Henry Ford Cancer Institute

Cancer Research Project Summaries

2017

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INTRODUCTION

Almost any new cancer medication, treatment or preventive measure can trace its origin back to an idea conceived and tested by a cancer researcher. Our research team at the Henry Ford Cancer Institute (HFCI) is committed to translating our research findings into effective cancer treatments and preventive measures that benefit our patients and the greater community that we serve. These advances will occur in a wide array of research, including clinical trials to test new cancer-fighting medications and treatments as well as discovering biomarkers and testing interventions that lead to better cancer prevention.

Historically, most of our research was funded by external grants received from the government and industry. However, in an era of tighter government budgets and industry cost-cutting, philanthropic gifts for research have become essential to ensure continuity of research programs that will advance our knowledge of cancer causes and treatments. To give an example of how government funding for cancer research has changed, in 1997, the National Cancer Institute funded 28 percent of the research grants it received allocating 272 million dollars in grant funding. In 2016, despite almost doubling the 1997 research grant funding allocation to $513 million, the National Cancer Institute could only fund 12 percent of the research grants it received. Even the research grants that were funded in 2016 were funded at levels that barely kept up with 1997 dollars. Simply put, if cancer research is to move significantly forward in the coming years, it will not be from government funding alone.

Every philanthropic research dollar we receive will be earmarked for specific funding needs that are vital to advance research in targeted areas. HFCI researchers are poised to make significant advances in multiple areas, including research in treatment and prevention of prostate, brain, and gynecologic cancers. In addition, our cancer researchers are testing new treatments and diagnostic procedures that can impact multiple cancers.

This Cancer Research Booklet is designed to provide you with a brief synopsis of the various cancer research projects our HFCI researchers are either conducting or hoping to start if funding resources become available. For each research project, some background on the research problem is included, along with the specific aims of the project, and the potential impact the research could have on fighting cancer. Most importantly, at the end of each cancer research project specific funding needs are listed. In essence, this booklet provides you with a "shopping list" of cancer research funding opportunities to allow you to target your gift to the research and research need that is most important to you.

We hope you take this opportunity to help fight the war on cancer and make a difference in one of our many exciting HFCI research programs. Your gift has the potential to accelerate the next new exciting cancer research discovery that can impact both present and future cancer patients leading to better curative treatments as well as preventing the cancer cases of tomorrow.

Thank you in advance for our generosity and interest in donating to the life-saving research we are doing at the Henry Ford Cancer Institute.

Benjamin A. Rybicki, Ph.D.
Associate Director for Research
Henry Ford Cancer Institute

Spencer Hoover
System Vice President & Executive Director
Henry Ford Cancer Institute

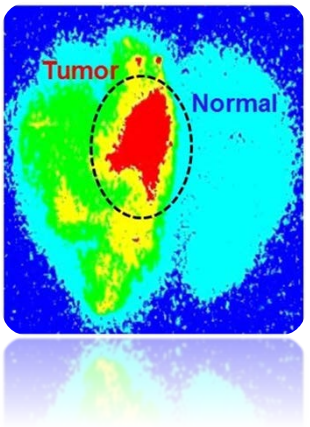
Steven Kalkanis, M.D.
Medical Director
Henry Ford Cancer Institute

A novel nanoformulation of DNA inhibitors: A new approach to selectively potentiate temozolomide in refractory GBM tumors

Principal Investigator: Meser M. Ali, Ph.D.
Co-Investigators: Ana deCarvalho, Ph.D., James Ewing, Ph.D. & Stephen Brown, Ph.D.

PROJECT DESCRIPTION:

Despite surgical resection and radiation therapy in combination with DNA alkylating agent temozolomide (TMZ), glioblastoma (GBM) remains one of the most lethal cancers, due in great part to the action of DNA repair mechanisms that drive resistance and tumor relapse. We introduce biodegradable small-sized nanoparticle (NP) for GBM targeted delivery of DNA repair inhibitors that are currently being tested with combination of TMZ and radiation therapy in vitro or preclinical animal models. The image shows the brain tissue section of a rat demonstrating the accumulation of NPs (red) at the tumor site selectively but not at the normal brain tissue.



SPECIFIC AIMS:

1. To incorporate DNA inhibitor into a nanoparticle platform that demonstrates full solubility in aqueous media.
2. To determine targeted therapeutic effect of nanoformulations of DNA inhibitors, especially in combination with TMZ and radiation therapy.
3. To understand the mechanisms of action and optimization of nanoformulation of DNA inhibitors.

WHY THIS RESEARCH MATTERS:

Temozolomide (TMZ)-based radiation therapy is the sole therapy available for patients with glioblastoma (GBM). The most pressing needs in clinical oncology are the development of novel approaches for treating drug-resistant GBM. The goal of this research project is to apply the most recent advances in nanotechnology for GBM targeted delivery of DNA inhibitors with combination of TMZ and radiation therapies for potential therapeutic impact and implications for personalized therapy.

FUNDING NEEDS

1. **2-year Post-Doctoral Fellowship in Chemical synthesis – *$150K***
Funds the salary of a newly graduated chemist for two years to help start his or her research career.

2. **Bridge Funding Grant – *$200K***
Funds an additional year of research allowing for completion of promising studies, publication of results and submission of federal grants for the next phase of studies.

3. **HPLC – *$120K***
High pressure liquid chromatography to purify and characterize nano-sized DNA inhibitors.

4. **UV-visible spectrometer – *$16K***
To characterize nanoformulation of DNA inhibitors.

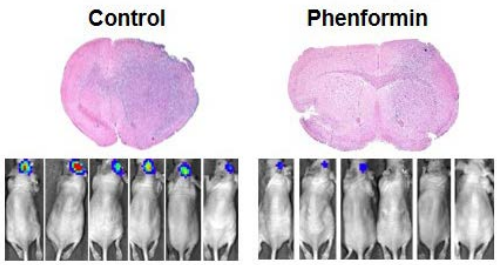
For more information, contact: **Meser M. Ali, Ph.D.**, Associate Scientist, at mali8@hfhs.org

An integrated approach for studying the role of cancer stem cells in brain tumor biology, identifying novel markers for brain tumor detection and developing novel therapeutics for the treatment of brain tumors

Principal Investigator: Chaya Brodie, Ph.D.
Co-Investigators: Steve Kalkanis, M.D., Zane Hammoud, M.D., Tom Mikkelsen, M.D. Walbert Tobias, M.D., Steve Brown, Ph.D., Laila Poisson, Ph.D., Houtan Noushmehr, Ph.D. & Ana DeCarvalho, Ph.D.

PROJECT DESCRIPTION:

Primary brain tumors such as glioblastoma and metastatic brain tumors are aggressive and incurable tumors with dismal prognosis. We have been studying the role of cancer stem cells in the progression and therapy resistance of these tumors and identified novel non-coding RNAs as potential promising therapeutic targets. In addition, we have demonstrated that some of these non-coding RNAs are secreted from the cancer stem cells via exosomes and can be employed as non-invasive circulating markers for the detection of tumor progression, metastatic activity and response to treatments. Finally, we are developing innovative therapeutic approaches combining the newly identified therapeutic targets and repurposing FDA-approved drugs. The figure shows that treatment of human tumors that were implanted in mouse brains with the diabetes drug, phenformin, kills cancer stem cells and decreases the size of brain tumor xenografts.



SPECIFIC AIMS:

1. Isolate and characterize cancer stem cells from glioblastoma and metastatic brain tumors for in vitro (spheroids and organoids) and in vivo (avatar) modeling.
2. Identify new non-coding RNAs that can serve as therapeutic targets
3. Identify circulating stem cells for diagnostic and prognostic purposes
4. Analyze novel therapeutic targets and repurposed FDA-approved drugs for the treatment of brain tumors.

WHY THIS RESEARCH MATTERS:

This integrated approach targets key elements related to brain tumors ranging from understanding cellular process to translational and clinical studies. Delineating the role of cancer stem cells and their secreted non-coding RNAs as a basis for developing novel therapeutic approaches can lead to a better prognosis of patients with both glioblastoma and metastatic brain tumors.

FUNDING NEEDS

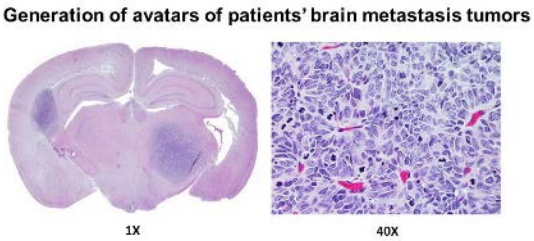
1. 2-year research fellow for performing in vitro and in vivo studies – ***$150K***
2. Generation of organoids and animals (nude mice) for xenografts – ***$120K***
3. Non-coding RNA sequencing of xenografted mice – ***$80K***
4. High throughput screening of drug libraries – ***$60K***

For more information, contact: **Chaya Brodie, Ph.D.**, Senior Staff Scientist, at cbrodie1@hfhs.org

Establishing novel models for studying cancer stem cells in lung tumor-derived brain metastases and for developing new therapeutics

Principal Investigators: Chaya Brodie, Ph.D. & Zane Hammoud, M.D.
Co-Investigators: Steve Kalkanis, M.D., Tom Mikkelsen, M.D., Walbert Tobias, M.D., Steve Brown, Ph.D. & Laila Poisson, Ph.D.

PROJECT DESCRIPTION:



Brain metastases are the most common secondary brain tumors in adults with a variety of primary cancers, including lung. Lung-derived brain metastases are invasive and exhibit resistant to current treatment modalities. These characteristics together with inability of complete resection predicts poor patient prognosis with a median survival of few months. Despite their high frequency and patient poor prognosis, very little research has been performed on brain metastases, mainly due to a lack of appropriate animal models. We have generated cultures of cancer stem cells from lung tumors and brain metastases and established novel in vitro (spheroids and organoids) and in vivo models (avatars) of these tumors. We currently employ these personalized models for delineating pathways that are involved in the progression of these tumors and for the identification of novel circulating markers. In addition, we are focusing on the development of innovative therapeutic approaches combining newly identified therapeutic targets, repurposed FDA-approved drugs and targeted delivery systems using extracellular vesicles.

SPECIFIC AIMS:

1. Establish a lung tumor and brain metastasis tumor bank
2. Isolate and characterize cancer stem cells from lung tumors and metastatic brain tumors for in vitro (spheroids and organoids) and in vivo (avatar) modeling.
3. Develop approaches for sensitizing cancer stem cells to radiation while minimizing radiation-induced injuries in normal tissues.
4. Identify circulating markers for diagnostic and prognostic purposes
5. Analyze novel therapeutic targets and repurposed FDA-approved drugs for the treatment of lung and metastatic tumors.

WHY THIS RESEARCH MATTERS:

These studies target cancer stem cells that are implicated in the generation of brain metastases, radiation-resistance and tumor recurrence and range from understanding cellular process to translational and clinical studies. Moreover, combining anti-tumor approaches while protecting the normal brain and lung tissues provide the basis for developing novel therapeutic approaches that can lead to a better prognosis of patients with lung and metastatic brain tumors.

FUNDING NEEDS
1. 2-year research fellow for performing in vitro and in vivo studies – ***$150K***
2. Generation of animals models of lung and brain metastasis xenografts – ***$120K***
3. Radiation studies – ***$100K***
4. High throughput screening of drug libraries – ***$50K***

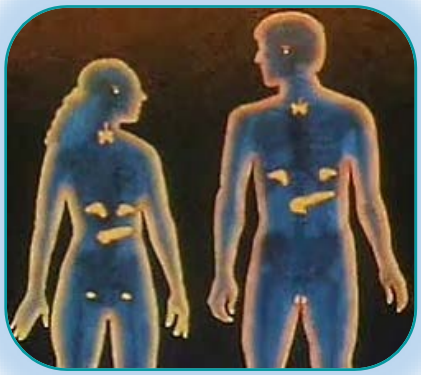
For more information, contact: **Chaya Brodie, Ph.D.**, Senior Staff Scientist, at cbrodie1@hfhs.org or **Zane Hammoud, M.D.**, Chief of General Thoracic Surgery, at zhammou1@hfhs.org

Epigenomic Landscape of Aggressive Endocrine Tumors

Principal Investigator: AnaValeria Castro, M.D., Ph.D.
Co-Investigators: Houtan Noushmehr, Ph.D., Ana deCarvalho, Ph.D., Laila Poisson, Ph.D., Albert Levin, Ph.D., Jack Rock, M.D., Todd Aho, M.D., Steven Chang, M.D., Michael Singer, M.D., Arti Bhan, M.D., Christian Keller, M.D. & Michelle Felicella, M.D.

Project Description:

Explore epigenetic alterations associated with aggressive or invasive behavior in endocrine tumors located in the, but not limited to, pituitary, thyroid and adrenal glands.



Specific Aims:

1. Explore epigenomic alterations in endocrine tumors
2. Integrate the molecular findings with their clinical, histological and radiologic and other molecular features
3. Chart predictive biomarkers of aggressive or invasive behavior in endocrine tumors.
4. Chart potential therapy targets to treat aggressive or invasive endocrine tumors.

Why This Research Matters:

Epigenetic alterations have a great impact on tumor behavior. Several FDA approved drugs targeting these changes benefit patients harboring aggressive tumors resistant to conventional therapy. The results of the current project will progress our knowledge on epigenetic/genetic alterations associated with aggressive/invasive behavior in endocrine tumors. This may help finding prognostic and predictive biomarkers and potential drug targets for aggressive endocrine tumors that may improve patient care.

Funding Needs

1. **Data generation – *$200K***
   E.g. kits, whole genome methylation data (Illumina human EPIC Array), Chromatin Immunoprecipitation sequencing and labor

2. **Data analysis – *$150 K***
   Bioinformatician (2 years)

3. **Data analysis – *$120K***
   Postdoctoral fellow (2 years)

4. **Bridge grant support – *$80 K***
   Funding an additional year while applying for internal and federal funding, publication fees.

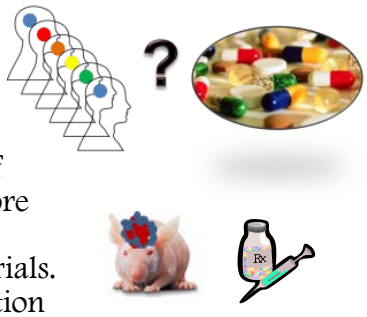
For more information, contact: **AnaValeria Castro, M.D., Ph.D.**, Assistant Scientist, at acastro1@hfhs.org

Patient avatars for personalized medicine for brain tumors

Principal Investigator: Ana C. deCarvalho, Ph.D.
Co-Investigators: Laila Poisson, Ph.D. & Ding Wang, M.D., Ph.D.

PROJECT DESCRIPTION:

Clinical trials for agents targeting specific molecular abnormalities in high grade gliomas have had disappointing results. More studies are needed to understand how the full molecular profile of the tumor affects drug sensitivity. To inform a personalized treatment choice that is based on patient-level evidence, we now have the capability of culturing the tumorigenic cells from tumor biopsies to create mouse 'avatars' of the patient in the laboratory. Using an avatar allows us to test a range of compounds and combination therapies for each patient. Our goal is to enroll the avatar models in pre-clinical trials of drugs based on their molecular profile. We will use the results of these trials to learn more about the mechanisms of resistance to therapy. The trials will inform us about the best treatment for each tumor and we will test these selections in confirmatory pre-clinical trials. The completion of this project will provide valuable information regarding patient selection and matching treatments for clinical trials.



