Grant Profile Information

Roger Abounader, MD, PhD

Institutional Research Grant

The Rector and Visitors of the University of Virginia
Department of Microbiology, Immunology and Cancer Biology
Room 4819
21 Hospital Drive
Charlottesville, VA 22908

Grant No. IRG-19-143-33-IRG
Division: Southeast
Term of Grant: 01/01/2020-12/31/2022
Total Award: $360,000
Total ACS Support: $2,990,000

Project Summary

For over 20 years, the American Cancer Society has supported the development of new cancer researchers at the University of Virginia (UVA) through the funding of the Institutional Research Grant (IRG). The IRG provides critical funds that enable new cancer investigators to conduct initial pilot research that is necessary for them to obtain larger national research support. The ACS support of the UVA IRG has been a fantastic investment and a great success. Over the most recent 7 years of the UVA IRG, 25 pilot projects were supported by $727,335 of ACS money. The 21 completed projects resulted in $11.5 million dollars in subsequent national research awards (a return of $15.84 for every dollar invested). In addition, the 21 completed pilot projects have already produced 18 publications. The number of funded research projects and publications from this latter investment will continue to grow as the pilot projects funded in the last few years are completed. The IRG has been a critical resource for UVA in terms of facilitating the success of our next generation of cancer researchers. As investment in cancer research and the hiring of new investigators at UVA has seen a substantial increase in the last few years, a continuation of the IRG is more critical than ever before.

Grant Profile Information

Katherine Aird, PhD

Cyclin E-Dependent Metabolic Vulnerabilities in Ovarian Cancer

Penn State University
Department of Cellular & Molecular Physiology
Office of Research Affairs, H138
500 University Drive
Hershey, PA17033

Grant No. RSG-19-113-01-CCG
Division: Northeast
Term of Grant: 01/01/2020-12/31/2023
Total Award: $780,000
Total ACS Support: $780,000

Area of Research: Cancer Initiation: Oncogenes and Tumor Suppressor Genes 100%

Types of Cancer: Ovarian Cancer 100%

Project Summary

Ovarian cancer is the most lethal gynecological malignancy in the United States. Excitingly, emerging therapies such as PARP inhibitors have recently been approved by the FDA. However, these inhibitors only work in a subset of ovarian cancer patients with mutations in BRCA1/2 or other genes in this pathway. Approximately 20% of ovarian cancer patients have high expression of a protein called cyclin E. These patients do not have BRCA1/2 mutations and are resistant to PARP inhibitor treatment. Therefore, it is critical to identify novel combination therapies that will sensitize this subset of patients to PARP inhibitors. Our long term goals are: 1) to understand the biology behind resistance of these patients to PARP inhibitors; and 2) to use this information as a way to sensitize cyclin E expressing ovarian cancers to PARP inhibitors. We recently discovered that targeting an enzyme called isocitrate dehydrogenase 1 (IDH1) may sensitize cyclin E-high ovarian cancer cells to PARP inhibitors. The goal of this proposal is to determine how inhibition of IDH1 sensitizes cyclin E-high ovarian cancer cells to PARP inhibitors and develop this combination as a new therapeutic strategy for these patients. PARP inhibitors are already FDA approved for ovarian cancer. As inhibitors to IDH1 have also been recently FDA approved, this combination could be quickly clinically applicable.

Grant Profile Information

Luis Batista, PhD

Telomerase Modulation prevents End-Stage Liver Disease and Cancer

Washington University, St. Louis
Department of Medicine
660 South Euclid Avenue
Saint Louis, MO 63110

Grant No. RSG-19-134-01-DMC
Division: North
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Cancer Initiation: Alterations in Chromosomes	60%
	Cancer Initiation: Oncogenes and Tumor Suppressor Genes	40%
Types of Cancer:	Liver Cancer	100%

Project Summary

Telomeres are repetitive DNA sequences that “cap” our chromosomes. Telomeres shorten with every cell division; when telomeres reach a critical length, they induce a growth arrest response that eliminates the cells" ability to divide, limiting the capacity of human tissues to self-renew. On the other hand, bypassing telomere induced growth arrest induces uncontrolled cellular proliferation, promoting tumor formation. Therefore, the control of telomere length has to be tightly managed for correct organismal function. The major mechanism responsible for telomere maintenance is a protein complex named telomerase. Not surprisingly, telomere dysfunction and telomerase are well accepted universal markers for cancer.

Of relevance for this application, multiple clinical studies have shown that telomere dysfunction represents a major risk factor for the development of end-stage liver disease (fibrosis and cirrhosis) and its progression to hepatocellular carcinoma. As hepatocellular carcinoma represents the fifth most common cancer worldwide, and the fourth most common cause of cancer-related death, novel strategies to prevent and treat this devastating disease are paramount.

In this proposal we will use genetically engineered human stem cells to elucidate how impaired telomere regulation contributes to end stage liver disease and its progression to liver cancer. We will focus on novel molecular targets that we have recently identified, using an in vitro platform where we can rigorously access the functionality of liver cells under different degrees of telomere dysfunction. These novel targets we have identified can be used as strategies to prevent the progression of end-stage liver disease into liver cancer. This would be extremely significant for the clinical management of liver cancer, as most cases of this devastating disease arise from fibrosis and cirrhosis. While our results will more directly impact patients that carry genetic mutations that predispose them to abnormal telomere shortening, these results will be broadly applicable to all patients with liver disease and cancer, since multiple lines of evidence show that abnormal telomeres are a universal aspect of this disease.

Our ultimate goal in this Research Scholar proposal to the American Cancer Society is to generate much needed molecular knowledge to devise novel treatment strategies to prevent end-stage liver disease and deter its progression into hepatocellular carcinoma, a cancer with increasing incidence and limited treatment options.

Grant Profile Information

Agata A. Bielska, MD, PhD

Defining and Targeting the Nutrient-Dependencies of mTOR-Driven Tumors

Memorial Sloan-Kettering Cancer Center
Department of Medicine
1275 York Avenue
Box 701
New York, NY 10065

Grant No. PF-19-125-01-CSM
Division: Northeast
Term of Grant: 01/01/2020-12/31/2022
Total Award: $163,500
Total ACS Support: $163,500

Mentor: Craig Thompson, MD

Area of Research: Cancer Progression and Metastasis 100%

Types of Cancer: Not Site-Specific Cancer 100%

Project Summary

The mechanistic target of rapamycin (mTOR) is a key regulator of cellular proliferation and growth, and is a downstream effector of many other cancer-associated genes including receptor tyrosine kinases (RTKs), PI3K mutations, and mutations of Akt. As a consequence, the RTK/PI3K/Akt/mTOR axis is defined as a major cancer signaling pathway, and it is thought that mutations in the upstream oncogenes ultimately converge upon increasing mTOR activation. However, using tumor sequencing data from over 27,000 patients at Memorial Sloan Kettering, mTOR was found to be mutated in only 3% of patients, despite being the final downstream effector of growth in this pathway. This represents a fundamental paradox, because if mTOR mediated biosynthesis is the final goal of this pathway, why is mTOR so rarely mutated? I hypothesize that oncogenic mTOR mutations, by committing cells to constitutive growth, render cells susceptible to nutrient depletion.

This hypothesis is supported by data showing that mTOR-driven tumors are dependent on unsaturated fatty acids in oxygen-limiting conditions, and by our preliminary data that shows oncogenic mTOR mutations have growth defects in amino acid-starved conditions. Consistent with this hypothesis, I have found that naturally occurring mTOR mutations are enriched in the subset of solid tumors that are clinically hypervascular and thus where nutrient limitations are unlikely. Upstream RTK and PI3K mutations are much more commonly mutated in cancers; 35% and 20%, respectively. I propose these mutations are favored because they activate alternative nutrient scavenging pathways, and are less susceptible to nutrient depletion because they retain mechanisms to inhibit mTOR. In the proposed work I will confirm and quantify the growth and survival defects of mTOR-driven cells as compared to PI3K-driven cells in amino acid and oxygen-limiting conditions. Then, in an in vivo model, I will investigate whether metabolic inhibitors can exploit this nutrient dependency to target and treat mTOR-driven tumors.

Grant Profile Information

Benjamin G. Bitler, PhD

Elucidating the role of Chromobox 2 in promoting Ovarian Cancer Progression

University of Colorado, Denver
Department of Obstetrics and Gynecology
12700 E 19th Avenue
Aurora, CO 80045

Grant No. RSG-19-129-01-DDC
Division: North
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Cancer Initiation: Oncogenes and Tumor Suppressor Genes	30%
	Cancer Progression and Metastasis	60%
	Localized Therapies - Discovery and Development	10%
Types of Cancer:	Ovarian Cancer	100%

Project Summary

Therapy resistance remains a significant clinical hurdle for almost every cancer type. For ovarian cancer, nearly all patients will develop therapy resistance within 2-years of the initial diagnosis, which is often the underlying cause of patient mortality. Ovarian cancer also has a unique metastatic process in which the tumor cells do not require blood vessels for metastasis. Through the support of an American Cancer Society Institutional Research Grant (ACS-IRG), my lab has recently linked this unique metastatic process to ovarian cancer therapy resistance. Thus, we propose to utilize ovarian cancer as our model system to further understand how cancer cells hijack the signaling pathways that promote metastasis and therapy resistance.

Our research proposal builds on our recent study that showed an epigenetic regulator, Chromobox 2 (CBX2/M33), regulates both ovarian cancer metastasis and therapy resistance. Epigenetics is the study of how cells reprogram themselves without changing the DNA sequence. CBX2 is part of an epigenetic complex that was initially found to be critical in sex determination during development. Consistently, we observed that loss of CBX2 in ovarian cancer cells resulted in a reduction of stem-like cells. Normally, stem cells are a critical cell population for the execution of normal developmental processes. Non-cancer cells express low levels of, CBX2, but cancer cells can express high CBX2 levels. Currently, there is no CBX2-specific inhibitor; however, through our collaboration with pharmaceutical sciences, we developed two CBX2-specific peptide inhibitors. To-date, there have been few published studies describing CBX2 activity in cancer. Notably, increased CBX2 correlates with metastatic prostate cancer. Also, CBX2 expression conveys a worse prognosis in multiple cancer types including ovarian, breast, sarcoma, and hepatocellular. Unfortunately, there is currently no mechanistic understanding as to how CBX2 is involved in promoting cancer progression. With our expertise in ovarian cancer and our novel CBX2 inhibitor, we feel that we are uniquely poised to make a significant contribution to the understanding of how CBX2 is involved in therapy resistance.

The objective of this Research Scholar award is to define how CBX2 is promoting ovarian cancer metastasis and therapy resistance. We hypothesize that elevated CBX2 expression is supporting an increased stem-like cell population that has heightened metastatic and therapy resistance capabilities. The short-term goal of the proposed research is to establish a rationale for therapeutically targeting CBX2 in ovarian cancer. The long-term goal will be to collaborate with clinical oncologists and ACS-IRG awardees to extend our findings into the clinic and other CBX2-relevant cancers, such as prostate and breast.

Grant Profile Information

Randy Carney, PhD

SERS Platform for Liquid Biopsy Analysis of Extracellular Vesicles

University of California, Davis
Department of Biomedical Engineering
451 Health Sciences Drive
Davis, CA 95616

Grant No. RSG-19-116-01-CDD
Division: West
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research: Technology and/or Marker Evaluation With Respect to Fundamental Parameters of Method 100%

Types of Cancer: Ovarian Cancer 100%

Project Summary

All cells dynamically excrete into circulation nano-sized packages termed extracellular vesicles (EVs), which contain an array of proteins and genes for cell-to-cell communication. This pathway can be hijacked by cancer cells for means of immune system suppression and metastasis. Innovative cross-disciplinary engineering methods are urgently needed to realize the diagnostic application of circulating cancer EVs to improve early detection of diseases like ovarian cancer, which do not have effective early screening tests. This project encompasses the design of highly multiplexed new nanoplasmonic probes for sensitive chemical fingerprinting of targeted circulating EVs. This project is to develop a reliable platform based on the use of these new nanoprobes to improve the limit of detection for diagnosing ovarian cancer compared to conventional methods.

Grant Profile Information

Leah M. Cook, PhD

Reprogramming the Immune-BME for Improving Outcomes of Bone Metastatic PCa

The Board of Regents of the University of Nebraska
Department of Pathology and Microbiology
985900 Nebraska Medical Center
Omaha, NE 68198-5900

Grant No. RSG-19-127-01-CSM
Division: North
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Cancer Progression and Metastasis	85%
	Complementary and Alternative Treatment Approaches	15%

Types of Cancer:	Bone Cancer	30%	Prostate Cancer	70%

Project Summary

Bone metastatic prostate cancer (BM-PCa) is the deadliest aspect of prostate cancer and is currently incurable. In bone, prostate cancer (PCa) cells induce excessive bone breakdown and abnormal bone formation resulting in the release of bone-derived growth factors, such as transforming growth factor beta (TGFbeta), which drive tumor growth. Although this seems like a straightforward process, current bone-targeting therapies have been unsuccessful in improving patient survival. Targeted immunotherapies have shown promising results for treating less advanced BM-PCa (i.e. patients with fewer than 20 bone lesions), but dismal impact in patients with more advanced disease, suggesting that PCa growth in bone contributes to immune response. Gaining a better understanding of the key immune cells involved in BM-PCa may present a new therapeutic approach.

Emerging data from my group demonstrates that polymorphonuclear neutrophils (PMNs), the most abundant immune cell in the bone marrow, heavily infiltrate the prostate tumor-bone microenvironment (T-BME), as identified in patient bone specimens. Recent studies demonstrated the existence of two distinct PMN populations in tumors: cytotoxic anti-tumoral (N1) and immunosuppressive pro-tumoral (N2) PMNs, with emergence of the latter being regulated by the accumulation of TGFbeta. Our preliminary studies revealed that: 1) BM-PCa, compared to non-metastatic PCa stimulates expansion of PMNs dependent on TGFbeta, 2) BM-PCa suppress N1 PMNs in vitro and 3) BM-PCa evades PMN cell killing to grow in bone. Thus, we hypothesize that bone metastatic PCa cells evade cytotoxic PMN cell killing potentially by TGFß-mediated skewing of PMN function. We will test this hypothesis in three aims. Aim 1. Determine the impact of bone metastatic PCa on PMN function and polarization. Aim 2. Define the therapeutic outcome of PMN polarization for treating PCa growth in bone. Aim 3. Define the importance of MSC-derived IL-8 on PMN function in the tumor-bone microenvironment. These aims will be implemented using analyses of BM-PCa media on PMN function, gene expression analyses of PCa patient-derived PMNs, and in vivo mouse bone metastasis models therapeutically targeting PMNs and models examining the role of MSCs on PMN polarization in bone.

Impact: Men with advanced stage prostate cancer frequently become resistant to androgen deprivation therapies and the disease progresses to the development of bone metastases, thereby limiting therapy options. The proposed research addresses the challenge to: develop effective treatments for men with metastatic prostate cancer. The proposed research will provide insight into immune regulation of prostate cancer and has the potential to present new therapeutic targets for improving outcomes of bone metastatic prostate cancer.

Grant Profile Information

Victoria C. Costales, MD, MPH

Physician Training Award in Cancer Prevention

Griffin Hospital
Department of Medical Education
130 Division Street
Derby, CT 06418

Grant No. PTAPM-19-186-18-PTAPM
Division: Northeast
Term of Grant: 01/01/2020-06/30/2024
Total Award: $300,000
Total ACS Support: $1,600,000

Area of Research:	Patient Care and Survivorship Issues	50%
	Surveillance	50%
Types of Cancer:	Not Site-Specific Cancer	100%

Project Summary

The Preventive Medicine Residency Program at Griffin Hospital with the support of the Yale School of Public Health and Yale Cancer Center will establish the Cancer Control and Prevention Track (CCPT), providing physician training in cancer prevention research, teaching, clinical practice, and community health/population health. The well-defined, robust curriculum includes cancer control and prevention experiences at Connecticut Tumor Registry, Yale-Griffin Prevention Research Center, Memorial Sloan Kettering Cancer Center, American Cancer Society, Griffin Hospital Accountable Care Organization, Griffin Hospital Center for Cancer Care/Smilow Cancer Hospital Care Center Derby, Yale Cancer Center, and the New Haven Health Department and academic training at the Yale School of Public Health and the National Cancer Institute. Our Department of Preventive Medicine stewards funding support from the Health Resources and Services Administration, Centers for Disease Control and Prevention, and the American Cancer Society in the areas of Cancer Control and Prevention, Preventive Medicine, Integrative Medicine, and Primary Care.

The Cancer Control and Prevention Track is designed to produce preventive medicine specialists with the passion and necessary skills to be future leaders in research, education/teaching, and clinical and community practice in cancer control and prevention. At the same time, the work of the CCPT Resident Physicians will advance cancer prevention in our local community the Lower Naugatuck Valley Region of Connecticut, where cancer is the leading cause of premature deaths. The research, teaching, and population health initiatives developed within the Cancer Control and Prevention Track will support the American Cancer Society''s ABCD strategy of being Activists (“convening relentless partners for awareness and impact”), delivering Breakthroughs (“investing in innovative research to develop game-changing approaches”), building Communities (“united to fight cancer with access to treatment and compassion”), and providing Direction (being “a passionate ally, empowering people with information and answers”) as well as our New England Region''s focus on Research, Colorectal Cancer, Human Papillomavirus vaccination, and Access to Care. Our Residency Program is excited to train the next generation of cancer prevention leaders and is confident that these collaborative efforts will have meaningful, measurable, and sustainable positive cancer control and prevention impact among our patients, local community, county, state, and beyond.

Grant Profile Information

Michael A. Davies, MD, PhD

Molecular Predictors and Vulnerabilities of Melanoma Brain Metastasis

University of Texas M.D. Anderson Cancer Center
Department of Melanoma Medical Oncology
Unit 0904
1515 Holcombe Boulevard
Houston, TX 77030

Grant No. MRAT-19-168-01-CCG
Division: South
Term of Grant: 01/01/2020-12/31/2022
Total Award: $500,000
Total ACS Support: $500,000

Project Summary

One of the most devastating complications of melanoma is spread of cancer cells to the central nervous system (the “CNS”), which includes the brain and the spinal cord. Melanoma has the highest risk of spreading to the brain among all common cancers. Once melanoma spreads to the brain, it is very challenging to treat effectively, and most patients will die from these tumors.

Despite the high risk and significance of CNS metastasis in melanoma, there are still many key gaps in our understanding of these tumors. First, at this time we do not know how to identify which melanoma patients have the highest risk of developing CNS metastases. If we could identify these patients, we could develop new strategies to try to detect such tumors when they are small and more easily treatable, or test treatments to prevent the spread of cancer cells to the brain. Second, our current treatments for metastatic melanoma are generally less effective for tumors that have spread to the brain compared to tumors in other organs. Developing new strategies that make our current treatments more effective against brain metastases would provide affected patients with an important new option and better outcomes.

Thus, our proposal brings investigators from many different specialties, and from two of the largest melanoma centers in the world, to address these key challenges.

First, we will test if molecular or immune features of melanomas can predict which patients will develop CNS metastases. This study builds upon a collaboration in which our teams have reviewed the records of more than 1,900 patients with stage III melanoma to identify clinical factors that predict an increased risk of developing CNS metastases. While we have identified novel factors, we will now determine if additional molecular or immune markers add to the accuracy of our predictors, and/or if they provide insights into why brain metastases develop. We will include markers that are also linked to the efficacy of targeted and immune therapies, so that we can translate findings into new treatments to reduce the risk of CNS metastases.

We will also test an experimental new treatment for brain metastases, IACS-010759. IACS-010759, which is currently in clinical trials, blocks a metabolic pathway in cells called oxidative phosphorylation (OXPHOS). We are conducting these experiments because we recently showed that melanoma cells growing in the brain specifically upregulate and depend upon OXPHOS for energy. Treatment with IACS-010759 blocked this pathway and slowed the growth of melanoma brain metastases in mice. Building upon those promising results, we will now test if IACS-010759 can improve survival further by combining it with FDA-approved targeted therapies. As our research showed that OXPHOS was increased in brain metastases from other cancers (i.e. lung cancer, breast cancer), we will also test if IACS-010759 can improve treatments used for brain metastases from those diseases.

Grant Profile Information

Bisrat Debeb, PhD

Novel Mechanisms of Brain Metastasis in aggressive Breast Cancers

University of Texas M.D. Anderson Cancer Center
Department of Breast Medical Oncology
1515 Holcombe Boulevard
Houston, TX 77030

Grant No. RSG-19-126-01-CSM
Division: South
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Cancer Progression and Metastasis	70%
	Systemic Therapies - Discovery and Development	30%
Types of Cancer:	Breast Cancer	100%

Project Summary

More than 90% of breast cancer-related deaths are due to metastasis, and as such, finding therapies to prevent and treat metastases is of the utmost clinical importance. Metastatic spread to the brain is a common and devastating manifestation of many types of cancer. In the United States alone, about 200,000 patients are diagnosed with brain metastases each year. With advances in diagnostic techniques and improved treatments for patients with breast cancer, the incidence of brain metastasis is increasing. The majority of patients with brain metastases die within months. Thus, there is an unmet clinical need to develop therapies against brain metastases. Understanding how breast cancer cells spread to the brain is critical to moving forward with developing new anti-brain metastasis agents. In the current application we will utilize our newly developed unique mouse models of brain metastasis to understand what drives metastatic dissemination to the brain and develop potential combinatorial therapies to prevent micrometastasis or treat established brain metastasis. In our preliminary data we have observed that elevated NDRG1 expression is associated with enhanced brain metastatic propensity and aggressiveness, and its silencing effectively inhibited migration, invasion and cancer stem cell properties suggesting that NDRG1 may play a crucial role in driving brain metastasis in aggressive breast cancers. However, no evidence is available on a direct functional link between NDRG1 and brain metastasis or aggressiveness in IBC. We will address the hypothesis that NDRG1 is a critical contributor in the metastatic spread of breast cancer cells to the brain by regulating downstream molecular factors that can be targeted to prevent or treat brain metastasis. In Specific Aim1 we will characterize newly generated brain metastasis sublines for tumorigenic properties as well as their interaction with the brain microenvironment, and examine if NDRG1 is required for brain metastasis initiation and colonization in our mouse models by genetic manipulation of the NDRG1 molecule. In Specific Aim 2 we will elucidate how NDRG1 enhances brain metastasis propensity and test the efficacy of anti-HER2 combinatorial approaches to prevent or treat brain metastasis using our HER2+ preclinical brain metastasis models. The proposed research will ultimately help women with breast cancer who develop brain metastasis particularly women with HER2+ breast cancer who are at high risk of developing brain metastasis. Upon completion, this work could lead to a breakthrough by significantly reducing the incidence of new brain metastases which improves survival of patients with breast cancer and accelerates progress toward ending breast cancer.

