonance spectroscopy (1H MRS) has become an innovative platform for the field of metabolomics. By utilizing this technique, several different biological samples can be analyzed, such as intact tissues, cell cultures, and biofluids. Although HRMAS 1H MRS has been employed extensively to study the underlying molecular mechanisms of diseases in animal models and humans, few studies have concentrated on the influence of various methodological and calibration parameters on the MRS measurements. Investigating this influence through a basic QA/QC procedure is important to ensure that existing biological variations are accounted for and to minimize systematic error on experimental results. The purpose of this report is to discuss a standard quality assurance protocol for performing HRMAS 1H MRS experiments with serum. To evaluate the effectiveness of the proposed protocol, the measurable peaks of the MRS spectral data from 12 individual de-identified Biobank serum samples were quantified. The study cohort consisted of two prostate cancer patient groups: progressive (n = 6), non-progressive (n = 6), and pooled control (n = 6). Multivariate statistical analysis was performed on the quantified data set to determine the influence of the parameters under study on measurements. The influence of multiple freezing and thawing cycles on the degradation of biological samples is a parameter that requires further investigation. Developing standard quality assurance protocols is necessary to advance to the field of metabolomics, which will play an important role in future diagnostic approaches and the development of precision medicine.

Sequencing T-Cell Receptor Variable Regions at Single-Cell Resolution

Jonathan Good

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T-cells are an important part of the human immune response and T-cell expansion is a key marker of some cancers. Knowing if the expansion is clonal or diverse is important for understanding the disease progression and the resulting immune response. Full-length single-cell RNA-sequencing (scRNA-seq) methods have the advantage of capturing the variable region genetic sequence with single-cell resolution, but they are time-consuming and expensive. High-throughput scRNA-seq reduces time requirements but are 3' biased missing the variable region and the primer-adapted methods lose the single-cell resolution. The Shalek lab developed a massively parallel protocol that created cDNA libraries with cell barcodes for single-cell resolution. These libraries can be aliquoted into various sequencing procedures and the information can be combined due to the cell barcodes. Building on these protocols, we created barcoded cDNA libraries from healthy bone marrow donors and used one portion to do scRNA-seq using the common 10x 3' scRNA-seq platform. In addition, we enriched another portion to select only the TCR transcripts which we amplified and prepared for TCR sequencing. We used a TapeStation to measure DNA concentration and length which were consistent with data from the Shalek protocol. The ability to perform multiple sequencing techniques and overlap the data due to cell barcoding can elucidate T-cell clonality or diversity and has the potential to compare healthy and diseased samples to better understand disease progression and immune response.

The Association Between Recent Influenza Vaccination and the Incidence and Severity of COVID-19

Simone Horowitz

Principal Investigator: JoAnn E. Manson, MD, DrPH

Brigham and Women's Hospital

With the outbreak of the COVID-19 pandemic, various interventions and safety measures worldwide have been evaluated to counteract the spread of this airborne virus. Current literature suggests that prior vaccination with the influenza vaccine may be associated with a protective immune response against the development of subsequent viral infections, including SARS-CoV-2, which causes the COVID-19 illness. We aim to explore the relationship between previously receiving the influenza vaccine after August 2019 and the risk of a positive test for SARS-CoV-2, the severity of COVID-19 symptoms, and associated clinical outcomes. Although a decreased rate of positive SARS-CoV-2 testing has been observed after influenza vaccination in several previous studies, a knowledge gap remains regarding the flu vaccine and the severity and duration of COVID symptoms due to the inability to account for possible confounders, such as behavioral factors and comorbidities, in most of these studies. To further investigate this issue, we analyzed three large-scale cohort studies (VITAL, COSMOS, and WHS) that contained extensive data about SARS-CoV-2 testing, COVID clinical diagnoses, symptoms, and hospitalizations, as well as information on recent flu vaccination, medical history, and other risk factors. In the three cohorts, 19,369 participants received the influenza vaccine compared to 3,374 participants who did not. Examining baseline characteristics by influenza vaccination status, those who were vaccinated were more likely to be older and to have comorbidities such as cancer, cardiovascular disease, autoimmune disorders, atrial fibrillation, and kidney failure. Furthermore, differences in racial/ethnic composition were apparent among those who were vaccinated compared to the unvaccinated population, with a greater percentage of Hispanic, African American/Black, and Native American/Alaskan patients in the unvaccinated group. Additionally, those who were vaccinated were more likely to use dietary supplements, such as multivitamins or vitamin D supplements, potentially reflecting a greater level of health consciousness. These results further support the need to adjust for potential confounding factors in analyses addressing the relationship between influenza vaccination and COVID-19. The findings of this study may inform the advice given to the public on preventive measures for COVID-19.

