

Pilot Project Award Program

2024 Awards

- ***Lung gamma delta T cells in a mouse model of non-small cell lung cancer***

Principal Investigator: Jonathan Boyson, PhD

Lay Summary: Gamma delta T cells are poorly characterized white blood cells that are enriched in mucosal tissues such as the lung. Recently, gamma delta T cells have been shown to play a “dual role” in cancer progression. In some instances, they effectively kill tumor cells and are beneficial. However, in other instances, they appear to promote tumor growth and metastasis. The current proposal is focused on investigating the underlying mechanisms that drive gamma delta T cell function in a model of lung cancer.

- ***Mechanistic Evaluation of PURA and PURB in Regulating the Phenotype of ER+ Breast Cancer Cells***

Principal Investigator: Robert Kelm, PhD

Lay Summary: Early detection and better treatments have led to great improvements in the prognosis and survival of breast cancer. The most common types of breast cancer express the estrogen receptor (ER+). These cancers are typically less aggressive and respond to endocrine therapy, however, there are still major challenges in the effective treatment of these breast cancers including resistance to endocrine therapies and relapse. Our preliminary data indicate that expression of the mRNA encoding the transcription factors PURA and PURB are prognostic indicators for ER+ breast cancer and may represent a potential target for ER+ breast cancer treatment. In this pilot proposal, we will test the overall hypothesis that PURA and PURB control certain ER+ breast cancer survival programs, including the regulation of gene expression associated with cell growth and DNA damage repair pathways. The proposed mechanistic studies will provide insight into the roles of PURA and PURB in regulating cancer cell characteristics, and the findings could pave the way for novel therapeutic interventions and prognostic markers in breast cancer treatment.

- ***Developing a Novel Analytical Tool for Prostate Cancer Diagnosis***

Principal Investigator: Scott Perrapato, DO

Lay Summary: Current prostate cancer diagnosis protocols frequently suffer from low sensitivity and false positives, leading to overtreatment, serious side effects, and unnecessary clinical expense. In this proposal, we focus on the analysis of proteins adsorbed onto mesoporous silica nanoparticles from patients at different stages of prostate cancer. Biostatistical analysis is used to identify a protein “fingerprint” of up- and down-regulated proteins specific to high-malignant prostate cancer patients with high predictive value ($\geq 90\%$).

- ***Identifying Communication Factors Influencing Connection in Telehealth Serious Illness Conversations with Rural Cancer Patients***

Principal Investigator: Elise Tarbi, PhD, MBE, APRN

Lay Summary: Telehealth offers a means to overcome critical disparities in cancer care access, expanding the delivery of specialty serious illness care, such as palliative care, to underserved rural areas; yet the optimal communication strategies to build connection in virtual settings have not been empirically established. Through interviews with rural-dwelling cancer patients, this study aims to explore the influence of communication features (i.e., what we say and how we say it) on the experience of building connection in telehealth serious illness conversations. This work will lead to a better understanding of the critical features of telehealth serious illness communication that support connection, ultimately informing the development of actionable, evidence-based communication training for clinicians.

2023 Awards

- ***Use of ctDNA to Predict Response to Intralesional Therapy for Melanoma***

Principal Investigator: Jessica Cintolo-Gonzalez, MD

Lay Summary: Melanoma that has spread to the skin, soft tissue, or lymph nodes can be treated by injection with an FDA-approved drug called talimogene laherparepvec (Imlygic®, T-VEC). This consists of injections every 2-3 weeks. While sometimes discontinuing therapy is a very clear decision due to either tumor progression or a complete clinical response resulting in no further injectable lesions, decisions to stop injections can be challenging when there is stability of a lesion over time. This can occur because physical exam or radiographic findings do not always indicate presence of viable tumor. Monitoring of tumor presence in the blood using circulating tumor DNA (ctDNA) is increasingly being used as a way to predict presence of disease and responses to cancer therapies. Therefore, we believe that testing a commercially-available ctDNA test, SIGNATERA™, for its ability to reflect presence/absence of viable tumor in patients with melanoma treated with TVEC could identify this platform as valuable as a tool that can inform these challenging treatment decisions.

- ***Determining Patient Outcomes in the Treatment of Mesothelioma with Proteomic Fingerprints***

Principal Investigators: Brian Cunniff, PhD & Christopher Landry, PhD

Lay Summary: The goal of this study is to use proteomics to identify patterns of protein up- and down-regulation in malignant pleural effusion (MPE) fluid of patients diagnosed with mesothelioma. Thiostrepton (RSO-021) is a new treatment being tested the phase 1 MITOPE trial by direct administration to the pleural cavity (NCT05278975). Given the rapid progression of mesothelioma from the point of diagnosis, and following first- and second-line therapy, it is important to develop effective treatment strategies at an early stage. Currently, an understanding of the factors impacting patient response to RSO-021 is lacking.