SPECIFIC AIMS:

1. Determine the molecular profile of the tumors and derived avatar models. Test 4 to 6 treatment arms for each tumor. Integrate the response data with molecular alterations prior to and in response to treatment, to propose the best treatment for each tumor type.
2. Design a second avatar trial based on the results of aim 1 to validate the findings and to test combination therapies that have the potential to overcome resistance to a single agent.

WHY THIS RESEARCH MATTERS:

The work proposed here overcomes the limitations of testing multiple therapies simultaneously in high grade glioma patients in the clinical setting. The information obtained in pre-clinical studies using patient avatars opens new horizons in the development of personalized therapy for brain tumor patients.

FUNDING NEEDS

1. **Research coordinators for Tumor Bank, Tissue Culture and Animal Work – *$150K***
Funds the salary of one research coordinator responsible for carrying on the work and overseeing research assistants for 2 years.

2. **Molecular profiling of tumor models –*$150K***
Covers the cost of next generation DNA and RNA sequencing, proteomics, immunohistochemistry and fluorescence in situ hybridization (FISH) to identify patient-specific tumor targets and biomarkers.

3. **Epifluorescence microscope and imaging software –*$50K***
For in house immunohistochemistry and FISH analysis.

4. **Pre-clinical trials – *250K***
Reagents for tissue culture and mouse care and housing.

5. **Statistics and Clinical Trials Office – *$150K***
Expert consultation on selection and procurement of therapeutic compounds, proper research design, data analysis and potential for clinical translation.

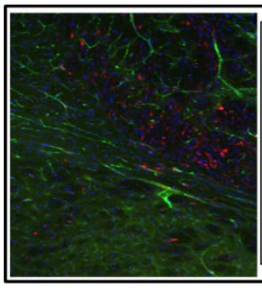
For more information, contact: **Ana deCarvalho, Ph.D.**, Assistant Scientist, at adecarv1@hfhs.org

Enhancing Brain Tumor Drug Delivery

Principal Investigator: Tavarekere N. Nagaraja, Ph.D.
Co-Investigators: James Ewing, Ph.D., Ian Lee, M.D., Tom Mikkelsen, M.D., Ana deCarvalho, Ph.D., Stephen Brown, Ph.D. & Robert Knight, Ph.D.

Project Description:

The goal of our research is to understand the critical role of brain blood vessels in and around a tumor in its treatment. Under normal conditions, brain blood vessels allow only essential nutrients to enter the brain to keep it protected from harmful substances. However, in disease conditions, these very properties limit drug entry and most drugs have extremely limited access to brain. In addition, there are transport molecules (cellular pumps) that actively prevent the entry of drugs into brain. Inhibiting such molecular pumps is one way of enhancing brain drug delivery. Some drugs in routine clinical use have properties that inhibit these cellular pumps. My laboratory is examining such drugs to increase the efficacy of radiotherapy and chemotherapy for brain tumors. This approach is called "drug repurposing". Such investigations are valuable because developing a new drug can take a decade and cost a billion dollars. Repurposing has the advantages of using an FDA-approved drug with known human safety profiles in treating another disease, either alone or in combination with other therapies. Therefore, the translation of our experimental work into the clinic will be quick. As of now, most patients with brain tumors have a short life span after diagnosis and do not have a high quality of life even after standard treatments. My colleagues and I believe that enhancing the efficacy of available treatments by drug repurposing will be of help to such patients.



Close association of infiltrating tumor cells and brain blood vessels.
Red: tumor cells
Green: blood vessels
Purple: normal brain cells

Specific Aims:

1. To characterize the transport properties of tumor vasculature in animal models of brain tumors using imaging and microscopy.
2. To measure the brain entry of chemotherapeutics into brain tumors and their tumor cell kill efficacy after inhibition of molecular pumps that limit brain drug access.
3. To measure the effects of such treatments in decreasing tumor growth and prolonging the life span using serial imaging.

Why This Research Matters:

Drug delivery to injured brain is considered the last frontier in treating brain tumors and other brain diseases. The success of this research positively impacts not only patients with brain tumors, but also victims of other neurological diseases that affect the brain.

Funding Needs

1. **Bridge Funding Grant – *$250K***
Funds an additional two years of research allowing for completion of studies, publication of results and submission of federal grants for the next phase of studies

2. **2-year Post-Doctoral Fellowship in Brain Tumor Biology – *$150K***
Funds the salary of a newly graduated PhD for two years to help start their research career.

For more information, contact: **Tavarekere Nagaraja, Ph.D.**, Assistant Scientist, at tnagara1@hfhs.org

Epigenomic Landscape of Brain Cancer

Principal Investigator: Houtan Noushmehr, Ph.D.
Co-Investigators: Laila Poisson, Ph.D., Ian Lee, M.D., Tobias Walbert, M.D., Steven Kalkanis, M.D., Ana Valeria Castro, Ph.D. & Ana deCarvalho, Ph.D.

PROJECT DESCRIPTION:

Our research goals are to understand and identify the changes at the epigenetics level associated with brain cancer. Epigenetics is a biochemical reaction frequently found in cancer cells that prevents the activation of the gene next to it. It differs from genetic mutation - in which the change in the DNA chain occurs within the gene – that's why it is called an "epigenetic" mechanism. Using advances in next generation sequencing, mathematics, and computer science we will elucidate the epigenomics of brain cancer. These findings will allow us to evaluate the effects of treatment, define candidate 'drugable' targets to improve therapy, and identify prognostic biomarkers for future screening in order to improve quality of life.

SPECIFIC AIMS:

1. To characterize the molecular epigenomic profile from primary and matched recurrent aggressive brain tumor samples.
2. To define predictive and diagnostic biomarkers associated with epigenomic markers that define when a brain tumor cell will progress to a more aggressive phenotype
3. To evaluate the effect of treatment (radiation, chemotherapy) on the epigenome of brain cancer.

WHY THIS RESEARCH MATTERS:

Gliomas are presently incurable. Diagnosis determines the type and intensity of treatment, but the relative lack of precision in the diagnosis often leads to the prescription of inappropriate treatments. We aim to utilize advanced biotechnology, mathematics and computers in collaboration with a team of clinicians and scientists to refine and improve treatment and diagnosis and thereby improve quality of life for brain cancer patients.

FUNDING NEEDS

1. **A 2-year Post-Doctoral research fellow in cancer epigenomics – *$150K***
Recent PhD graduate with high motivation to conduct independent research work and to help start his or her research career.

2. **Research Assistant with bioinformatics experience – *$75K/year***
To support the informatics of the lab and to provide bioinformatics support for the cancer epigenomics project.

3. **Epigenomic profiling of tumor specimens – *$350K***
Covers the cost of DNA, RNA extractions and next generation sequencing.

4. **Data infrastructure and computing – *$75K***
Covers cost of computer hardware, informatics software and related costs for storage of the epigenomic data.

For more information, contact: **Houtan Noushmehr, Ph.D.**, Associate Scientist, at hnoushm1@hfhs.org

Genomic Characterization of Brain Tumor Bank Tissues

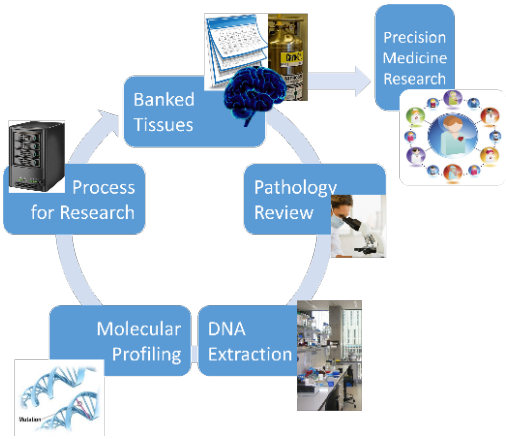
Principal Investigator: Laila Poisson, Ph.D.
Co-Investigators: Ian Lee, M.D, Tobias Walbert, M.D., MPH, Ana deCarvalho, Ph.D., Houtan Noushmehr, Ph.D. & Michelle Felicella, M.D.

PROJECT DESCRIPTION:

In 2016, the World Health Organization officially decided that, in combination with physical characteristics seen under a microscope, glioma should be diagnosed according to two alterations that occur in the patient's tumor DNA -- mutation in the IDH gene and a joint loss of sections of chromosome 1 and chromosome 19. These ground breaking changes happened with the help of the Hermelin Brain Tumor Tissue Bank and the help of our cutting edge research at Henry Ford. Meningioma is another brain tumor that shows distinct molecular forms, in this case based on the functional ability of the NF2 gene. Evidence has shown that specific features of the tumor DNA can predict tumor behavior better than can be done by microscopic images alone. Further, metastatic cancer in the brain is expected to carry alterations from its primary tumor. The Hermelin Brain Tumor Center has one of the most extensive brain tumor tissue banks nationally and worldwide. Over the last 24 years, more than 3100 frozen brain tumor samples were collected at Henry Ford and can be linked to clinical information for research. Yet, many of the samples were collected before these characteristic DNA changes were even discovered. Their tumor DNA profiles therefore remain unknown at this point. Health insurance ensures that all newly diagnosed brain tumors undergo genetic analysis, however, to truly take advantage of our extensive brain tumor collection, we need to know the genetic changes of our historic samples.

SPECIFIC AIMS:

1. Profile tumor DNA of the 1890 glioma specimens so that each can be updated to meet the 2016 World Health Organization diagnosis criteria.
2. Profile tumor DNA of the 430 meningioma specimens to determine the functional status of the NF2 gene so that focused research efforts can applied separately to these two distinct groups.
3. Profile tumor DNA of the 395 metastatic brain cancer specimens to identify which molecular classes of tumors migrate to the brain and to inform studies that help targeted therapies gain access the brain.



WHY THIS RESEARCH MATTERS:

This research infrastructure development will have a multiplicative return on investment by supporting the many researchers using our banked tumor specimens. Knowing the characteristic DNA alterations in each tumor will enhance studies that drive precision medicine opportunities for current and future patients.

FUNDING NEEDS

1. **Research coordinator and technician for DNA extraction and Molecular Profiling – *$150K per year***
2. **Molecular profiling of tumor specimens – *$30K per 100 specimens***
3. **Neuropathology consultation – *$150K***
4. **Data infrastructure and computing – *$100K***

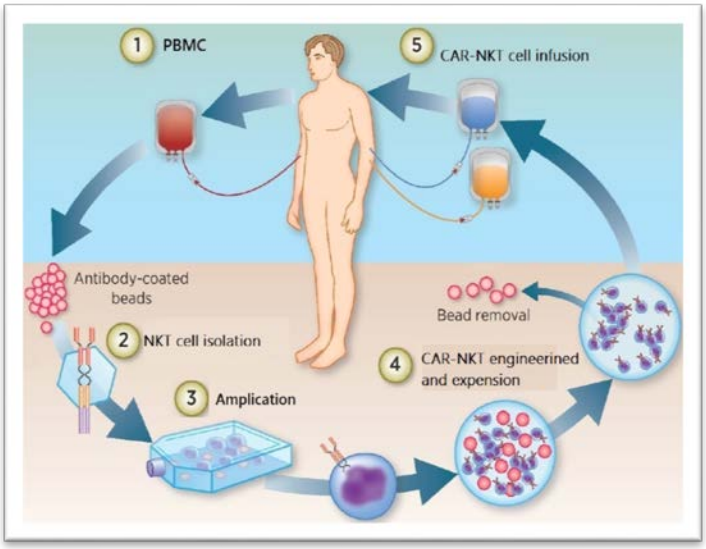
For more information, contact: **Laila Poisson, Ph.D.**, Associate Scientist, at Laila.poisson@hfhs.org

Brain cancer immunotherapy: a novel chimeric antigen receptor (CAR) NKT cell-based immunotherapy

Principal Investigators: Qing-Sheng Mi, M.D., Ph.D. & Steve Kalkanis, M.D.
Co-Investigators: Li Zhou, M.D., Xiaojun Wu, Ph.D., Hongmei Peng, M.D. & Ana DeCarvalho, Ph.D.

PROJECT DESCRIPTION:

Natural killer T (NKT) cells, a special subset of immune cells, are potent warriors against solid tumor cancers. They can localize to tumors, where they attack the tumors. Defective NKT cells in blood or tissue may contribution to cancer development. We previously identified some genes that can regulate NKT cell development and developed a method to multiply NKT cells outside of the body, which could be used for cancer therapy. Recently, the tumor specific markers are selectively identified in the specific tumor but not in normal tissue, called chimeric antigen receptor (CAR). Recent studies from the clinical trials indicated that when CAR is engineered with T cells, it showed success in fighting certain types of cancer. Given the natural anti-tumor properties and ability to localize to the tumor, NKT cells appear an attractive alternative for CAR-directed immunotherapy of cancer. Here, we aim to generate brain cancer specific CAR-NKT cells for brain cancer immunotherapy.



SPECIFIC AIMS:

1. Use a mouse model of brain cancer, to investigate the role of CAR-NKT cells in preventing brain cancer development
2. Optimize NKT cell expansion protocol to obtain FDA approval to initiate clinical trial
3. To generate human brain cancer CAR-NKT cells

WHY THIS RESEARCH MATTERS:

One of the greatest challenges in treating brain tumors is finding an effective way to eliminate the entire disease, making sure no cancer cells are left behind, while minimizing damage to healthy brain tissue. A special form of immunotherapy known as CAR-T cell therapy is showing tremendous promise. Our study may bring a new hope to effectively treat brain cancer by using CAR-NKT immunotherapy.

FUNDING NEEDS

1. **3-year Post-Doctoral Fellowship – *$200K***
   Funds the salary of a newly graduated cancer biologist for two years
2. **Mouse brain cancer model with CAR-NKT immotherapy – *$250K***
3. **Generate human brain cancer CAR-NKT cells and optimize NKT cell expansion protocol – *$250K***

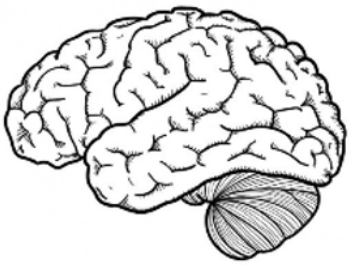
For more information, contact: **Qing-Sheng Mi, M.D., Ph.D.**, Senior Scientist, at qmi1@hfhs.org

The Impact of Advance Care Planning on Quality of Life and End-of-Life Decision Making in Brain Tumor Patients

Principal Investigator: Tobias Walbert, M.D., Ph.D., M.P.H.