A Content Analysis of E-Cigarette Apps in the Apple App Store

Tia Joseph

Principal Investigator: Bettina B. Hoeppner, PhD, MS

Scientific Advisor: Kaitlyn Siegel

Massachusetts General Hospital

The rise of electronic nicotine delivery system (END) technology has public health implications for current and non-smokers alike. Though e-cigarettes can have a positive impact on public health by being used as smoking cessation supports, the long-term effects of vaping remain unclear, and reports from the Centers for Disease Control and Prevention reveal that ingredients in e-cigarette aerosol, such as diacetyl, may be harmful to the lungs. With the Pew Research Center reporting that 85% of Americans own smartphones, apps are widely accessible and can shape public perception and knowledge regarding e-cigarettes. However, what remains unknown in e-cigarette apps are the types of messaging being conveyed to the public, how these messages are targeting app users, and how effective these messages are in impacting the habits of vape users. To this end, we conducted a qualitative content analysis of the top fifteen e-cigarette apps in the Apple App Store under the keywords "vaping" and "e-cigarettes" to evaluate elements contained in these types of apps. In this analysis, the investigators developed a codebook capturing app descriptors, sophistication, whether the app targeting vaping promotion or cessation, and if it used scientific concepts. Then, two independent raters rated each identified app based on these codes. The final consensus-rated descriptors will be tabulated to provide an overview of the content of the apps. The findings from this content analysis will provide insight on public health messages being conveyed in e-cigarette apps, and what tools these apps offer.

The Role of FGFR1 and BRAF Genes and How it Can Change Primary Treatment in Pediatric Low-Grade Gliomas Research

Syeda Kazmi

Principal Investigator: Pratiti Bandopadhayay, MD, PhD

Scientific Advisors: Eric Morin; Alexandra Condurat

Dana-Farber Cancer Institute

Pediatric low-grade gliomas are a type of brain tumor where only one main mutation is enough to drive the cell to become cancerous. Most commonly, these mutations are found in the FGFR gene and the BRAF gene. Currently, there are two main forms of first-line treatment: chemo/radiotherapy and surgical resection. However, both treatments are not ideal as they cause killing of healthy tissue cells in surrounding areas. The brain cells of a pediatric patient are programmed to perform functions of a developing brain, whereas in adults these cells oversee homeostatic maintenance and respond to damage. Therefore, killing healthy cells needed for full development of the brain would cause neurological issues for the patient as they grow older. To provide a fulfilling lifestyle and limit the neurological issues associated with current therapy treatments, the lab is focusing on the role the FGFR gene and the BRAF gene play in the MAPK/mTOR pathway for a targeted gene therapy. This would allow only the gene causing the mutation to be targeted as opposed to healthy cells in an area as well. Currently, using analysis procedures such as Incubators and western blots, these genes are being observed under different conditions to see whether there is still activity downstream in these two pathways. For example, the FGFR-1 project observed high levels of phosphorylation occurring in the mutant FGFR-1 protein in 0% growth factor, which means that this gene is still being activated without there being a growth factor to initiate this. This suggests that a point-mutation in FGFR-1 is causing the gene to continuously be turned on and sending growth signals down the pathways, as compared to a normal FGFR gene which would not work under those conditions. The goal of this study is to create a targeted gene therapy which would get rid of the cancer, as well as not inhibit the patient's brain development and allow them to live a fulfilling life.