- ***Impact of environmental toxins on BRPF1 bromodomain acetylated lysine recognition in leukemogenesis***

Principal Investigator: Karen C. Glass, PhD

Lay Summary: Leukemia is a cancer of the blood caused by both genetic and environmental factors that cause the bone marrow cells to grow too rapidly, which interferes with the function of normal red blood cells in transporting oxygen around our body. Exposure to toxic substances (i.e. benzene and tobacco smoke), pesticides, and even nickel in the soil are known to be risk factors for developing leukemia. They are also known to alter chemical signaling patterns within our cells that are important for regulating cell growth. We are proposing to develop new methods to identify and characterize the interaction of proteins that bind to these chemical signals to determine how environmental toxins alter the binding interaction and promote leukemia development.

- ***Estrogen Modulates Dexamethasone Responsiveness in Acute Lymphoblastic Leukemia***

Principal Investigator: Jessica L. Heath, MD

Lay Summary: Adolescents with acute lymphoblastic leukemia (ALL) have a decreased survival rate compared with younger children. The factors underlying these survival differences are poorly understood; however, one significant biological change that happens in the transition to adolescence is the increase in hormones associated with puberty. It is not known how this hormonal shift influences leukemia development or response to treatment. We hypothesize that increased concentrations of pubertal hormones in the bone marrow, specifically estrogen, modulate the way leukemia cells behave, and influence the efficacy of standard chemotherapy.

- ***PEPrMINT' – A Pipeline to Enhance Precision Medicine through Identification of Novel Therapeutics***

Principal Investigators: Doug J. Taatjes, Ph.D. and Alan K. Howe, Ph.D.

Lay Summary: The term 'precision medicine' refers to the goal of delivering medical care that is tailored to the individual patient and their disease, in order to increase effectiveness and minimize side effects. The realization of precision medicine in cancer treatment is complicated and hindered by limits in both our understanding of fundamental cancer cell biology as well as in our capacity for the efficient design and discovery of newer, better anti-cancer drugs. Our proposal is a budding attempt to address the critical need for methods and infrastructure that facilitate and expedite cancer drug discovery. Specifically, we have proposed to develop 'PEPrMINT', a pipeline to enhance precision medicine through identification of novel therapeutics. This pipeline will procure tumor samples from patients and grow them into miniature, three-dimensional models called 'tumor organoids', which retain key characteristics of the patient's own tumor. Importantly, these patient-derived tumor organoids can be greatly expanded in number, which allows them to be used as targets for drug screens in the laboratory. We will test this aspect of the pipeline initially by screening a library of approximately 500 new chemicals that are known to alter cellular metabolism - the various ways that cells produce, convert, and store energy. It is well known that cancer cells grow and divide much faster than normal cells and therefore have many significant changes in their metabolism. However, there are few – if any – current anti-cancer drugs that target this metabolic

reprogramming, making this library a particularly intriguing first choice. We hope that these initial efforts will support and inspire many future projects aimed at enhancing the development of precision cancer medicine and accelerating the pace at which discoveries made through basic research are turned into new clinical treatment options for cancer.

- ***Investigating Heterogenous Preferences for Screening Mammography Among Non-White and Underserved Populations in Vermont***

Principal Investigator: Eline van den Broek-Altenburg, Ph.D., MSc, MA

Lay Summary: Mammography (breast x-ray) can help identify breast cancer early and is recommended every year for women over age 40. Currently, non-white women are underrepresented among those eligible for mammography screening in Vermont. We are interested in conducting a study to try to understand why more white women, than non-white women receive mammography screening in our state in order to more effectively recommend programs to motivate these women to get screened. We are seeking to understand where the gaps and barriers are in the current system, and to identify what can be done to improve access to mammography screening among nonwhite women in Vermont. We have been working with Vermont Department of Health's YouFirst program, aiming to have access to non-white women who do not necessarily have access to, and are not within the health system.