Project Description:

Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults. Despite optimal treatment with surgery, radiation therapy and chemotherapy, the prognosis remains poor and the median survival is 14.6 months. Patients' preferences regarding care should guide care and this is especially true during the end-of-life process. Open and respectful communication is of importance to evaluate patients' preferences. However patients have a high symptom burden and frequently lose their ability to make end-of-life decisions in the final stages of the disease and are therefore unable to participate in end-of-life decision making and advance care planning. Advance care planning (ACP) is a formalized process of communication between patients, relatives and caregivers about patients' care preferences. We will evaluate in this trial with 50 patients, if patients have a better quality of life in the end-of-life phase and if care givers have better bereavement when they address advance care planning proactively with specially trained health care facilitators. We are using an established advance care planning program that has been shown to be successful in other diseases (Respecting Choices Program®).



Specific Aims:

1. To understand if patients and caregivers are more "at peace" with their decision making after participating in the standardized advance care planning program.
2. To establish if patients and their caregivers have lower levels of anxiety and depression and higher levels of quality of life after participating in the standardized advance care planning program.
3. To find out if patients have less symptoms during the end-of-life phase and if caregivers have improved bereavement after participating in the standardized advance care planning program.

Why This Research Matters:

There is no established method to date on how to approach advance care planning and how best to communicate with patients and their caregivers about end-of-life. The goal of this trial is to apply the most advanced communication strategies to improve end-of-life care

Funding Needs

1. **Cost for facilitator training, program fees and data base – *$10K***
   Funds the training of the facilitator, to obtain access to program and to create data base
2. **Cost for clinical trials data management and assessment – *$15K***
   Funds the costs associated with collecting data and analyzing it
3. **Facilitator (Clinical trials personal) – *$30K***
   Funds the salary needs of the facilitator discussing advance care planning with patients

For more information, contact: **Tobias Walbert, M.D., Ph.D., M.P.H.**, at twalber1@hfhs.org

A comparison of traditional cancer treatment to traditional cancer treatment with the addition of integrative services for patients experiencing muscle, joint and back pain during care

Principal Investigator: Eleanor M. Walker, M.D.
Co-Investigator: David Betts, Chiropractor

PROJECT DESCRIPTION:

For patients undergoing cancer treatment who are experiencing muscle, joint and back pain we wish to determine whether the use of integrative services such as massage therapy, chiropractic therapy and acupuncture can help to improve patient morale, decreased stress and pain levels and increase overall satisfaction with care. The study would be comparing patients undergoing cancer treatment (surgery, chemotherapy and radiation) who are receiving standard treatment for their side effects (ie., medication alone) to those who are treated with the addition of acupuncture, chiropractic, and massage therapy.

SPECIFIC AIMS:

1. To see if traditional cancer supportive treatment by itself or in conjunction with integrative services is a better option for patients undergoing cancer treatment
2. To see if patients undergoing cancer treatment and integrative services are able to increase their activity level during care.
3. To see if adding integrative services during cancer treatment improves patients' morale during care.

WHY THIS RESEARCH MATTERS:

67-84% of cancer patients use alternative medical therapies because they desire a more humanistic and holistic approach to their care. They desire:

1. Relief of cancer or treatment related symptoms and side effects
2. For improved quality of life
3. To give themselves greater control during their medical treatment
4. To boost their immune system
5. To possibly improve their survival

FUNDING NEEDS

1. **Cost of acupuncture treatments $ 88/visit for 12-16 treatments**
2. **Linens, massage oils, acupuncture needles, face paper, and face cradles. $ 600**
3. **Chiropractic, acupuncture, and massage tables if we are not able to use our own in office**

For more information, contact: **Eleanor M. Walker, M.D.**, Director of Breast Radiation Oncology, at ewalker1@hfhs.org

Acupuncture for the treatment of Chemotherapy-Induced Peripheral Neuropathy

Principal Investigator: Eleanor M. Walker, M.D.
Co-Investigator: Zeyeid Elias

Project Description:

Chemotherapy-induced peripheral neuropathy (CIPN) is recognized as one of the most common adverse reactions related to cancer treatment. Among side-effects, neurotoxicity is second only to hematologic toxicities. The symptoms of CIPN can be debilitating causing both motor and sensory symptoms, including severe pain, paresthesias, dysesthesias, and increased sensitivity to even normal touch. CIPN is associated with several of the drugs routinely used in many malignancies. While CIPN may improve after stopping the drug treatment, some patients may experience persistent or worsening symptoms as a result of permanent nerve damage. Oncologists must resort to 'off-label' use of drugs, such as antiepileptics, antidepressants, and opioids to help manage their patient's symptoms. These, of course, come with their own toxicities, side effects, and problems. Acupuncture has been shown to have a positive effect on a number of physiological processes, both peripherally and centrally. While acupuncture is often associated with pain management, its extension of study into CIPN has been limited. Cancer patients in the HFHS have been treated with acupuncture for CIPN with excellent results. Since there is limited data in this area we wish to study this treatment option and expand the literature.

Specific Aims:

1. To study the effects of acupuncture on CIPN prevention.
2. To study the effects of acupuncture once CIPN is established; can it decrease it or reverse it.
3. To study the duration of the effect of acupuncture on CIPN.

Why This Research Matters:

Although the incidence of chemotherapy-induced peripheral neuropathy varies depending on the chemotherapy regimen and the duration of exposure, it is estimated to occur in approximately 38% of patients treated with multiple agents. The likelihood of developing the condition increases if the patient receives combinations of agents such as platinum drugs, vinca alkaloids, bortezomib (Velcade), or taxanes. Acupuncture is effective for alleviating chemotherapy-induced peripheral neuropathy.

Funding Needs

1. **Cost of the treatments since acupuncture has limited insurance coverage in this state – *$60K***
2. **Cost of needles and supplies associated with acupuncture use – *$800***
3. **Cost of statistical evaluation of the study results – *$4K***

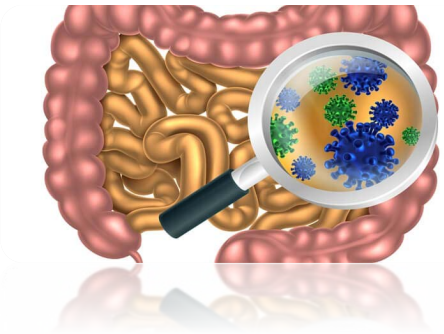
For more information, contact: **Eleanor M. Walker, M.D.**, Director of Breast Radiation Oncology, at ewalker1@hfhs.org

Clinical Analysis of Gut Health of HFHS Employees with Cancer

Principal Investigator: M. Elizabeth Swenor, DO
Co-Investigator: Eleanor M. Walker, M.D.

Project Description:

The hypothesis is that cancer patients will have moderate to severe microbial imbalances to the 25 main gut commensal bacteria and disruption to the protective gut lining as measured through fecal analysis of bacteria and inflammatory markers. This study would focus on 10 employees who have cancer compared with healthy controls. These measurements would be performed using an approved comprehensive diagnostic stool analysis with a 3 day stool collection. We feel that an intervention of an evidence based nutritional whole food plant based dietary intervention for 3 months will decrease markers of inflammation and poor bacterial mechanistic processes and will improve the diversity and abundance of the healthy commensal 25 bacteria. Microbial gut imbalances left untreated empirically translate to whole body inflammation and propagation of chronic disease and cancer.



Specific Aims:

1. To analyze the gut flora of cancer patients verses healthy cohorts.
2. To use an evidence based nutrition plan to decrease markers of inflammation and improve gut health.

Why This Research Matters:

Research has demonstrated that whole food plant based diets reverse chronic disease such as coronary vascular disease and diabetes. This research is important in that if the findings demonstrate an outcome similarly favorable to the reversal of chronic disease, then we are reducing the inflammatory burden, improving the immune system, improving the quality of life and possibly longevity, and improving the patient's ability to pursue recommended cancer treatments. If the results demonstrate reduction in inflammation and improvement of gut health, this would then become a recommended dietary intervention for all cancer patients.

Funding Needs

1. **Kits and analysis of results – *$1690***
   The cost of the kits are $169.00 each with insurance. Each patient would need to complete 4 tests. (Baseline and one at the end of each month). Total of 40 kits x $169.00 = $1690
2. **Baseline routine labs billable to insurance**
3. **Diet – *$2K***
   Each patient will be placed on a whole food plant based diet. Recipes, patient information booklets, dietary food journals will be provided to each patient. $200 each patient = $2K
4. **$200 monthly food stipend – *$2K***
5. **Statistical analysis – *$3K***

For more information, contact: **Eleanor M. Walker, M.D.**, Director of Breast Radiation Oncology, at ewalker1@hfhs.org

Toward Precision Medicine in Radiation Oncology: Using Magnetic Resonance Guided Radiation Therapy to See, Track, and Adapt

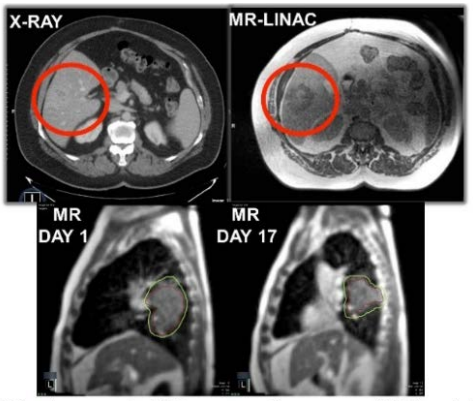
Principal Investigator: Carri Glide-Hurst, Ph.D.
Co-Investigators: Benjamin Movsas, M.D. & Indrin Chetty, Ph.D.

PROJECT DESCRIPTION:

Sixty percent of all cancer patients receive radiation therapy. Many deadly cancers in the abdomen (liver, pancreas), breast, and pelvis (prostate and gynecological) are best visualized using magnetic resonance imaging (MRI) because it highlights soft tissue boundaries. We recently installed *one of the world's first* MRI-guided radiation therapy machines where we can use MRI's soft tissue contrast to identify tumors for daily radiation therapy. By **SEE**ing these tumors on MRI, we can better target them with radiation (Figure, top). Because MRI does not use radiation, we can **TRACK** moving anatomy, acquiring 4 snapshots of tumor motion in 1 second, and turn the radiation beam off when the tumor moves. Finally, we can tailor, or **ADAPT**, the radiation to the patient each day to spare nearby healthy tissues. This offers potential to reduce side effects from radiation while better targeting tumors (Figure, bottom). MRI-guided radiation will enable **PRECISION MEDICINE** techniques in radiation oncology. Your investment in our research will help us quantify the accuracy and determine clinical benefits of being able to **SEE** tumors, **TRACK** during radiation, and **ADAPT** plans to yield higher tumor control while sparing critical organs.

SPECIFIC AIMS:

1. To use an MRI-safe motion platform to quantify the accuracy and efficiency of tracking moving objects to determine how to best target moving tumors like lung, pancreas, and liver.
2. To perform a virtual clinical trial (i.e. using patient data) to quantify the impact of tracking vs. non-tracking on how long a treatment takes and potential dose differences.
3. To perform a virtual clinical trial on adaptive radiation therapy to evaluate tumor response/reduction over time to determine clinical benefits and determine high priority cases for adaptive.



(Top) Liver tumor can be **SEE**n on magnetic-resonance (MR) linac but not on x-ray scan. (Bottom) Lung cancer reducing over time, showing **TRACK**ing and potential for **ADAPT**ing (Images from ViewRay)

WHY THIS RESEARCH MATTERS:

MRI-guided radiation therapy will enable us to see deadly cancers and treat them like we have never been able to before. This work will impact patient care, offering potential for increased cure and reduced toxicity.

FUNDING NEEDS

1. **MRI Testing Equipment – *$75K***
   Magnetic resonance (MR)-safe motion platform to test tracking accuracy.
   MR-safe ion chamber, gel dosimetry, and film to test dose delivery during tracking.
2. **2-year Post-Doctoral Fellowship in Radiation Oncology – *$150K***
   Funds the salary of a newly graduated PhD for two years to help start their research career.
3. **Funding a Clinical Trial – *$100K***
   Clinical trial to assess adaptive radiation therapy in disease sites such as pancreas or liver.

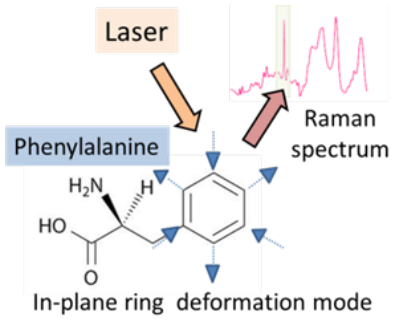
For more information, contact: **Carri K. Glide-Hurst, Ph.D.**, Director of Translational Research, at churst2@hfhs.org

Development of a novel Raman spectroscopy-based, early predictor of tumor response and normal tissue damage following radiation therapy

Principal Investigator: Suneetha Devpura, Ph.D.
Co-Investigators: Stephen L Brown, Ph.D., Kenneth Barton, Ph.D., Farzan Siddiqui, M.D., Ph.D., George Divine, Ph.D. & Indrin J Chetty, Ph.D.

PROJECT DESCRIPTION:

Our long range goal is to improve radiotherapy effectiveness and to limit the damaging effects of radiation by developing a novel tool that can predict early response of tissue to radiation. The benefit of curing a tumor with radiation is questionable, if surrounding normal tissue is destroyed and quality of life permanently degraded. An early measurement of tumor and normal tissue sensitivities to radiation is a first step in evaluating improvements in radiation therapy. Raman spectroscopy, which uses laser light to measure molecular components of cells (see image), is well-suited for this purpose. Our aim is to identify biomarkers that predict lung and prostate cancer responses and their normal tissue toxicities to radiation therapy using Raman spectroscopy. The information about these biomarkers before the radiation treatment can be used to personalize radiation therapy treatment and will improve the quality of lives of the cancer patients.



SPECIFIC AIMS:

1. To identify Raman signatures associated with malignant progression in a spontaneous prostate cancer model and to assess response to radiation therapy.
2. To identify and correlate radiation-induced biochemical markers of normal tissue damage using Raman spectroscopy.
3. To identify and correlate radiation-induced biochemical markers of tumor response using Raman spectroscopy.

WHY THIS RESEARCH MATTERS:

The goal of this research is to use Raman spectroscopy to assess radiation response within minutes, giving clinicians an indication of individual tumor radio-response and a warning system that allows them to detect the earliest signals of toxicities in patients receiving radiation therapy. This method will have the potential to benefit all cancer patients, improve their tumor responses and their quality of life.

FUNDING NEEDS

1. **Raman spectrometer – *$200K***
   Funds for a Raman spectrometer with additional imaging/mapping capability and xyz control.
2. **Pre-clinical testing & pathology services – *$90K***
   Funds to support animal model experiments, pathology evaluations and laboratory supplies.
3. **Funds to support clinical trials – *$50K***
   Funds for clinical trials

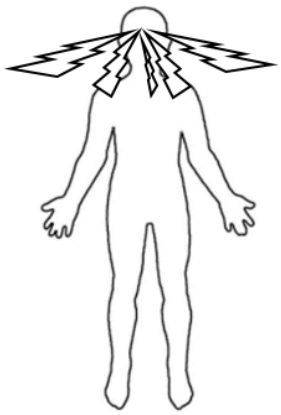
For more information, contact: **Suneetha Devpura, Ph.D.**, Senior Associate Physicist, at sdevpur1@hfhs.org

Normal Tissue Protection from Radiation Injury

Principal Investigator: Stephen Brown, Ph.D.
Co-Investigators: Ben Movsas, M.D., Jae Ho Kim, M.D., Ph.D., James Ewing, Ph.D., Tavarekere Nagaraja, Ph.D., Ana deCarvalho, Ph.D. & Chaya Brodie, Ph.D.