Grant Profile Information

Wendy Demark-Wahnefried, PhD, RD

Clinical Research Professor

The University of Alabama at Birmingham
Department of Nutrition Sciences
Room 650
1675 University Boulevard
Birmingham, AL 35294

Grant No. CRP-19-175-06-COUN
Division: South
Term of Grant: 01/01/2020-12/31/2024
Total Award: $400,000
Total ACS Support: $800,000

Area of Research:	Interventions to Prevent Cancer: Personal Behaviors (Non-Dietary) that Affect Cancer Risk	20%
	Patient Care and Survivorship Issues	20%
	Resources and Infrastructure Related to Cancer Control/ Survivorship/ and Outcomes Research	20%
	Dietary Interventions to Reduce Cancer Risk and Nutritional Science in Cancer Prevention	20%
	Education and Communication Research	20%

Types of Cancer:	Breast Cancer	12%	Kidney Cancer	12%
	Cardiotoxicity / Heart Cancer	16%	Myeloma	12%
	Colon and Rectal Cancer	12%	Ovarian Cancer	12%
	Endometrial Cancer	12%	Prostate Cancer	12%

Project Summary

A healthy diet, weight control, and a physically-active lifestyle are important for all individuals, but are even more important for cancer survivors, who are at higher risk for recurrence as well as second malignancies, heart disease, diabetes, osteoporosis, and functional decline. Unfortunately, many cancer survivors have suboptimal diet and physical activity behaviors. Nutrition scientist, Dr. Wendy Demark-Wahnefried, has made significant advances in developing and testing diet and exercise interventions among cancer survivors, and was awarded an ACS Clinical Professorship to adapt her effective mailed material and telephone counseling interventions for cancer survivors to a web-based platform. As a result, the SurvivorSHINE website (https://survivorshine.org) was created and beta-tested. This website is currently being used by approximately 400 cancer survivors in 38 states and four countries, and is endorsed by the Cancer and Aging Research Group. The SurvivorSHINE website is being refined further through an NCI-funded Program Project Grant (P01 CA22997), which will allow the addition of other web-based strategies that involve web chat interactions, text messaging, enhanced animation, and modularization. These additions should improve engagement and long-term use. The resulting intervention will be tested in a 2-year randomized controlled trial among 652 cancer survivors across the southeastern United States entitled AMPLIFI (Adapting MultiPLe behavior Interventions that eFfectively Improve) Cancer Survivor Health. Given the high risk of cancer survivors for developing sarcopenia that subsequently leads to functional decline, and which ultimately threatens independence, continued ACS funding is requested to assure evaluation of muscle mass - a critical endpoint. D3 Creatine, a field technique to measure muscle, is especially promising and has been strongly correlated with physical functioning in recent studies. Continued ACS support also is requested to provide Dr. Demark-Wahnefried with dedicated release time so that she can obtain the needed expertise in dissemination and implementation (D&I) research to optimize the dissemination potential of this newly-adapted intervention. The D3 creatine evaluation of muscle mass to substantiate the critical role of diet and exercise for cancer survivors, as well as the support and resources to optimize further broad scale dissemination of AMPLIFI can play a crucial role in advancing the science of lifestyle interventions among cancer survivors - a vulnerable population in need of interventions aimed at enhancing long-term health, physical functioning, and overall quality of life, and who will number over 20 million in the next 5 years.

Grant Profile Information

Christina Fitzsimmons, PhD

Investigating Molecular and Cellular Roles of Metabolism in RNA Epigenetics

NIH/National Cancer Institute
Laboratory of Cell Biology
Suite 3A19
31 Center Drive
Bethesda, MD 20892

Grant No. PF-19-157-01-RMC
Division: Northeast
Term of Grant: 01/01/2020-12/31/2021
Total Award: $111,500
Total ACS Support: $111,500

Mentor: Pedro Batista, PhD

Area of Research:	Endogenous Factors in the Origin and Cause of Cancer	50%
	Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors	50%

Types of Cancer:	Kidney Cancer	90%	Not Site-Specific Cancer	10%

Project Summary

Normal cells grow and divide in response to signals from their environment. Changes in the availability of nutrients or metabolic building blocks can influence cell growth. In cancer cells, metabolism is reprogrammed to meet the demands for higher energy and faster growth. Not only does metabolic rewiring provide energy advantages to cancer cells, but metabolic changes also influence the epigenetic landscape. Epigenetic modifications are like accent marks in a language--by changing the placement of an accent, we can completely change the meaning of the sentence, without changing the underlying alphabet. Similarly in cells, epigenetic changes can help determine whether genes are turned on or off. We believe that when cancer cells rewire metabolism, they affect the enzymes that "erase" the accent marks on RNA. In this proposal, we want to understand how changes in metabolism and accent marks are linked, and how alterations in the pattern of accent marks might influence the development of cancer. RNA epigenetic dysregulation has been implicated in many cancers, including acute myeloid leukemia, glioblastoma, and hereditary kidney cancers. We believe that this work will help us understand the development of cancer, and that it may lead to new methods for early cancer detection and cancer treatment.

Grant Profile Information

Danielle Friedman, MD

Metabolic Risk and Adipose Function After Childhood Total Body Irradiation

Memorial Sloan-Kettering Cancer Center
Department of Pediatrics
1275 York Avenue
New York, NY 10065

Grant No. CSDG-19-117-01-CPHPS
Division: Northeast
Term of Grant: 01/01/2020-12/31/2022
Total Award: $437,000
Total ACS Support: $437,000

Area of Research: Patient Care and Survivorship Issues 100%

Types of Cancer: Not Site-Specific Cancer 100%

Project Summary

Dr. Friedman''s long-term goal is to become an independent, patient-oriented clinician scientist focused on understanding radiation-related complications affecting cancer survivors, particularly related to metabolic and cardiovascular outcomes. Formal mentoring, coursework in cellular metabolism and molecular epidemiology, and protected research time will give Dr. Friedman the tools needed to achieve her goals and grow as a doctor caring for cancer survivors. The proposed research will investigate the determinants and mechanisms leading to diabetes, abnormal lipids, and hypertension, collectively known as ''cardiovascular disease (CVD) comorbidities'' after exposure to total body irradiation (TBI). Specifically, it will explore whether changes in adipose tissue contributes to these risks.

By the year 2026, an estimated 20 million cancer survivors will live in the United States, a subset of whom will be adult survivors of childhood malignancies treated with TBI-based hematopoietic cell transplantation. While refinements in therapy have led to improvements in survival, survivors face an excess lifelong risk of treatment-related late toxicity, including CVD comorbidities, which are associated with increased CVD and mortality. Retrospective studies have identified that childhood cancer survivors treated with TBI are at increased risk for these problems; the mechanisms underlying this risk remain unclear. In the general population, recent work has identified changes in adipose tissue as important factors in the development of cardiometabolic dysfunction. The current proposal seeks to investigate whether radiation-exposed adipose tissue plays a similar role in cancer survivors, while also assessing sociodemographic, treatment, and environmental/lifestyle factors that modify risk of CVD comorbidities after TBI. Through the Childhood Cancer Survivor Study cohort, Dr. Friedman proposes to study population-level determinants of cardiometabolic risk in a cohort of 571 five-year survivors of childhood cancer treated with TBI from 1970-1999; this cohort includes detailed treatment exposures, longitudinal outcomes data, and key information on lifestyle factors, such as physical activity, smoking, and alcohol use. In parallel, Dr. Friedman will conduct a translational research study of childhood cancer survivors treated at Memorial Sloan Kettering to assess adipose tissue features and gene expression profiles, as well as inflammatory markers, glucose/insulin, lipids, blood pressure, and body composition, in 15 individuals exposed to TBI, relative to 15 matched survivors treated with chemotherapy only and 15 healthy controls. We hypothesize that radiation results in primary defects in adipose tissue structure and function that results in preferential lipid storage in visceral fat depots, leading to insulin resistance and increased cardiometabolic risk. These studies will clarify the biological basis of cardiometabolic disease after TBI, and will provide important foundations for future trials to modify these risks and improve the health of cancer survivors.

Grant Profile Information

Dmitry I. Gabrilovich, MD, PhD

Regulation of Tumor Development and Progression by Myeloid Cells

Wistar Institute
Department of Immunology, Microenvironment and Metastasis
3601 Spruce Street
Philadelphia, PA 19104

Grant No. RP-19-179-01-LIB
Division: Northeast
Term of Grant: 01/01/2020-12/31/2024
Total Award: $400,000
Total ACS Support: $400,000

Area of Research:	Cancer Progression and Metastasis			40%
	Systemic Therapies - Discovery and Development			60%
Types of Cancer:	Breast Cancer	10%	Lung Cancer	80%
	Colon and Rectal Cancer	10%		

Project Summary

Myeloid derived suppressor cells are pathologically activated neutrophils and monocytes that are expanded in almost all types of cancer and represent critical component of tumor microenvironment. These cells directly support tumor cell survival and growth. These cells playa major role in tumor metastasis by establishing pre-metastatic niche that allows tumor cells to seed distant sited. Myeloid-derived suppressor cells severely limit antitumor immune responses. Recently, large number of studies demonstrated that these cells are critical in blocking the effect of cancer immunotherapy. The clinical significance of myeloid-derived suppressor cells was established in large number of studies. It suggests that these cells may be an attractive target for cancer therapy. However, the approaches to selective targeting of these cells are lacking. In this proposal we will identify the specific markers of these cells in cancer patients and mice, determine the mechanism of these cells promotion of tumor metastasis and will investigate the approaches to therapeutic targeting of these cells. We will explore novel concept that myeloid-derived suppressor cells can be converted to antitumor activated neutrophils and monocytes by regulating several metabolic processes in these cells including ferroptosis (recently discovered form of cells death), lipid metabolism, and endoplasmic reticulum stress. Our studies will discover previously unknown features of myeloid cells in cancer and, more importantly, will provide new approaches to their therapeutic targeting.

Grant Profile Information

Michael L. Gatza, PhD

Dissecting the Role of BRG1-SOX4 in Triple Negative Breast Cancer - Resub 2

Rutgers, The State University of New Jersey
Department of Radiation Oncology
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New Brunswick, NJ 08901

Grant No. RSG-19-160-01-TBE
Division: Northeast
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research: Cancer Initiation: Oncogenes and Tumor Suppressor Genes 100%

Types of Cancer: Breast Cancer 100%

Project Summary

Triple negative breast cancer (TNBC) is an aggressive form of breast cancer that disproportionately affects younger women and women of African American decent. This disease accounts for approximately 20,000 new cases and 10,000 deaths, or 1 in 4 breast cancer-related deaths, each year in the United States. TNBC tumors lack expression of many commonly targeted drug-able proteins and genes. As a result, this disease is largely treated using chemotherapy which, despite toxic side-effects, has a limited durable response. Therefore, the goal of our proposed research is to identify alterations in genetic signaling pathways that are commonly present in TNBC as a means to understand what alterations are responsible for tumor development and to use this information as a guide to develop rational therapeutic strategies based on the underlying biology of this disease.

By analyzing genetic data from more than 3,000 breast cancer patients, we have identified a series of mutated and improperly over-expressed genes that cooperate to mediate a novel signaling pathway activated in TNBC tumors and which is essential for TNBC cell viability. Our initial experimental studies have shown that expression of SOX4 and BRG1 results in activation of oncogenic signaling pathways, including PI3K/Akt activity, as well as increased cell proliferation and viability. Therefore the proposed studies will test the hypothesis that BRG1-SOX4 constitutes a novel signaling pathway that mediates tumor development, progression and therapeutic response through modulation of a novel gene expression program.

In the proposed studies we seek to define a novel signaling pathway and to identify the specific mechanisms by which BRG1-SOX4 promotes tumor development and progression. The proposed research will identify the mechanisms by which SOX4 modulates aberrant PI3K/Akt signaling leading to tumor cell growth and proliferation; will demonstrate the mechanisms by which BRG1 modulates SOX4 expression and cooperates with SOX4 to mediate PI3K signaling; and will determine the therapeutic potential of the BRG1-SOX4 axis by identifying additional drug-able signaling pathways activated by BRG1-SOX4 overexpression in TNBC. The results of the proposed studies will delineate a novel signaling pathway in TNBC and provide the foundation for rational, personalized therapeutic strategies for a subset of breast cancer patients with few therapeutic options.

Grant Profile Information

Jessica Gorman, PhD, MPH

Opening the Conversation for Couples with Reproductive Health Concerns

Oregon State University
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2250 SW Jefferson Way
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Grant No. RSG-19-123-01-CPPB
Division: West
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research: Patient Care and Survivorship Issues 100%

Types of Cancer: Breast Cancer 100%

Project Summary

Young adult survivors of breast and gynecologic cancer face a number of challenges, including interrupted life plans. As many as two-thirds of these young survivors experience negative effects of cancer and cancer treatment on their reproductive health, including sexual function and ability to have children. These are among the most distressing aspects of life after cancer for young survivors and their partners, and when left unaddressed, lead to poorer mental health and quality of life. Effective communication and coping are important for couples struggling with reproductive distress after cancer. Through our research, we have learned that many couples encounter significant challenges when faced with the reproductive health consequences of cancer. Yet, surprisingly, evidence-based programs are not available to help young couples manage this aspect of life after cancer.

We will adapt an existing program so that it specifically fills this gap. To do this, we will incorporate advice from young survivors, survivors'' partners, clinicians, and researchers. The new program will focus on fertility/family building and sexual health concerns after cancer, be tailored to meet the needs of young adult breast and gynecologic cancer survivors and their partners, include information about strategies shown to be effective to cope with reproductive health concerns after cancer, and be delivered by videoconference to reach couples living in rural and urban Oregon. We will enroll 100 couples in this study to compare this newly adapted program to the original program, which focuses on managing the impact of cancer more generally. Fifty couples will be randomly assigned to receive the new program and 50 couples will receive the original program. We will evaluate whether the new program leads to greater improvements in reproductive distress than the original program. We also expect to see improvements in other aspects of relationships, sexual functioning, and well-being. Additionally, we are interested in gaining knowledge about how the program works. We will study possible mechanisms, including improved coping and communication between couples, using data from both survey questions and interviews. We expect this study to yield a feasible and effective program to reduce reproductive distress, which will lay the groundwork for making this program available to a wider audience in real-world settings. In the long term, this is expected to improve equity of access to information and supportive care for young survivors and their partners.

Grant Profile Information

Lipika Goyal, MD

Overcoming Resistance and Heterogeneity in FGFR2+ Cholangiocarcinoma

Massachusetts General Hospital
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55 Fruit Street
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Grant No. CSDG-19-163-01-TBG
Division: Northeast
Term of Grant: 01/01/2020-12/31/2024
Total Award: $729,000
Total ACS Support: $729,000

Area of Research:	Cancer Progression and Metastasis	50%
	Systemic Therapies - Clinical Applications	50%
Types of Cancer:	Gastrointestinal Tract	100%

Project Summary

Understanding why patients develop resistance to anticancer drugs is a fundamental unsolved question in oncology. Drug resistance is a barrier that curtails the benefit of even the most promising drugs and leads to frustration for patients, their families, and their oncologists. A new class of drugs, FGFR inhibitors, is having dramatic benefit for patients with a type of primary liver cancer called bile duct cancer. Scientist discovered that up to 20% of these patients have a gene mutation called an FGFR2 fusion, and these tumors are exquisitely sensitive to FGFR inhibitors. Up to 85% of patients with FGFR2 fusion positive bile duct cancer benefit from these drugs and up to 40% of patients enjoy dramatic tumor shrinkage. This is compared to a 40% rate of benefit and 5% rate of shrinkage with chemotherapy. Importantly, FGFR inhibitors are relatively well tolerated, and patients prefer these drugs over chemotherapy. However, while we as oncologists are very excited about this breakthrough for our patients, the duration of benefit from these drugs is unacceptably low at less than 6 months. One of the main reasons for this is that the tumors become resistant to the FGFR inhibitors. The aim of this proposal is to understand why tumors become resistant to FGFR inhibitors in bile duct cancer and what we can do about this. Our approach to studying this will be two-fold. First, we will gather data from patients. We will do this by collecting and sequencing tumor and liquid biopsies at the time of tumor growth on the FGFR inhibitors to find new mutations that may be causing resistance. Next, we will use this mutational data to select drug combinations that might help these patients get longer benefit from FGFR inhibitors, and we will test these drugs in mouse models and other models in the lab so we can rapidly come up with the most promising combinations. All the data from this proposal are aimed at coming up with the next clinical trial (of an FGFR inhibitor plus a second drug) that will improve survival and quality of life for patients with this awful disease. MGH is a high volume center for bile duct cancer, and specifically for FGFR2 fusion positive bile duct cancer, and we have a world renown bile duct cancer scientist, Dr. Nabeel Bardeesy, here who likely has the largest collection of bile duct cancer models in the lab when comparing worldwide. Thus, I am confident that we can execute this project and come up with new promising treatments for our patients.

Grant Profile Information

Kira Gritsman, MD, PhD

RON Kinase as a Therapeutic Target in Myeloproliferative Neoplasms

Albert Einstein College of Medicine
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Chanin 410
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Bronx, NY 10461

Grant No. RSG-19-130-01-DDC
Division: Northeast
Term of Grant: 01/01/2020-12/31/2023
Total Award: $660,000
Total ACS Support: $660,000

Area of Research: Cancer Progression and Metastasis 50%

Systemic Therapies - Discovery and Development 50%

Types of Cancer: Blood Cancer 100%

Project Summary

The myeloproliferative neoplasms (MPNs) are a group of blood cancers that include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). PV and ET are characterized by an expansion of red blood cells, white blood cells, and/or platelets. These diseases can progress to leukemia or myelofibrosis. Patients with myelofibrosis suffer from low blood counts due to inflammation, spleen enlargement, and scarring of the bone marrow. In most cases, MPN cells have mutations in proteins that activate the JAK/STAT signaling cascade, which relays messages by growth factors from outside to inside the cell. These growth factors normally bind to receptor proteins on the cell surface to stimulate blood cell division at the appropriate time. However, activation of the JAK/STAT pathway causes blood cells to divide out of control, without the need for growth factors. Existing inhibitors of the JAK/STAT pathway, such as ruxolitinib, can reduce spleen size and improve symptoms. However, these drugs can worsen blood counts, and do not reduce bone marrow scarring. The only cure for patients who have developed myelofibrosis is stem cell transplantation. Therefore, new treatments for MPN are urgently needed that can interfere with inflammation that causes bone marrow scarring and do not worsen blood counts.

We unexpectedly found that the drug crizotinib, which is approved for patients with lung cancer, also has activity in a patient with PV. Crizotinib is a potent inhibitor of the kinase enzymes c-MET and RON, which activate multiple signaling cascades in cancer.
We found that crizotinib also blocks activation of the JAK/STAT pathway in patient MPN cells, and impairs their growth. Furthermore, we discovered that genetic inactivation of RON has similar effects to crizotinib in inhibiting cell growth and JAK/STAT signaling.

Our hypothesis is that crizotinib interferes with expansion of MPN cells by inhibiting the JAK/STAT pathway through RON, and that inhibition of RON can also prevent changes to the bone marrow in MPN that result in scarring. In this proposal we will (1) determine using two different mouse models of MPN with genetic deletion of Ron whether RON is important for disease initiation and progression, (2) determine whether inactivation of RON can prevent bone marrow scarring in a mouse model of PMF, and (3) explore the mechanisms by which RON promotes JAK/STAT activation and resistance to JAK inhibitors in MPN patients. Therefore, we want to test whether blocking RON could be an effective strategy to delay MPN progression and reduce bone marrow scarring. Because crizotinib is already clinically approved for the treatment of lung cancer, it could rapidly enter clinical trials for MPN patients.

Grant Profile Information

Yanxiang Guo, PhD

Targeting Metabolic Vulnerabilities to Improve Kras-driven NSCLC Treatment

Rutgers, The State University of New Jersey
Department of Medicine Oncology
195 Little Albany Street
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Grant No. RSG-19-165-01-TBG
Division: Northeast
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Cancer Initiation: Oncogenes and Tumor Suppressor Genes	30%
	Complementary and Alternative Treatment Approaches	70%
Types of Cancer:	Lung Cancer	100%

Project Summary

KRAS, TP53 and Liver Kinase B1 (LKB1) are three most frequent mutations detected in human lung cancer patients, leading to aggressive tumors with limited treatments. LKB1 or TP53 comutations define different subgroups of KRAS-mutant non-small cell lung cancer (NSCLC) with distinct biology, therapeutic vulnerabilities and immune profiles. Thus, new therapies for different subtypes of KRAS-mutant NSCLC are urgently needed.

KRAS mutation triggers many cancer pathways that enhance tumor cell growth and survival. However, blocking these pathways (PI3K and MAPK) has not made much progress in the clinical setting of KRAS-mutant NSCLC. Additionally, dose-limiting toxicities of dual PI3K and MEK inhibitors was observed. Recent clinical trials show that immunotherapies could be a new strategy for treating KRAS-mutant NSCLC. However, the objective response rate is different in subgroups of KRAS-mutant NSCLC. Particularly, LKB1 mutation causes KRAS-mutant lung cancer patients to resist anti-PD1 treatment. Therefore, developing strategies to improve the efficacy of dual PI3K and MEK inhibitors or immunotherapy to treat KRAS-mutant NSCLC is imperative.