2022 Awards

- ***Thyroid hormone receptor beta (TRβ) agonists: Novel applications in anaplastic thyroid cancer***

Principal Investigator: Frances E. Carr, PhD

Lay Summary: Thyroid cancer is the most common cancer of the endocrine system and is now the fastest growing cancer worldwide. There are no effective, long lasting treatments for poorly differentiated and undifferentiated anaplastic thyroid cancer (ATC), which has a median survival of 5-6 months. Decreased levels and activity of a tumor suppressor, thyroid hormone receptor beta (TRβ), is characteristic of advanced endocrine cancers including ATC suggesting the potential importance of increasing the activity of TRβ to counter tumor progression. Based upon our earlier work, this study will establish the proof-of-concept that activation of TRβ with a synthetic thyroid hormone selective for this tumor suppressor counters the aggressive ATC phenotype, inhibits tumorigenic signaling, and increases the efficacy of current therapeutics to improve clinical outcomes with fewer negative sides effects for this aggressive cancer.

- ***Characterization of talin as a putative, mechanically-gated A-Kinase Anchoring Protein in Ovarian Cancer Cell Migration and Invasion***

Principal Investigator: Alan K. Howe, PhD

Lay Summary: Ovarian cancer cells sense and utilize the rigidity of their surrounding tissues – the more rigid the tissue, the better the cells invade and metastasize. The proposed research will investigate talin, a protein that changes shape in response to the high cellular tension, and its role in coordinating a rigidity-dependent signaling pathway that governs cell shape and migration, and thus may contribute to ovarian cancer metastasis.

- ***GLUTAREDOXIN, GLUTATHIONE METABOLISM AND LUNG CANCER***

Principal Investigator: Yvonne Janssen-Heininger, PhD

Lay Summary: The environment of lung tumors is hostile requiring tumors to adapt in order to survive and grow. Part of this adaptation is a change in metabolism and increases the antioxidant, glutathione, to combat the increased oxidative stress. In this proposal we will address the mechanism whereby this increase in glutathione occurs and offer new strategies to prevent the increases in glutathione from happening. We will test whether this strategy can be used to increase the therapeutic efficacy of the chemotherapeutic drug cisplatin.

- ***A novel in vitro system to determine the role of macrophages in cancer cachexia***

Principal Investigator: Michael J. Toth, PhD

Lay Summary: Cancer cachexia is a syndrome characterized by weight loss, secondary to skeletal muscle and fat wasting, that occurs in certain cancer types, such as lung, pancreatic, head and neck cancer, and advanced stages of other cancer types. Cachexia reduces physical function and quality of life and increases treatment toxicities mortality. Despite the scope and gravity of this syndrome, the mechanisms underlying cancer cachexia remain unknown and there are currently no available treatments. The proposed studies are designed to address the critical barrier of translating the wealth of data on cancer cachexia from animal models into human cancer using novel cell culture models designed in our laboratories using materials from both mouse models and human patients.

2021-2022 Awards

- ***Examining the Relationship Between Rural Social Networks and Tobacco and Alcohol Use in Northern New England***

Principal Investigator: Sarah Nowak, PhD

Lay Summary: While cancer deaths are declining in the United States overall, deaths that could potentially be prevented through changes to behavior are not declining as quickly in rural areas as in non-rural areas. Tobacco and alcohol use are two behaviors that influence cancer risk and may explain some differences between rural and non-rural mortality declines. Social networks can influence health behavior in important ways and this project will examine whether differences in social networks in rural and non-rural areas of Northern New England (NNE) are related to differences in alcohol and tobacco use.

- ***Linking differential immune cell recruitment with STK11 loss using an inducible mouse model of lung adenocarcinoma***

Principal Investigator: David J. Seward, MD, PhD

Lay Summary: Each year lung cancer kills more people in the United States than breast, colorectal and prostate cancer combined. Advances in immunotherapy promise to reduce lung cancer mortality but we lack the tools to accurately predict which patients will benefit. The goal of my research is to delineate the molecular mechanisms linking STK11 loss with anti-PD-1 therapy resistance in KRAS-driven non-small cell lung adenocarcinoma and exploit that

knowledge to restore sensitivity to current therapies while also working to identify new treatment strategies.