Project Description:

The goal of our research is to reduce the inadvertent normal tissue injury that could occur during the course of cancer radiation therapy. Based on exciting pre-clinical studies, anti-inflammatory agents applied days or weeks after the radiation exposure effectively preserve normal tissue function, including that of skin, lung and brain. Importantly, reducing inflammation has an additional beneficial effect, in that tumor growth is slowed. Our group is studying anti-inflammatory agents including FDA approved drugs and newly synthesized compounds developed by collaborators from universities and commercial sponsors. Our studies span basic laboratory through clinical trials. The work being done at Henry Ford Hospital is helping to change the field of radiation biology with the hope of improving the quality of life of patients.



Specific Aims:

1. To measure the therapeutic gain of new promising cancer therapeutics, especially in combination with radiation therapy.
2. To elucidate the mechanisms of action of and optimize new promising cancer therapeutics.

Why this Research Matters:

All tumors are potentially curable with sufficient radiation dose however radiotherapy effectiveness is limited by adjacent normal tissue radiation damage. Reducing radiation damage, especially skin, lung and brain could benefit hundreds of thousands of people a year.

Funding Needs

1. **2-year Post-Doctoral Fellowship in Cancer Radiation Biology – *$150K***
Funds a newly graduated cancer radiation biologist for two years to help start his/her research career.

2. **Bridge Funding Grant – *$200K***
Funds an additional year of research allowing for completion of promising studies, publication of results and submission of federal grants for the next phase of studies.

3. **Microscope – *$25K***
To capture publication grade images that will facilitate dissemination of study results.

4. **Temperature-controlled cell culture incubator – *$12K***
To grow cancer cells in a controlled environment.

5. **Experimental Irradiator – *$450K***
To allow for precise x-ray therapy and imaging.

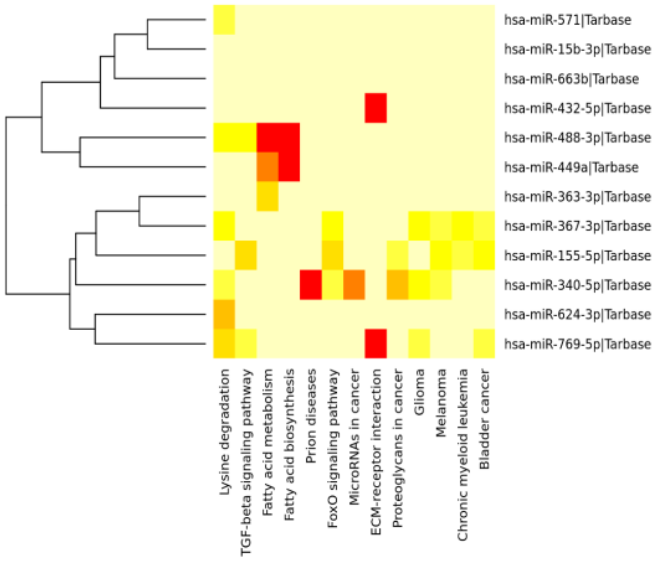
For more information, contact: **Stephen Brown, Ph.D.**, Senior Scientist, at sbrown1@hfhs.org

Biomarkers of Response to Immunotherapy in Bladder Cancer

Principal Investigator: Shaheen Alanee M.D., MPH, MBA, FACS, FRCS(C)
Co-Investigator: Qing-Sheng Mi, M.D., Ph.D.

PROJECT DESCRIPTION:

The blockade of the programmed death 1 (PD1) pathway, an important immunregulatory pathway, has been shown recently to be effective in cancer therapy. As more clinical trials evaluating anti-PD1 drugs are published, the potential of these agents in managing treatment resistant cancers is becoming more obvious. MicroRNAs (miRNA) are small molecules involved in cancer development. Altered miRNA levels in tumor cells are found in variety types of cancer and contribute to resistance to therapy in some cancers, suggesting tumor miRNAs can serve as biomarkers for early diagnosis and prediction of therapeutic responses. This proposal is designed to test the hypothesis that different miRNA expression profiles can be detected, either in bladder tumor or blood, in patients who are responsive and those who are resistant toanti-PD1 therapy . These differences could potentially serve as convenient, noninvasive biomarkers for prediction of response to immunotherapy.



SPECIFIC AIMS:

1. Identification of tumor-specific miRNAs associated with therapeutic responsiveness or resistance- Studies using tumor tissues.
2. Identification of immune cells-related miRNAs related to immunotherapy resistance

WHY THIS RESEARCH MATTERS:

Bladder cancer is the fifth most common cancer in the United States. Anti-PD1 therapy is the most important development in treating bladder cancer over the past 2 decades. Predicting response to this treatment would allow many patients to receive the benefit of the drug while minimizing side effects miRNA pathway analysis in bladder cancer.

FUNDING NEEDS

1. **Salary support for investigators and laboratory technicians involved in the study – *$225K***
Funds the salary of two investigators and two research assistants to isolate and detect miRNA from bladder tumors and patient's blood for the first 2 years of research.

2. **Bridge Funding Grant – *$110K***
Funds an additional year of research allowing for completion of studies, publication of results and submission of federal grants for the next phase of studies.

3. **Supplies – *$165K***
Allows for equipment and supplies required to detect miRNA and bioinformatics analysis of the data over 3 years of research.

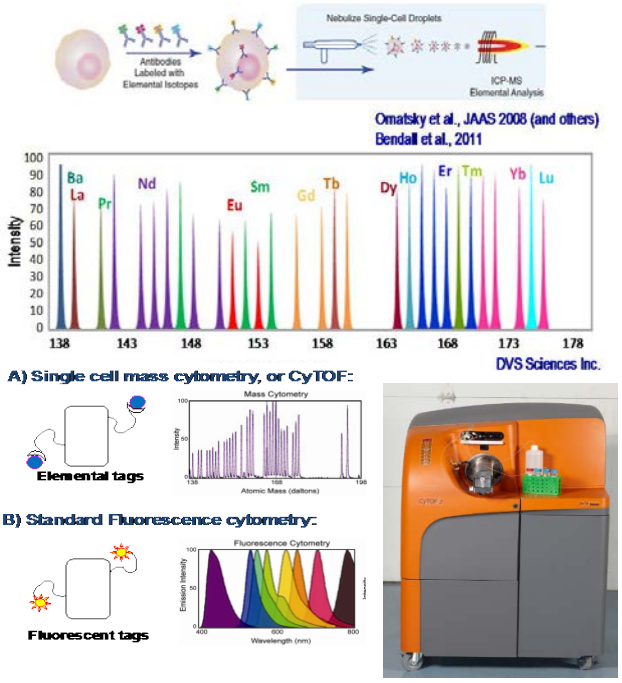
For more information, contact: **Shaheen Alanee, M.D., MPH, FACS, FRC(S)**, Urologist, at salanee1@hfhs.org

Establishing a CyTOF core for high-throughput single-cell analysis of immune cell phenotypes in cancers

Principal Investigator: Li Zhou, M.D.
Co-Investigators: Qing-Sheng Mi, M.D., Ph.D. & Yi Yao, Ph.D.

PROJECT DESCRIPTION:

Tumor infiltrating Immune cells modulate cancer progression and are attractive immune therapeutic targets. However, their phenotypes in the tumor and their relationship with clinical outcomes after immunotherapy are poorly defined. The Single-Cell Mass Cytometry (CyTOF) is a cutting edge technology only ~6 years old. There are ~50 CyTOF instruments in the US. The key feature of CyTOF is to use metal element-tagged antibodies that enable detection of up to 100 markers on a single cell, as compared to ~12 parameters for the staple flow cytometery technology that uses fluorescently labeled antibodies. The exquisite multiplexed detection capability of CyTOF enables a much more comprehensive assessment of complex immunological systems with both breadth (detect many cell populations at once) and depth (detect many markers on each of the populations). This systematic approach is critical for advancing our understanding of the complex immune cells in cancer, especially in cancer biology and cancer immunotherapy. The first NIH-funded CyToF grant was in 2010. In 2016, NIH funded 80 CyToP related grants. We want to establish a CyTOF core in HF for high-throughput single-cell analysis of immune cell phenotypes in different cancers, especially before and after cancer immunotherapy.



SPECIFIC AIMS:

1. Phenotyping immune cells in tumor microenvironments at a single-cell level using CyTOF.

WHY THIS RESEARCH MATTERS:

This research will not only lead to groundbreaking results to establish new knowledge of immunoregulation in tumor microenvironments, but may also contribute to discovery of potential biomarkers and development of immunotherapeutic targets for cancer.

FUNDING NEEDS

1. **Establish a CyTOF core – *$1,000,000***
   Funds the salary of a newly graduated cancer biologist for two years CyTOF2 instrument (700K) and service contract (10% of the instrument purchase price) as well as room reconstruction ($200K)

2. **Annual maintenance – *$50K/year***
   Funds for annual maintenance of CyTOF core, including argon gas ($10-20K/year), reagents and supplies (startup cost: $15-30K/panel), as well as data analysis software ($1-2K/license/year).

3. **Core operating staff – *$100K/year***
   Funds to support an operating staff in the core.

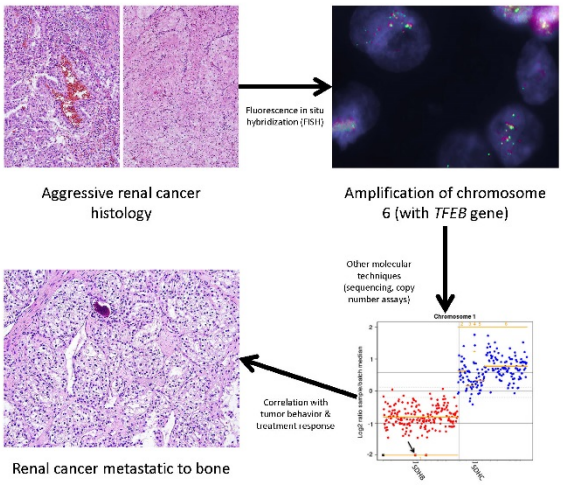
For more information, contact: **Li Zhou, M.D.,** Assistant Scientist, at lzhou1@hfhs.org

Histologic and molecular reclassification of kidney cancer

Principal Investigator: Sean R. Williamson, M.D.
Co-Investigators: Nallasivam Palanisamy, Ph.D., Nilesh S. Gupta, M.D. & Craig G. Rogers, M.D.

PROJECT DESCRIPTION:

Now entering the era of personalized medicine based on genetics and molecular technology, it is possible to reclassify tumors based on the combination of their microscopic appearance (histology), production of proteins (immunohistochemistry), and genetics. In our research, we aim to define distinct subsets of tumors with unique genetic underpinnings that may have importance for patient counseling, such as tumors with very favorable or very aggressive behavior. In particular, we are interested in tumors of the kidney (renal cancer or renal cell carcinoma / RCC), in which some tumor types (or histologies) are associated with very favorable behavior (such as clear cell papillary RCC), others may be associated with inherited gene mutations (such as SDH-deficient RCC), and others may be highly aggressive (chromosome 6p21 amplified RCC). After studying these tumors with molecular techniques, it then becomes possible to define for pathologists which features allow them to recognize these tumors in diagnostic practice, leading to the appropriate confirmatory testing, patient treatment, and counseling.



SPECIFIC AIMS:

1. To critically reappraise known renal tumor histologies based on integration of histology, immunohistochemistry, and genetics, to define distinct tumor subgroups.
2. To correlate these distinct tumor subgroups with clinical behavior to define categories of relevance for patient treatment and follow-up strategies.

WHY THIS RESEARCH MATTERS:

Although most tumors of the kidney are considered together under the umbrella of "kidney cancer," the behavior of these tumors is variable. Patients will benefit from knowing whether a kidney tumor is of high or low risk for determining their future treatment and surveillance.

FUNDING NEEDS

1. Seed Funds – *$25K*

Seed funds to purchase reagents and fund technicians to perform molecular assays on patient tumor tissues (including next-generation genetic sequencing, array-based comparative genomic hybridization, and fluorescence in situ hybridization)

2. Salary Support – *$50K*

Stipend/salary support for a pathology research fellow to support a junior doctor to begin his or her experience in pathology research under the mentorship of Dr. Williamson

3. Journal Publication Fees – *$4K*

Journal publication fees (journals that are open access are able to disseminate research around the world for free; however, these require the authors to pay for the costs of printing, often over $2000 per article. Other journals have similar costs if images are printed in color)

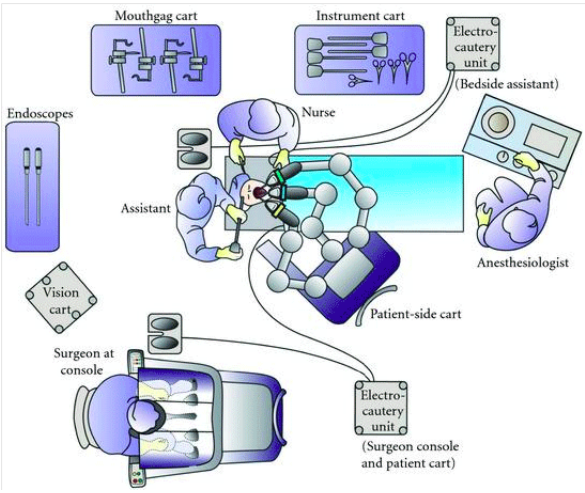
For more information, contact: **Sean R. Williamson, M.D.**, Pathologist, at swilli25@hfhs.org

Outcomes of Transoral Robotic Surgery for Oropharyngeal Cancers

Principal Investigator: Tamer Ghanem, M.D., Ph.D.
Co-Investigator: Amy Williams, Ph.D.

PROJECT DESCRIPTION:

Throat cancers are becoming a more common problem reaching epidemic proportions, mainly due to the rise of the Human Papilloma Virus (HPV) driven squamous cell cancers (SCCA). These cancers occur in younger patients typically, who are non-smokers, non-drinkers, physically active, and otherwise healthy. The survival outcomes of these cancers has been shown to better than SCCA which are not related to HPV (caused usually by heavy smoking and alcohol). The traditional treatments involved radiation therapy alone or a combination of radiation therapy. These worked well but came at a high price with respect to swallowing dysfunction, dry mouth, loss of taste, and feeding tube dependency. Transoral robotic surgery (TORS) for throat cancers, has been FDA approved since 8 years ago and has shown very promising cancer control results equivalent to or better than the non-surgical treatments. At Henry Ford, the TORS program has started soon after the FDA approval and has been following patients for 8 years tracking cancer survivorship and quality of life outcomes. Furthermore, new reconstructive techniques using TORS have been developed at Henry Ford to help improve quality of life for throat cancer patients.