Cancer cells alter metabolism for tumorigenesis. Autophagy is a normal cellular process to clean up debris in the cells but this process is also used by cancer cells to recycle cellular components to maintain cellular metabolism when extracellular nutrients are limited. Our previous studies have demonstrated that autophagy supports lung tumorigenesis by using genetically engineered mouse models (GEMMs) for Kras-mutant NSCLC, suggesting that targeting autophagy could be a potential approach to improve KRAS-mutant NSCLC treatment. Indeed, supported by ACS Early Investigator Pilot Award (8/2017-8/2018), we found that cell-autonomous autophagy ablation significantly improved the anti-tumor efficacy of dual PI3K and MEK inhibitors at lower doses, which leads to the reduced drug toxicity in KrasG12D/+; p53-/- (KP) GEMMs for NSCLC. In addition, using KrasG12D/+; Lkb1-/- (KL) GEMMs for NSCLC, we found that autophagy ablation significantly reduced the frequency of tumor initiation and tumor growth, and extended mouse life span, which is associated with increased T cell infiltration in KL tumors, suggesting that autophagy may promote immune escape for KL tumorigenesis. Here, we will evaluate potential clinical translatability of our findings by testing the central hypothesis: autophagy is required to maintain cellular metabolism, which may cause KRAS-mutant lung cancer to be resistant to chemotherapy or immunotherapy. Therefore, inhibition of autophagy could circumvent resistance and significantly enhance the efficacy of anticancer therapies for KRAS-mutant NSCLC.

The overall goal of this project is to provide novel therapeutic combinations that effectively improve the efficacy of treating KRAS-mutant NSCLC and elucidate the underlying mechanism.

Grant Profile Information

Denis C. Guttridge, PhD

Insitutional Research Grant

Medical University of South Carolina
Department of Pediatrics
Drug Discovery Building, 305
70 President Street
Charleston, SC 29425

Grant No. IRG-19-137-20-IRG
Division: Southeast
Term of Grant: 01/01/2020-12/31/2022
Total Award: $450,000
Total ACS Support: $3,157,500

Project Summary

The American Cancer Society Institutional Research Grant (ACS IRG) is an essential mechanism used by the Medical University of South Carolina"s (MUSC) Hollings Cancer Center (HCC) to recruit new faculty into cancer research and to nurture the ideas of junior faculty already involved in cancer research. Over the past 25 years, the ACS IRG has successfully fostered cancer interests among young investigators, providing them with an opportunity by which they can obtain small grants for testing their ideas and positioning them to successfully compete for extramural peer-reviewed research grants. In fact, ACS IRG-funded awards from 2012-2018 will yield a 20-fold return. As the recipient of one of the largest ACS IRG awards in the United States, MUSC/HCC has clearly continued to demonstrate its ability to draw highly motivated and productive applicants. Additionally, with the recent recruitment of a new Director of the HCC, Dr. Gustavo Leone, and in collaboration with the Dean of the College of Medicine, university-wide strategic plans include a priority for expanding the faculty with an emphasis on cancer-related researchers in diverse disciplines that range from basic molecular biology to clinical investigations to population-based sciences. HCC is strategically positioned to meet that goal having just received its five year redesignation from the National Cancer Institute.
The mission of the HCC is to reduce the cancer burden in South Carolina (SC) through the highest quality care, innovative research, outstanding professional education, and statewide cancer prevention programs with a focus on reaching underserved populations. The HCC focuses on serving SC, its catchment area, to address the disproportionate burden cancer places on the state in terms of incidence, mortality, morbidity, and quality of life. Many contextual and sociocultural factors impact SC"s cancer burden. For instance, the SC Rural Health Association designates greater than 75% of SC as rural. When compared to national levels, SC ranks among the lowest education and income levels. SC"s population is racially diverse; 36% are minorities, with 29% African American (AA) and 5% Hispanic/Latino. SC"s tobacco control efforts face many challenges with 23% of the residents continuing to smoke. This combination of factors contributes to SC being ranked 13th highest in the nation for cancer mortality rates. Additionally, mortality rates for numerous cancer types are significantly higher in the AA population in SC than the national average. Given the enormous cancer burden in SC, all ACS IRG applicants are encouraged to design research which addresses the most significant needs in SC through scientific approaches spanning basic, translational and clinical disciplines. This ACS IRG competing renewal application requests ACS IRG Review Committee to support projects of up to $30,000 each year, with the HCC contributing an additional $5,000 per project awarded.

Grant Profile Information

Sarah R. Hengel, PhD

Elucidating the Role of Human RAD51 Paralogs in DNA Damage Repair

University of Pittsburgh
Department of Microbiology and Molecular Genetics
University Club
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Grant No. PF-19-132-01-DMC
Division: Northeast
Term of Grant: 01/01/2020-12/31/2022
Total Award: $163,500
Total ACS Support: $163,500

Mentor: Kara A. Bernstein, PhD

Area of Research:	Endogenous Factors in the Origin and Cause of Cancer	50%		
	Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors	50%		
Types of Cancer:	Breast Cancer	50%	Prostate Cancer	5%
	Endometrial Cancer	45%		

Project Summary

We are studying genetic factors that make some individuals more susceptible to cancer, particularly breast, uterine/endometrial, and prostate cancers. When cancer is identified in the clinic, these individuals undergo genetic testing. In addition to the genes that are currently being screened, we study related genes that are also found in cancers. These new genes are not yet included on the screening panels but may also be a cause of cancer. If our research project is successful we will be able to 1) better predict who is likely to develop cancer based upon their genetics and 2) to understand why they developed cancer. The genes we study are important for fixing damaged DNA. If these genes are not operating properly and DNA damage goes unrepaired then cancer can develop. Changes in DNA are called mutations and are found in cancers. While scientists have identified mutations in cancer, doctors do not always know which mutations are important and may be the cause of a person''s cancer. To overcome these obstacles, we are combining biochemical and genetic approaches to study how our DNA is protected and why unrepaired DNA leads to cancer. These biochemical and genetic approaches allow us to determine which mutations are important in cancers. In the short term, we are working towards better predicting who may be at risk to develop cancer. In the long term, we are working towards identifying the most effective treatment strategies for cancer patients. Our ultimate goal is to prevent cancer from forming at all.

Grant Profile Information

Eva Hernando, PhD

Role of Amyloid Beta in Brain Metastasis

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New York, NY 10016

Grant No. MRAT-19-169-01-CSM
Division: Northeast
Term of Grant: 01/01/2020-12/31/2022
Total Award: $500,000
Total ACS Support: $500,000

Area of Research:	Cancer Progression and Metastasis			80%
	Systemic Therapies - Discovery and Development			20%
Types of Cancer:	Breast Cancer	15%	Melanoma	70%
	Lung Cancer	15%		

Project Summary

Some cancers, including melanoma, lung and breast adenocarcinomas often reach and disseminate through the brain. Patients with brain metastasis have limited therapeutic options and generally poor prognosis. The mechanisms underlying a tumor''s ability to reach and colonize the brain remain vastly unknown. We have developed a new model for the study of melanoma brain metastasis, consisting of pairs of cultured cells from a brain metastasis and a non-brain metastasis from the same patient. We have shown that the brain-derived melanoma cells have higher ability to colonize the brains when transplanted to mice than cells derived from other locations, such as lymph nodes or subcutaneous tumors. This suggests that those cells have acquired properties advantageous for brain colonization, and represent a good model to study melanoma brain metastasis. We analyzed the protein content of these brain-derived cultures and compared it to that of cultures obtained from extra-cranial metastases. Surprisingly, most of the proteins found increased in brain-derived melanoma cells were related to Alzheimer''s disease, and particularly to the Amyloid Processing Protein (APP), which plays a central role in Alzheimer''s.
We have demonstrated experimentally that APP is essential for melanoma cell adaptation to the brain. We propose that APP or some of its products (such as amyloid-beta) allow melanoma cells to communicate with the surrounding astrocytes, which in turn support melanoma growth. Here we propose to: 1) investigate how APP influences melanoma growth within the brain microenvironment or the interactions between melanoma cells and astrocytes; 2) determine the therapeutic potential of targeting APP pharmacologically, using antibodies and compounds that have already being tested clinically in Alzheimer''s patients; 3) assess if APP is required for brain metastasis of other tumors, such as lung and breast cancers.
Our studies have revealed an unexpected connection between brain metastasis and Alzheimer''s disease. As we are testing reagents that have already shown a favorable safety profile in humans, successful completion of our preclinical studies will result in rapid transition to clinical use. Our findings may dramatically change the clinical management and outcomes of patients with brain metastasis.

Grant Profile Information

Daniel Herranz, PhD

The role of SIRT1 in T-Cell Acute Lymphoblastic Leukemia

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Department of Pharmacology
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195 Little Albany Street
New Brunswick, NJ 08901-1914

Grant No. RSG-19-161-01-TBE
Division: Northeast
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research: Cancer Initiation: Oncogenes and Tumor Suppressor Genes 50%

Cancer Progression and Metastasis 50%

Types of Cancer: Leukemia / Leukaemia 100%

Project Summary

T-ALL is an hematological malignancy that affects children and adults. Cure rates have increased due to recent advances; however, 20-50% of patients still relapse, and therapeutic options are scarce at that point, leading to high mortality rates. Thus, we need to discover new targets for the treatment of T-ALL. The main cause of T-ALL are activating mutations in a gene called NOTCH1. Related to this, my findings suggest that inhibition of NOTCH1 has drastic consequences in cancer cell metabolism and identified novel potential therapeutic targets. Of note, our preliminary results demonstrate that NOTCH1 directly activates SIRT1, and SIRT1 itself plays a critical role in T-ALL generation and progression, such that inhibiting SIRT1 might be an attractive therapeutic strategy. To this end, we will use cutting-edge techniques in combination with unique novel mouse models to study the mechanism of regulation of SIRT1 by NOTCH1, as well as the mechanistic and therapeutic effects of SIRT1 inhibition in T-ALL. Thus, our results might translate into better treatments for T-ALL patients in the short term.

Grant Profile Information

Erin K. Hertlein, PhD

Investigating the Role of BCL3 in Ibrutinib Resistant CLL

Ohio State University
Department of Internal Medicine
420 W 12th Avenue
Columbus, OH 43210

Grant No. RSG-19-151-01-LIB
Division: North Central
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Cancer Initiation: Oncogenes and Tumor Suppressor Genes	50%
	Cancer Progression and Metastasis	50%
Types of Cancer:	Leukemia / Leukaemia	100%

Project Summary

Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia in the US. It is characterized by the slow accumulation of malignant B-cells that resist apoptosis and evade immune surveillance. While chemotherapy (with or without therapeutic antibodies) is still used for some patients, with the recent results of several definitive clinical trials most patients are now receiving inhibitors of a protein called Bruton"s tyrosine kinase (BTK) in the front line setting. However, for patients who relapse on BTK inhibitors such as ibrutinib, progression to death is rapid as salvage therapy is only palliative. Identifying prognostic factors that predict risk of relapse is of high interest, as is an understanding of the underlying biology and development of treatment strategies toward these factors.

B-cell Leukemia 3 (BCL3) is a signaling protein that is over-expressed in some patients with CLL, but BCR signaling or promotes tumor cell survival is unknown. Our group has observed that a significant proportion of CLL patients with a chromosome translocation which results in BCL3 upregulation progress on ibrutinib. The mechanism of resistance in these patients is frequently the acquisition of a mutation in BTK that prevents ibrutinib from binding BTK. We hypothesize that BCL3 supports the survival and subsequent outgrowth of this mutant BTK clone in ibrutinib-resistant CLL.

A promising clinical strategy in patients with ibrutinib resistant, aggressive CLL is to harness the immune system to fight the cancer cells. Correcting deficiencies in the immune cell function, or “re-educating” the immune cells to recognize the tumor cells has the potential to provide long term remission for CLL patients. Our data indicates that the BCL3 protein is important to direct how the tumor cells regulate the surrounding immune cells. Our current investigation will identify ways in which the BCL3-expressing CLL cells learn to evade or hide from the immune cells which would otherwise target the tumor for destruction. This research will therefore identify a novel therapeutic target in ibrutinib resistant CLL, the BCL3 protein.

Grant Profile Information

Scott W. Hiebert, PhD

Institutional Research Grant

Vanderbilt University Medical Center
Department of Biochemistry
2220 Pierce Avenue
Nashville, TN 37232

Grant No. IRG-19-139-59-IRG
Division: North Central
Term of Grant: 01/01/2020-12/31/2022
Total Award: $360,000
Total ACS Support: $3,670,000

Project Summary

For 58 years, Vanderbilt has been privileged to be a recipient of an American Cancer Society Institutional Research Grant (ACS IRG). We view these funds as an essential part of our efforts to recruit new investigators into cancer research and to nurture new ideas from junior faculty members already involved in cancer research. Over the past 58 years, the ACS IRG has continued to foster the cancer interests of many young investigators, providing them with a mechanism by which they can obtain their first independent grant for testing new ideas, and positioning them to successfully compete for extramural peer-reviewed research grants. A key component of the Vanderbilt IRG is our extensive mentoring of young investigators. One of the best measures of success of the Vanderbilt ACS IRG awards and our mentoring is that over the last reporting period, a relatively small ACS investment has turned into over $20 million in other grant funds.

The leadership of the Vanderbilt-Ingram Cancer Center (VICC), Vanderbilt University Medical Center, and Vanderbilt University understands the need for new ideas and fresh perspectives that new investigators bring to their first faculty positions. As such, the institution has committed significant funds and space to the VICC for new faculty recruitment. This will allow us to maintain a very strong applicant pool with the recruitment of at least 15-18 new faculty members each year doing cancer-related research. We are continuing the expansion of our Cancer Epidemiology and Cancer Control and Health Outcomes programs. This recruitment will help us target many populations that the ACS has identified as needing special emphasis including increasing access to health care for rural populations and populations that are obese or have little physical activity. These are populations that are prevalent in our catchment area and we look forward to working with the mid-south ACS to address these issues.

The VICC has extensive interactions with the local chapter of the ACS and the ACS IRG plays an integral role in fostering these interactions. A highlight is our yearly ACS IRG symposium and this year we are working closely with the mid-South ACS chapter to include even more local ACS staff and donors and incorporating tours of the VICC into this event. We are especially proud of our extensive support of the regional Relay For Life fundraisers, our support for the Hope Lodge, and the many personal appearances made by ACS funded investigators at Mid-South chapter events. Over the past 58 years, this relationship has been mutually beneficial to both organizations in terms of media exposure, fund raising and, most importantly, ensuring that this region''s cancer patients and their families have the best care and the newest therapies.

Grant Profile Information

Andrew J. Holland, PhD

Targeting a Novel synthetic-lethal Interaction in Breast Cancer

Johns Hopkins Hospital
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615A PCTB
725 North Wolfe Street
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Grant No. MBG-19-173-01-MBG
Division: Northeast
Term of Grant: 01/01/2020-12/31/2021
Total Award: $240,000
Total ACS Support: $240,000

Area of Research:	Cancer Initiation: Oncogenes and Tumor Suppressor Genes	15%
	Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors	15%
	Systemic Therapies - Discovery and Development	50%
	Systemic Therapies - Clinical Applications	20%
Types of Cancer:	Breast Cancer	100%

Project Summary

Drugs that target cell division and destroy rapidly dividing tumor cells have been in clinical use for a long time. Unfortunately, these drugs also kill healthy dividing cells, leading to severe side effects such as diarrhea, nausea, and exhaustion. In this proposal, we develop a novel anti-cancer strategy that allows for the specific killing of proliferating tumor cells without affecting healthy dividing cells. Many tumor cells express high levels of a protein called TRIM37. We recently discovered that inhibiting the action of the enzyme Polo-like kinase 4 (PLK4) triggers massive cell death in dividing tumor cells with elevated levels of TRIM37. Importantly, because healthy cells express lower amounts of TRIM37, suppressing PLK4 does not affect their proliferation, and they keep dividing. This phenomenon is known as “synthetic lethality” because a tumor cell"s genetic makeup renders an otherwise harmless drug lethal. In this proposal, we will undertake an effort to test new PLK4 inhibitors in cell culture and animal models of human breast cancers expressing high levels of TRIM37. We have included experienced translational and clinical researchers at Johns Hopkins School of Medicine who have vast experience in taking similar studies rapidly to trials in patients. The work is innovative and impactful, with tremendous potential to positively affect the lives of cancer patients.

Grant Profile Information

Jenna Jewell, PhD

Regulation of mTORC1 by Glutamine

University of Texas Southwestern Medical Center, Dallas
Department of Molecular Biology
5323 Harry Hines Boulevard
Dallas, TX 75390-9148

Grant No. RSG-19-162-01-TBE
Division: South
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Cancer Initiation: Oncogenes and Tumor Suppressor Genes			50%
	Cancer Progression and Metastasis			50%
Types of Cancer:	Colon and Rectal Cancer	30%	Pancreatic Cancer	40%
	Lung Cancer	30%		

Project Summary

The mammalian target of rapamycin complex 1 (mTORC1) signaling pathway is frequently elevated in human disease, including cancer, type 2 diabetes, metabolic disorders, and neurodegeneration. We recently discovered a novel pathway where the amino acid, glutamine, activates mTORC1. The goal of this American Cancer Society Research Scholar Grant is to decipher the molecular mechanisms by which glutamine activates mTORC1, in order to develop more effective therapeutics to inhibit mTORC1.

Grant Profile Information

Christopher Jondle, PhD

Gammaherpesvirus hijacks Host IL-17A Production to establish Latency

Medical College of Wisconsin
Department of Microbiology and Immunology
8701 Watertown Plank Road
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Grant No. PF-19-176-01-MPC
Division: North
Term of Grant: 07/01/2019-06/30/2022
Total Award: $163,500
Total ACS Support: $163,500

Mentor: Vera L. Tarakanova, PhD

Area of Research:	Exogenous Factors in the Origin and Cause of Cancer			100%
Types of Cancer:	Hodgkin's Disease	80%	Kaposi's Sarcoma	20%

Project Summary

Human specific gammaherpesviruses, Epstein-Barr virus (EBV) and Kaposi''s Sarcoma associated herpesvirus (KSHV), currently infect over 95% of all adults. These viruses are associated with multiple cancers, including Burkitt''s lymphoma, Hodgkin''s lymphoma and Kaposi''s sarcoma. Unfortunately, we do not fully understand how these gammaherpesviruses drive cancer development.

IL-17A is a functionally diverse cytokine that is associated with certain autoimmune diseases and whose expression is increased in almost every type of cancer. It has been found to support tumor growth as well as suppress tumor growth depending on the type of cancer, indicating that its role in cancer development is complex. Interestingly, Herpesvirus saimiri (HVS), a simian gammaherpesvirus, creates its own IL-17A, which acts like human IL-17A. Surprisingly, nothing is known about the role of IL-17A in gammaherpesvirus infection and associated cancers, a gap in knowledge that my study will begin to address.

I found that IL-17A promotes the establishment of chronic gammaherpesvirus infection. In the first part of my study, I want to identify the cells that produce IL-17A during gammaherpesvirus infection and then determine which cells respond to IL-17A to aid gammaherpesvirus infection. The second part of my study will look into two potential ways gammaherpesvirus infection causes release of IL-17A and how IL-17A directly acts on infected cells to promote gammaherpesvirus replication. Successful completion of the proposed studies will pave the way for future translational studies and ultimately new therapies against virus driven cancers.

Grant Profile Information

Minal Kale, MD

Personalizing Lung Cancer Screening for Smokers with Comorbidities

Icahn School of Medicine at Mount Sinai
Department of Medicine
Box 1087
One Gustave L. Levy Place
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Grant No. RSG-19-118-01-CPHPS
Division: Northeast
Term of Grant: 01/01/2020-12/31/2023
Total Award: $734,000
Total ACS Support: $734,000

Area of Research:
- Resources and Infrastructure Related to Detection/ Diagnosis/ or Prognosis — 50%
- Education and Communication Research — 50%

Types of Cancer:
- Lung Cancer — 100%

Project Summary

Lung cancer screening, consisting of an annual low-dose computed tomography (LDCT) is currently recommended to 8 million smokers who are at high risk of developing lung cancer. However, many individuals who are eligible for lung cancer screening also have comorbid conditions (such as chronic obstructive pulmonary disease [COPD], cardiovascular disease [CVD], and stroke) due to the shared risk factor with lung cancer (i.e., tobacco exposure). Others have comorbid diabetes mellitus (DM), another condition that is prevalent among middle aged and older individuals eligible for screening. These chronic conditions substantially alter the benefits from lung cancer screening in the following ways: 1) influence risk of complications from work-up of positive screening tests; 2) modify eligibility to lung cancer treatments; 3) vary the risk of treatment-related complications; 4) influence quality of life; and 5) substantially modify an individuals'' life expectancy. While current guidelines acknowledge that screening should not be offered or should be discontinued in individuals with health problems that substantially limit life expectancy, there is little guidance to clinicians or persons with comorbidities regarding whether to pursue screening and the optimal screening regimen.

Medicare policy requires that providers engage in shared decision making with patients who are eligible for lung cancer screening, wherein a decision aid is used to illustrate the benefits and harms of screening. However, currently available decision aids fail to address how comorbidities might attenuate the benefits of screening or even lead to a net harm, as they mostly represent the results of the National Lung Screening Trial, a study that disproportionately included healthier and younger individuals compared with the majority of candidates for screening encountered in routine practice. Additionally, the decision aids fail to offer estimates of when screening might be stopped. Discontinuing screening is a critical element to discussing the benefits and harms of cancer prevention as evidence from other studies suggest that cancer screening may persist beyond what is recommended by national guidelines.

In this proposal, we seek to personalize lung cancer screening decisions in patients with comorbidities using mixed research methods. Using a well-validated mathematical model, we will generate quantitative data to incorporate into a novel, tailored decision support tool that will enhance the ability of individuals with comorbidities to make informed decisions about lung cancer screening in alignment with their preferences and values. Our decision support tool will fulfill a significant research and clinical gap and will reflect more closely the clinical scenarios under which lung cancer screening is currently being considered.