Establishing Background Fluorescence in Bimolecular Fluorescence Complementation Assays in the Context of Cell Signaling

Maddison Lessard

Principal Investigator: Alexey Veraksa, PhD

Scientific Advisor: Claire Jackan

University of Massachusetts, Boston

Protein-protein interactions are the basis of many cellular activities, including metabolism, altered gene expression, and proliferation. Improving techniques to identify and validate protein-protein interactions is key to understanding complex biological processes. One such technique is bimolecular fluorescence complementation (BiFC), in which protein-protein interactions are visualized in vivo through the formation of a functional fluorescent protein from the reassociation of non-fluorescent fragments that are attached to the proteins of interest. However, the fluorescent protein fragments are capable of self-assembling spontaneously. How much this occurs when BiFC is applied to cell signaling pathways is not well understood. Establishing this background fluorescence is important for optimizing BiFC assays in cell communication studies. Thus, we created a negative control that can be used to quantify the amount of self-assembly of fluorescent fragments. We generated a Drosophila line in which the transcriptional activators of the Hippo pathway, Yorkie (Yki) and Scalloped (Sd), are unable to interact. The results of this study will determine the amount of fluorescent protein self-assembly in cell communication BiFC assays. These findings will facilitate the identification of true protein-protein interactions in signaling pathways in vivo.

RIG-I After Chemotherapy And Breast Cancer Cells

Alisha Marte

Principal Investigator: Shobha Vasudevan, PhD

Scientific Advisor: Rasika Kunden, PhD

Massachusetts General Hospital

Breast cancer is commonly treated with chemotherapy. Chemotherapy is used to kill fast growing cells and can be effective. Although chemotherapy is used to kill cancer cells, some cancer cells survive after the process. These cells that survive chemotherapy cause the regrowth of the breast cancer tumor and lead to the recurrence of breast cancer that is usually untreatable. This brings up the question of what causes and influences the survival of these cells. The lab detected a significant upregulation of the RNA virus detecting protein, RIG-I, in chemotherapy surviving breast cancer cells. Based on the upregulation of RIG-I, it is possible it has an influence in these surviving breast cancer cells. Finding the influence RIG-I has on breast cancer cells has the potential to allow us to find ways to inhibit this activation and terminate breast cancer tumor progression after chemotherapy. It is important for us to find what the role of RIG-I is in chemotherapy breast cancer surviving cells. We approached this by using PCR to detect the RNA of the RIG-I protein. This allows us to measure the upregulation of RIG-I in cells that survive various chemotherapies. PCR data affirmed that RIG-I is upregulated significantly upon doxorubicin chemotherapy treatment. We are currently testing other chemotherapies and testing the impact of RIG-I on breast cancer cells. This research will allow us to understand the role of a chemotherapy induced factor, RIG-I, and how it is activated, in therapy-resistant breast cancer cells. These data will allow us to find ways to stop the survival of breast cancer cells after chemotherapy.

The Emergence of CIML NK Cells in Targeted Cancer Immunotherapy for AML

Alijandro Mendoza

Principal Investigator: Rizwan Romee, MD

Scientific Advisor: Grace Birch, PhD

Dana-Farber Cancer Institute

Cytokine-induced memory-like (CIML) NK cells are an investigational therapy in which NK cells are preactivated with a combination of IL-12, IL-15, and Il-18. These CIML NK cells are currently in the clinical stage of testing for safety and efficacy. CIML NK cell infusions are being investigated as a potential treatment for acute myeloid leukemia (AML), which has poor outcomes in the clinical setting. Much study has been done investigating CIML NK cell's antitumorigenic properties, but the hope is that treatment with CIML NK cells can be optimized to be most safe and effective for patient care. To better do this, we have to understand why patients in the current study have relapsed following CIML NK cell treatment, and how it can be prevented. Using blood samples from AML patients treated with CIML NK cell infusion post-haploidentical stem cell transplant relapse, and running flow cytometry, we looked at percentages of NK cells, T cells, B cells, macrophages, and dendritic cells over increments within 60 days. This data will allow us to better understand immune cell reconstitution following CIML NK cell infusion post-haploidentical stem cell transplant relapse in patients with AML. Utilizing the data from flow cytometry will conceptualize how the collective immune system fluctuates and adapts to the treatment and this will help contribute to a greater understanding of how relapse transpires. This will allow us to recognize a pathway or point of approach to streamline CIML NK cell treatment for patients with AML.

