

**Pilot Project Award Program**

**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

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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.

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- ***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 $\beta$ ) 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 $\beta$  are found in malignant white blood cells from patients with acute myeloid leukemia (AML), particularly those with poor prognosis

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characteristics. Our working hypothesis is that disruption of Pur $\beta$  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 $\beta$ -nucleic acid interaction using computational approaches and our unique structural models of the distinct ssDNA-binding domains present in Pur $\beta$ . 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 $\beta$  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)***

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**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.