Grant Profile Information

Yibin Kang, PhD

Stromal Niche as Regulators of Breast Cancer Metastasis

Princeton University
Department of Molecular Biology
255 Lewis Thomas Laboratory
Princeton, NJ 08544

Grant No. RP-19-180-01-CSM
Division: Northeast
Term of Grant: 01/01/2020-12/31/2024
Total Award: $400,000
Total ACS Support: $400,000

Area of Research:	Normal Functioning	10%
	Cancer Progression and Metastasis	90%
Types of Cancer:	Breast Cancer 100%	

Project Summary

Breast cancer is a complex disease that kills patients by invading adjacent tissue and spreading to other organs in a process called metastasis. The accounts for over 40,000 deaths in the United States each year, the vast majority of which are due to deadly spread of metastatic cancer cells to organs such as bone and lung. While prevention, diagnosis, and therapy of breast cancer are improving steadily due to intensive research and clinical development efforts, we are still far from being able to cure advanced late-stage cancers. Improved treatments critically rely on better understanding of the molecular mechanisms driving breast cancer metastasis to distant organs.

It has become increasingly clear that interactions between tumor cells and normal organ cells, also called “stromal cells”, are critical for tumor growth and metastasis. These “tumor-stromal” interactions are often mediated by cellular signaling pathways that relay information from tumor cells to stromal cells, or vice versa. In metastasis, stromal cells in secondary organs provide cellular “niches” for seeding and outgrowth of metastases. It has also been recognized that the resistance of many breast cancers to various therapies is in part caused by such stromal components surrounding tumor cells. During cancer progression, bone marrow (BM)-derived cell populations are influenced by factors released by tumors, and in turn contribute crucial functions in every step of cancer development. Furthermore, bone is also an organ frequently colonized by the metastatic spread of solid tumors. Research on bone metastasis in my lab and others has revealed extensive molecular mechanisms that mediate the intricate interactions between tumor cells and various bone stromal cells during the seeding, dormancy and outgrowth of bone metastasis. While tumor-bone crosstalk has been studied extensively in the context of primary tumor growth and bone metastasis formation, very few studies have explored such interactions in the context of common cancer therapeutics and physio-psycological stress, conditions commonly experienced by cancer patients. The proposed study will build on our extensive experience in the study of tumor-stromal interactions in breast cancer bone metastasis, and will investigate the poorly explored questions of how therapy- and stress-induced BM changes influence the metastatic recurrence in bone and other organs.

The new insights that we will gain from our studies will have important implications in improving the treatment of metastatic breast cancer. By better understanding tumor-stromal interactions in breast cancer metastasis, new treatments can be designed to target stromal cells to prevent or reduce metastasis, or improve the efficacy of existing treatments. Patients with metastatic cancer will benefit from better targeted therapy to slow down or revert disease progression, while patients with localized early stage breast cancer will have better preventive treatments and sensitive diagnostic markers for early detection of emerging metastasis.

Grant Profile Information

John Karijolich, PhD

Innate Immune Sensing in Primary Effusion Lymphoma

Vanderbilt University Medical Center
Department of Pathology, Microbiology, and Immunology
Suite 970
3319 West End Avenue
Nashville, TN 37203

Grant No. RSG-19-152-01-MPC
Division: North Central
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Endogenous Factors in the Origin and Cause of Cancer	50%
	Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors	50%
Types of Cancer:	Blood Cancer 50%	Kaposi's Sarcoma 50%

Project Summary

Current estimates suggest ~15% of all cancers are caused by viral infections. Kaposi''s sarcoma-associated herpesvirus (KSHV) is the causative agent of Kaposi''s sarcoma (KS) and primary effusion lymphoma (PEL). Both of these cancers are more prevalent in individuals that are immunocompromised, including HIV-positive individuals that have progressed to AIDS, or organ transplant recipients receiving immunosuppressive therapy to prevent organ rejection. The increased incidence of both cancers in the setting of immunosuppression suggests that our immune system is capable of defending against the virus. Thus, understanding how the virus is detected by the human immune system will be critical for the development of therapeutics against these malignancies. Data from my laboratory has discovered that an arm of the immune system, called the cell intrinsic immune system, is capable of recognizing and suppressing the replication of KSHV. Interestingly, we have discovered that the immune system, rather than detecting the virus , actually recognizes specific defects in cellular RNAs that occur as a result of KSHV infection. Here, we propose to investigate how KSHV infection results in defects in cellular RNAs. Given that up to 50% of patients with KS never achieve total remission, and the lack of an effective treatment for PEL, these studies will provide key information to evaluate the potential of therapeutics that treat KSHV-associated disease through activation of the cell intrinsic immune response.

Grant Profile Information

Anne E. Kazak, PhD, ABPP

Implementing Family Psychosocial Risk Screening for Pediatric Health Equity

Alfred I. duPont Hospital for Children of The Nemours Foundation
Department of Research/Pediatrics
Suite 160
1701 Rockland Road
Wilmington, DE 19803

Grant No. RSG-19-122-01-CPPB
Division: Northeast
Term of Grant: 01/01/2020-12/31/2024
Total Award: $1,638,000
Total ACS Support: $1,638,000

Area of Research:	Patient Care and Survivorship Issues	50%
	Population-based Behavioral Factors	50%
Types of Cancer:	Not Site-Specific Cancer	100%

Project Summary

The diagnosis and treatment of pediatric cancer adversely affects patient and caregiver physical and psychosocial health. Particularly at risk for disparities in care and health are families with limited instrumental and social resources and pre-existing child and family problems. Both the Institute of Medicine Report Cancer Care for the Whole Patient: Meeting Psychosocial Health Care Needs and the Standards of Psychosocial Care in Pediatric Cancer call for improvement in delivery of psychosocial care. The first standard, “youth with cancer and their family members should routinely receive systematic assessment of their psychosocial healthcare needs” is the starting point for ensuring evidence-based care for all patients and families to improve health, increase access to care, and reduce health disparities. Screening is not routinely implemented in pediatric cancer care due to multi-level patient/family, provider, and institutional barriers. With support from the ACS, we validated in English and Spanish a web-based, parent report screener of family psychosocial risk-the Psychosocial Assessment Tool (PAT). The PAT is now ready for broad dissemination across pediatric cancer centers. The ultimate goal of this proposal is to create and broadly disseminate an implementation toolkit to facilitate acceptable, feasible, and sustainable family psychosocial risk screening in English and Spanish.

Guided by strong dissemination and implementation research methods, the PAT will be implemented across a national sample of 18 pediatric cancer programs in a comparative effectiveness study. Prior to the trial, we will obtain input from an 18-member stakeholder Implementation Team consisting of parent advocacy groups, health care providers, pediatric oncology organization representatives (Association of Pediatric Oncology Social Workers, Association of Pediatric Hematology/Oncology Nurses), and pediatric health care industry leaders. With this information, we will finalize two strategies (Training, Training + Enhanced Resources) to implement family psychosocial risk screening with the PAT in English and Spanish. Then we will compare the two strategies across 18 children''s cancer centers of different sizes. We believe that Training + Enhanced Resources will be more successful than Training alone at the patient/family (all patients screened), provider (job satisfaction/burnout), and institution (cost-effectiveness) levels. Finally, with feedback from the Implementation Team, we will develop and distribute a web-based PAT Implementation Toolkit. This proposal is highly responsive to the mission of the ACS to improve access to care and reduce health disparities. By identifying strategies for the successful and sustainable implementation of universal, family psychosocial screening across children''s cancer centers, we can achieve the assessment Standard and deliver psychosocial care matched to family need for all patients, especially those most impacted by health inequities.

Grant Profile Information

Mark R. Kelley, PhD

Institutional Research Grant

Indiana University, Indianapolis
Department of Pediatrics
1044 West Walnut
Indianapolis, IN 46202

Grant No. IRG-19-144-34-IRG
Division: North Central
Term of Grant: 01/01/2020-12/31/2022
Total Award: $270,000
Total ACS Support: $3,289,000

Project Summary

The American Cancer Society Institutional Research Grant (ACS-IRG) is a key program used by Indiana University to recruit and mentor junior faculty who are pursuing research in basic/translational, clinical, and behavioral oncology. The ACS-IRG provides pilot funding on a competitive basis to help junior faculty become productive, independent researchers with strong external peer-reviewed support.

The IU ACS-IRG is a critical program that over the years has launched outstanding cancer research careers for over 200 faculty members on the IUPUI campus. Over the past seven years, the ACS with matching funds from IUSM has invested $878,327 to fund cancer-based pilot project and this has led to the acquisition of $6.9M of extramurally funded grants by recipients of ACS-IRG pilot projects as well as 44 publications in peer review journals. Thus, the ACS-IRG program has had an outstanding return on investment (ROI of $7.81 in extramural funding for every $1 of ACS-IRG funding).

The proposed IRG program builds on this success by integrating project management, mentoring, career development, and translational research support processes (ITRAC, CITE, CTSI) to facilitate the advancement of junior faculty. A vigorous committee review process and increased interaction between the IU ACS-IRG awardees and ACS staff and donors, including participation in ACS events and activities is described. Extensive mentoring and faculty development opportunities throughout the IUSCC and the IUSM are also presented.

As the IUSCC continues to expand its programs, its faculty, and its space, the ACS-IRG pilot project funding will be even more important to the Cancer Center''s growth. For this reason, the IU School of Medicine will supplement the ACS-IRG award with $10,000 additional funds per award, raising the total value of each award to $40,000; the School of Medicine has committed to providing $30,000 per year over the three years of the ACS-IRG for a total of $90,000. This will encourage more applications and increase the program''s competitiveness.

Grant Profile Information

Ruth Keri, PhD

Institutional Research Grant

Case Western Reserve University
Department of Pharmacology
10900 Euclid Avenue
Cleveland, OH 44106

Grant No. IRG-19-141-24-IRG
Division: North Central
Term of Grant: 01/01/2020-12/31/2022
Total Award: $360,000
Total ACS Support: $3,768,000

Project Summary

The ACS IRG provides foundational support for newly-established investigators associated with the Case Comprehensive Cancer Center (Case CCC). Eligible individuals include any researcher with interests in cancer that is affiliated with the Case CCC"s constituent institutions, including University Hospitals Cleveland Medical Center (UHCMC), Cleveland Clinic (CCLCM), Case Western Reserve University (CWRU), and MetroHealth Medical Center. The Case CCC includes >380 members spanning 7 research programs with expertise in diverse cancer disciplines, including clinical oncology, cancer biology, cancer immunology, population sciences, disparities, prevention, drug development, biomedical engineering, nursing, genomics, etc. The Case CCC integrates basic, translational, and clinical research, and all applicants for ACS pilot funds become members of one of its core research programs. Based on previous recruitment rates, we will add ~60 IRG eligible investigators over the next three years. The availability of ACS pilot funds is a major recruitment incentive that grows the pool of next-generation researchers at the Case CCC. Discoveries made by these investigators begin within the community by studying patients, their diseases, and basic mechanisms, with the goal of expanding globally through translational breakthroughs.

The ACS IRG gives investigators an opportunity to initiate cancer research projects and generate data needed for successful applications for national funding. By providing critical support early in their careers, the ACS IRG motivates new faculty members to build laboratories focused on cancer research. New faculty have an opportunity to formulate hypothesis-driven applications and receive constructive feedback via review. All applicants receive formal written critiques from two reviewers as well as additional input from the review panel. In addition, the review panel provides rigorous feedback for developing a competitive, innovative, and impactful research program that improves our understanding of cancer.

The Case CCC has built a comprehensive mentoring program around the ACS IRG, ensuring career guidance by established investigators. All awardees must participate in this bipartite program that includes group meetings with the Case CCC Director and ACS IRG PI as well as individual meetings with mentoring committees that focus on research and career development. Written feedback/follow-up is given to ensure accurate and sustained communication between new investigators and their mentoring teams.

In addition to growing as cancer researchers, awardees of the ACS IRG pilots develop an appreciation of the importance of building and sustaining cancer research programs. Many awardees, in addition to the members of the Case CCC, actively participate in ACS activities including grant reviewing, fundraising, advocacy, volunteering, and providing seminars on research that was supported by the ACS IRG and discussing its long-term impact.

Grant Profile Information

Mary-Claire King, PhD

ACS-Disney Foundation Professor for Breast Cancer Research

University of Washington
Department of Medicine and Genome Sciences
Room K-160 Health Sciences Building Box 357720
1959 NE Pacific Street
Seattle, WA 98195

Grant No. RP-19-177-25-COUN
Division: West
Term of Grant: 01/01/2020-12/31/2024
Total Award: $400,000
Total ACS Support: $2,045,000

Area of Research:	Cancer Initiation: Oncogenes and Tumor Suppressor Genes	60%
	Resources and Infrastructure Related to Prevention	20%
	Technology and/or Marker Testing in a Clinical Setting	20%

Types of Cancer:	Breast Cancer	70%	Prostate Cancer	10%
	Ovarian Cancer	20%		

Project Summary

In 1994, the Walt Disney family established the ACS-Disney Foundation Professorship for Breast Cancer Research, to provide partial salary support for an investigator whose research addressed prevention and/or treatment of breast cancer. The ACS-Disney Professorship differed from other ACS professorships in that it focused on a particular cancer problem (breast cancer) and provided support for the academic life of the investigator. I was honored, indeed overwhelmed, to be named the ACS-Disney Breast cancer Research Professor, and have found it to be a defining feature of my scientific life.

This report is my every-5-year progress report to the ACS community on my activities under the professorship and plans for my next five years of work. My professorship began just after BRCA1 and BRCA2 were cloned. In the 25 years since, I have worked to understand the genetics and biology of inherited breast cancer in the light of BRCA1 and BRCA2 and their sister genes also involved in homologous recombination repair, and to apply that knowledge to prevent breast cancer for women with inherited mutations leading to very high risks of breast and related cancers.

My progress report includes details of my research in breast cancer genetics over the past five years. The themes of my research have been: (1) development of new genomic technologies for characterization of inherited breast cancer; (2) characterization of the role in inherited breast cancer of mutations that alter regulation of the estrogen receptor; (3) understanding the very wide variety of biological effects, and therefore of clinical consequences, of mutations in breast cancer genes; (4) investigating inherited breast cancer in populations from all parts of the world; (5) demonstrating that genetic testing for inherited predisposition to breast cancer can provide accurate and useful information for all women, regardless of personal or family history of cancer.

All these activities will continue in the next five years of my professorship. In the strategic plans section of the report, I describe in detail a new genomic approach that we are developing that will, I hope, resolve the remaining unsolved component of inherited predisposition to breast cancer. If successful, this approach can be applied straightforwardly to all forms of inherited cancer.

I am also active in the ACS, both locally (the Washington-Alaska chapter) and nationally, and will of course continue these activities. Finally, in the past five years, I am proud to have been recognized for my breast cancer research, most notably by the Lasker Foundation Special Achievement Award in 2014 and by a US National Medal of Science from President Obama in 2016. I am very proud to be the ACS-Disney foundation professor for Brest Cancer Research and plan to continue this work for the foreseeable future.

Grant Profile Information

Dorothy Lane, MD

Physician Training Award in Cancer Prevention

Stony Brook University
Department of Family, Population and
Preventive Medicine
Renaissance School of Medicine
Health Science Center Level 3 Room 086
Stony Brook, NY 11794-8036

Grant No. PTAPM-19-156-30-PTAPM
Division: Northeast
Term of Grant: 01/01/2020-06/30/2024
Total Award: $300,000
Total ACS Support: $2,297,500

Area of Research: Population-based Behavioral Factors 100%

Types of Cancer: Not Site-Specific Cancer 100%

Project Summary

The ACGME accredited residency program in general preventive medicine and public health at Stony Brook University School of Medicine will provide physician training in cancer prevention and control through a well-defined and enriched cancer prevention and control curriculum track for the Physician Training Award in Cancer Prevention (PTACP) residents, featuring a variety of cancer prevention and control research, teaching and practice rotations and related academic coursework. An MPH will be awarded by the CEPH accredited Stony Brook Program in Public Health. The training is designed to develop board certified preventive medicine specialists who will be future leaders in research, education and interventions in cancer prevention and control and will contribute to the accomplishment of national objectives for cancer control. The Department of Family, Population and Preventive Medicine at Stony Brook has a track record of NIH and CDC supported research and demonstration projects in cancer prevention and control, and operates cancer prevention clinical services for hospital employees, other occupational populations, and primary care patients visiting our wellness and chronic illness program and family medicine patient-centered medical home. The training program is building upon this rich resource in cancer control research and service, as well as longstanding affiliations with health departments, hospitals, and other practicum training sites with expertise and programs in cancer prevention and control. Our grant application also proposes the addition of new content to our standardized cancer prevention and control track, including an innovative curriculum for: the further development and understanding of the evidence-base for cancer prevention and control; improving interprofessional practice of cancer prevention and control; increasing access and extending cancer prevention and control through the use of tele-preventive medicine; as well as continuing the implementation of a cancer center rotation designed to increase collaborations with cancer specialists and increase cancer center community outreach to broaden the impact of cancer prevention and control on the health of our community.

Grant Profile Information

Kate Lawrenson, PhD

Decoding the Core Regulatory Circuitry of High-Grade Serous Ovarian Cancers

Cedars-Sinai Medical Center
Department of Gynecologic Oncology
290W
8700 Beverly Boulevard
Los Angeles, CA 90048

Grant No. RSG-19-135-01-DMC
Division: West
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Endogenous Factors in the Origin and Cause of Cancer	50%
	Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors	50%
Types of Cancer:	Ovarian Cancer	100%

Project Summary

In recent decades, technological advances have vastly improved our ability to sequence large amount of genetic material from patient tumors and have led to the development of targeted therapies for many tumor types. These targeted therapies have revolutionized cancer therapy and are so successful that these new agents have significantly improved outcomes for many cancers. In the future, we hope that all cancer patients will be offered ‘personalized medicine'' – drugs that specifically and potently target vulnerabilities present in a patient''s own tumor. However for epithelial ovarian cancer, treatment options are very limited, particularly for recurrent disease. Moreover those therapies that are available are associated with severe side-effects which in the most extreme cases can even lead to patients discontinuing treatment. Consequently, 5-year survival rates remain under 40% and ovarian cancer is expected to cause over 14,000 deaths in 2018 in the United States.

To address this unmet need, our proposed research project strives to validate a select group of target proteins that we have strong evidence to believe will be effective therapeutic targets for the treatment of high-grade serous ovarian cancer, the most common subtype of epithelial ovarian cancer. We developed a tool, the ‘Cancer Core Transcription factor Specificity (CaCTS)'' algorithm, to prioritize ‘master regulators'' for 33 tumor types, including ovarian cancer. To characterize the role of these novel master regulators in ovarian cancer development, we will take an integrated approach that combines state-of-the-art molecular assays to comprehensively evaluate these factors as novel drivers and candidate therapeutic targets for ovarian cancer. This research focuses largely on the non-coding portion of the genome, which harbors elements that control the expression of key ovarian cancer genes, but which has been little studied in ovarian tumorigenesis. We hope that by developing targeted therapeutics that interfere with key proteins that regulate gene expression in ovarian cancer cells specifically, we can create drugs that preferentially kill ovarian cancer cells with reduced off-target effects and minimal systemic toxicities. Following successful execution of this proposed project we will work with drug development experts at our Medical Center to develop drugs that potently inhibit the HGSOC master regulators, after which we will work with clinical trial experts to perform Phase 0 trial in ovarian cancer patients. We therefore expect to translate these findings into a new ‘targeted therapy'' within a 5-10 year timeframe.

Grant Profile Information

Allison J. Lazard, PhD

Engaging Adolescents and Young Adults with Cancer via a Social Support App

University of North Carolina, Chapel Hill
School of Media and Journalism
Suite 2200 CB1350
104 Airport Drive
Chapel Hill, NC 27599-1350

Grant No. PEP-19-154-01-PCSM
Division: Southeast
Term of Grant: 01/01/2020-12/31/2021
Total Award: $144,000
Total ACS Support: $144,000

Area of Research: Patient Care and Survivorship Issues 50%

Education and Communication Research 50%

Types of Cancer: Not Site-Specific Cancer 100%

Project Summary

Adolescents and young adults (AYAs) affected by cancer are a health disparity group with few age-appropriate resources dedicated to their unique psychosocial and health needs, despite the approximately 70,000 diagnoses each year in the US. Specifically, social support is one of the most prominent unmet issues AYAs face. AYAs struggle to find peers experiencing their diagnoses and often suffer from social isolation, compounded by debilitating life disruptions, such as extended absences from school and work. Lack of social support is associated with poorer physiological and physical functioning and increased sensitivity to stressors; conversely, AYAs who experience adequate social support report less psychological distress and improved quality of life. There is a critical need to find ways to improve social support among AYAs. Considering that AYAs report the two most important criteria for a cancer support resource are connection with peers and convenience, preferring technology-based support over face-to-face, peer support mobile apps offer a viable solution. Our goal is to identify ways to enhance and evaluate the design of a social support app to increase engagement (seeking and sharing support in the app) and perceived social support. The interactive app, the Stupid Cancer app, directly addresses the critical need in AYA cancer care for age-appropriate supportive resources and addresses priorities for support among AYAs: choice, flexibility, convenience, and similarity to peers. The Stupid Cancer app provides AYAs access to instant, anonymous peer support and cancer information through private, one-to-one messaging and group chats. Through this social support app, AYAs may access emotional, informational, and/or practical support about specific concerns at any time, while maintaining control of the process and anonymity. Our team will investigate how to increase engagement (seeking and sharing) with a social support app in 3 phases. In Phase 1, we will identify design cues that increase feelings of being with others (social presence) and develop app prototypes enhanced with these design cues. Design cues increase feelings of peer connections are necessary to encourage AYAs to engage in reciprocal communication with peers within the social support app, and in turn increase perceived social support. In Phase 2, we will examine the impact of these designs on engagement (seeking and sharing support in the app). In phase 3, we will assess the feasibility of using in-app behavioral data to examine the influence of app engagement on perceived social support. We aim to identify evidence-based designs to increase AYAs" willingness to seek and sharing support with a peer-to-peer app, and in turn, perceived social support among AYAs with cancer, who consistently rate their desire to connect with peers with shared experiences as top priority for unmet support needs. In all phases, we will engage with the AYAs, an underserved population, to directly address their unique needs for age-appropriate supportive care.