2021 Awards

- ***Unraveling REV1 functions in cancer resistance to therapy***

Principal Investigator: Nimrat Chatterjee, MSc, PhD

Lay Summary: Cancer resistance to chemotherapy and radiotherapy is associated with relapse, poor prognosis, and reduced survival of patients, but biomarkers that might explain the mechanisms are limited. Recent evidence suggests that a possible strategy to sensitize tumors and reduce chemotherapy resistance is to inhibit the mutagenic translesion-synthesis (TLS) pathway by targeting REV1 TLS polymerase. Translesion synthesis is a DNA-damage bypass process involving a set of specialized DNA polymerases that collectively tolerate DNA damage and cause mutations. However, recent data suggest that REV1 inhibition unexpectedly triggers radioresistance by a remarkable induction of autophagy stress response. In this study, we seek to 1) determine the role of REV1 in cancer cell response to radiation treatment by investigating the biological role of translesion synthesis, doublestrand break repair, and autophagy in radioresistant cells; and 2) determine whether REV1 is a stress-regulated protein that drives cancer cell response to therapy based on a given tumor microenvironment. Collectively, the proposal aims to further our understanding of mechanisms that propel cancer resistance to therapy by investigating novel phenotypes of the REV1 protein.

- ***Translation of an evidence-based exercise program for remote delivery to rural, older cancer survivors***

Principal Investigator: Nancy Gell, PT, PhD, MPH

Lay Summary: Older cancer survivors living in rural areas have limited opportunities to engage in health-promoting exercise. However, due to the COVID-19 pandemic, Enhance Fitness, an evidence-based, group exercise program, has recently transitioned to remote delivery through videoconference technology. The pivot from a community-based program to an online platform provides a unique and timely opportunity to pilot test Remote-Enhance Fitness for rural, older cancer survivors. The results will provide important information for demonstrating feasibility and acceptability of Remote-Enhance Fitness, and therefore building evidence for designation as a nationwide exercise program for aging cancer survivors.

- ***Understanding Dis3 Mutation and Its Role in Multiple Myeloma Gene Regulation and Genome Structure***

Principal Investigator: Dev Majumdar, PhD

Lay Summary: Multiple Myeloma is a cancer of the plasma cell, and is a very aggressive cancer affecting 0.7% of the US population. Enigmatically, one of the top mutated genes in myeloma is Dis3, a regulator of RNA degradation. Here, we propose to understand the molecular basis of myeloma by utilizing new technologies that allow us to understand the 3D relationships in the genome of RNA and DNA. New structures in the nucleus have been discovered in the past few

years that allow us to envision that Dis3 dysregulation might be causing global changes in the nucleus of myeloma cells. By leveraging these new technologies, we propose to map the nuclei of several types of myeloma so we can understand the role of the mutated Dis3 proteins and fully understand the role of RNA hubs we have discovered in these cancer cells. By better understanding myeloma at a molecular level, we hope to gain insights that will inform new therapeutic strategies into myeloma progression and disease.

2020 Supplemental Awards

- ***Targeting Glycogen Metabolism as a Novel Therapeutic Approach in Aggressive, Poorly Differentiated Thyroid Cancer***
Principal Investigator: Eyal Amiel, PhD
Lay Summary: Thyroid cancer is the most common cancer of the endocrine system, and the incidence has tripled in the past thirty years. There are no effective, long-lasting treatments for anaplastic thyroid cancer, which has a median survival of 5-6 months. However, it may be possible to target glycogen metabolism to prevent the tumor from having access to stored glucose supplies to fuel cell division and metastasis. This study will be significant for exhibiting a unique, targetable oncogenic feature of anaplastic thyroid cancer that offers a potentially improved clinical outcome.
- ***Investigating the impact of micronuclei on genomic stability of primary tumor cells***
Principal Investigators: Jason Stumpff, PhD & Julie Dragon, PhD
Lay Summary: Cancer cells often contain genetic abnormalities that allow them to proliferate uncontrollably. Our understanding of how these defects arise and how they contribute to tumor initiation and development remains incomplete. The proposed work will use tumor models of lymphoma and glioblastoma to investigate the origin and impact of a specific type of genetic defect, called chromothripsis (“shattered chromosome”), which has been implicated as an initiating event for a wide range of tumor types.

2020 Awards

- ***Evaluation of purine-rich element binding protein B as a druggable target in cancer therapy***
Principal Investigator: Robert J. Kelm, PhD
Lay Summary: Purine-rich element binding protein B (aka Pur β) is a sequence-specific, single-stranded DNA (ssDNA) and RNA binding protein implicated in the repression of cardiac, vascular, and blood cell differentiation. Consistent with its role as a repressor of cell differentiation, we recently reported that elevated levels of Pur β are found in malignant white blood cells from patients with acute myeloid leukemia (AML), particularly those with poor prognosis characteristics. Our working hypothesis is that disruption of Pur β function in AML cells may provide a therapeutic advantage by enhancing the chemosensitivity of malignant cells to standard of care drugs that interfere with DNA replication and transcription. The first objective