Equity in Early-Stage Immunotherapy Research

Paulkichna Merove

Principal Investigator: Latrice G. Landry, PhD, MS, MMSc

Harvard Medical School

Past research on various immunotherapies has shown promising results and researchers believe that this form of treatment will be crucial to the fight against cancer and other diseases. However, clinical research populations tend to lack individuals from a variety of racial, ethnic, geographic, and socio-economic backgrounds. The scarce representation of diverse populations in clinical trials often leads to insufficient knowledge regarding an intervention's effects in diverse populations. This can lead to a lack of effective treatment options for some individuals, contributing to disparities. The goal of this study is to analyze the landscape and populations studied in early-stage immunotherapy research to determine whether there is a need for equity in these studies. To accomplish this goal, we extracted the top 100 immunotherapy studies from the US National Library of Medicine's database of clinical studies (clinicaltrials.gov) and carefully curated the database. Then, we coded the database, and finally, used the information to create graphs to visually analyze the data. The results would be useful for research and policy considerations.

Identifying Barriers and Facilitators to Minority Recruitment in Clinical Trials

Katie Mohammed

Principal Investigator: Aruna Pradhan, MD, MPH

Brigham and Women's Hospital

Peripheral artery disease (PAD) is the accumulation of fatty deposits in the arteries that limits the blood flow to the lower limbs and leads to over 150,000 limb amputations annually. Patients with PAD, in particular, minorities, are often undiagnosed, and therefore live with the unrelenting symptoms of this disease and are often first treated by physicians at late stages of their disease. Screening for PAD at earlier disease states may lead to improved symptoms and prevent limb loss. However, due to low participation of minority patients in clinical trials, we have limited information about the effectiveness of this approach. In preparation for a clinical trial that will test whether screening for PAD improves cardiovascular health, we first sought more information about barriers and facilitators to minority recruitment. We developed a short, elaborate, culturally and academically appropriate and easy to distribute survey designed to better understand the reasons for low minority representation and recruitment in clinical trials. Before developing the survey and by thorough research, we identified similar themes across racial and ethnic minority groups in medicine that may potentially inhibit their engagement in clinical trials. We found little contemporary data for cardiovascular trials and little information about facilitators. Potential impediments include socioeconomic status, medical mistrust, prejudicial treatment, and existing or past health conditions. Our questionnaire begins with a comprehensive demographic section to first determine the survey population and socioeconomic characteristics. It then proceeds to ask about three additional domains: medical mistrust, barriers to clinical trials participation, and facilitators to clinical trials participation. Although data have yet to be collected, we plan to disseminate our survey in local ethnically diverse communities. Our findings will allow us to modify the planned clinical trial (and future clinical trials) in ways that improve minority enrollment.

Antidepressant Use and its Effects on Human Gut Microbiota

My Nguyen

Principal Investigators: Raaj S. Mehta, MD; Andrew Chan, MD, MPH

Scientific Advisors: Curtis Huttenhower, PhD; Shelley Tworoger, PhD; Long H. Nguyen, MD; Wenjie Ma, ScD

Massachusetts General Hospital; Harvard Medical School

Introduction: Considerable evidence suggests that the trillions of microorganisms in the intestines — collectively known as the gut microbiome — are linked to neuropsychiatric illness, including depression, schizophrenia, autism, and anxiety. At the same time, increasing data supports the role of medications in modifying microbial composition in the gut. Despite this, there is little known about the impact of antidepressants on gut bacterial species.

Methods: We conducted a cross-sectional among 210 participants in the Mind Body Study, a sub-study nested within the ongoing Nurses' Health Study II. Between 2013 and 2014, participants provided up to 4 stool samples, which were profiled by metagenomics to identify species-level taxonomic information. With each sample, participants also completed questionnaires reporting medication use, comorbidities, dietary intake, and stool quality. Multivariate mixed-effects regression models were used to assess if antidepressant use was associated with microbial features.

Results: Among 827 stool samples profiled, we identified 144 bacterial species. 208 were antidepressant users. After multivariate adjustment, antidepressant use was associated with a greater relative abundance of Bacteroides Uniformis (beta: 0.067, $p<0.000001$), Clostridium Asparagiforme (beta: 0.004, $p<0.000001$), and Ruminococcaceae bacterium D16 (beta 0.004, $p<0.000001$). In contrast, antidepressant use was inversely linked with Bacteroides Finegoldii (beta: -0.017, $p<0.000001$) and Dorea Formicigenerans (beta: -0.008, $p<0.000001$)

Conclusions: Antidepressant use is associated with large-scale differences among a small number of intestinal microbes. Future studies are needed to determine if these differentially abundant species are implicated in treatment-refractory depression.