Grant Profile Information

Michelle M. LeBeau, PhD

Institutional Research Grant

University of Chicago
Comprehensive Cancer Center
5841 South Maryland Avenue
Chicago, IL 60637

Grant No. IRG-19-136-59-IRG
Division: North Central
Term of Grant: 01/01/2020-12/31/2022
Total Award: $270,000
Total ACS Support: $2,866,500

Project Summary

The American Cancer Society Institutional Research Grant (ACS IRG) will provide funds to the University of Chicago Medicine Comprehensive Cancer Center (UCCCC) to award pilot project grants to early-stage investigators without national peer-reviewed research grant support. The goal is to support junior faculty so they can obtain preliminary results that will enable them to compete successfully for national research grants. The UCCCC will use the ACS IRG program to: a) support the development of new investigators to conduct independent cancer research; b) foster direct relationships between funded investigators and the local ACS; and c) support research by newly independent investigators in areas of special interest to the ACS.

In each year of the grant cycle, the UCCCC will issue, and broadly publicize, a Request for Applications (RFA) describing the ACS IRG funding opportunity. The RFA will be promoted through multiple avenues, including email, website, e-newletters, and targeted invitations to eligible faculty. Using an online portal, candidates will submit applications that include a description of the planned research and discussion of its cancer relevance, biographical sketch, description of other research support, and budget with budget justification. Proposals will be assigned primary and secondary reviewers from the UCCCC Standing Review Committee, using ad hoc reviewers when specific expertise is needed. This Committee will be chaired Dr. Michelle Le Beau, director of the UCCCC, and comprised of senior and junior faculty, including past IRG recipients. The applications will be reviewed and scored in a manner similar to that used by National Institutes of Health review panels using the following criteria: a) overall scientific merit, b) cancer relevance, c) feasibility of timely completion of the project, and d) likelihood of project leading to peer-reviewed funding. Three proposals will be funded at the level of $35,000, with $30,000 coming directly from the ACS IRG award and the remainder from UCCCC philanthropic funds. The UCCCC will ensure that all recipients are informed of the source of their support, and awardees will be required to acknowledge the ACS IRG in publications of their work. All applicants will receive reviewers'' critiques and senior UCCCC scientific staff and Standing Review Committee members will discuss comments with those applicants not selected for funding. Finally, the UCCCC encourages ACS IRG recipients to take advantage of existing institutional and Cancer Center mentoring and career development opportunities, including the UCCCC''s recently-initiated Grant Writers'' Group.

In summary, support of early-stage investigators provided by the ACS IRG award is critical for the success of the UCCCC and its mission of reducing the devastating effects of cancer through innovation in cancer prevention, diagnosis, and treatment.

Grant Profile Information

Andrew T. Lenis, MD

Checkpoint Inhibition and TLR Agonism for Upper Tract Urothelial Carcinoma

University of California, Los Angeles
Department of Urology
Suite 331
300 Stein Plaza
Los Angeles, CA 90095

Grant No. PF-19-114-01-CDD
Division: West
Term of Grant: 01/01/2020-12/31/2020
Total Award: $53,500
Total ACS Support: $53,500

Mentor: Karim Chamie, MD, MSHS

Area of Research:	Localized Therapies - Discovery and Development			80%
	Localized Therapies - Clinical Applications			20%
Types of Cancer:	Bladder Cancer	20%	Urinary system	80%

Project Summary

Treatment for patients with aggressive cancer of the upper urinary tracts (renal pelvis and ureter) is limited to complete removal of the kidney, ureter, and segment of bladder. Currently, there is no organ-sparing treatment option for patients with the aggressive, high-grade form of the disease. Unfortunately, many patients are elderly with several comorbidities, including chronic kidney disease, that preclude major surgery. Our study investigates a novel combination of immunotherapy as a localized treatment that could be instilled into the kidney via a small camera placed into the bladder during a brief clinic procedure. This combination of immunotherapy will be delivered in a hydrogel formulation that improves delivery to the upper urinary tracts. The gel is liquid when cooled during instillation and when warmed in the body forms a semisolid gel. This gel then slowly releases the treatment over several hours and is eliminated out of the body through the urine. This overcomes many of the current limitations with local treatment of the upper urinary tracts. Our current study will evaluate the efficacy of this combination treatment in a mouse model of the disease.

Additionally, our research proposal asks a fundamental question in urologic oncology related to the practice-changing class of checkpoint inhibitors. While these medications are given systemically for metastatic disease, their mechanism of action is localized to the tumor microenvironment. As interventionalists, urologists have unrestricted access to the tumor via cystoscopy and upper tract endoscopy. Local treatment also has the potential to reduce side effects seen with systemic delivery. What role checkpoint inhibitors have as intraluminal agents has been incompletely investigated. If successful, this would be the first study to demonstrate feasibility of intraluminal checkpoint inhibitors. Our vision is to utilize our experience with the hydrogel delivery system to deliver combination immunotherapy to the upper tracts in patients with aggressive upper tract cancer. This treatment strategy could fundamentally change the treatment paradigm for patients with this disease and address a critical unmet need in urologic oncology.

Grant Profile Information

Yong Lu, PhD

A Novel Strategy for Immunotherapy to Kill the Escaped Variant Tumor Cells

Wake Forest University Health Sciences
Department of Microbiology and Immunology
Medical Center Boulevard
Winston-Salem, NC 27157

Grant No. RSG-19-149-01-LIB
Division: Southeast
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research: Systemic Therapies - Discovery and Development 100%

Types of Cancer: Melanoma 100%

Project Summary

Cancer recurrence may cause cancer treatment failure and death in more than 90% of patients with advanced tumors especially with metastatic disease. Patients may initially sensitive to the treatment or combinational treatments, but may have a recurrence because of the heterogeneous nature of cancer cell population. In the heterogeneous cancer cells, those small percentage of resistant cells due to somatic mutation will be iteratively selected and escaped from treatment, and finally, leads to the relapse of cancer. The relapsed tumors may contain a large percentage of resistant cells, and always do not respond to the retreatment of the initial therapies, which is the leading cause of cancer-related death.

In the field of cancer immunotherapy, a very similar situation happens and lead to the relapse of cancer. For example, despite high initial response rates, more than 70% of leukemia patient after CD19 chimeric antigen receptor (CAR)-T cell treatment suffers from regrowth of cancer cells about 6 months to 2 years after transfer. The relapsed leukemia cells are characterized by the loss of CD19 antigen target, rendering the malignant cells invisible to CD19-specific CAR-T cells (T cell-resistant cancer cells).

In this proposal, we will use a strategy (transfer of CD39KO T cells) discovered by us recently to target this most important issue of cancer therapy. In this project, we will determine the roles of specialized white blood cells, called CD39KO tumor-specific T cells, in preventing the tumor recurrence for cancer immunotherapy. We hypothesize that transfer of tumor-specific CD39KO T cells for T cell therapy will eradicate large established tumors and prevent recurrence of T cell-resistant tumors, due to their ability to 1) directly kill the tumor cells; 2) induce intratumor release of cytokines (type I interferons) to promote host antitumor immune responses; and 3) effectively eradicate large established human tumors in vivo in humanized mice model. These innovative and mechanistic studies will shed light on the mechanisms underlying CD39KO T cell-mediated antitumor immunity and will thus establish a foundation for translating this discovery into more effective immunotherapies in human cancers.

Grant Profile Information

Leyuan Ma, PhD

A Universal Booster Vaccine for Chimeric Antigen Receptor T cells

Massachusetts Institute of Technology
Koch Institute
76-211
500 Main Street
Cambridge, MA 02139-4822

Grant No. PF-19-147-01-LIB
Division: Northeast
Term of Grant: 01/01/2020-12/31/2022
Total Award: $163,500
Total ACS Support: $163,500

Mentor: Darrell J. Irvine, PhD

Area of Research:	Vaccines			40%
	Systemic Therapies - Discovery and Development			30%
	Combinations of Localized and Systemic Therapies			30%
Types of Cancer:	Brain Tumor	40%	Melanoma	40%
	Leukemia / Leukaemia	20%		

Project Summary

Adoptive cell therapy (ACT) with genetically engineered T cells-chimeric antigen receptor (CAR) T cells has shown dramatic clinical responses in blood cancer. This success has led to a strong commercial investment in establishing adoptive cell therapy as a viable clinical therapy and the first licensure of CAR T therapy by the FDA in 2017. However, this type of cell therapy has failed to induce an optimal response in solid tumor. A key challenge is maintaining a sufficient pool of functional CAR T cells in vivo. In addition, even in blood cancer treated effectively with CAR T cells, pre-conditioning with highly-toxic chemotherapy or irradiation is often required to ensure the initial expansion of infused CAR T cells. A unique vaccine design, amphiphile-vaccine, recently discovered in Irvine lab offers a convenient way to deliver a small molecular entity into the lymph node, where T cells are naturally activated and expanded. This small molecular entity could insert in cell membranes on arrival in lymph nodes, thus being able to engage CAR T cells and trigger their expansion like natural T cells. We propose here to employ this amphiphile vaccine design to repeatedly expand and rejuvenate CAR T cells, enhance their persistence and functionality in the patient and potentially allowing a lower number of CAR T cell infusion and eliminating the need of toxic pre-conditioning. We envision this CAR T booster vaccine strategy could dramatically reduce the cost and also substantially enhance the success rate of current CAR T therapy in both blood cancer and solid tumor.

Grant Profile Information

Robert S. Mannel, MD

Institutional Research Grant

University of Oklahoma Health Sciences Center
Department of Obstetrics and Gynecology
800 NE 10th Street
Oklahoma City, OK 73104

Grant No. IRG-19-142-01-IRG
Division: South
Term of Grant: 01/01/2020-12/31/2022
Total Award: $270,000
Total ACS Support: $270,000

Project Summary

This is a new application for an American Cancer Society Institutional Research Grant (ACS-IRG). Funding an ACS-IRG application in Oklahoma would provide an essential resource for both The University of Oklahoma Health Sciences Center (OUHSC) and the Stephenson Cancer Center (SCC). An ACS-IRG will help OU and the SCC both to recruit new faculty into cancer research positions and to advance new and early stage cancer-research faculty already at OU and the SCC. Supporting pilot studies though an ACS-IRG mechanism would also provide a dedicated resource to successfully foster cancer research interest among young investigators and provide them with a mechanism by which they can obtain small grants for testing their innovative ideas, thus positioning them to be competitive for extramural peer-reviewed research grant awards. The leadership of the OUHSC and the SCC fully understand that the most innovative and novel ideas often come from new researchers as they embark on their first full-time faculty position. The OU campus system, which includes OUHSC, OU-Norman, and OU-Tulsa, currently has over 40 eligible junior faculty that could compete for ACS-IRG funding in the future. The OUHSC also has agreed to recruit at least 12 new faculty researchers in the cancer research mission over the next five years, which ensures there will be a strong need for ACS-IRG pilot award funds for the future. This new recruitment will also enlarge the already substantial pool of eligible applicants for future ACS-IRG funding.

The current application includes a mentoring and career development plan that will ensure all ACS-IRG awardees are properly mentored by senior faculty as they gain credentials and achieve early milestones. The mentoring process will not only include two senior faculty that will oversee each ACS-IRG awardee, but the SCC program members from each of the four research programs in the SCC will also provide input and oversight to ensure all awardees receive diverse and important feedback and training as they secure their own independent, peer-reviewed funding. The OU system and SCC fully recognize the importance and prestige of an American Cancer Society Institutional Research Grant for young investigators and understand how it will help us attract top research talent in the future. In fact, to help leverage the ACS resources, the SCC has committed $20,000 in matching funds for each ACS-IRG pilot project award ($60,000/year in total), which will allow us to bring the $30,000 ACS award up to a $50,000 award per investigator.

An ACS-IRG award will play an important role in fostering even more interaction between OUHSC, the SCC, and the ACS. Over the years, our relationship has been beneficial to both organizations and, more importantly, this collaboration has had an important impact on cancer screening and community outreach to both patients and their families in Oklahoma. We look forward to continuing this important relationship with the ACS.

Grant Profile Information

Julia Maxson, PhD

Targeting Oncogene Interaction in Acute Myeloid Leukemia

Oregon Health and Science University
Division of Medicine
3181 SW Sam Jackson Park Road
Portland, OR 97239

Grant No. RSG-19-184-01-LIB
Division: West
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Cancer Initiation: Oncogenes and Tumor Suppressor Genes	67%
	Systemic Therapies - Discovery and Development	33%
Types of Cancer:	Blood Cancer	100%

Project Summary

My motivations for pursuing scientific research changed fundamentally when my father was diagnosed with lymphoma. Fortunately for my family, a targeted therapy had been developed to combat lymphoma. This targeted therapy worked wonderfully for my dad, and he has been in remission for many years. This personal experience led me to pursue a postdoctoral fellowship with Dr. Brian Druker, whose discovery of the kinase inhibitor Gleevec has revolutionized the treatment of CML.

As a postdoctoral fellow, I discovered a gene mutation that exists in almost all patients with a rare form of leukemia called CNL. I was able to find a drug that shuts down this bad gene and kills the leukemia cells. It was incredibly gratifying to start with a sample from a patient, study the cancer cells in the laboratory, and then see a patient improve based on the research. This targeted therapy is now in clinical trials for patients with this rare leukemia.

The gene mutation that I studied in CNL also exists in AML. AML is a life-threatening type of blood cancer that kills 10,000 Americans per year. Only one in four patients with AML will survive for 5 years after their diagnosis. While much effort has been invested in developing drugs to cure AML, survival of patients with this disease has not substantially improved in the past thirty years. Numerous genetic mutations play a significant role in causing AML.

Unfortunately, targeted therapies directed against individual gene mutations in AML have not worked very well. One explanation for the lack of long lasting responses is the complexity of gene mutations in AML. If you are able to shut down one mutation, another one may still allow the cancer cells to grow. Based on our initial work, we propose that multiple mutations cooperate to cause this type of cancer.

My laboratory has developed an innovative approach for studying how gene mutations cooperate in blood cancers. This new approach taught us that the order in which gene mutations arise is fundamentally important. Our goal is to harness these new tools to better understand the biology of AML so that we can uncover its Achilles" heel. Clarifying the way in which cancer causing mutations work together will allow us to design better treatments for AML, with the goal of helping patients survive this terrible disease. I am committed to paving the way for lifesaving treatments for patients with this devastating blood cancer through research.

Grant Profile Information

Katherine McKenney, PhD

Role of Human Pumilio Proteins in Acute Myeloid Leukemia

University of Minnesota
Department of Biochemistry, Molecular Biology and Biophysics
450 McNamara Alumni Center
200 Oak Street S.E.
Minneapolis, MN 55455

Grant No. PF-19-128-01-DDC
Division: North
Term of Grant: 01/01/2020-12/31/2022
Total Award: $163,500
Total ACS Support: $163,500

Mentor: Aaron Goldstrohm, PhD

Area of Research: Cancer Initiation: Alterations in Chromosomes 100%

Types of Cancer: Leukemia / Leukaemia 100%

Project Summary

Acute myeloid leukemia (AML) is the most prevalent form of leukemia in adults with 19,500 new cases of AML reported in 2018. The ACS estimates that AML claims more than 10,670 deaths per year in the United States alone. In the bone marrow, the differentiation and proliferation of hematopoietic (blood) stem cells requires exquisite regulatory precision to generate over 10 essential blood types. AML occurs when genetic mutations produce leukemia stem cells that evade crucial regulatory mechanisms allowing them to divide uncontrollably and invade other tissues throughout the body, eventually leading to organ failure.

Gene expression involves decoding the information in DNA, transmission through messenger RNA (mRNA) intermediates, to produce the proteins a cell needs at the right time and amount. Proper expression is crucial and must be exquisitely regulated at all stages whereas defects in gene expression can cause a range of human diseases, particularly cancer. Over 7.5% of the human genome is dedicated to the production of more than 1,000 RNA binding proteins (RBPs), many of which are critical regulators of gene expression. The Pumilio (PUM) RBPs repress the translation of proteins primarily by facilitating mRNA degradation. PUMs have conserved roles in fundamental biological pathways including development, fertility, neurological processes, and stem cell maturation.

Recently, PUMs were implicated in the regulation of gene expression during hematopoiesis with potential impacts on AML pathogenesis. Thus, we plan to elucidate the network of genes controlled by human PUM1 and PUM2 in normal hematopoietic and AML cancer cells. We predict that the PUM regulated genes identified in this study will have important functions in cell proliferation, differentiation, and cancer pathways. We will establish their precise effects on gene expression at the levels of protein synthesis and mRNA decay by probing the mechanism of regulation and identifying protein partners. We will then examine the effects of PUMs and their cofactors in leukemia cell proliferation. By discerning the underlying genetic mechanisms of AML progression, this project aims to improve standard therapeutic strategies for treating AML, which have remained largely unchanged for the past 30 years.

Grant Profile Information

Matthew Meyerson, MD, PhD

Genome-inspired Approaches to Cancer Discovery and Therapeutics

Dana-Farber Cancer Institute
Department of Medical Oncology
DA-1540
450 Brookline Avenue
Boston, MA 02215-5450

Grant No. RP-19-178-06-COUN
Division: Northeast
Term of Grant: 01/01/2020-12/31/2024
Total Award: $400,000
Total ACS Support: $800,000

Area of Research:	Cancer Initiation: Alterations in Chromosomes	20%
	Cancer Initiation: Oncogenes and Tumor Suppressor Genes	30%
	Exogenous Factors in the Origin and Cause of Cancer	20%
	Systemic Therapies - Discovery and Development	30%

Types of Cancer:	Colon and Rectal Cancer	30%	Lung Cancer	70%

Project Summary

The goal of our research is to understand the causes of cancer and how we can use this information to cure cancer. Specifically, we want to understand the genome, the DNA that is in every cell of our bodies. Every cell has its own DNA, which provides instructions for cell growth and activity. The DNA of most normal cells is similar to one another and has changed little since we were born. In contrast, cancer cell DNA exhibits many changes that have occurred during the development of the cancer. Knowledge of these alterations allows us to improve the diagnosis and treatment of cancer.

In the past five years, we have made significant breakthroughs in cancer genomics and genome-associated drug discovery. We have found new types of alterations in cancer genomes, beyond the genes, that are important in understanding cancer progression for lung cancer and prostate cancer. We have identified new drug candidates based on our understanding of the cancer genome. And we have provided a deeper understanding of the role that bacteria might play in the development of colon cancer. These various discoveries promise both an improved understanding of lung and colon cancer, and new treatments for these and other cancers.

Grant Profile Information

Adriana M. Mujal, PhD

Investigating Post-Transcriptional Regulation of Antitumor NK Cells

Memorial Sloan-Kettering Cancer Center
Department of Immunology Program
ZRC Room 1429
408 East 69th Street
New York, NY 10065

Grant No. PF-19-148-01-LIB
Division: Northeast
Term of Grant: 01/01/2020-12/31/2022
Total Award: $163,500
Total ACS Support: $163,500

Mentor: Joseph Sun, PhD

Area of Research:	Normal Functioning			25%
	Cancer Progression and Metastasis			75%
Types of Cancer:	Blood Cancer	33%	Not Site-Specific Cancer	34%
	Melanoma	33%		

Project Summary

Cancer immunotherapies have emerged as highly effective interventions that help to improve patient immune responses against cancer. For example, immune checkpoint blockades block inhibitory regulators on immune T cells, which can enable them to better kill tumor cells. Yet despite the benefits appreciated by certain patients across a number of different cancer indications, many patients do not respond to these therapies. For these patients it is therefore critical to identify additional immune pathways that, when targeted therapeutically, will drive an effective antitumor response. Natural killer (NK) cells, like T cells, are immune lymphocyte cells that can directly kill tumor cells, but also can provide distinct and complementary benefits. For example, NK cells are primed to respond quickly following detection of a tumor cell and are thus especially skilled at controlling systemically dispersed cancer, as in the case of leukemias or metastasis. They are also able to recognize cancer cells that lose immunogenic markers to evade T cell detection. NK cells are thus emerging as a promising therapeutic target and boosting their antitumor activity across different types of cancer may expand and enhance patient responses to immunotherapies.

How NK cells can quickly and robustly exert antitumor activity, however, is poorly understood, as are the ways in which NK cells are disabled during cancer progression. Development of novel therapies that harness NK cell responses in patients will therefore require a better understanding of how NK cells can become potent effector antitumor cells. There is emerging evidence that RNA-binding proteins (RBPs) may restrict immune cells from making effector proteins needed to control tumor growth, but RBP functions have not been extensively studied in NK cells. The studies proposed here will specifically investigate how RBPs in NK cells manage precise deployment of potent responses and whether they impair NK cell antitumor immunity. These findings will advance our understanding of the key processes underlying antitumor NK cell function and will contribute to the development of novel therapies that improve NK cell control of cancer in patients.

Grant Profile Information

Barzin Y. Nabet, PhD

Identification and Mechanisms of Innate Resistance to PD-1 Blockade

Stanford University, Stanford CA
Stanford Cancer Institute
265 Campus Drive
Stanford, CA 94305

Mentor: Maximilian Diehn, MD, PhD

Grant No. PF-19-164-01-TBG
Division: West
Term of Grant: 01/01/2020-12/31/2022
Total Award: $163,500
Total ACS Support: $163,500

Area of Research:	Technology Development and/or Marker Discovery	50%
	Systemic Therapies - Clinical Applications	50%
Types of Cancer:	Lung Cancer	100%

Project Summary

Lung cancer is the leading cause of cancer-related death worldwide and in the United States. One in 15 people will be diagnosed with lung cancer in their lifetime. Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancers. The majority of NSCLC cases are diagnosed after the cancer has metastasized; therefore, overall survival for NSCLC is poor. Immunotherapy such as PD-1 blockade has transformed the treatment of NSCLC. These therapies function by blocking signaling checkpoints on T cells to enhance anti-tumor immune function. While PD-1 blockade generally outperforms alternative therapies long-term, only a minority of patients will respond to these therapies. Therefore, there is significant need to both identify patients who will benefit from PD-1 blockade and to delineate mechanisms underlying innate resistance. The current best methods for predicting response to PD-1 blockade prior to therapy include assessment of tumor mutational burden (TMB) and tumor PD-L1 expression. Once therapy has been initiated, response is evaluated by conventional imaging no earlier than eight weeks due to accuracy concerns. Therefore, there is no reliable method for identifying who will respond to therapy either prior to or early during the course of treatment. The first Aim of this proposal will develop a method based on tumor and immune factors to predict response to therapy prior to therapy with high accuracy and from a simple blood draw, rather than an invasive test. If successful, this Aim will provide sound evidence for testing this type of approach in a clinical trial. This approach could then personalize therapy so as to only give PD-1 blockade to those who will benefit, rather than treat with a potentially dangerous drug that will not be successful and withhold a different therapy that may be effective. The second and third Aims of this proposal focus on using the same patient samples to understand why only a minority of patients respond to PD-1 blockade. Based on published results and our preliminary findings, we believe that two major immune-mediated mechanisms are responsible for response to PD-1 blockade. First, we will test the hypothesis that patients who respond to PD-1 blockade have fewer CD8 T cells in their circulation and more in their tumor. Further, we hypothesize that the subset of T cells that respond to PD-1 blockade and can kill tumor cells, are present at higher rates in the blood of responders. This understanding can then eventually lead to new treatment strategies to benefit significantly more NSCLC patients. In summary, the aims presented in this proposal will identify and understand response and resistance to PD-1 blockade in the most common type of cancer.