SPECIFIC AIMS:

1. Prospectively and retrospectively evaluate survival and quality of life outcomes patients undergoing TORS surgery for throat cancers.
2. Develop new minimally invasive surgical techniques for throat cancer resection and reconstruction.
3. Utilize this data to develop new surgical clinical trials to evaluate the efficacy of robotic surgery in the treatment of throat cancers.

WHY THIS RESEARCH MATTERS:

By conducting this research, we learn the impact of different therapies on cancer patients' quality of life, ability to swallow. Through this type of research we can propose new clinical trials to improve quality of life while maintaining excellent cancer survival and tumor control.

FUNDING NEEDS

1. **Study coordinator – *$72K***
   To enroll patients, administer questionnaires at baseline and set time intervals to track the patients' progress.

2. **Database manager – *$150 K***
   To record clinical data and quality of life questionnaires results.

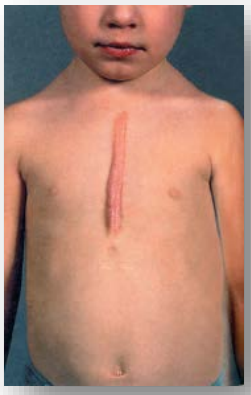
3. **Statistical support from the Bioepidemiology Department – *$150 K***
   To analyze the results and make valid statistical conclusions.

For more information, contact: **Tamer Ghanem, M.D., Ph.D.,** Otolaryngologist, at tghanem1@hfhs.org

Molecular and Clinical Signatures of Keloids

Principal Investigator: Lamont R. Jones, M.D., MBA
Co-Investigator: Maria J. Worsham, Ph.D., FACMG

PROJECT DESCRIPTION:



Keloids are fibroproliferative tumors which occur during normal wound healing following injury to the skin such as after surgery, trauma and burns. They affect 11 million people in the developing world and there are 425,000 clinic visits yearly in the United States. Keloids are often symptomatic with pain, puritis, emotional distress and loss of function. Keloids have many characteristics akin to cancer such as hyperplasia, recurrence and tissue invasion, but do not cross the threshold to malignancy. Medical treatment is fraught with recurrence rates of up to 100% following surgery and 50% after surgery and adjuvant therapies, mainly because of an incomplete understanding of keloid pathogenesis. The objective of this study is to provide novel insights into the formation and treatment of keloids.

SPECIFIC AIMS:

1. To determine biomarkers for the pathogenesis and treatment of keloids.
2. To study the impact of keloid microenvironment on its pathogenesis.
3. To identify novel therapies for keloids.

WHY THIS RESEARCH MATTERS:

The significance of the proposed research is that it will lead to an enhanced understanding of keloid pathogenesis and the potential for novel therapy. The positive impact of the proposed research will help to improve treatment outcomes for millions of patients affected by keloids.

FUNDING NEEDS

1. **2-year Post-Doctoral Fellowship in wound healing – *$150K***
Funds the salary of a newly graduated PhD student for two years to help start his or her research career.

2. **Bridge Funding Grant – *$200K***
Funds an additional year of research allowing for completion of promising studies, publication of results and submission of federal grants for the next phase of studies.

3. **Keloid animal model – *$25K***
Funds the development of a keloid animal model for in vivo assessment of novel drugs for treatment of keloids.

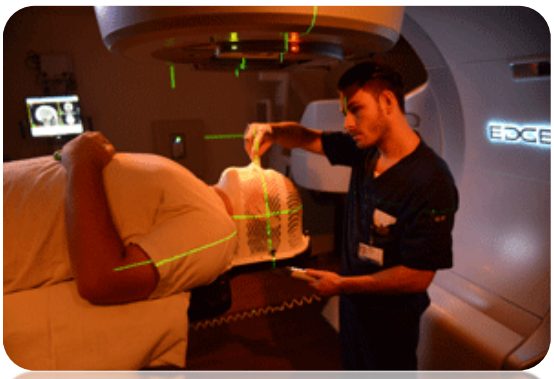
For more information, contact: **Lamont R. Jones, M.D., MBA**, Vice Chair of the Department of Otolaryngology, at ljones5@hfhs.org

Randomized Study Using Gabapentin to Reduce Radiation Therapy Induced Pain during the Treatment of Head and Neck Cancer

Principal Investigator: Ankit Modh, M.D.
Co-Investigator: Farzan Siddiqui, M.D.

PROJECT DESCRIPTION:

Therapies to alleviate pain from radiation to the head and neck cancers are limited. Doctors are generally limited to using opioids (narcotic medication) to help patients, which come with their own set of drawbacks. We propose to evaluate using gabapentin, a cost effective and readily available medication used for pain from other conditions, to minimize the pain experienced and to lower the amount of opioid medication needed during cancer treatment.



SPECIFIC AIMS:

1. Evaluate the reduction or delay of treatment related pain with the use of gabapentin in patients with head and neck cancer undergoing radiation and chemotherapy compared to standard supportive care.
2. Assess opioid use with the addition of gabapentin during radiation treatment.
3. Evaluate side effects associated with gabapentin.

WHY THIS RESEARCH MATTERS:

The Centers for Disease Control and Prevention reported that narcotics such as opioid pain medication killed more than 33,000 people in 2015 – half of these overdoses involved prescription medication. If physicians can reduce the need of opioid medication with agents such as gabapentin, we can not only improve the quality of life of our patients, but we can help fight a growing epidemic.

FUNDING NEEDS

1. **Medication (including gabapentin and placebo) – *$30K***
   This will support the medication and placebo required for the study.
2. **Clinical Trial Office support – *$5K***
   The Clinical Trials Office supports these trials and aids in the patient accrual process.
3. **Research staff support – *$5K***
   Research staff is required to consent patients, distribute medication, collect and analyze the data.

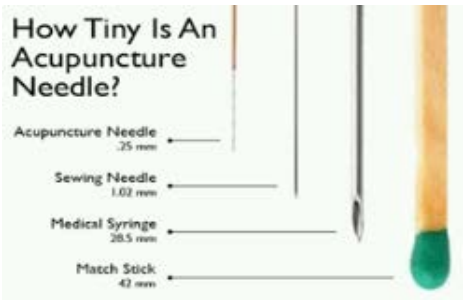
For more information, contact: **Ankit Modh, M.D.,** Resident Physician, at amodh1@hfhs.org

Acupuncture vs. Gabapentin for the treatment of pain syndrome related to chemoradiation-induced mucositis in H&N cancer patients

Principal Investigator: Eleanor M. Walker, M.D.
Co-Investigator: Zeyeid Elias

PROJECT DESCRIPTION:

Pain is a very common problem in the treatment of H&N cancer patients receiving chemoradiation therapy especially due to the development of mucositis. Opioids are typically used to treat this side effect, however, addiction can become a problem long term. Recently the use of Gabapentin in these patients seems to decrease the need for high doses of pain medicine. But as with all medications, there can be side effects such as dizziness, drowsiness, weakness, tired feeling, nausea, diarrhea, constipation, blurred vision, headache, breast swelling, dry mouth, loss of balance or coordination. Acupuncture, a traditional Chinese medicine technique is known to treat many disease processes including pain. This study is to evaluate the efficacy of acupuncture compared with gabapentin in (1.) decreasing pain and the requirement for high doses of opioids and (2.) avoiding treatment interruption in Head & Neck cancer patients treated with concurrent chemoradiation.



SPECIFIC AIMS:

1. Determine if acupuncture is equivalent if not better in preventing and/or controlling the pain syndrome related to radiation induced mucositis in H&N cancer patients.
2. Determine whether acupuncture will have less side effects & be more cost effective than drug treatment.
3. Determine if acupuncture will decrease the xerostomia (dry mouth) generally seen with radiation treatment of H&N cancers.

WHY THIS RESEARCH MATTERS:

Cancer pain is typically treated with opioids and with interventional anesthetic or neurosurgical procedures. Despite the maximal use of pain medications and the application of interventional procedures, a significant portion of cancer patients still suffer from pain. In addition, the undesired side effects of long-term use of opioid pain medication, which include changes in mental status as well as constipation, nausea, and fear of dependency, are issues of concern. Acupuncture treatments significantly reduced pain and improved function in cancer patients with chronic pain or dysfunction due to neck dissection, vs standard care alone. Given more holistic option of treatment for pain like acupuncture that has limited side effects which while effectively controlling pain, most patients would prefer acupuncture for treatment of their side effects. Also acupuncture allows patients some control over their cancer treatment.

FUNDING NEEDS

1. Cost of acupuncture treatments per patient ~ 30 patients – ***$50K***
2. Cost of 2 months of gabapentin ~ 30 patients – ***$5K***
3. Cost of 2 IPADs for patient surveys – ***$1500***
4. Cost of statistical analysis – ***$4K***
5. Cost of acupuncture needles and supplies – ***$600***

For more information, contact: **Eleanor M. Walker, M.D.**, Director of Breast Radiation Oncology, at ewalker1@hfhs.org

An anti-cancer nutrient-based novel prodrug for head and neck cancer

Principal Investigator: Maria J Worsham, Ph.D., FACMG
Co-Investigators: Meser Ali, Ph.D., Josena K Stephen, M.D. & Kang Mei Chen, M.D.

PROJECT DESCRIPTION:

We recently synthesized a new generation 3 (G3) dendrimer-based curcumin (Curc) conjugate which demonstrated full solubility in aqueous media. G3-Curc, as a prodrug, is a promising new formulation that overcomes a major impediment critical for clinical translation of Curc to cancer patients by improving systemic bioavailability, tumor location specificity, and by extension, therapeutic efficacy. The in vitro study showed enhanced bioavailability of G3-Curc conjugate with improved therapeutic efficacy against different cancers cells, including human papilloma virus (HPV) positive and negative head and neck cancer (HNC) cell lines. While small molecule chemotherapeutic drugs are insensitive against HPV negative cells, interestingly G3-Curc was more sensitive against HPV negative cells than that of HPV positive cells. We also demonstrated in vivo that G3-Curc nanoparticles were internalized into glioma U-251 cells with preferential accumulation in an orthotropic preclinical glioma model minimizing systemic toxic effect. Multicolor microscopy of the tumor tissue showed that G3-Curc particles were internalized inside tumor cells selectively and further localized within nuclei. The next stage of our technology development is to demonstrate in vivo the preferential sensitivity of G3-Curc for HPV negative HNC. Also, because CUR has been reported as a demethylating agent in prostate cancer, we will test whether G3-Curc restores gene expression silenced by methylation as an anti-cancer drug mechanism.

Solubility in water:
G3-(Curc) (A),Curc (B'

SPECIFIC AIMS:

1. Confirm the preferential sensitivity of G3-Curc for HPV negative HNC using 10 HPV positive and 10 HPV negative cell lines and demonstrate *in vivo* the preferential sensitivity of G3-Curc for HPV negative HNC using orthotropic preclinical HPV positive and HPV negative HNC mouse models.
2. Assess global methylation patterns and associated gene expression patterns for correlation of gene expression and methylation status with tumor regression.

WHY THIS RESEARCH MATTERS:

We expect these investigations to 1.) further provide a supportive basis of G3-Curc as a potential pre-clinical drug for treatment of HNC that will also be patient-centered for HPV negative patients, and 2.) as a milestone for pursuing commercialization for G3-C derivatives.

FUNDING NEEDS

1. **Bridge Funding Grant – *$200K***
   Funds an additional year of research allowing for completion of studies, publication of results and submission of federal grants for the next phase of studies
2. **Tissue Culture and Cell lines – *$25K***
   Will support in vitro cell line experiments for Aim 1
3. **Animal Models – *$25K***
   Will support the construction of HNC mouse models for in vivo evaluation of the prodrug
4. **Comprehensive methylation and expressions assays for Aim 3 – *$120K***
   Support for Illumina platform methylation, validation, and expression assays.

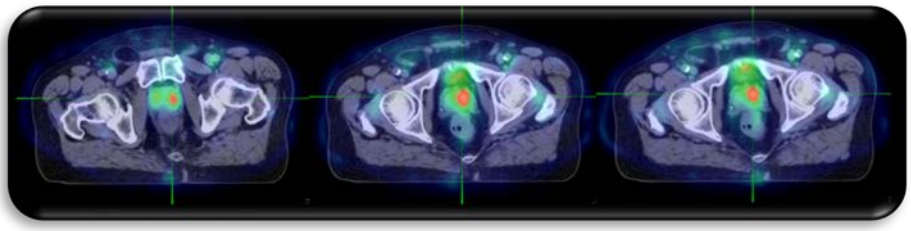
For more information, contact: **Maria Worsham, Ph.D.,** Senior Scientist, at mworsha1@hfhs.org

Lung Cancer Clinical Trial

Principal Investigator: Svend O Freytag, Ph.D.
Co-Investigators: Benjamin Movsas, M.D., Munther Ajlouni, M.D., Michael Simoff, M.D., John Fallucca, M.D., Zane Hammoud, M.D., Kenneth Levin, M.D., Ibrahim Aref, M.D., Igor Rybkin, M.D., Indrin Chetty, Ph.D., KC Karvelis, M.D. & Kenneth Barton, Ph.D.

Project Description:

For the past 23 years we have been developing a multi-faceted, gene therapy-based approach for the treatment of cancer. We have evaluated the safety and effectiveness of our approach in five clinical trials of prostate cancer including a multi-center, prospective, randomized, controlled, phase 2 trial. These clinical studies have demonstrated that our approach is safe and it can significantly reduce the percentage of patients who have detectable cancer 2 years later. Based on our encouraging results in prostate cancer, we plan to explore the potential of our multi-faceted approach in other cancers. Towards this end, we have opened a new clinical trial in early stage lung cancer combining our approach with stereotactic radiation therapy. We believe our work will have high impact because it will ultimately lead to better treatments for lung cancer.



Specific Aims:

1. Conduct a phase 1 clinical trial to assess the safety and tolerability of combining our multi-faceted approach with stereotactic radiation therapy in early stage lung cancer.
2. Conduct preclinical studies combining our multi-faceted approach with immune checkpoint blockade in a model of lung cancer.

Why This Research Matters:

Over 1.6 million people were diagnosed with cancer in the United States in 2016 accounting for almost 600,000 deaths. Lung cancer is the leading cause of cancer death and claims 158,000 lives each year. Median survival for patients who present with early stage disease is less than 5 years. New therapies that may improve the outlook for this devastating disease are needed.

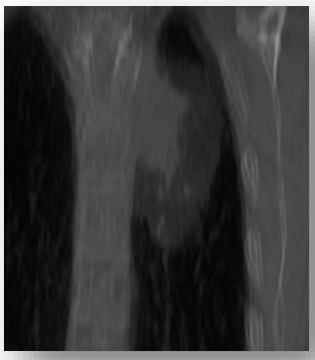
Funding Needs
1. **Patient care costs for phase 1 clinical trial in lung cancer – *$100K***
2. **Supply costs for preclinical studies in lung cancer – *$50K***

For more information, contact: **Svend O Freytag, Ph.D.**, Division Head, Radiation Oncology and Wendell Anderson Chair in Cancer, at sfreyta1@hfhs.org

To improve the efficacy of radiation treatment for patients with locally advanced lung cancer

Principal Investigator: Hualiang Zhong, Ph.D.
Co-Investigators: Indrin Chetty, Ph.D. & Benjamin Movsas, M.D.