Hippo Signaling and Liver Cell Fate

Amanda Oliveira

Principal Investigator: Yingzi Yang, PhD

Scientific Advisors: Yuchen Liu, PhD; Qian Cong, PhD; Yizhong Hu, PhD; Caiqi Cheng, DMD; Yaxing Zhou

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Understanding the mechanisms behind cell proliferation and apoptosis remains a fundamental process in cancer research. This paper is an updated review on the hippo signaling pathway and the roles it plays regarding human liver cancer. The Hippo signaling cascade is an evolutionarily conserved molecular pathway that plays a major role in different variations of cancer such as hepatocellular carcinoma and intrahepatic cholangiocarcinoma. The Hippo signaling pathway is known to control liver size and growth, however, much remains unknown regarding the functions of signaling components in the Hippo pathway and the cells it affects. MST1/2 are Hippo kinases that have been identified as tumor suppressors in the mouse liver. Understanding the Hippo signaling cascade considering specific proteins such as MST1/2 and their functions within liver cells in terms of gene expression regulation, and cell fate maintenance is critical in cancer research to identify potential therapeutic targets. AVV-TBG-Cre and Ck19- CreERT2 are molecular tools that can be used to manipulate gene expression. Here we discuss the need for understanding and discovering more specific genes and their roles within this pathway for regulating cell fates.

Examining Post-Transplant Diabetes Mellitus with Regulatory T-cells and Immunosuppressives

Fidias Orlando Soto Pena

Principal Investigator: Eva C. Guinan, MD

Scientific Advisors: Urvashi Bhatia, PhD; Laura Contreras-Ruiz, PhD; Sofia Sousa, PhD; Katelyn Powell, PhD

Dana-Farber Cancer Institute

Regulatory T-Cells (Tregs) are important factors when considering modern medicine around cell immunotherapy in organ transplants. Graft rejection, aside from infection and sepsis, is the primary concern when it comes to organ transplants. To be able to prevent the host from ultimately destroying the newly introduced graft is imperative for long-term survival in a transplanted patient. Immunosuppressive drugs exist as a counterbalance to this by suppressing and regulating the immune system that is attacking the graft. However, the long-term effects on the host can produce complications such as metabolic and cardiovascular disease, an increased risk of secondary cancers, an increased susceptibility to infection, and ultimately graft rejection by the body. Tregs are a “natural” approach to dealing with allografts and rejection that avoid the toxicity of the immunosuppressives; however, figuring out how to prepare Tregs, when to infuse them, and for how long to continue to prescribe them is the current research problem along with long-term data not being available. The primary approach was to examine the post-transplant outcomes of patients that develop Post-Transplant Diabetes Mellitus (PTDM) under the use of Immunosuppressants versus under the use of Cell Immunotherapy with Tregs. The collected data indicate that there was a lower percentage of patients who developed PTDM and cardiovascular complications using the Treg therapy.

Effects of Sleeve Gastrectomy Surgery in B-Cells of Visceral Adipose Tissues

Shamiza Quader

Principal Investigator: Eric Sheu, MD, PhD

Scientific Advisor: Renuka S.Haridas, DVM, PhD

Dana-Farber Cancer Institute

Sleeve gastrectomy (SG) is a metabolic surgery attributed to not only weight loss, but also to rapid metabolic health benefits in type 2 diabetes (T2D). SG improves insulin sensitivity and alters levels of hormones secreted by the gut, causing increased insulin secretion. In fact, nearly 40% of patients with diabetes who undergo SG leave the hospital without needing anti-diabetic medications.

Here we investigated the immediate effects of bariatric surgery for weight loss in type 2 diabetes (T2D) patients regarding insulin production and necessity of anti-diabetic medications. We aimed to study how SG changes the B-cell functions that mediates the visceral adipose tissue metabolic remodeling. To achieve this purpose, an in vivo system was designed using two groups of high-fat diet (HFD) mice. The control group was treated with placebo or sham surgery while the experimental group was treated with SG. Flow cytometry was optimized to detect and measure B-cells, total visceral adipose immune cells were isolated, in vitro stimulation of total immune cell with lipopolysaccharide (LPS) was conducted, and immunoglobulins and cytokines were measured by enzyme-linked immunosorbent assay (ELISA) in culture supernatant.