Grant Profile Information

Edward L. Nelson, MD

Institutional Research Grant

University of California, Irvine
Department of Medicine
Cancer Research Institute
Sprague Hall, Room 127
Irvine, CA 92697-3905

Grant No. IRG-19-145-16-IRG
Division: West
Term of Grant: 01/01/2020-12/31/2022
Total Award: $270,000
Total ACS Support: $1,720,000

Project Summary

The recent, exciting clinical advances in molecular therapies, immunotherapy, and prevention strategies for cancer can be traced to fundamental scientific insights made more than twenty years ago by ground breaking researchers often early in their careers. It is this drive and innovation that must be fostered and nurtured. If we are to see continued rapid advancement in the treatment and prevention of cancer, the support of junior researchers, as they launch their career, will be critically important whether they work at the bench or the bedside.

At the University of California Irvine (UCI) the American Cancer Society Institutional Research Grant (ACS-IRG) is unique; it is the only award program specifically dedicated to the support of junior faculty cancer researchers. This is codified in the eligibility criteria that; 1) applicants must be within the first six years of their their first faculty appointment, and 2) they are not the P.I. on any other nationally funded, peer-reviewed grant, with the exception of training awards used primarily for P.I. salary support. In addition, ACS-IRG awards are open to eligible faculty from all schools within the university who have cancer research proposals. These characteristics make the ACS-IRG award of unique value to UCI and set it apart from the only other major form of support for cancer research pilot projects, which is managed through the NCI-designated Chao Family Comprehensive Cancer Center (CFCCC). Unlike the ACS-IRG, applications for CFCCC seed funds are restricted to cancer center members and are not restricted to junior investigators. Thus, the ACS/IRG funds allow junior investigators, including newly recruited faculty, the opportunity to establish new cancer research projects with the aim of successfully competing for national peer-reviewed funding. Indeed, the potential availability of support through an ACS/IRG grant is a valuable recruitment tool for new, exceptional junior faculty. Given the highly competitive nature of external peer-reviewed national funding, the importance of the availability of the ACS/IRG grant to young faculty cannot be overstated.

A measure of this importance, the Office of the Vice-Chancellor for Research and the Director of the CFCCC have each pledged $30,000 annually (totaling $60,000) in matching funds. This will allow funding of 12, one year, seed grants at $45,000 per award. The ACS-IRG also provides a structure for accelerating the career development of junior faculty cancer researchers, which requires both mentorship and opportunities to gain valuable experience communicating with the public and peers. Through a number of mentorship mechanisms, presentation venues, and local ACS chapter interactions, junior faculty cancer researchers derive benefit, regardless of their funding status under the ACS-IRG. Thus, the exceptional impact of the ACS-IRG is not just restricted to 12 awardees, but includes UCI as a whole and our surrounding community.

Grant Profile Information

Jonathan O. Nelson, PhD

Uncovering the Activity of Retrotransposons in Ribosomal DNA Maintenance

Life Sciences Institute, University of Michigan
Life Sciences Institute
210 Washtenaw Avenue
Ann Arbor, MI 48109

Mentor: Yukiko Yamashita, PhD

Grant No. PF-19-133-01-DMC
Division: North Central
Term of Grant: 01/01/2020-12/31/2021
Total Award: $111,500
Total ACS Support: $111,500

Area of Research:	Normal Functioning	80%
	Cancer Initiation: Oncogenes and Tumor Suppressor Genes	20%
Types of Cancer:	Not Site-Specific Cancer 100%	

Project Summary

A major feature of cancer cells is their ability to overcome the challenges that normally limit the amount that a cell can divide. Cancer cells usually achieve this cell immortality by acquiring the features that are used by germ cells (the cells that make sperm and eggs) to pass their genetic information from generation to generation without accumulating any defects. This proposal seeks to understand how germ cells protect their genome so that we can understand how these functions act in cancer cells. Repetitive DNA, regions where a pattern of DNA sequence is repeated over and over again hundreds of times, in particular requires this protection because it is difficult to copy the exact number of repeats during cell division without accidentally gaining or losing a few copies. Our labs recent work found that the germ cells of the fruit fly Drosophila melanogaster can identify when the number of repeats is dangerously low and rapidly create more copies, maintaining repetitive DNA from generation to generation. My preliminary work has surprisingly found that genes that normally hurt the genome, called retrotransposons, are necessary for this maintenance. The work proposed for this fellowship will understand how these retrotransposons create new repetitive DNA and how the germ cells manage to use them for their benefit while preventing them from harming the genome. In addition to explaining why these harmful retrotransposons exist in the genome, this work will reveal how cells achieve the fundamental features necessary for immortality. The knowledge learned from this proposal will lead to understanding how cancer cells can divide indefinitely so that new and more effective methods to detect and treat cancer can be developed.

Grant Profile Information

Marja Nevalainen, MD, PhD

Institutional Research Grant

Medical College of Wisconsin
Department of Pathology
8701 Watertown Plank Road
P.O. Box 26509
Milwaukee, WI 53226-0509

Grant No. IRG-19-138-34-IRG
Division: North
Term of Grant: 01/01/2020-12/31/2022
Total Award: $270,000
Total ACS Support: $2,530,000

Project Summary

The ACS Institutional Research Grant (ACS-IRG) provides pilot money for research projects to junior faculty at the Medical College of Wisconsin (MCW) and its affiliated institutions. The ACS-IRG supports independent, self-directed junior investigators and is essential to developing the next generation of cancer researchers. Pilot grants give junior investigators the opportunity to study novel ideas and obtain the preliminary data required to compete for national research funding.

The ACS-IRG program is administered by the MCW Cancer Center, a consortium of five independent institutions (MCW, the BloodCenter of Wisconsin, Froedtert Hospital, Children''s Hospital of Wisconsin, and Zablocki Veterans Administration Medical Center) consisting of over 318 members. The ACS-IRG program is the sole mechanism used by the MCW Cancer Center for junior faculty research applications. To drive the career development of these young faculty members, a mentoring committee of 2-3 senior faculty members is assigned to each ACS-IRG recipient. These junior faculty members have access to development opportunities and research resources, including weekly forums, annual programs and center research retreats, and translational research clubs.

The Principal Investigator, Marja Nevalainen, MD, PhD, is an internationally recognized expert in prostate cancer research. Dr. Nevalainen is the Associate Director of Cancer Research Career Enhancement and Related Activities for the MCW Cancer Center, the Assistant Dean of Research at MCW and the Director of the MCW Prostate Cancer Center of Excellence. She has a long-standing record of training and mentoring MS, PhD, and MD/PhD students, postdoctoral fellows, medical students and residents in her laboratory.

A 22-member review committee reviews all ACS-IRG applications. ACS-IRG awards have broadened the base of cancer research at MCW by attracting young investigators to focus their research on cancer. Collaboration between MCW basic scientists and physicians has facilitated the transfer of laboratory research into clinical trials and innovative therapies. The ACS-IRG is instrumental in facilitating translational research to bring the basic science findings and developments in cancer treatment to patients by fostering the careers of scientists with high potential to impact diverse fields of cancer treatment and research.

From 1989 to 2018, 109 ACS-IRG awards have been made to 65 PhD or ScD scientists and 44 MD or MD/PhD physician scientists from 30 different institutes, departments and divisions at MCW contributing to a steady increase in cancer-related peer-reviewed research funding at MCW over the last decade. In this renewal, three years of funding is requested to support four pilot grants per year at up to $30,000 each. MCW will supplement the ACS-IRG grants with up to $20,000 for each original award upon peer review of progress reports.

Grant Profile Information

Paul Nghiem, MD, PhD

A Therapeutic Vaccine for Merkel Cell Carcinoma

University of Washington
Department of Medicine
850 Republican Street
Seattle, WA 98109

Grant No. MBG-19-171-01-MBG
Division: West
Term of Grant: 01/01/2020-12/31/2021
Total Award: $240,000
Total ACS Support: $240,000

Area of Research:	Vaccines	50%
	Systemic Therapies - Discovery and Development	50%
Types of Cancer:	Skin Cancer (non-melanoma) 100%	

Project Summary

Merkel cell carcinoma is a skin cancer that affects about 3000 Americans per year. About 35% of persons diagnosed with MCC die of the disease, making it far more aggressive than melanoma. I have focused on MCC since 2000, leading a team of medical oncologists, surgeons, radiation oncologists, and allied professionals to care for MCC patients. This is a new initiative to provide a novel form of immunotherapy for MCC patients.

I led a clinical trial, published in The New England Journal of Medicine, which demonstrated that a recent class of immune therapy called PD-1 blockers helps many patients with advanced MCC. PD-1 blockers are now standard care endorsed by national experts. These drugs work by releasing the tumor-killing potential of a patient''s killer immune cells (CD8 T cells), but can''t work if a patient does not have appropriate CD8 T cells. Because these drugs only persistently help about half of MCC patients, there is a great need to help the other half, perhaps by augmenting the CD8 T cell response to coordinate with PD-1 blockers.

It was discovered in 2008 that about 80% of MCC tumors are caused by the Merkel cell polyomavirus (MCPyV). A portion of this virus forces MCC cells to proliferate uncontrollably. We have evidence that the CD8 T cell immune system can recognize this key viral protein and then eliminate MCC cells. The goals of this PMBG are to create a MCPyV therapeutic vaccine and test if the vaccine has the potential to work in a broad population of MCC patients, test if is safe in the test tube, and study if it safe and works to eliminate tumors in animals.

There are two patient groups for whom an MCC therapeutic vaccine would help. The first is MCC patients who are diagnosed before metastatic spread. Standard care is excision and sometimes radiation. Unfortunately, about 40% of these patients will have a recurrence of MCC in the next 2 years. Bolstering the immune response against MCPyV, using a vaccine, we hope to wipe out any microscopic residual areas of MCC cells and prevent recurrences. The second group is patients with advanced MCC who have no improvement, or only temporary improvement, with PD-1 blockers. A cancer vaccine may synergize with continuing PD-1 blockers by supplying the CD8 T cells to kill tumors, which are then potentiated by PD-1 blockers.

Our team will make candidate MCC vaccines containing a specific portion of the MCPyV virus. We will ensure safety with help from Dr. Denise Galloway, a world-renowned expert in how viruses cause cancer. The first Milestone will ensure that killer CD8 T cells from at least 90% of MCC patients can be stimulated by the vaccine, to enable “off the shelf” use for almost all Merkel patients. The second Milestone will test efficacy in a mouse model of MCC.

If we reach the pre-specified Milestones, we will apply for an ACS Secondary MBG. This will provide essential “bridge” funding prior to the actual clinical trial and administration of the vaccine to MCC patients.

Grant Profile Information

Kathleen L. O'Connor, PhD

Institutional Research Grant

University of Kentucky Research Foundation
Markey Cancer Center - Department of Biochemistry
HKRB 344
760 Press Avenue
Lexington, KY 40536

Grant No. IRG-19-140-31-IRG
Division: North Central
Term of Grant: 01/01/2020-12/31/2022
Total Award: $360,000
Total ACS Support: $2,260,000

Project Summary

The American Cancer Society (ACS) Institutional Research Grant (IRG) is awarded by the ACS. This grant provides funds that are distributed to promising new investigators at the University of Kentucky (UK) and UK''s Markey Cancer Center (MCC) who are performing cancer-related research. The primary objective of the ACS IRG is to help new faculty develop their research program and establish a track-record of peer-reviewed funding. This funding mechanism, in turn, will enhance their efforts to build their cancer research programs and compete for larger extramural grants. The success of previous ACS IRG awardees in obtaining extramural funding reflects the value of this program.

Dr. Kathleen O''Connor will continue to serve as PI of the ACS IRG. Funds from the ACS IRG will be distributed to new faculty on a competitive basis. Briefly, grants will be solicited from potential candidates two times per year, and guidelines are provided to each grantee. Submitted grant applications will be reviewed by Dr. O''Connor and a panel of UK faculty with expertise in all areas of cancer research. This process will select grants with the highest scientific merit and greatest likelihood of future extramural funding. We anticipate the awarding of 12 grant applications over the three-year period of the ACS IRG. Awardees must spend the funds within one year, although no-cost extensions of up to one additional year can be requested if justified. Awardees are expected to acknowledge ACS IRG funding, when appropriate, in abstracts and papers.

Grant Profile Information

Richard Possemato, PhD

Targeting Cell Cycle and Transformation Specific Metabolic Processes

New York University School of Medicine
Department of Pathology
MSB 504
550 First Avenue
New York, NY 10016

Grant No. RSG-19-159-01-TBE
Division: Northeast
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Normal Functioning	15%
	Cancer Initiation: Oncogenes and Tumor Suppressor Genes	50%
	Exogenous Factors in the Origin and Cause of Cancer	20%
	Technology Development and/or Marker Discovery	15%

Types of Cancer:	Breast Cancer	25%	Liver Cancer	75%

Project Summary

The metabolic processes of the cell are responsible for the acquisition of raw materials, such as glucose and amino acids, from the extracellular space and the assembly of those raw materials into new cancer cells. Over the past decade there has been increased attention paid to understanding how the metabolism of a cancer cell contributes to the transformed state. Indeed, one of the most frequently used diagnostic tests to identify tumors within the body, the FDG-PET scan, relies on the massive uptake of glucose by cancer cells. Approaches to target tumor metabolism have been successful, but have focused on therapies which block metabolic processes common to all dividing cells, resulting in toxicity to the patient. Here, we propose to address this problem using a combination of cell based cancer models and liver models in mice. The mouse liver is a particularly appropriate model because we can remove part of the liver and induce the remaining liver tissue to grow. In separate animals, we can injure the liver with a chemical known to cause liver cancer in mice. We can then compare the metabolism of normal liver, growing liver, and liver tumors by measuring the levels of small molecule building blocks with the tissue or tumor, and following those small molecules as the cell incorporates them into biomass. We have identified one metabolic pathway in particular, serine metabolism, which we believe will be an important and specific target in several types of cancer, including estrogen receptor negative breast cancer, a particularly intractable form of the disease. In a separate aim, we will use mice in which serine production or utilization can be turned off to ascertain whether targeting these genes will affect normal growing cells, like those in the growing liver, differently than those that have become cancerous. We will assess the metabolism of these liver models to determine how targeting these pathways affects the tissue or the tumor. Finally, we will assess how different phases of cell growth and division (termed the cell cycle) coordinates cellular metabolism in general and serine metabolism specifically. These approaches will allow us to understand whether targeting serine metabolism will be efficacious in potential future anti-tumor therapies, while providing opportunities to identify novel targets in cancer cell metabolism.

Grant Profile Information

Melanie Potiaumpai, PhD

Exercise for Sarcopenia in Hematopoietic Stem Cell Transplant Patients

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Grant No. PF-19-109-01-CCE
Division: Northeast
Term of Grant: 01/01/2020-12/31/2022
Total Award: $163,500
Total ACS Support: $163,500

Mentor: Kathryn Schmitz, MD, PhD

Area of Research:	Patient Care and Survivorship Issues			100%
Types of Cancer:	Blood Cancer	45%	Myeloma	10%
	Hodgkin's Disease	45%		

Project Summary

Allogeneic hematopoietic stem cell transplant (HSCT) is a medical treatment for patients with blood cancers. HSCT consists of ablating a patient''s immune system using high-dose chemotherapy or total body irradiation followed by an infusion of stem cells harvested from a matched donor. The stem cells will then reconstitute the patient''s immune system. HSCT recipients face a 60-70% survival rate during the first two years after a HSCT due to complications such as relapse of their primary disease, chronic whole body inflammation, and toxicity to their cardiovascular and muscular systems. Additional side effects such as nausea, body pain, and fatigue discourage patients from staying active, thus, increasing sedentary behavior which can lead to severe muscle wasting, and significant bone density loss.

Exercise has been employed as a successful rehabilitation therapy after numerous cancer treatments, including HSCT. Exercise can help patients recuperate losses in muscle mass, increase bone density, regain muscular strength, improve aerobic endurance, and maintain levels of physical function and independence. While rehabilitation exercises are effective after HSCT, it does not provide a method to improve patients'' physical condition before HSCT and prevent drastic declines in physical function and psychological well-being. Prehabilitation, defined as exercise training prior to the start of a medical therapy, has been shown to be beneficial in colon and lung cancer patients. Prehabilitation exercises can reduce recovery time, improve walking capacity, mood, and physical function, and reduce the severity of symptoms associated with treatment.

Despite the benefits of prehabilitation in other cancer entities and the potential for HSCT recipients, there is a lack of studies utilizing prehabilitation in HSCT patients and investigating the impact of exercise on long-term health outcomes in survivors. This project will investigate how a combined resistance and aerobic exercise prehabilitation program will affect body composition and bone health in HSCT recipients and survivors. My fellowship research project will build on an existing clinical trial titled, Impact of Prehabilitation in Oncology via Exercise- Bone Marrow Transplant (IMPROVE-BMT). I will evaluate changes in skeletal muscle mass and visceral fat tissue, and bone mineral density. We will achieve this by adding a full-body dual energy x-ray absorptiometry exam (DXA) at two time points- before the start of prehabilitation and 100 days post-HSCT in 33 patients. The DXA scan will help us identify and describe the long-term impact of HSCT and the possible mitigating effects of prehabilitation. This grant will allow us to identify the proper intervention to help condition patients to receive a HSCT and what role exercise has to improve survival outcomes. These findings will have the direct potential to change the time and way exercise is delivered to best benefit HSCT recipients.

Grant Profile Information

Sarah Prinsloo, PhD

Optimizing Treatments for Chemotherapy-Induced Peripheral Neuropathy

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Grant No. RSG-19-155-01-PCSM
Division: South
Term of Grant: 01/01/2020-12/31/2023
Total Award: $738,000
Total ACS Support: $738,000

Area of Research: Complementary and Alternative Treatment Approaches 50%

Patient Care and Survivorship Issues 50%

Types of Cancer: Not Site-Specific Cancer 100%

Project Summary

Chemotherapy-induced peripheral neuropathy (CIPN) is often a side effect of cancer treatment, and can diminish a patient''s quality of life (QOL) by affecting everyday activities such as driving a car, putting on clothing, using utensils, and walking. CIPN also leads to treatment delays, dose reductions, and chemotherapy discontinuations which negatively affect treatment outcomes. Only two therapies have been shown to be effective to treat CIPN, neurofeedback (NFB) and duloxetine. NFB is a treatment that is customized to the individual, relatively inexpensive, non-invasive, and provided alongside conventional medicine. In a completed study of NFB to treat CIPN (ACS postdoctoral award of the applicant) we found that patients with CIPN can learn to control activity in brain areas that are associated with CIPN, leading to QOL improvements such as restoration of normal exercise and recreational activities. Duloxetine is the only medication shown to be effective for treatment of CIPN. The proposed study will attempt to maximize benefit for patients by combining neurofeedback with duloxetine. Further, and through the use of placebo, we will attempt to understand the mechanisms by which these interventions could be helpful.

Patients will complete assessments that determine the brain activity related to their pain, mental health, and QOL. Patients will be randomized to one of four groups: 1) neurofeedback + duloxetine 2) neurofeedback + placebo pill, 3) duloxetine + placebo neurofeedback, or 4) placebo neurofeedback + placebo pill. The neurofeedback groups will have a minimum of three sessions of NFB training each week for 6 weeks where their brain activity is monitored by EEG while the patients play a computer game. The neurofeedback game rewards the participants when they successfully modify their brainwave activity in a targeted area, hence pairing a stimulus with a reward. Over time, the patient will learn to modify that activity without the game. Patients will also either be given duloxetine or a placebo pill regimen in conjunction with NFB, as listed above. Patients in the placebo condition will have the same NFB treatment although they will not be taught to modify their brain activity. Follow-up measures will be collected at the end of treatment. After the placebo groups finish their part of the study, all participants will be offered true NFB to help them with symptoms.

This project is the next step in understanding a common side effect of cancer treatment. The project will help us understand CIPN at the level of individual brain function and will explore neurofeedback training, a non-invasive therapy, in conjunction with duloxetine to maximize benefit to patients. We hypothesize neurofeedback in combination with duloxetine will decrease pain perceptions and improve other symptoms related to quality of life such as anxiety and depression to a greater extent than either neurofeedback or duloxetine alone. Lastly, this project will provide valuable information on the interplay between pain perceptions, treatments, and brain function.

Grant Profile Information

Zhaoxia Julia Qu, PhD

Specifically Targeting Oncogenic NF-kappaB for Cancer Therapy

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Grant No. RSG-19-166-01-TBG
Division: Northeast
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Cancer Progression and Metastasis			50%
	Combinations of Localized and Systemic Therapies			50%
Types of Cancer:	Lung Cancer	80%	Not Site-Specific Cancer	20%

Project Summary

The transcription factor NF-kappaB plays a causative role in the development, maintenance, and therapeutic resistance of many human cancers, including lung cancer, the leading cause of cancer-related deaths in both women and men in the US. However, it is unfeasible to block NF-kappaB for cancer therapy because currently available NF-kappaB inhibitors also block the important physiological function of NF-kappaB. In fact, human clinical trials show that classical NF-kappaB inhibitors actually kill patients. On the other hand, despite recent breakthrough in immunotherapies and in particular immune checkpoint PD-1/PD-L1 blockade for lung and several other cancers, the majority of cancer patients do not respond and benefit from those novel cancer therapies. Revolutionary ideas and approaches are thus direly needed to specifically target oncogenic, but not physiological, NF-kappaB, and to improve PD-1/PD-L1 blockade therapy for effective cancer treatment. Another major obstacle in cancer research is the lack of animal models that can faithfully recapitulate human cancers for determining the mechanisms of cancer development and progression and testing new therapeutics. This is particularly true for lung cancer. Accordingly, although it kills about 160,000 Americans each year, the 5-year survival rate for lung cancer patients has not improved significantly in the past 30 years and is currently only 18%.