PROJECT DESCRIPTION:



While dose escalation in radiation treatment improves tumor local control, it may increase radiation toxicity to surrounding tissues, especially for locally advanced lung cancer patients who usually have large bulky tumors. It has been found that tumor volumes change during the course of fractionated radiotherapy. This may facilitate dose escalation to the remaining tumor target without increasing radiation toxicity to surrounding healthy organs. The purpose of this study is to develop a novel adaptive treatment planning technique to reduce the potential radiation toxicity. Development of this technique is of central importance to the success of radiation therapy for locally advanced lung cancer. This technique combined with a tumor response model will be implemented in a prospective clinical trial to evaluate the efficacy of the adaptive treatment strategy.

SPECIFIC AIMS:

1. To develop novel image registration and response assessment techniques for adaptive planning.
2. To conduct a prospective clinical trial to evaluate the safety and benefits of adaptive radiotherapy.
3. To develop treatment response models to predict clinical outcomes.

WHY THIS RESEARCH MATTERS:

Adaptive radiotherapy has not been adopted in clinic, partly due to the lack of efficient tools to adapt treatment plans safely and accurately. We developed an image matching technique based on a reliable biomechanical model and proposed a novel method for quantitative assessment of tumor response. These techniques will help develop a high quality treatment plan for individual patients.

FUNDING NEEDS

1. **2-year Post-Doctoral Fellowship in Medical Physics – *$150K***
The candidate will help validate and improve the techniques mentioned above.

2. **Clinical acquisition of PET/4DCT images – *$200K***
The acquisition of PET/4DCT images is required for the clinical trial

3. **A high speed computer with 1 TB RAM and software – *$150K***
The computer is required for PET image reconstruction for response assessment

4. **A PET phantom for validation of the PET reconstruction algorithm – *$100K***

For more information, contact: **Hualiang Zhong, Ph.D.**, Senior Staff Physicist, at hzhong1@hfhs.org

A new lung cancer immunotherapy: targeting tumor associated macrophages

Principal Investigators: Qing-Sheng Mi, M.D., Ph.D. & Li Zhou, M.D.
Co-Investigators: Ding Wang, M.D., Yi Yao, Ph.D. & Hongmei Peng, M.D.

PROJECT DESCRIPTION:

The lung is home to many types of immune cells. It is known that tumors typically have an influx of macrophages, a kind of innate immune cells, known as tumor associated macrophages (TAM), which are involved in tumor development. We recently uncovered a key gene that specifically targets lung macrophage development and survival. We will first use a mouse lung cancer model to test if the deletion of this gene in the macrophages in mice can alter the tumor development. If successful, we then will propose to start a clinical trial to inhibit TAM in lung tumors using known the drug to block this gene function.

SPECIFIC AIMS:

1. Use a mouse model of lung cancer, with specific gene deletion in the macrophages, to investigate the role of TAM in lung cancer.
2. Characteristics of TAM in lung cancer, before and after immunotherapy.

WHY THIS RESEARCH MATTERS:

Lung cancer kills more people per year than any other form of cancer, and the 5 year survival rate is only around 18%. Given the prevalence of lung cancer in the US, it is important to understand all of the mechanisms that surround tumor development so that patients can be properly treated and experience the fewest adverse effects. We expect that the gene we identified for TAM will be a new target for lung cancer.

FUNDING NEEDS

1. **2-year Post-Doctoral Fellowship – *$150K***
   Funds the salary of a newly graduated cancer biologist for two years
2. **Mouse lung cancer model with a gene mutation – *$100K***
3. **Biorepository funds – *$100K***
   Allows for the collection of lung cancer patient specimens

For more information, contact: **Qing-Sheng Mi, M.D., Ph.D.**, Senior Scientist, at qmi1@hfhs.org

Pancreatic Cancer Clinical Trial

Principal Investigator: Svend O. Freytag, Ph.D.
Co-Investigators: David Kwon, M.D., Farzan Siddiqui, M.D., Ph.D., Munther Ajlouni, M.D., Robert Pompa, M.D., Gazala Khan, M.D., KC Karvelis, M.D. & Kenneth Barton, Ph.D.

Project Description:

For the past 23 years we have been developing a multi-faceted, gene therapy-based approach for the treatment of cancer. We have evaluated the safety and effectiveness of our approach in five clinical trials of prostate cancer including a multi-center, prospective, randomized, controlled, phase 2 trial. These clinical studies have demonstrated that our approach is safe and it can significantly reduce the percentage of patients who have detectable cancer 2 years later. Based on our encouraging results in prostate cancer, we now plan to explore the potential of our multi-faceted approach in other cancers. Towards this end, we have opened a new clinical trial in metastatic pancreatic cancer using a new agent that can attack both local and metastatic disease. We believe our work will have high impact because it will ultimately lead to better treatments for pancreatic cancer.

Specific Aims:

1. Conduct a phase 1 clinical trial to assess the safety and tolerability of combining our multi-faceted approach with chemotherapy in metastatic pancreatic cancer.
2. Conduct preclinical studies combining our multi-faceted approach with immune checkpoint blockade in a model of pancreatic cancer.

Why This Research Matters:

Over 1.6 million people were diagnosed with cancer in the United States in 2016 accounting for almost 600,000 deaths. Pancreatic cancer is the fourth leading cause of cancer death and claims 42,000 lives each year. Median survival for patients who present with metastatic disease is less than 6 months. New therapies that may improve the outlook for this devastating disease are needed.

Funding Needs

1. **Patient care costs for phase 1 clinical trial in metastatic pancreatic cancer – *$150K***
2. **Supply costs for preclinical studies in pancreatic cancer – *$50K***

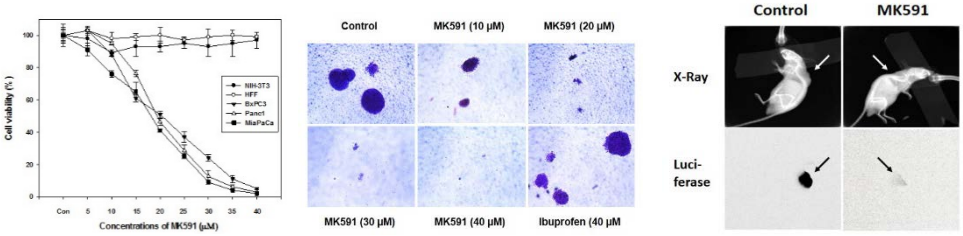
For more information, contact: **Svend O Freytag, Ph.D.**, Division Head, Radiation Oncology and Wendell Anderson Chair in Cancer, at sfreyta1@hfhs.org

Development of Novel Agents for Targeted Pancreatic Cancer Therapy

Principal Investigator: Jagadananda Ghosh, Ph.D.
Co-Investigators: Siva Sarveswaran, Ph.D. & David Kwon, M.D.

PROJECT DESCRIPTION:

Pancreatic ductal-adenocarcinoma (PDAC) has an abysmal prognosis mainly due to its late diagnosis and the aggressive nature of the PDAC cells. FDA-approved Gemcitabine-based therapy is the mainstay for treatment of pancreatic cancer (PanCan), but therapy-resistance develops invariably and rapidly, which leads to widespread metastatic tumor growth causing excruciating pain and suffering. No remedy is available for therapy-resistant pancreatic cancer. We recently found that a few of the anti-inflammatory compounds, which block metabolism of arachidonic acid via 5-lipoxygenase (5-Lox), dramatically kill PanCan cells, but does not affect normal, non-cancer cells in the same experimental conditions. Interestingly, PanCan cells express high levels of 5-Lox but its expression in non-cancer cells is undetectable. Thus, 5-Lox-targeting agents may emerge as new promising therapy for deadly pancreatic cancer. We found that these compounds strongly inhibit the K-ras > c-RAF pathway in PanCan cells. Detailed mechanism of downregulation of K-ras > c-RAF pathway in PanCan cells is yet to be characterized, and the new 5-Lox-targeting agents need to be tested *in vivo* for their efficacy to block tumor growth for development of a new therapy against PDAC.



SPECIFIC AIMS:

1. To characterize the molecular mechanism how acetyl-keto-beta-boswellic acid (AKBA), AM803 and N-oleoyl-dopamine (ODA) block the Ras > RAF pathway and induces apoptotic death in PDAC cells.
2. To determine the *in vivo* effects of AKBA, AM803 and ODA against PanCan using cell line, patient-derived xenografts (PDX), and transgenic PanCan mouse models.

WHY THIS RESEARCH MATTERS:

PDAC is a deadly disease for which no remedy is available because currently available treatments cannot effectively kill these cancer cells. We found that a few anti-inflammatory compounds strongly affect and kill PDAC cells via inhibition of the Ras > RAF pathway without affecting normal cells. Thus, evaluation of these compounds may provide us with a new treatment option for PDAC and save thousands of human lives.

FUNDING NEEDS

1. **Bridge Funding Grant – *$200K***
   Funds an additional year of research allowing for completion of promising studies, publication of results and submission of federal grants.

2. **2-year Post-Doctoral Fellowship in Cancer Biology – *$150K***
   Funds the salary of a newly graduated Cancer Biologist for two years to help start his or her research career.

3. **Microscope – *$25K***
   Allows slide viewing at the highest level of resolution and clarity. It also captures publication-grade images that will facilitate dissemination of the study results.

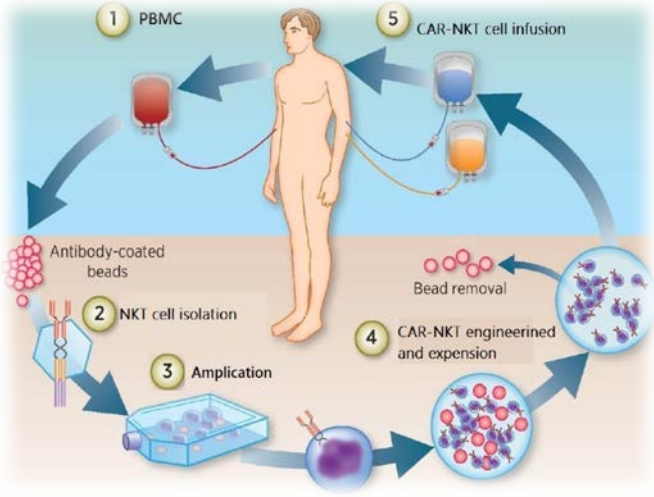
For more information, contact: **Jagadananda Ghosh, Ph.D.**, Associate Scientist, at jghosh1@hfhs.org

Pancreatic cancer immunotherapy: a novel chimeric antigen receptor (CAR) NKT cell-based immunotherapy

Principal Investigators: Qing-Sheng Mi, M.D., Ph.D. & Li Zhou, M.D.
Co-Investigators: Ding Wang, M.D., Xiaojun Wu, Ph.D. & Hongmei Peng, M.D.

PROJECT DESCRIPTION:

Natural killer T (NKT) cells, a special subset of immune cells, are potent warriors against solid tumor cancers. They can localize to tumors, where they attack the tumors. Defective NKT cells in blood or tissue may contribution to cancer development. We previously identified some genes that can regulate NKT cell development and developed a method to multiply NKT cells outside of the body, which could be used for cancer therapy. Recently, the tumor specific markers are selectively identified in the specific tumor but not in normal tissue, called chimeric antigen receptor (CAR). Recent studies from the clinical trials indicated that when CAR is engineered with T cells, it showed success in fighting certain types of cancer. Given the natural anti-tumor properties and ability to localize to the tumor, NKT cells appear an attractive alternative for CAR-directed immunotherapy of cancer. Here, we aim to generate brain cancer specific CAR-NKT cells for pancreatic cancer immunotherapy



SPECIFIC AIMS:

1. Use a mouse model of pancreatic cancer, to investigate the role of CAR-NKT cells in preventing pancreatic cancer
2. Optimize NKT cell expansion protocol to obtain FDA approval to initiate clinical trial
3. To generate human pancreatic CAR-NKT cells

WHY THIS RESEARCH MATTERS:

Pancreatic cancer is the fourth leading cause of cancer death. Worldwide efforts on many levels are underway to understand pancreatic cancer, but progress has been slow. Because it is often found late and it spreads quickly, pancreatic cancer can be hard to treat. Our study may bring a new hope to effectively treat pancreatic cancer by using CAR-NKT immunotherapy.

FUNDING NEEDS

1. **3-year Post-Doctoral Fellowship – *$200K***
   Funds the salary of a newly graduated cancer biologist for two years
2. **Mouse pancreatic cancer model with CAR-NKT immunotherapy – *$250K***
3. **Generate human pancreatic CAR-NKT cells and optimize NKT cell expansion protocol – *$250K***

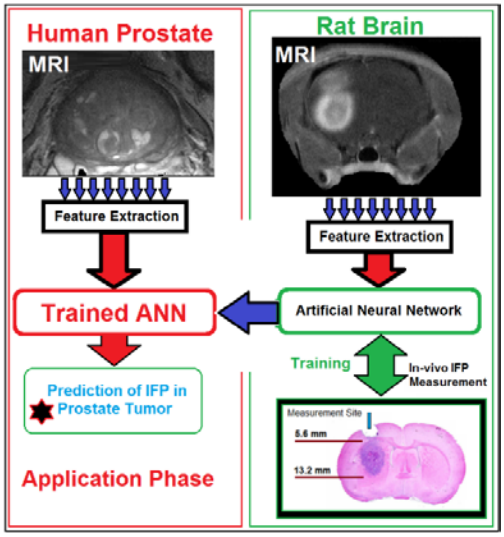
For more information, contact: **Qing-Sheng Mi, M.D., Ph.D.**, Senior Scientist, at qmi1@hfhs.org

Prediction of Response to Treatment and Tumor Grading in Patients with Prostate Cancer Using an Artificial Neural Network

Principal Investigator: Hassan Bagher Ebadian, Ph.D.
Co-Investigator: Ning Wen, Ph.D.

PROJECT DESCRIPTION:

Recent studies have shown that tumor interstitial fluid pressure (IFP) can be related to tumor aggressiveness and an elevated IFP adversely affects drug therapy in embedded tumors. Thus, estimation of tumor IFP can play an important role in diagnosis, grading, treatment planning, drug delivery, and response to treatment in patients with prostate cancer (Pca). Our group has recently constructed an Artificial Neural Network (ANN) for non-invasive prediction of tumor IFP from MR images acquired from cerebral tumors in rats. We have also shown that physical properties of *embedded tumors* control their physiology. The aim of this study is to apply an animal trained-ANN on the MR data of patients with Pca to non-invasively estimate their IFP. We will also construct a new ANN for predicting the probability of response to Radiation Therapy (RT) in patients with Pca. In addition to the MR data of the Pca that is collected at Henry Ford Hospital, this study will use the MRI data of Pca that is publicly shared by the cancer imaging archive (TCIA).



SPECIFIC AIMS:

1. A trained ANN with animal data can be applied to the MR data of human with prostate cancer to non-invasively estimate the tumor IFP. The predicted IFP should be proportional and correlated with the tumor Gleason number and inversely correlated to tumor response to RT.
2. An ANN can be trained from MR data of human for predicting their response to RT using the known outcome of patients with prostate cancer.