of this pilot project is to identify small molecule inhibitors of Pur β -nucleic acid interaction using computational approaches and our unique structural models of the distinct ssDNA-binding domains present in Pur β . In silico screening will be conducted in collaboration with a commercial partner utilizing a novel artificial intelligence-based platform. Putative inhibitory compounds identified via in silico screening will then be tested for possible therapeutic bioactivity using a combination of biochemical and cell-based assays designed to assess how selective modulation of Pur β function affects the phenotype of leukemia and other cancer cell lines. As a complement to the pharmacological studies, a genome editing approach will also be employed to confirm the putatively beneficial effect of genetic ablation of PURB expression on the phenotypic properties of leukemia and other cancer cell lines.

- ***Addressing DNA Damage Response in organoids***

Principal Investigators: Delphine Quénet, PhD & David Pederson, PhD

Lay Summary: Previous attempts to design efficient therapy to treat brain tumors like glioblastoma have been unsuccessful. Describing glioblastoma progression and identifying biomarkers and promising drugs is challenging due to the lack of a reliable model that mimics this specific cancer. In this proposal, we aim to establish the ex vivo 3-dimensional tissue system, called organoid, that will recapitulate the architecture of the brain invaded by glioblastoma tumor. Using this approach, we will both characterize the biology of glioblastoma and test potential new drugs, such as PARP inhibitors, which are already used in the treatment of BRCA mutated breast and ovarian cancers.

- ***Point of Care (POC) Testing for Patients with Advanced Cancer (PoC-TAC): A feasibility study***

Principal Investigators: Marie E. Wood, MD & Marc Greenblatt, MD

Lay Summary: The field of cancer genetics has changed significantly over the past 5 years, with increased numbers of genes associated with hereditary cancer identified. Current indications for cancer genetic testing include several cancer types and the most appropriate individuals to undergo genetic testing are individuals with cancer, as they are the most likely individuals to carry a gene associated with hereditary cancer (compared to an individual without cancer). Testing patients with cancer can have significant impact on their management (cancer treatment, risk of second primary) as well as management of family members. Our goal is to establish the prevalence of germline mutations in high and moderately penetrant cancer associated genes in patients with advanced cancer and to test the feasibility and impact of testing patients at diagnosis.

2019 Awards

- ***Prostate Cancer-Circulating miRNA for Precision-based Medicine (PROMISE)***

Principal Investigators: Steven Ades, MD; Jane Lian, PhD; Scott Perrapato, DO; & Thomas Ahern, PhD

Lay Summary: A large percentage of men at low risk receive immediate treatment; yet only a very small fraction are at risk of disease progression and death. Further, radiation treatment, surgery, and hormonal therapy have many associated risks. Current tools to assess prostate cancer biology rely on marker genes or proteins identified in tumor tissue, requiring invasive techniques. The epigenetic microRNA biomarkers can be measured from a non-invasive blood draw and could reflect cancer-related and other biological pathways prior to detection of PCa progression.

- ***Mitochondrial positioning determines subcellular redox modifications supporting cell migration and metastasis***

Principal Investigators: Brian Cunniff, PhD & Albert van der Vliet, PhD

Lay Summary: Tumor metastasis is the spread of cancer cells from the primary tumor to a secondary site in the body, and is the primary cause of most cancer-related deaths. Tumor metastasis is a multistep process that requires local invasion and active cell migration. Our research focuses on identifying molecular mechanisms supporting tumor cell migration in order to elucidate novel avenues of therapeutic intervention.

- ***Evaluating the impact of policy and public education on tobacco and substance use: Feasibility of recruiting and retaining an online cohort of young adults***

Principal Investigator: Andrea C. Villanti, PhD, MPH

Lay Summary: Population-level interventions like health policy and public education efforts that decrease alcohol and tobacco consumption are likely to reduce cancer incidence and mortality. These benefits are likely to be even greater if patterns of consumption are disrupted early in youth and young adulthood. The proposed pilot study demonstrates the feasibility of recruiting and retaining a cohort of Vermont young adults (aged 18-25) who respond to online surveys on awareness of state-level substance use policy and communication efforts and tobacco, alcohol, and substance use attitudes, beliefs, and behaviors at baseline, 3 months, and 6 months. This project builds on an ongoing collaboration between Dr. Villanti and the Vermont Department of Health (including Drs. Searles and Singer) that aims to seek external funding for such a cohort of Vermont youth and young adults that is sufficiently representative of the VT population and sufficiently flexible to address rapid changes in policy, communication, and interventions at the state-level.