To overcome those outstanding challenges, we have recently made the following groundbreaking discoveries and technical achievements: generation of the first and only available animal model faithfully recapitulating the full processes of lung cancer from initiation to regional and distant metastasis with 100% penetrance; identification of a tumor suppressor that specifically represses oncogenic, but not physiological, NF-kappaB and is repressed in many cancer types, including lung cancer; and linking it to PD-1/PD-L1 blockade immunotherapy resistance. Moreover, we have developed an oncolytic virus-mediated tumor cell-specific gene delivery system that shows promising efficacy and safety in human. In this application, we will employ the innovative lung cancer model and the clinically feasible tumor cell-specific gene delivery system we developed, to define and selectively target oncogenic NF-kappaB activation for lung cancer treatment, by re-expressing the unique tumor suppressor alone or in combination with PD-1/PD-L1 blockade. These studies will provide fundamental knowledge on oncogenic NF-kappaB activation and lung cancer pathogenesis, and more importantly, may lead to novel effective approaches to treat lung cancer and other NF-kappaB-associated cancers.

Grant Profile Information

Amanda Roca, PhD

Defining the Role of SUMOylation in Dynamic Kinetochore Function

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Grant No. PF-19-112-01-CCG
Division: West
Term of Grant: 01/01/2020-12/31/2022
Total Award: $163,500
Total ACS Support: $163,500

Mentor: Susan Biggins, PhD

Area of Research:	Normal Functioning	50%
	Cancer Initiation: Alterations in Chromosomes	50%
Types of Cancer:	Not Site-Specific Cancer 100%	

Project Summary

Each time a cell needs to make an exact copy of itself, it must first duplicate each of its chromosomes and then equally segregate them into two daughter cells. This process of cell division is essential for cell replacement and organismal development and growth. If chromosomes are not accurately segregated, the resulting daughter cells often become aneuploid, meaning they have too many or too few chromosomes. Notably, aneuploidy is a common characteristic of cancer cells.

In order to properly divide their chromosomes, cells build a large structure called a spindle. A spindle is made of filamentous proteins called microtubules, which make connections to each chromosome via a large protein machine called a kinetochore that forms on each chromosome. Then, the microtubules pull the chromosomes to opposite sides of the cell. This process is extremely complex and requires tight regulation. First, the kinetochore is made up of over fifty distinct proteins present in multiple copies, and the composition and function of the kinetochore changes slightly throughout cell division. Furthermore, the kinetochore is able to distinguish between correct microtubule attachments (emanating from the correct side of the cell) and incorrect attachments (emanating from the wrong side). Thus, I am interested in understanding how cells regulate kinetochores in order to accurately divide their chromosomes.

During complex cellular processes such as cell division, the proteins involved can be “decorated” with reversible modifications, and this allows the proteins to temporarily alter their functions, locations, or interacting partners. One such modification is called SUMO, and recent studies have shown that SUMO decorates many kinetochore proteins. Although, it is not understood how SUMO specifically affects most of these kinetochore proteins, other more general studies have shown that cell division is defective when SUMO is not present, often leading to cell death or aneuploidy. Therefore, I aim to elucidate the role of SUMO in kinetochore function using a multidisciplinary approach. I will specifically investigate a regulatory role of SUMO in kinetochore assembly and error-correction in the context of kinetochore-microtubule attachments. My findings are essential for two reasons. First, in order to determine how cell division becomes defective and contributes to tumorigenesis and cancer, we must understand how this process occurs normally. Second, many cancers make too much or too little of the proteins related to SUMO and this likely contributes to the disease state. Therefore, we need to understand what SUMO is doing in cancer cells and how it effects cell division. In closing, I believe my studies will result in significant foundational knowledge for cancer cell biology.

Grant Profile Information

Davide Ruggero, PhD

Mechanisms of Translation Control in Cancer & its Therapeutic Implications

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Grant No. RP-19-181-01-RMC
Division: West
Term of Grant: 01/01/2020-12/31/2024
Total Award: $400,000
Total ACS Support: $400,000

Area of Research:	Cancer Initiation: Oncogenes and Tumor Suppressor Genes	50%
	Cancer Progression and Metastasis	50%

Types of Cancer:	Blood Cancer	17%	Liver Cancer	33%
	Brain Tumor	10%	Lung Cancer	10%
	Kidney Cancer	10%	Prostate Cancer	10%
	Leukemia / Leukaemia	10%		

Project Summary

Historically, cancer research has focused on how normal cells are reprogrammed to become cancer cells by altering how DNA, the genetic material in a cell, is transcribed into the messenger RNA molecule. However, these studies focus on only half of the overall process of gene expression, and do not take into account the ultimate end product of gene expression: protein production. Exciting developments in cancer biology, of which my lab has been at the forefront, show that many genetic alterations directly impact the process by which mRNAs are translated to produce a protein. Translational control can become deregulated, leading to grave consequences such as uncontrolled cell growth and division. Therefore, there is a growing appreciation for the importance of restoring normal translational control as a novel paradigm for cancer treatment.

My lab has pioneered the study of translational control and cancer. Among my lab"s major contributions is the discovery that cancer cells usurp the cell"s translation machinery as a means of uncontrolled production of proteins that selectively fuel cancer cell growth. Importantly, we have shown that it is possible to reprogram aberrant translational control of protein synthesis back to normal level and these findings are changing the outlook for cancer therapies.

Our short-term goal is to employ state-of-the-art technologies to discover novel molecular connections between oncogenic signals and deregulations of protein production. We will map new points of vulnerability specific to cancer, but not normal cells, that impinge on translation control. In addition, based on our exciting preliminary results, we will investigate new causes for alterations in protein synthesis in obesity-induced cancer. Roughly 30% of the world is currently obese, with increasing rates each year. Better treatments and ways to inhibit metabolic alterations are greatly needed to prevent the health risks associated with cancer formation. We will also establish a new line of cancer research focusing on a paradigm shifting idea that oncogenes remodel major components of the translation machinery, particularly the ribosome (responsible for converting mRNA into protein), in order to produce specific proteins that are tailor made for cancer cell growth.

In the long term, our efforts are to translate our findings directly to the clinic by the development of new small molecules that target aberrant protein production in cancer cells as well as the development of novel biomarkers that detect alterations of protein production in cancer. In this respect, I am a co-founder of eFFECTOR Therapeutics, the first biotech company that has pioneered the development of specific pharmaceutical agents to restore the aberrant translational landscape of cancer cells. In just a short period of time, one of our lead compounds that targets the phosphorylation of the major translation factor eIF4E is currently in advanced phase II clinical trials. With this exciting progress, I will be able to directly translate our findings in the lab to the clinic.

Grant Profile Information

Rebeca San Martin, PhD

Microenvironment Influence on the 3D Genome Structure of Prostate Cancer

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Grant No. PF-19-183-01-CSM
Division: North Central
Term of Grant: 01/01/2020-12/31/2022
Total Award: $163,500
Total ACS Support: $163,500

Mentor: Rachel P. McCord, PhD

Area of Research:	Cancer Initiation: Alterations in Chromosomes	50%
	Cancer Progression and Metastasis	50%
Types of Cancer:	Prostate Cancer 100%	

Project Summary

Cancer does not exist in a vacuum: the environment of the tissue in which it grows plays a critical role in the development, and survival, of tumors. In glands like the prostate, this microenvironment is primarily a connective- tissue that supports structure and function, called stroma. Stroma reacts in response to non-cancerous events (like inflammation, trauma, and infection), by making new proteins, degrading others, and recruiting the immune system. This process changes the local microenvironment through a wound repair-like response aimed to keep the tissue healthy. The stroma reacts to cancer in the same manner but with one significant difference: as cells grow uncontrollably and invade the surrounding healthy tissue, the stroma attempts to fix a wound that does not heal. Highlighting the importance of the tissue environment in cancer progression, abundance of reactive stroma in prostate cancer tumors has been correlated with decreased patient survival.

What happens inside the cancer cell to make it more aggressive and metastatic? Many changes occur at the genomic level: key genes change expression, pieces of DNA get broken and repaired, and the whole nucleus changes shape and rigidity. The 3D folding and organized packing of the 6 feet of DNA into a microscopic nucleus affects all these processes. Thus, the primary goal in this proposal is to evaluate whether a reactive stroma microenvironment will foster a different chromosome and nuclear architecture, which in turn can result in expression of genes that relate to cancer progression and nucleus malleability that favors invasiveness. This abnormal 3D genome structure may in turn affect how the cancer cell responds to drugs that block testosterone action, which is among the first therapies used to treat prostate cancer. Prostate cancer that survives this “androgen ablation” therapy, is the main cause of death in patients.

Given that reactive stroma can occur independently of prostate cancer, the genome''s structural changes derived from an interaction with this microenvironment can happen before the onset of disease, influencing later cancer-related events, like metastasis. A better understanding of these early events will help develop better personalized diagnostics of whether a patient''s localized cancer is likely to progress. Our immediate contribution to the field of genomic cancer research will be the production of high-quality 3D genome conformation datasets from the different cell lines that are used to model the disease, providing a new toolset that is not restricted to microenvironment biology, but usable in prostate cancer genomic studies at large. Ultimately, by characterizing how the reactive microenvironment effects genome structure, particularly around genes known to be therapeutically relevant, our studies can reveal new opportunities for targeting disease progression in all prostate cancer patients.

Grant Profile Information

David Sarlah, PhD

Isocarbostyril Alkaloids as Templates for Small Molecule Chemotherapeutics

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Grant No. RSG-19-115-01-CDD
Division: North Central
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Chemoprevention	50%
	Localized Therapies - Discovery and Development	50%
Types of Cancer:	Not Site-Specific Cancer	100%

Project Summary

History has proven that significant advancements in cancer therapy come from novel drugs that eradicate cancer in new ways. The immense number and rich diversity of anticancer molecules found in nature (natural products) presents medicinal chemists with a variety of molecular blueprints and templates from which they may design and construct safer and more effective medicines. For decades, easily acquired natural products have played a central role in providing and inspiring new chemotherapeutics, and their derivatives have undoubtedly improved the lives of many cancer patients. The high structural complexity and limited availability of some natural products are the principal obstacles preventing medicinal chemists from exploring their properties, modifying them, and developing them into new medicines; nonetheless, in recent years there have emerged numerous success stories in which modern synthetic chemistry campaigns enabled practical access to complex anticancer natural products and analogues thereof, accelerating their progression all the way through clinical trials to FDA approval. Our laboratory is focused on the chemistry of anticancer natural products and fundamental studies related to their chemical biology. We have situated our research program at the crossroads of chemistry and biology, and our mission is to provide efficient synthetic routes to desirable molecular scaffolds and to uncover their biological targets and mechanisms of action through the development and study of molecular probes. Our expertise in the creation of powerful new chemical reactions affords us the opportunity to streamline the construction of complex molecules through the application of customized, target specific transformations, and to eliminate natural product supply problems via sustainable multigram-producing syntheses that are amenable to further modifications for the preparation of potentially superior analogues. We envision our research program to be at the base of a resonant feedback loop where biological studies on novel molecules can inform future chemical synthesis; thus, in collaboration with experts in chemical biology, anticancer medicinal chemistry, and comparative tumor oncology, we are positioned to rapidly evaluate our newly synthesized compounds and to elucidate their precise modes of action in relevant tumor models. This information in turn can aid in the evolutionary design of new drugs inspired by nature with capabilities beyond those of the parent natural products themselves.

Grant Profile Information

Adam Schmitt, MD

Examining a Candidate Long Noncoding RNA Tumor Suppressor in p53 Signaling

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Grant No. RSG-19-158-01-RMC
Division: Northeast
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research: Cancer Initiation: Oncogenes and Tumor Suppressor Genes 100%

Types of Cancer: Non-Hodgkin's Lymphoma 33% Sarcoma (soft tissue) 33%
Not Site-Specific Cancer 34%

Project Summary

To understand how human cancers form and in order to develop new and effective cancer treatments, it is imperative that we characterize the cellular alterations that drive cancer growth. The most frequently altered gene across all types of human cancer, TP53, encodes the p53 tumor suppressor protein, which is the central hub for cellular stress responses. p53 coordinates the cellular responses to many types of cellular insults that cause cancer, such as DNA damage and oncogenic stress, in order to prevent tumor formation. The cellular responses that p53 is responsible for include inhibiting cell growth, activating cell death pathways, and altering cellular metabolism.

It is thought that all cancers need to overcome the tumor suppressor functions of the p53 pathway in order to develop. Indeed, approximately 50% of all human cancers are known to have mutated or deleted the TP53 gene or one of the other known the genes that are components of this pathway. Yet, it remains a major unresolved question how the other 50% of human cancers that have no mutations in these genes are able to develop. One appealing hypothesis holds that there are alternative, and as yet undiscovered, mechanisms for inactivating the p53 pathway. Discovery and characterization of these mechanisms will provide greater insight into the

We have recently discovered a new mechanism of p53 regulation whereby a long noncoding RNA (lncRNA) called DNA Damage Induced Noncoding RNA (DINO) is required for many of p53"s functions. LncRNAs are a new class of cellular macromolecules which are now known to be pervasive features of the mammalian genome, but still very little is known about their function in cells. Instead of severing as a messenger used for the synthesis of protein, long nonconding RNAs can fold into complex three-dimensional structures and interact with proteins, chromatin, RNA and other cellular molecules in order to regulate various processes. We found that loss of DINO in both human and mouse cells results in cellular behaviors that are similar to loss of p53 function, such as impaired cell cycle arrest and cell death. In this proposal, we will examine whether DINO is necessary for the most important function of p53, the suppression of cancer formation.

Our proposal is based on the hypothesis that the lncRNA DINO, a component of the p53 pathway, is necessary for the function of the p53 tumor suppressor pathway and that alterations of the DINO gene is an alternative means of inhibiting the p53 tumor suppressor pathway during the process of cancer formation. In order to examine this hypothesis, we will (1) examine whether loss of DINO is associated with tumor formation in humans and mice, and (2) investigate the mechanism by which DINO is altered in cancer, and (3) characterize the molecular mechanism by which DINO enhances p53 function. This study could provide important new insights into how p53 suppresses cancer formation that may create an opportunity to reactivate p53 function in some human tumors for therapeutic gain.

Grant Profile Information

Stephanie Seidlits, PhD

Tissue-Engineered Models of Glioblastoma for Evaluating Treatment Responses

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Grant No. RSG-19-167-01-TBG
Division: West
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors	20%
	Technology and/or Marker Evaluation With Respect to Fundamental Parameters of Method	80%
Types of Cancer:	Brain Tumor	100%

Project Summary

Glioblastoma (GBM) is a highly lethal brain cancer that inevitably acquires resistance to multiple treatments. Although many treatments have shown promise in the laboratory studies, these results have not translated to clinical efficacy. We posit that these disappointments are because common experimental test beds do not account for 1) the extracellular matrix (ECM) or 2) the diverse cell population present within a single tumor. The ECM, proteins and sugars that make up the space surrounding cells, interacts with tumor cells, facilitating their ability to acquire resistance to multiple treatments. In addition, different cells within a single tumor acquire diverse functions, acting together in a complex ecosystem to fuel cancer progression.

Thus, we are engineering artificial tumor tissues that incorporate key aspects of the brain ECM and a patient''s own tumor cells. The proposed approach, in which patient-derived tumor cells are cultured in brain-mimetic biomaterials, is less costly, more time efficient and better controlled than animal studies — yet, unlike other cell culture methods, yields results with comparable clinical relevance. Using a patient''s own cells to create patient-tailored test beds for treatment screening will allow these test beds to capture the unique characteristics of each patient''s disease. While the majority of approaches to personalized cancer treatment rely solely on a patient''s genetic characteristics, this proposal aims to integrate this genetic information with patient-specific functional assessments to better predict treatment response.

Ultimately, we anticipate these patient-specific tumor models will be able to directly inform clinical actions to improve patient outcomes. This proposal describes the next steps towards accomplishing this long-term goal. First, we propose to evaluate the ability of these tissue-engineered tumor models to predict responses to a variety of treatments across a heterogeneous patient population. Second, we aim to improve the ability of tissue-engineered tumors to capture the heterogeneous cell population that composes an individual GBM tumor. Together, we expect the proposed studies will improve robustness of tissue-engineered models of GBM tumors by characterizing their ability to faithfully capture heterogeneity both across patients and within individual patient tumors.

Grant Profile Information

David B. Shackelford, PhD

Targeting Metabolic Dependencies in Therapy-Resistant Tumors

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Grant No. MBG-19-172-01-MBG
Division: West
Term of Grant: 01/01/2020-12/31/2021
Total Award: $240,000
Total ACS Support: $240,000

Area of Research:	Cancer Progression and Metastasis	25%
	Systemic Therapies - Discovery and Development	25%
	Systemic Therapies - Clinical Applications	25%
	Complementary and Alternative Treatment Approaches	25%

Types of Cancer:	Bone Cancer	12%	Head and Neck Cancer	25%
	Breast Cancer	13%	Lung Cancer	50%

Project Summary

The overarching focus of this study is to identify more effective therapies that will improve the overall survival of cancer patients. Recent breakthroughs with immune based therapies are now able to induce durable responses in approximately 20-30% of patients with lung, brain and renal cell cancers. However, the majority of patients who do not qualify for immune therapy will receive standard of care chemotherapy with most patients developing resistance to treatment. Therefore we sought to identify effective new treatment strategies that target and inhibit nutrient consumption in aggressive tumors. Fast growing tumors require excessive nutrients to support tumor cell metabolism and growth. Importantly, the restriction of key metabolic pathways causes “energetic crisis” that results in tumor cell death. Simply put, if a tumor cannot eat it cannot survive. This approach represents a paradigm shift in the treatment of cancer as we move towards developing personalized therapeutic strategies that selectively target the metabolic needs unique to each tumor as a novel means to overcome therapy resistance. This strategy has proved highly effective for squamous cell lung tumors, a particularly aggressive and metabolically active subtype of lung cancer that has a voracious appetite for sugar and amino acids, which are the building blocks of protein. By restricting specific nutrients such as sugar and the amino acid glutamine we are able to selectively kill highly aggressive lung tumors while preserving the normal healthy surrounding tissue. Using imaging and molecular analysis we are able to profile the nutrient requirements of metabolically active tumors and tailor precise therapies to inhibit tumor cell metabolism and growth. Importantly, we have identified that metabolically active tumors of the head, neck, breast and bone share the same metabolic signatures identified in lung cancer. We predict that metabolically active therapy-resistant cancer across a broad set of tumor types can be successfully treated by inhibiting sugar and amino acid metabolism and will be the focus of our proposed study.

Grant Profile Information

Vanessa Sheppard, PhD

Improving Communication and Adherence in Black Breast Cancer Survivors

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Grant No. RSG-19-182-01-CPPB
Division: Southeast
Term of Grant: 01/01/2020-12/31/2024
Total Award: $1,536,750
Total ACS Support: $1,536,750

Area of Research:	Interventions to Prevent Cancer: Personal Behaviors (Non-Dietary) that Affect Cancer Risk	33%
	Population-based Behavioral Factors	33%
	Education and Communication Research	34%
Types of Cancer:	Breast Cancer	100%

Project Summary

Black women continue to experience worse breast cancer outcomes, which may be due to inadequate adherence to systemic therapies that can be improved via patient centered communication. We developed and piloted the Sisters Informing SistersSM (SIS) intervention (survivor-led skill-building sessions and culturally tailored materials to activate Black breast cancer survivors in their medical encounters) and obtained promising findings. This project will compare in a two-arm RCT the impact of SIS vs. enhanced usual care (treatment recommendation summary form) on patient centered communication and systemic treatment adherence; SIS tools may be integrated within existing clinical and support services.

Grant Profile Information

David Soto-Pantoja, PhD

Targeting CD47 Prevents Cancer Therapy Adverse Effects

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Grant No. RSG-19-150-01-LIB
Division: Southeast
Term of Grant: 01/01/2020-12/31/2023
Total Award: $782,000
Total ACS Support: $782,000

Area of Research:	Combinations of Localized and Systemic Therapies	50%
	Patient Care and Survivorship Issues	50%

Types of Cancer:	Breast Cancer	50%	Cardiotoxicity / Heart Cancer	50%

Project Summary

Several studies show that many patients treated with chemotherapy develop cardiovascular complications during and long after treatment with chemotherapy. In particular a drug known as Doxorubicin is known to cause cardiovascular complications. Doxorubicin is a highly effective drug that inhibits the growth of breast tumors. It is particularly used in patients that have a type of cancer known as “triple negative” due to the fact that the tumors of these patients do not respond to stimulus from the hormones estrogen and progesterone or respond to the activation of a receptor known as HER2. This type of breast cancer is prevalent in young and African American women. Therefore while these patients don''t have an effective therapy to target their cancer they are also more susceptible to developing cardiovascular issues after treatment.
Another emerging treatment is the use of drugs that activate our immune system to attack the tumor. These drugs known as immune checkpoint inhibitors are currently tested in clinical trials for the treatment of TNBC. While the treatment holds great promise there are cases where patients develop cardiovascular complications associated with treatment.
A molecule known as CD47 is overexpressed in Triple-negative breast cancer. We have shown that while blockade of CD47 reduced tumor growth in combination with radiotherapy it also protected normal tissue from death associated to off target effects or radiotherapy. Therefore we hypothesize that blockade of CD47 will reduce tumor growth in combination with doxorubicin or immune checkpoint inhibitor therapy while also protecting from the cardiovascular side effects associated with this drug. Our data in animal models shows that blocking this receptor in combination with doxorubicin reduces breast tumor growth and metastasis.
The preclinical data generated by this application will serve as a basis to design clinical regimens that can be translated to the clinic. We believe that agents targeting CD47 will be translated quickly since drugs targeting this molecule are currently being tested in other cancer types. Therefore the completion of these studies could lead to the reduction in triple-negative breast cancer patient mortality while preserving long-term breast cancer patient quality of life.