WHY THIS RESEARCH MATTERS:

We have shown that *physical properties* of embedded tumors are not strongly dependent on the site of the tumor, thus, two seemingly unrelated but clinically significant tumors will be studied: a rat model of cerebral tumor, and human prostate cancers. This work makes a paradigm shift in non-invasive estimation of tumor IFP and its response to treatment in patients with prostate cancer.

FUNDING NEEDS

1. Year Post-doctoral fellowship – *$60K*

Funds a post- doc candidate with working knowledge of MR imaging and familiarity with signal processing, adaptive models and information theory to closely work with PI to acquire the data from HFHS and the cancer imaging archive (TCIA). The candidate will help process different MR image modalities, apply the trained-ANN on the MR data of human, construct, train, and validate a new ANN for prostate tumor grading and predicting the response to RT.

2. Equipment – *$5K*

In order to construct, train, and validate an ANN and also modeling and processing different MR information, this project needs a couple of workstations with high computational power. The workstations should have fast CPU (preferably with GPU capability) with large memory (16 or 32 GB) and high storage capacity (2-3 TB of HDD).

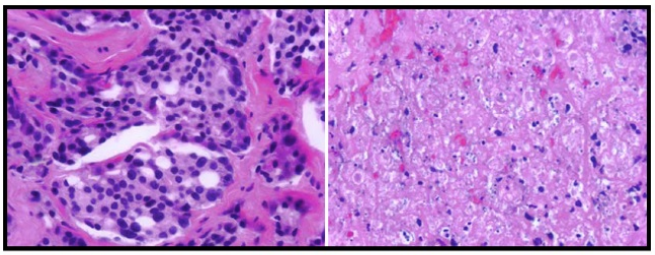
For more information, contact: **Hassan Bagher Ebadian, Ph.D.**, Assistant Scientist, at hbagher1@hfhs.org

Prostate Cancer Clinical Trial

Principal Investigator: Svend O. Freytag, Ph.D.
Co-Investigators: Hans Stricker, M.D., Mohamed Elshaikh, M.D., Farzan Siddiqui, M.D., Ph.D., Haythem Ali, M.D., Clara Hwang, M.D., James Peabody, M.D. & Benjamin Movsas, M.D.

Project Description:

For the past 23 years we have been developing a multi-faceted, gene therapy-based approach for the treatment of cancer. We have evaluated the safety and effectiveness of our approach in five clinical trials of prostate cancer including a multi-center, prospective, randomized, controlled, phase 2 trial. These clinical studies have demonstrated that our approach is safe and it can significantly reduce the percentage of patients who have detectable cancer 2 years later. Based on these encouraging results, we have opened a new clinical trial in radio-recurrent prostate cancer using a new agent that can attack both local and metastatic disease. We believe our work will have high impact because it will ultimately lead to better treatments for aggressive forms of prostate cancer.



Biopsy before- cancer present Biopsy after- cancer destroyed

Specific Aims:

1. Conduct a phase 1 clinical trial to assess the safety and tolerability of our multi-faceted approach in radio-recurrent prostate cancer.
2. Conduct preclinical studies combining our multi-faceted approach with immune checkpoint blockade in a model of prostate cancer.

Why This Research Matters:

Over 1.6 million people were diagnosed with cancer in the United States in 2016 accounting for almost 600,000 deaths. Prostate cancer is the second leading cause of cancer death in men and claims 26,000 lives each year. Men with radio-recurrent prostate cancer are at high risk for developing metastatic disease, which is presently incurable. New therapies that may improve the outlook for this devastating disease are needed.

Funding Needs

1. **Patient care costs for phase 1 clinical trial in radio-recurrent prostate cancer – *$100K***
2. **Supply costs for preclinical studies in prostate cancer – *$50K***

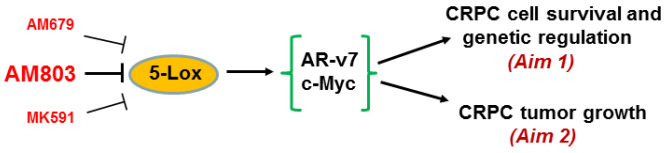
For more information, contact: **Svend O Freytag, Ph.D.**, Division Head, Radiation Oncology and Wendell Anderson Chair in Cancer, at sfreyta1@hfhs.org

Development of a New Targeted Therapy against Castration-Resistant Prostate Cancer

Principal Investigator: Jagadananda Ghosh, Ph.D.
Co-Investigators: Siva Sarveswaran, Ph.D. & Dan Chitale, M.D.

PROJECT DESCRIPTION:

Androgen-deprivation therapy (ADT) is the mainstay for treatment of advanced prostate cancer. However, therapeutic-resistance invariably develops, which progresses to widespread metastatic disease and brings demise to prostate cancer patients because no effective remedy is available for castration-resistant prostate cancer (CRPC). We found that metabolism of arachidonic acid via 5-lipoxygenase (5-Lox) plays an essential role in the survival of CRPC cells but not of non-cancer cells, and that CRPC cells express high levels of 5-Lox but its expression in non-cancer cells is undetectable. Thus, 5-Lox emerges as a new promising target for therapy of castration-resistant prostate cancer. However, details of the molecular regulation of CRPC cell survival by 5-Lox is unknown and suitable agents need to be developed to appropriately block the activity of 5-Lox. Recently we found that 5-Lox regulates the androgen receptor splice variant-7 (AR-v7) and the c-Myc oncogene which are well characterized to play important roles in the development and maintenance of CRPC. Now we are screening new 5-Lox-targeting compounds for molecular understanding, and testing them *in vivo* for therapy of CRPC.



SPECIFIC AIMS:

1. To characterize the molecular mechanisms how 5-Lox inhibitors block AR-v7 and c-Myc in CRPC cells, and induce apoptotic cell death.
2. To determine the *in vivo* effects of new compounds against CRPC using cell line and patient-derived xenograft (PDX) models.

WHY THIS RESEARCH MATTERS:

Most of the deaths due to prostate cancer happen because of CRPC for which no effective therapy is available. We discovered that CRPC cells critically depend on fatty acid metabolism via 5-Lox, and that inhibition of 5-Lox dramatically kills CRPC cells, but not normal cells. Thus, we have an opportunity to develop a new targeted therapy by selectively killing and eliminating CRPC cells without affecting non-cancer cells.

FUNDING NEEDS

1. **2-year Post-Doctoral Fellowship in Cancer Biology – *$150K***
   Funds the salary of a newly graduated Cancer Biologist for two years to help start his or her research career.

2. **Bridge Funding Grant – *$150K***
   Funds an additional year of research allowing for completion of promising studies, publication of results and submission of federal grants.

3. **Microscope – *$25K***
   Allows slide viewing at the highest level of resolution and clarity. It also captures publication-grade images that will facilitate dissemination of the study results.

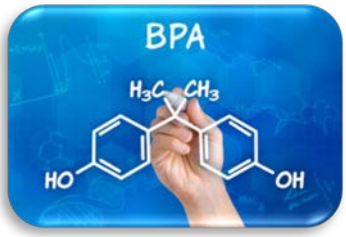
For more information, contact: **Jagadananda Ghosh, Ph.D.**, Associate Scientist, at jghosh1@hfhs.org

Environmental Exposures and Race Disparities in Prostate Cancer

Principal Investigator: Chris Neslund-Dudas, Ph.D.
Co-Investigators: Albert Levin, Ph.D., Dhanajay Chitale, M.D., Nilesh Gupta, M.D., Clara Hwang, M.D., Craig Rogers, M.D. & Sean Williamson, M.D.

Project Description:

African American men are more likely than White men to develop prostate cancer and to die from the disease. Reasons for these race disparities in prostate cancer are as yet unknown. Our current work is looking at interactions between environmental exposures. Our team has identified a difference by race in the relationship between the heavy metal cadmium and the androgen receptor. The androgen receptor is the key driver of prostate cancer. Our team has also identified a potential interaction between heavy metals and a gene known as JAZF1 (Juxtaposed with another zinc finger protein 1). JAZF1 has been linked to prostate cancer and another disease common in African-Americans, diabetes. Due to our current findings, we would like to expand our work on environmental exposures and race disparities in prostate cancer.



Specific Aims:

1. Determine if there are interactions between heavy metals, phthalates, and/or bisphenol A and genes linked to prostate cancer. Further, determine if these environmental factors or interactions differ by race.
2. Determine if metals, which can be measured in prostate tissue, impact important downstream targets of the androgen receptor and JAZF1. Further, determine if relationships between metals and downstream targets differ by race.

Why This Research Matters:

African American men are more than twice as likely to die of prostate cancer then white men. They develop the disease at younger ages and many reports suggest prostate cancer in African American men is more aggressive. If we are able to identify environmental factors that African American men either have higher exposure to or have greater susceptibility to, we can potentially intervene to reduce race disparities in prostate cancer.

Funding Needs

1. **Genotyping Arrays – *$100K***
Funds genotyping of JAZF1 and related pathway genes for 400 individuals

2. **RNA-Transcriptome Arrays – *$100K***
Funds the assessment of the expression of genes downstream of the androgen receptor and JAZF1

3. **Circulating Tumor Cell Capture and Analysis – *$30K***
Circulating tumor cells allow us to monitor the status of the androgen receptor across the course of prostate cancer.

4. **K-XRF Bone Lead measurement equipment – *$40K***
Bone lead, rather than lead in blood or urine samples, is the best measurement of lifetime lead exposure. Having access to the best measurement method is important for conducting high quality science.

5. **Study Coordinator – 1 year – *$72K***
The coordinator is responsible for consenting and enrolling patients into the study.

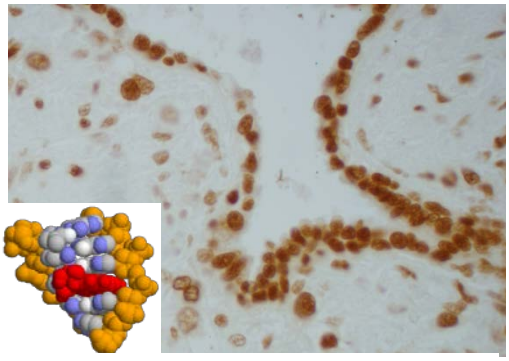
For more information, contact: **Christine Neslund-Dudas, Ph.D.**, Assistant Scientist, at cdudas1@hfhs.org

Biomarkers of Prostate Carcinogenesis

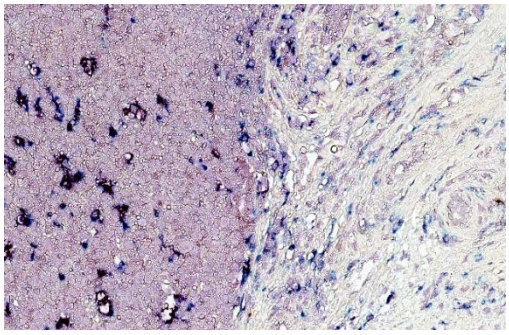
Principal Investigator: Benjamin A. Rybicki, Ph.D.
Co-Investigators: Dhananjay Chitale, M.D. & Nilesh Gupta, M.D.

Project Description:

The earliest stages of prostate carcinogenesis involve subtle changes to the DNA molecule and transition from a tumor protective to a tumor promotive inflammatory environment. We have identified a cohort of over 10,000 men in the Henry Ford Health System at high risk for prostate cancer, and performed molecular studies to better understand why some men progress to cancer and others do not. Using their pre-malignant prostate biospecimens, we have measured DNA adducts, environmentally-derived compounds that bind to DNA molecules, as prostate cancer biomarkers that increase risk of disease susceptibility and/or progression. Inflammatory biomarkers are also being measured in pre-malignant prostate tissue to better quantify on a molecular level the key indicators of an inflammatory response that promotes prostate cancer.



Staining for DNA adducts (adduct model left bottom insert) in prostate



Multi-color staining of different inflammatory markers

Specific Aims:

1. To characterize the molecular, histological, and cellular components of inflammation in benign prostate tissue and to determine how these markers of inflammation are associated with prostate carcinogenesis.
2. To measure biomarkers indicative of DNA damage and a "prostate cancer field effect" – premalignant molecular changes indicative of cells ready to transform to cancer - in benign prostate and determine their role in prostate carcinogenesis.

Why This Research Matters:

Nearly 1 Million men a year have a negative prostate biopsy, but remain at high risk for prostate cancer. Determining the best tissue-based biomarkers of prostate cancer progression can aid in clinical management and development of chemoprevention strategies to lower cancer risk.

Funding Needs

1. **2-year Post-Doctoral Fellowship in Cancer Epidemiology – *$150K***
   Funds the salary of a newly graduated cancer epidemiologist for two years to help start his or her research career

2. **Bridge Funding Grant – *$400K***
   Funds an additional year of research allowing for completion of studies, publication of results and submission of federal grants for the next phase of studies

3. **Microscope – *$25K***
   Allows for slide image viewing at the highest level of resolution and clarity. It also captures publication grade images that will facilitate dissemination of study results.

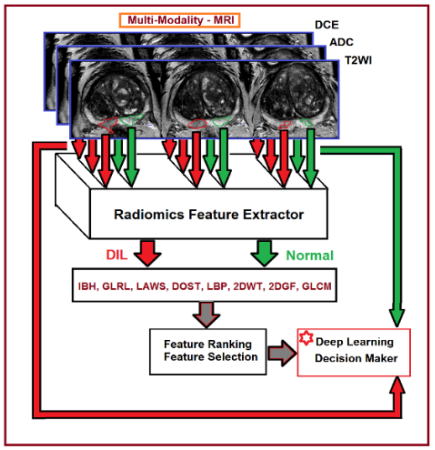
For more information, contact: **Sudha Sadasivan, Ph.D.**, Project Manager, at ssadasi3@hfhs.org

Physiological Adaptive Radiotherapy for Prostate Cancer Treatment

Principal Investigator: Ning Wen, Ph.D.
Co-Investigators: Hassan Bagher Ebadian, Ph.D. & Branislava Janic, M.D., Ph.D.

PROJECT DESCRIPTION:

There has been evidence from pathology studies that dominant lesions exist within the prostate gland. Pilot studies have also shown an ability to increase probability of tumor control by administering a boost dose to the dominant intraprostatic lesions (DILs). Simultaneous dose escalation to the DILs without increasing the risk of late complications has potential to increase local control rates for prostate cancer patients. We propose to develop a deep machine learning algorithm to identify the DILs from multiparametric MRI sequences and implement a treatment strategy that can be a valuable middle ground between radical treatment and focal therapy and potentially very effective at controlling low risk or intermediate risk, localized prostate cancer. A median dose to the entire gland could prevent the disease recurrence in the prostate from satellite tumors and significantly reduce the side effects associated with escalated radiation dose to the entire gland. A boosting dose to the DIL can maintain the effectiveness of focal therapy to treat the index lesion that is the main determinant for tumor progression and prognosis.