The results showed that total adipose B-cells and natural IgM antibody secretion >8 fold significantly increased in HFD mice following SG, while IL-10 and TNFα secretion was reduced. Natural IgMs and anti-inflammatory B-cells are known to improve insulin resistance. Therefore, changes witnessed in adipose B-cell function likely contribute to diabetes resolution after SG. These results suggest SG as an exciting operation which could be explored further by human trials to develop a breakthrough treatment for obese T2D patients.

The Cyclical Links Between BMAL1 Dysregulation and the Synaptic Abnormalities of Tuberous Sclerosis Complex

Victoria Sles

Principal Investigator: Jonathan Lipton, MD, PhD

Scientific Advisor: Ilaria Barone, PhD

Boston Children's Hospital

Regulated by the body's biological clock, otherwise known as the circadian rhythm, sleep is one of the most essential developmental behaviors in humans. Disruptions in circadian rhythms are known to exacerbate the neuronal abnormalities of Tuberous Sclerosis Complex (TSC), a neurodevelopmental disorder whose psychiatric and cognitive manifestations are referred to as TAND (TSC Associated Neuropsychiatric Disorders); sleep irregularity remains as one of the most common TAND manifestations. Despite its importance, this continues to be understudied while the molecular links between TAND abnormalities and circadian dysfunctions are unknown; investigation of such links proves to be essential to the treatment of TAND. The dysregulation of the core clock protein, BMAL1, and its phosphorylated state at Serine 42, pBMAL1 (S42), is elevated in TSC mutant mice and has demonstrated abnormal synaptic function underlying the disturbed circadian rhythm. It is hypothesized that the genetic lowering of pBMAL1 (S42) will mitigate TAND-associated symptoms in mutated TSC mice models. Analysis of immunohistochemistry images from adult mice brains that lack pBMAL1 (S42) compared to the brains of standard wildtype (WT) littermates suggests that there is a daily variation in BMAL1 expression in WT conditions, but that this oscillation is lost in the absence of pBMAL1(S42). In addition, the quantification of pBMAL1(S42) is essential for the accurate distribution of BMAL1. To conclude, these findings will help us to better define the mechanisms by which TSC deregulates BMAL1 and synaptic abnormalities in the TSC background.

Premature and Accelerated Aging in Cancer Survivors

Maria Torres

Principal Investigator: Yangming Ou, PhD

Scientific Advisors: Mohamad Arafat Hussain, PhD; Danielle LaMay, MS

Boston Children's Hospital

Successful cancer treatments are potent, but such therapeutics are being associated with premature aging. ΔBrainAGE — the difference between Artificial Intelligence (AI) — predicted brain age from a survivor's brain magnetic resonance images (MRI) and the actual chronological age, is a rising biomarker with potential to be an essential indicator for cognitive health and mortality risk. In pediatric populations, ΔBrainAGE cannot effectively predict brain aging because there is a lack of data describing MRI scans of healthy developing brains. To solve this data gap, the largest sample size of brain MRI data of normal-developing children was collected to build a highly accurate AI-based brain age predictor for children 0-22 years of age, with hopes of quantifying normal vs. abnormal child brain aging in pediatric brain tumor survivors. Thus, we developed a research report analyzing findings found in multiple research publications on premature aging to investigate the extent tumor diagnosis and cancer treatment accelerate aging in young survivors. Increasing evidence suggests cancer treatments cause accelerated aging in survivors; therefore, their health and quality of life rapidly decreases years after diagnosis. The study's purpose is to quantify the (ΔBrainAGE) biomarker in pediatric brain tumor survivors and establish it as a quantitative and objective biomarker that retrospectively predicts a survivor's future neurocognitive outcomes, given their demographics, tumor, and treatment information. Such predictions can identify high-risk survivors for developing neurocognitive impairment, who should be ideal targets included in interventional trials that aim to further optimize treatment and post-treatment management for improving neurocognitive outcomes in cancer survivors.