Grant Profile Information

Ishwaria M. Subbiah, MD

Technology-enhanced Palliative Care for Cancer Patients in Phase 1 Trials

University of Texas M.D. Anderson Cancer Center
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1515 Holcombe Boulevard
Houston, TX 77030

Grant No. CSDG-19-153-01-PCSM
Division: South
Term of Grant: 01/01/2020-12/31/2023
Total Award: $582,000
Total ACS Support: $582,000

Area of Research:	Resources and Infrastructure Related to Treatment and the Prevention of Recurrence	70%
	End-of-Life Care	30%
Types of Cancer:	Not Site-Specific Cancer	100%

Project Summary

BACKGROUND: Phase I clinical trials are studies conducted to find a new drug''s dose that is best tolerated (with limited side effects) and can be taken safely. These trials are extremely important as a 1st step in bringing new drugs to patients who might benefit from them. When cancer grows on standard treatments, many patients with advanced cancer consider participating in phase I trials for several reasons, including the sense of hope and purpose that participation can give them. However, these patients often have very severe symptoms such as pain, fatigue, neuropathy, anxiety, and depression because of their cancer and/or side effects from previous treatments like chemotherapy and radiation. These side effects can cause problems for their participation in the clinical trial. This has negative consequences for both the person taking part in the trial and the trial itself.

Palliative care is a field of medicine that treats the symptoms of people facing serious illness at all stages of their disease, and can help people with advanced cancer. Exciting new research has shown that increased contact between the palliative care team and patients, including telephone calls and app-based contact, can make palliative care more effective, meaning the patient''s symptoms are under better control and consequently that patient reports a better overall quality of life. Our study will test three methods for frequent contact using simple smartphone technology to improve symptom relief for cancer patients preparing to participate in phase I trials: standard palliative care, palliative care with occasional patient contact, and palliative care with frequent patient contact.

QUESTIONS TO BE ASKED: For each of the three different symptom management methods, we will ask how patients'' symptoms change over a period of two weeks prior to starting their phase I trial. Next, we will ask how symptoms change 4, 8, and 12 weeks later. We will ask about survival of patients receiving palliative care by each of the three methods, their intensive care unit admissions, and the quality of their care. Importantly, we will interview the patients and their caregivers to find out about their experiences and perceptions of palliative care, technology use, and participation in phase I trials.

INFORMATION TO BE OBTAINED: The information that we will obtain from this study will be critical for our future studies aimed at improving the care and quality of life of patients on phase I clinical trials, as well as other cancer patients and those with other serious illnesses. Understanding how symptoms are impacted in patients receiving each of the three palliative care methods will help us to decide how many patients to enroll in our subsequent study to determine which of the methods is best for patients. We will also get some early information on outcomes like survival, intensive care admissions, and quality of care that we can test in our future research. Patient and caregiver interviews will help us design our future studies and give us new ideas to improve delivery of care.

Grant Profile Information

Bill Sugden, PhD

Institutional Research Grant

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Grant No. IRG-19-146-54-IRG
Division: North
Term of Grant: 01/01/2020-12/31/2022
Total Award: $270,000
Total ACS Support: $2,441,270

Project Summary

Cancer is a complex and multifaceted disease. At the cellular level, basic research has uncovered mechanisms by which cancer cells arise and progress. At the clinical level, testing of innovative diagnostic tools has helped to detect cancer sooner, and ongoing clinical trials seek to improve outcomes for cancer patients. At the population level, expanded understanding of how to prevent and detect cancer has helped us reduce the burden of the disease on patients, families and communities. Despite progress in all these areas, much remains to be done, and research in all three areas, Basic, Clinical, and Population studies, continues to advance treatment and understanding of cancer. Moreover, while cancer incidence and mortality have decreased over the last few decades, not all people have benefited equally from these successes, and more needs to be done to address health disparities in the context of cancer. This proposal seeks funds to support four pilot projects per year at the University of Wisconsin in the areas of Basic, Clinical, and Population Sciences, with a focus on health disparities in cancer in the poor and underserved. Additional funds from the University of Wisconsin Carbone Cancer Center supplements each pilot project by another $20,000 for a total added value of $80,000 per year towards the goals of the American Cancer Society. With these funds, we have and will support the meritorious, innovative, and cancer-relevant projects of junior investigators on campus. In this way, the ACS not only funds essential cancer research, but also supports the development of the next generation of cancer researchers across all colleges and schools at the University of Wisconsin-Madison.

Grant Profile Information

Normarie Torres-Blasco, PhD

Cultural Adaptation of Meaning-Centered Psychotherapy for Latino families

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Grant No. PF-19-120-01-CPPB
Division: Southeast
Term of Grant: 01/01/2020-12/31/2022
Total Award: $163,500
Total ACS Support: $163,500

Mentor: Eida Castro, PsyD

Area of Research: End-of-Life Care 100%

Types of Cancer: Not Site-Specific Cancer 100%

Project Summary

Family issues are a crucial component of adjustment and well-being of advanced cancer and family caregivers. This critical component of care has led to the development of effective interventions in family care. However, there is an absence of therapeutic intervention for Latino families coping with advanced cancer. To address this need, this project will develop a culturally adapted Family Meaning-Centered Psychotherapy (FMCP) for advanced cancer patients and caregivers to improve the quality of life in Latino cancer patients and their family caregiver (FC). The FMCP will be developed from the Meaning Centered Psychotherapy (MCP) and culturally adapted through data analyzed from Puerto Rican patients, easily translating to multiple Latino subcultures throughout the United States and Latin America. Meaning Centered Psychotherapy (MCP) is an evidence-based treatment that aims to sustain or enhance a sense of meaning, peace, and purpose as patient"s approach end-of-life. The study team will use questionnaires aimed to assess the need to culturally adapting the MCP intervention to a Family Meaning Centered Psychotherapy (FMCP). The primary outcome of the FMCP proposed psychotherapeutic adaptation is to improve the spiritual well-being of Latino cancer patients and family caregivers (FCs). This study will focus on a population composed of Latino, Puerto Rican women and men, patients, and caregivers to culturally adapt Family Meaning-Centered Psychotherapy for cancer families. In order to Identify the foundational information needed to culturally adapt the MCP to FMCP; and by determine the association between meaning & spirituality with secondary outcomes (hopelessness, anxiety, and depression symptomatology) in Latinos diagnosed with advanced cancer and their family caregivers (FCs); and moderation effect of caregiving burden and family function (communication, conflict and cohesion). This Aim will be achieved by exploring the 57 dyad"s and 15 key informants (caregivers who score above >4 in Distress Thermometer) advanced cancer experience, strategies used to cope, caregiving burden, and the family function (communication, conflict and cohesion) and by identifying factors that will facilitate the cultural adaptation, use, and dissemination of FMCP. The study agenda is innovative and will allow the applicant to acquire the research skills necessary to become a successful independent investigator in the field of cultural adaptation of Latino families coping with advanced cancer. The study findings are expected to position the candidate to submit a competitive NIH R21 application to conduct a large pre-pilot and pilot study of Family Meaning-Centered Psychotherapy with Latinos patients. The cultural adaptation of the intervention will also advance the field of healthcare services on families coping with cancer. These findings will have the direct potential to improve the quality of life of Latinos dealing with advanced cancer.

Grant Profile Information

Jennifer Urban, PhD

How is Asymmetric Histone Deposition coupled to DNA Replication?

Johns Hopkins University
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Grant No. PF-19-131-01-DMC
Division: Northeast
Term of Grant: 01/01/2020-12/31/2021
Total Award: $111,500
Total ACS Support: $111,500

Mentor: Xin Chen, PhD

Area of Research:	Normal Functioning	50%
	Cancer Initiation: Alterations in Chromosomes	50%
Types of Cancer:	Not Site-Specific Cancer 100%	

Project Summary

Many mammalian tissues rely on a subpopulation of adult stem cells to remain healthy. Adult stem cells often divide to produce two different cells. One cell maintains the stem cell population while the other one replaces damaged cells. This mechanism is called asymmetric cell division (ACD). Disruptions in ACD can lead to the initiation of several different cancers. Therefore defining the mechanisms that regulate normal ACD is imperative to understanding the earliest steps in tumor formation.

Much of what we know about ACD comes from studies on Drosophila male germline stem cells (GSCs). In GSCs, asymmetry is introduced long before ACD occurs. First, the GSC duplicates its genome to produce two identical copies in the form of chromosomes. Each set of chromosomes is coated with a different factor that will dictate which set of chromosomes remains in the stem cell and which set is segregated to the cell that will become sperm. Disrupting the pattern of these factors results in mixing of the chromosome sets such that they no longer segregate to the correct cell, causing GSC tumors. This indicates that preserving the asymmetries on chromosomes prior to ACD is an essential mechanism for preventing tumor initiation. Identifying the molecular players involved in generating these asymmetries will lead to a better understanding of how cancers initiate.

Our laboratory has evidence that the process of duplicating the genome, called DNA replication, plays a key role in establishing the asymmetries of these factors on chromosomes. However, this has never been explored. In this proposal, I will investigate how DNA replication introduces asymmetries on chromosomes that lead to their proper segregation during ACD. First, I will gain a better understanding of where DNA replication initiates in the genome and how it proceeds in GSCs. Then I will define the molecular players involved in ensuring the correct placement of factors required for proper ACD. To complete the proposed project, I created an unprecedented germline stem cell system that allows us to probe questions in the germline stem cell and cancer biology fields that were previously difficult to address. This system will transform the types of studies we can perform, significantly impacting how we approach cancer research. With this powerful system, this proposal will significantly contribute to our understanding of asymmetry-producing mechanisms. Ultimately, this knowledge can be translated into developing therapies to prevent and potentially correct abnormal ACD.

Grant Profile Information

Jordan M. Winter, MD

Targeting Wild type IDH1 in Pancreatic Cancer

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Grant No. MBG-19-174-01-MBG
Division: North Central
Term of Grant: 01/01/2020-12/31/2021
Total Award: $240,000
Total ACS Support: $240,000

Area of Research:	Systemic Therapies - Discovery and Development	100%		
Types of Cancer:	Breast Cancer	2%	Lung Cancer	2%
	Colon and Rectal Cancer	2%	Pancreatic Cancer	92%
	Gallbladder Cancer	2%		

Project Summary

Pancreatic cancer is the most aggressive common cancer. Over 50,000 new cases present annually in the United States, and nearly as many patients die from the disease. Due to a lack of effective new therapies and its aggressive biology, pancreatic cancer is now the 3rd leading cause of cancer death in this country. Novel therapies are needed. The PI is a pancreatic cancer surgeon and scientist. Thanks to the American Cancer Society-sponsored Mentored Research Scholar Grant, the PI discovered a new molecular vulnerability in pancreatic cancer biology: antioxidant defense. Pancreatic cancer, perhaps more than any other cancer, has a profoundly austere and nutrient-deprived microenvironment. These challenging conditions result in the generation of toxic waste or metabolites called reactive oxygen species. These metabolites chemically modify essential cellular components. Therefore, in order to survive, pancreatic cancer cells recruit pathways to neutralize these oxidants. We determined that one metabolic enzyme, isocitrate dehydrogenase 1 (IDH1), is particularly important. Although the enzyme is present in normal tissues, its expression is markedly elevated in pancreatic cancer cells. Moreover, its function is far more important under ‘desert-like'' conditions encountered by pancreatic cancer cells, than more comfortable conditions encountered by normal cells. Mice that lack only the IDH1 gene do not have health abnormalities. However, they typically die if the mice are severely stressed, revealing the essentiality of this enzyme under specific conditions. When we deleted the IDH1 gene from pancreatic cancer cells, the cells were extremely sensitive to low glucose culture conditions, as well as to chemotherapy. Supplementing the tissue culture media with an antioxidant compound proved that the antioxidant capabilities of IDH1 were critical for survival. Additionally, when we implanted IDH1-deficient pancreatic cancer cells in mice, the tumors failed to grow. In contrast, pancreatic cancer cells with IDH1 expression flourish. Our lab recently demonstrated that under nutrient-deprived conditions, standard chemotherapy actually is less effective. Pancreatic cancer cells adapt to low nutrient conditions, and these adaptations double as a protective shield against chemotherapy. IDH1 inhibition has the opposite effect. Cancer cells are more susceptible to IDH1-targeted therapy under nutrient withdrawal. Amazingly, we are targeting the wrong pathways in patients! In recent months, we discovered a compound that potently inhibits IDH1. Fortunately, patients use this compound for another cancer type, and the drug is safe. In this proposal, we definitively prove drug efficacy in cell culture and in mouse models of pancreatic cancer. These experiments will pave the way for a clinical trial in the Secondary Boost, in order to demonstrate efficacy in patients with pancreatic cancer. Moreover, we expect this compound to work against other common cancers with nutrient-deprived microenvironments, like breast and colon cancer.

Grant Profile Information

Trisha Wise-Draper, MD, PhD

Harnessing the Natural Killer Cytotoxic Response in Head and Neck Cancer

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Grant No. RSG-19-111-01-CCE
Division: North Central
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research: Systemic Therapies - Discovery and Development 60%

Systemic Therapies - Clinical Applications 40%

Types of Cancer: Head and Neck Cancer 100%

Project Summary

A patient''s own immune system is critically important for preventing and fighting cancer. A properly functioning immune system recognizes a tumor as foreign and serves to eliminate the cancer. Unfortunately, this fighting mechanism is often turned off by the tumor itself through a variety of processes including upregulation of a protein called programmed death-ligand 1 (PD-L1). When PD-L1 binds another protein called PD-1, which is often expressed on cancer fighting immune cells, these immune cells are turned off and the cancer is no longer recognized and removed by the immune system. Based on our understanding of this “checkpoint” controlling tumor growth, a promising strategy for improving cancer treatment is to block this inhibitory pathway, thereby recovering the capacity for the patient''s own immune system to eliminate the cancer. In fact, nivolumab, a PD-1 antibody that blocks this negative interaction between PD-L1 and PD-1, has been shown to dramatically improve cancer outcomes in some patients. However, for unclear reasons, the majority do not achieve such an impressive response. Any new research that explains the basis for this frustrating spectrum of complete cure in some patients to no response in the majority, would have an enormous impact on cancer treatment outcomes.

Although it is known that nivolumab can activate the adaptive immune cell response resulting in tumor reduction in some patients, components of the innate immune system, specifically natural killer (NK) cells, may also be vitally important for robust immunogenic tumor cell killing. For this study, we propose to use a diabetic medication with minimal side effects called metformin, which we have shown activates a person''s own NK cells likely through a specific cancer signaling pathway. Importantly, as NK cells also express PD-1, we hypothesize that blocking both the PD-1/PD-L1 checkpoint with nivolumab, and negative signaling pathways with metformin in NK cells, will result in activation of both the adaptive and innate immune response leading to a more robust cytotoxic response. Here we propose to combine both treatments in patients in a clinical trial and to utilize patient''s tumor tissue and blood from the trial to determine why some patients respond and even more importantly, why some patients do not respond. We will use novel model systems such as organoids, three dimensional cell collections that are derived from individual patients, to allow us to directly test and predict patient responses in the laboratory. We will also analyze differential gene expression patterns in patients and relate to various responses to treatment. This will give vital insight to not only better understand and tailor specific treatment for each individual patient but also developing new more effective combinations for the future. We expect that the addition of metformin will increase the number of patients who respond to nivolumab and, in some cases, make the tumor disappear completely.

Grant Profile Information

Yelena P. Wu, PhD

Family-focused Melanoma Preventive Intervention for Children of Survivors

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Grant No. RSG-19-121-01-CPPB
Division: North
Term of Grant: 01/01/2020-12/31/2023
Total Award: $789,000
Total ACS Support: $789,000

Area of Research:	Interventions to Prevent Cancer: Personal Behaviors (Non-Dietary) that Affect Cancer Risk	100%		
Types of Cancer:	Melanoma	90%	Skin Cancer (non-melanoma)	10%

Project Summary

Melanoma is the most deadly form of skin cancer. Strategies to prevent melanoma are best if they are used in childhood. These strategies include applying sunscreen, wearing long-sleeved shirts, pants, broad-brimmed hats and sunglasses, avoiding outdoor daylight when it is strongest, using shade when outdoors, and avoiding intentional tanning. A growing number of children are at increased risk for melanoma because they have a parent with a history of the disease. The only way to reduce melanoma risk for these children is to help them avoid excess ultraviolet radiation exposure leading to sunburn. Unfortunately, children with higher risk for melanoma do not use sun protection strategies consistently due to a variety of reasons and get sunburns. Existing melanoma prevention programs do not teach children and their parents how to work together to improve child sun protection, and they have not been able to target child sunburns which make children more at risk for developing melanoma.

We designed a family-focused program for melanoma survivors and their children that is delivered via a website, through live video sessions with an educator, and through text message or email. The program provides essential information about the child"s higher risk for melanoma and teaches parents and children how to work together to improve child sun protection use. In our early test of the program, we saw that it helped to lower child sunburns and improve child sun protection. It was practical for families and both parents and children liked the program.

We will compare our program to a standard sun safety program consisting of general melanoma prevention information, to see if children who receive our program experience fewer sunburns than those who receive the standard sun safety program. We will also study which survivors and children benefit most from our program so that in the future, we can better tailor melanoma prevention programs for particular groups of individuals. This project will also study ways survivors and children interact to increase child use of sun protection and decrease sunburn occurrence. Survivors and children will be asked to complete questionnaires before, during, and after receiving the programs, for up to one year. Our program could help prevent melanoma in at-risk children who require effective prevention programs so that they do not get a costly and deadly skin cancer.

Grant Profile Information

Liiangzhong Xiang, PhD

In Vivo Dosimetry with X-ray-induced Acoustic Computed Tomography

University of Oklahoma
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Grant No. RSG-19-110-01-CCE
Division: South
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research: Technology Development and/or Marker Discovery 60%

Technology and/or Marker Testing in a Clinical Setting 40%

Types of Cancer: Prostate Cancer 100%

Project Summary

Cancer is a major public health problem and remains a leading cause of death globally. As one of the main treatment options for cancer, radiation therapy is received by roughly two-thirds of all cancer patients. Radiation dosimetry is crucial to continued success and improvement in cancer treatment, ensuring that a correct and accurate dose is delivered to the desired location. However, in such a widely used clinical intervention, the delivered radiation dose can only be planned and/or verified via simulation with phantoms, and an in vivo and in-line verification of the delivered dose is still absent in the clinic.

This proposal seeks the development of a completely novel in vivo dosimetry, X-ray-induced Acoustic Computed tomography (XACT), for real-time monitor radiation dose during radiation therapy. Our overall strategy is to use computer simulations to optimize imaging parameters, then to further design/construct a 3D XACT dosimetric scanner, and to test/refine the imaging prototype on a tissue-mimic phantom in clinic. The impact of the proposed XACT imaging is not only to provide a novel imaging tool to accurately verify in-patient radiation doses, but also to provide real time feedback for adaptive therapy during treatment. The technological advancements in XACT imaging as an in vivo dosimetry will decrease radiation treatment toxicity and improved clinical outcomes for cancer patient.

Grant Profile Information

Ji Young Yoo, PhD

Impact of Focal Adhesion Kinase (FAK) Signaling on Oncolytic HSV Therapy

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Grant No. RSG-19-185-01-MPC
Division: South
Term of Grant: 01/01/2020-12/31/2023
Total Award: $792,000
Total ACS Support: $792,000

Area of Research:	Localized Therapies - Discovery and Development	80%		
	Localized Therapies - Clinical Applications	20%		
Types of Cancer:	Brain Tumor	80%	Neuroblastoma	20%

Project Summary

Glioblastoma (GBM) is the most malignant primary brain tumor. Nearly all tumors recur and are often resistant to radiation and chemotherapy, leaving few options available to delay disease progression. Oncolytic viruses (OV) are viruses designed to selectively replicate in and kill cancer cells without harming surrounding normal cells and activate an anti-tumor immune response. Thus, OV therapy offers the potential to increase patient survival and quality of life. Since the FDA approval of the first Herpes simplex virus type 1-derived OV (oHSV) therapy, Talimogene Laherparepvec, in the United States, various second generation of oHSV have been introduced and are currently being evaluated in clinical trials for efficacy against brain tumors. Past clinical trials utilizing oHSV therapy for GBM have demonstrated safety and promising clinical outcomes. However, the use of oHSV has not been approved yet for GBM therapy. Therefore, an innovatively improved therapeutic strategy is still in need.

OHSV-treated tumors often initially respond well, with cessation of tumor growth and even tumor shrinkage observed. However, some tumors do not respond well and regrow after viral clearance. oHSV therapy-induced changes in the environment that encompasses the tumor, known as the tumor microenvironment (TME), can lead to activation/inhibition of signaling pathways in tumor and surrounding cells, decreasing the therapeutic efficacy of oHSV therapy. The proposed research is based on our recent unpublished key findings that oHSV treatment of glioma cells leads to increased activation of focal adhesion kinase (FAK) in glioma and TME cells. FAK plays critical roles in tumor progression and regrowth. The proposed research outlined in this grant will elucidate the mechanism of oHSV therapy-induced FAK signaling activation, which is implicated in enhanced tumor regrowth after viral clearance. Recent findings indicate that FAK signaling is strongly activated in GBM and strategies to therapeutically modulate FAK signaling are of interest for GBM therapy. Although several small molecule FAK inhibitors have been shown to decrease tumor growth and metastasis in several preclinical models, its clinical activity remains to be determined. In this proposal, we will evaluate the impact of combining oHSV therapy with Penfluridol, an FDA approved anti-psychotic drug which inhibits FAK signaling. Repurposing drugs clinically approved for other indications towards cancer therapy has several advantages including decreased development costs, higher success rates, and an expedited drug approval process. Thus, the repurposing of Penfluridol to enhance oHSV cancer therapy is highly significant. Data obtained from this proposed study will provide the rationale to design a novel OV and to develop promising oHSV combination strategies. We anticipate that the discoveries herein will accelerate the successful translation of oHSV therapy into an efficient and improved treatment option for GBM patients, bringing this therapy closer to becoming a standard of care for GBM patients.