The Assessment of Smoking Cessation Therapies in Cancer Patients

Leila Wirth

Principal Investigators: Elyse R. Park, PhD, MPH; Jamie S. Ostroff, PhD

Scientific Advisors: Angela Walter, PhD; Brett Goshe, PhD; Laura Malloy, LICSW; JoRean Sicks, PhD

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Different evidence-based therapies bring about smoking cessation more effectively than others. There is a massive field of evidence-based therapies available to help with nicotine cravings and withdrawals, including a range of counseling and pharmaceutical aids. Understanding which therapies can bring high rates of success, relative to how efficient, affordable, and accessible they are, is crucial when dealing with a demographic of cancer patients. Smoking cessation can increase the quality of life and decrease overall mortality rates in cancer patients. Cessation studies on cancer patients are frequently unreliable, often lacking a defined definition of tobacco usage and using self-reported data to draw conclusions. Our goal is to understand what the scope and effectiveness of evidence-based treatments for tobacco cessation look like in cancer patients. This will be found through the analysis of past studies on the relationship between tobacco usage, cancer, and smoking therapies. Additionally, data from the EAQ171CD Smokefree Study 2.0 (SSS 2.0) will be examined to compare standard smoking treatment with a Virtual Intervention Therapy. This study is part of the ECOG-ACRINE cancer research group and takes place at various NCORP sites participating in the SSS 2.0 trial. Through the analysis of a case from this study, we will collect data on patient-counselor interactions, reductions in smoking, and external factors that impact cessation efforts in each patient. This will allow us to accurately assess tobacco usage and understand the efficacy of various evidence-based therapies in cancer patients.

Epigenetics Therapeutics in Advanced Thyroid Cancer

Grant Wu

Principal Investigator: Inigo Landa, PhD

Scientific Advisors: Jingzhu Hao, MS; Jacob Hasse, PhD

Brigham and Women's Hospital

Anaplastic thyroid cancers (ATC) have poor prognosis and lack effective treatments. Genomic studies on ATC have unveiled the importance of members of the SWI/SNF chromatin remodeling complex in thyroid cancer progression and paved the way for the potential application of epigenetic inhibitors in this disease. While the inhibition of EZH2 in other cancers harboring SWI/SNF mutations has shown the potential to improve prognosis, whether it has the same effect in SWI/SNF-mutant ATC has yet to be answered. This summer, I assessed the effect of EZH2 inhibition on ATC-derived cell lines with mutations in subunits of the SWI/SNF complex. To study this, thyroid cancer cell lines with mutations in SWI/SNF members ARID1A and SMARCA4, as well as their wild-type counterparts, were treated with the EZH2 inhibitor tazemetostat. Cell growth and Western blot analysis of H3 lysine 27 trimethylation (H3K27me3), a chromatin mark catalyzed by EZH2 activity, was performed to determine tazemetostat's efficacy. While we expected SWI/SNF-mutant cell lines to be more dependent on tazemetostat treatment, i.e., more dramatic decrease of H3K27me3 marks and diminished proliferation, so far, the results have been inconclusive. Despite that, my summer research experience will contribute to the growing understanding of molecular therapeutic applications in thyroid and other tumor types.

Notable Achievements 2021

In the past year a student participating in our CURE and YES for CURE programming:

- Was accepted and will be pursuing their education at one of the following institutions: Tufts University, Boston College, Harvard University, Morehouse College, New York University, Johns Hopkins University, Simmons University, Stanford University, Massachusetts College of Pharmacy and Health Sciences
- Graduated from one of the following colleges and universities: Northeastern University, Harvard College, Boston College, Tufts University, College of the Holy Cross
- Successfully defended their dissertation: Rollins School of Public Health at Emory University in Epidemiology and Università Bocconi in Milan, Italy in Public Policy and Administration
- Received acceptance to Northeastern University (Physician Assistant), Yale University (School of Public Health), and Brown University (Medical School)
- Secured employment at: Boston Children's Hospital Stem Cell Neurology and Dana-Farber Cancer Institute; Shepherd Therapeutics
- Became HOPE Award recipients from the Biomedical Science Careers Program
- Received acceptance into the RISE (Research Initiative for Scientific Enhancement) program at Spelman College
- Was awarded the UMass Boston's Beacon Student Success Fellowship
- Became a published author
- Was an invited guest on the Health Design podcast
- Gained acceptance into the U54 Research Education Post-Baccalaureate Program

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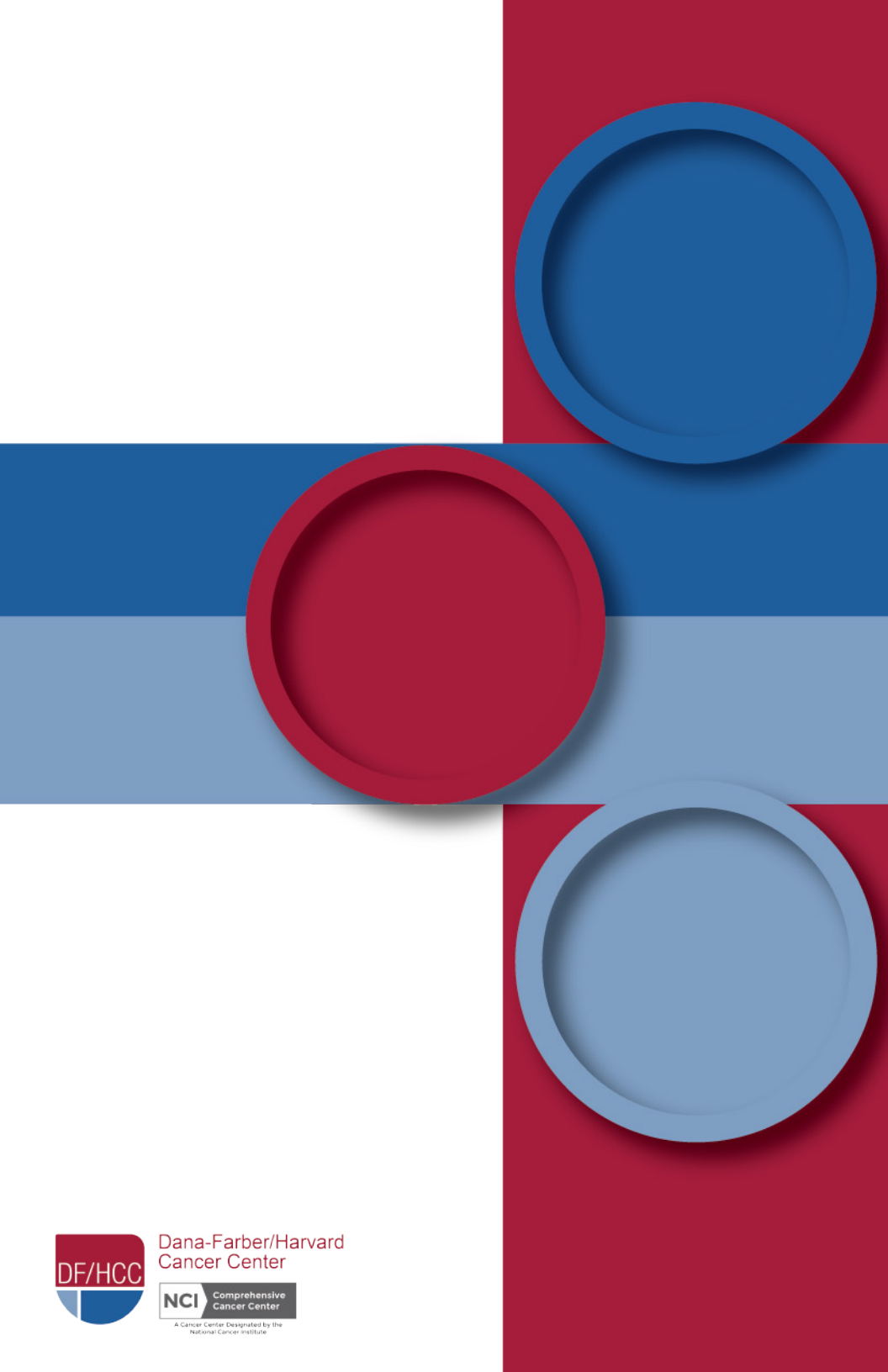
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