SPECIFIC AIMS:

1. Develop a multiparametric MRI model using deep machine learning algorithm with quantitative measures to detect, characterize and assess treatment response of DILs of prostate cancer.
2. Investigate the dosimetric benefits of a simultaneous boost dose given to dominant intraprostatic lesions defined by MRI.
3. Investigate the optimal reoptimization schedule for adaptive radiotherapy using radiobiological dose indices.

WHY THIS RESEARCH MATTERS:

There has been increased evidence from pathologic studies that DILs play an important role in prostate cancer progression and may be considered the epicenter of local recurrence post-treatment. Combining deep machine learning algorithm with multiple MR Imaging techniques can help clinicians recognize cancer patterns, identify DILs, evaluate treatment response and predict treatment outcomes.

FUNDING NEEDS

1. Two 2 Year Postdoctoral fellowship in deep machine learning algorithm – *$240K*

Funds a postdoctoral fellow to develop the artificial neural network to train the radiomics features collected from both morphological and functional imaging. The other postdoctoral fellow is expected to perform research in functional MRI, image processing, and the clinical applications in cancer treatment.

2. MR Imaging Fees – *$300K*

Funds technical and professional charges for multiple MR scans that need to be arranged for each patient.

3. Equipment – *$6K*

Given the size and 3D nature of the data we are working with and the memory and speed needed for the processing, we request funding for two workstations, each powered by Intel i7 3rd generation CPUs, 16Gb RAM, 120Gb SSD HDD for OS and 1Tb for storage.

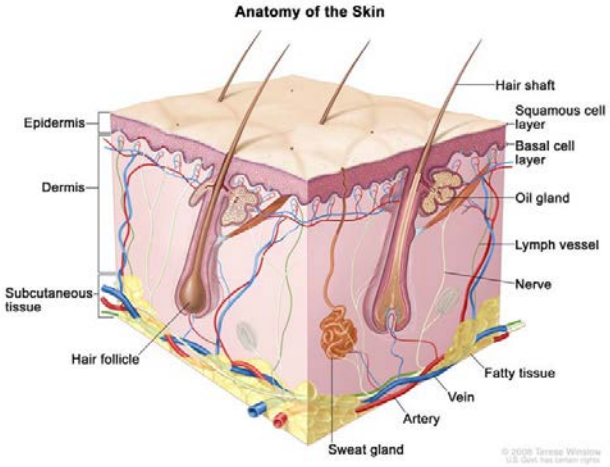
For more information, contact: **Ning Wen, Ph.D.**, Director of Clinical Physics, at nwen1@hfhs.org

MiRNAs as New Therapeutic Targets for Skin Cancer

Principal Investigator: Qing-Sheng Mi, M..D., Ph.D. & David Ozog, M.D.
Co-Investigators: Li Zhou, M.D., Mark Balle, M.D. & Hongmei Peng, M.D.

Project Description:

The skin is the largest organ in the body. Skin cancer is an abnormal growth of skin cells. Exposure to ultraviolet (UV) rays is thought to be the major risk factor for most skin cancers. The two most common kinds of skin cancers are Basal cell cancer which starts in the lowest layer of the skin and Squamous cell cancer which starts in the top layer of the skin. MicroRNAs (miRNA), small non-coding RNAs which regulate gene expressions, are involved in cancer development. Our recent studies have identified some key miRNAs related to mouse skin cancer as well as in human skin cancer. Here we test if miRNAs can serve as new therapy targets for skin cancer.



Specific Aims:

1. To develop nanoparticles of miRNA inhibitors or mimics
2. To test miRNA nanoparticles in skin cancer in a mouse model
3. To test therapeutic effects in human skin cancer

Why This Research Matters:

Each year in the U.S. over 5.4 million cases of nonmelanoma skin cancer are treated, and more than 5 million new cases are diagnosed in the U.S. Over the past three decades, more people have had skin cancer than all other cancers combined. Between 40 and 50 percent of Americans who live to age 65 will have either basal cell carcinoma or squamous cell carcinoma at least once. The new reliable therapies are needed for skin cancer. This study will facilitate the development of new intervention strategies for skin cancer.

Funding Needs

1. **2-year Post-Doctoral Fellowship in Skin Cancer Dermatology – *$150K***
   Funds the salary of a newly graduated cancer epidemiologist for two years to help start his or her research career
2. **Bridge Funding Grant – *$400K***
   Clinical trial
3. **Supplies – *$150K***
   Animals and molecular biology reagents

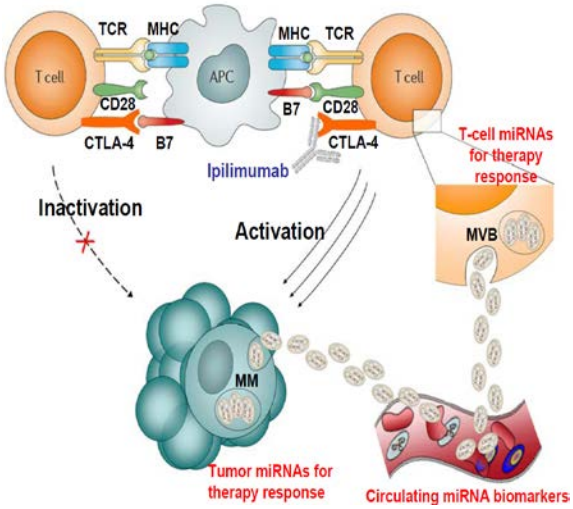
For more information, contact: **Qing-Sheng Mi, M.D., Ph.D.**, Senior Scientist, at qmi1@hfhs.org

MiRNAs serve as the early diagnostic biomarkers and immunotherapy responsive biomarkers in melanoma

Principal Investigator: Qing-Sheng Mi, M.D., Ph.D. & Li Zhou, M.D.
Co-Investigators: Ding Wang, M.D., Laurie Kohen, M.D. & Hongmei Peng, M.D.

PROJECT DESCRIPTION:

Malignant melanoma (MM) is one of the most invasive human cancers with high potential for metastasis. The management of MM has been challenging due to the lack of reliable early diagnostic biomarkers for screening and its relative resistance to conventional chemotherapy and radiotherapy; only a small percentage of patients demonstrated durable responses to immunotherapy. Thus, a personalized strategy are urgently needed to develop assays which may guide the individual patient in the selection of appropriate therapy. Discovery of early diagnostic noninvasive biomarkers and predictive biomarkers for immunotherapy response is an important strategy to attain this objective. MicroRNAs (miRNA), small non-coding RNAs which regulate gene expressions, are involved in cancer development. Our recent studies indicate that cell-free serum from MM patients contains MM-specific miRNAs, which may serve as early diagnostic biomarkers and predictors or surrogates of immunotherapeutic response. Here we aim to further validate and confirm these biomarkers.



SPECIFIC AIMS:

1. Identification of MM-specific miRNAs associated with therapeutic responsiveness or resistance- Studies using tumor tissues.
2. Identification of immune cells-related miRNAs related to MM immunotherapy resistance - Studies using immune cells.
3. Identification of serum miRNAs as predictive biomarkers for responsiveness to MM immunotherapy - Studies using sera.

WHY THIS RESEARCH MATTERS:

The results from the proposed pioneering studies enable us to further confirm and validate the early diagnostic biomarkers as well as the biomarkers to predict MM patients who will respond to immunotherapy. This study may also facilitate the development of new intervention strategies for increasing immunotherapy for MM.

FUNDING NEEDS

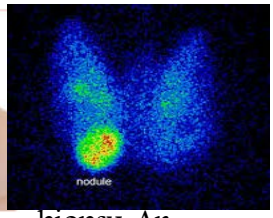
1. **Next generation sequencing, comprehensive miRNA expression profiles – *$250K***
2. **2-year Post-Doctoral Fellowship in next generation sequencing – *$150K***
   Funds the salary of a newly graduating cancer biologist for two years
3. **Biorepository – *$100K***
   Allows for collection of patient specimens

For more information, contact: **Qing-Sheng Mi, M.D., Ph.D.**, Senior Scientist, at qmi1@hfhs.org

Methylation Biomarkers in Thyroid Cancers & Benign Nodules

Principal Investigator: Josena K. Stephen, Ph.D.
Co-Investigators: Dhananjay Chitale, M.D., George Divine, Ph.D., Indrani Datta, M.S., Arti Bhan, M.D. & Maria Worsham, Ph.D.

PROJECT DESCRIPTION:



Thyroid cancer (TC) accounts for 95% of all endocrine malignancies, tends to occur more often in younger people and is three times more common in women than men. Of the four main types of TC, papillary (PTC) and follicular (FTC) account for >90%, followed by medullary (MTC) with 3% to 5%, and anaplastic with <3%. The standard diagnostic tool for preoperative diagnosis of TC is the fine-needle aspiration (FNA) biopsy. An FNA allows for the assessment of cellular morphologic features that cannot be identified by clinical exam or ultrasound imaging. However, thyroid FNA is limited by the skill of the aspirator and expertise of the cytologist and is inconclusive for certain histological subtypes, especially between follicular adenomas (FA) and FTC. The challenge is therefore to accurately diagnose cancer in thyroid nodules. Thus, there is a pressing need for reliable, preoperative markers, usable independently or in conjunction with FNA cytology, to help differentiate benign and malignant thyroid nodules, which may aid in early diagnosis, and in the long term contribute to personalized clinical management and surveillance. Biomarkers that can help distinguish malignant from benign nodules would reduce over-diagnosis and unnecessary surgeries currently associated with TC. Our focus is on identifying novel genetic and epigenetic markers that differentiate benign and malignant thyroid nodules and help with the early detection of thyroid cancers.

SPECIFIC AIMS:

1. Identify novel genetic (mutations) & epigenetic (DNA methylation) markers of benign and malignant thyroid nodules as well as markers of aggressive thyroid cancers (MTC & ATC) for early detection of thyroid cancer.
2. Develop diagnostic gene panels, used alone or in conjunction with FNA, to improve diagnosis and decrease unnecessary surgeries, and identify targets against which novel therapies can be developed and directed.
3. Detect the presence of residual disease or recurrence by identifying thyroid cancer specific markers in blood/serum.

WHY THIS RESEARCH MATTERS:

The current clinical challenge is to accurately diagnose cancer among thyroid nodules. Overcoming this hurdle will help reduce over-diagnosis and the unnecessary surgeries currently associated with TC which results in lifelong hormone replacement therapy for thousands of people.

FUNDING NEEDS

1. **Next generation sequencing, comprehensive methylation and expression assays – *$225K***
   Funds the use of Illumina EPIC methylation platform, expression assays and sequencing of samples.
2. **Bridge Funding Grant – *$200K***
   Funds an additional year of research allowing for completion of promising studies, publication of results and submission of federal grants for the next phase of studies.
3. **Temperature-controlled cell culture incubator – *$10K***
   To grow cancer cells in the laboratory.
4. **-80°C Freezer – *$20K***
   To store FNA, surgical specimens and cultured cancer cells.

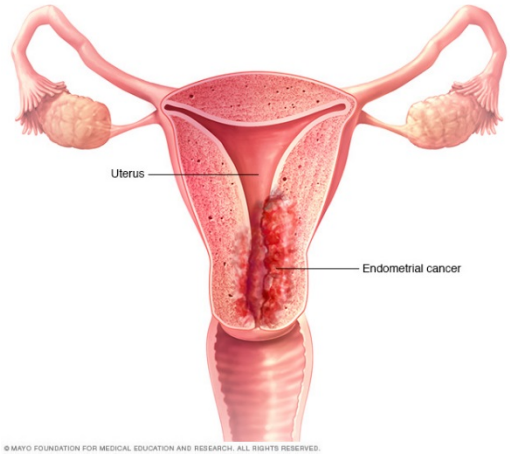
For more information, contact: **Josena Stephen, Ph.D.**, Research Scientist, at jstephe2@hfhs.org

Teaming Up for Women's Health, Cure Uterine Cancer

Principal Investigator: Mohamed Elshaikh, M.D.
Co-Investigators: Ramandeep Rattan, Ph.D. & Nallasivam Palanisamy, Ph.D.

Project Description:

Uterine cancer is the most common gynecologic cancer in USA. We are one of the most active research programs in the country involved in Uterine Cancer Research. We would like to expand our research program and learn more about molecular and genetic factors that might predict for uterine cancer development, recurrence and tumor response to treatment by using advanced and available research technologies such as next generation gene sequencing.



Specific Aims:

1. To create pairs of tissue specimens from women with uterine cancer who developed tumor recurrence after surgery (hysterectomy) (one sample from the original hysterectomy specimen and one sample from the recurrent tumor. To create a third sample from matched women with endometrial cancer who were cured) (based on the same stage and tissue type) (a total of 300 specimens from 200 women).
2. To determine gene or protein expression between the different specimens using next generation sequencing technique and protein expression.

Why This Research Matters:

Using the most advanced technology, if we predict molecular differences between the tissue specimens, this will serve as novel predictive markers for future patients with endometrial cancer. These predictive markers could potentially help to intensify or de-intensify treatment or screening process according to the results of gene expression

Funding Needs

1. **2-year Post-Doctoral Fellowship in next generation gene sequencing – *$150K***
Funds the salary of a newly graduated scientist for 2 years to help start his or her research career.

2. **The cost of next generation gene sequencing at a specialized research core – *$300K***
The average cost of running each sample is $1000 x 300 samples ($300K).

3. **Bridge funding grant – *$100K***
Funds an additional year of research allowing for completion of promising studies, submission of federal grants for the next phase of studies.

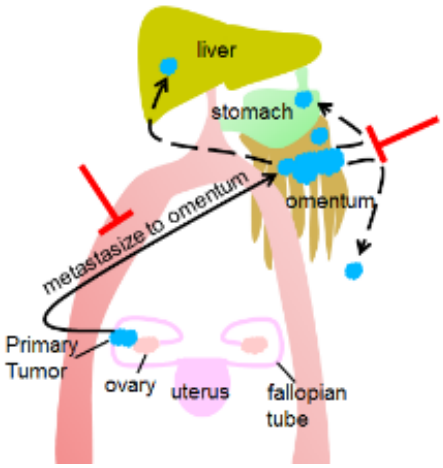
For more information, contact: **Mohamed Elshaikh, M.D.**, Clinical Professor, at melshai1@hfhs.org

Inhibiting the First Step of Ovarian Cancer Metastasis

Principal Investigator: Ramandeep Rattan, Ph.D.
Co-Investigator: Adnan Munkarah, M.D

Project Description:

Almost 80% of women diagnosed with ovarian cancer present with metastasis to the omentum, an organ rich in adipocytes (fat storing cells). In fact, the reason why ovarian cancer cells colonize omentum first is to gain access to the fat (lipids, fatty acids) and other growth factors that aid and provide ovarian cancer cells with extra resources to sustain, grow and spread to other organs. With the aim to disrupt the dependency of ovarian cancer cells on omental as well as other adipocytes, we have identified two growth factors that attract the ovarian cancer cells towards adipocytes. We are targeting these growth factors to restrict the ovarian cancer cells reaching out to adipocytes. Second, we are investigating, that once the fat from the adipocytes relocate into the tumor cells, how exactly is it is getting incorporated into the cancer cells and helping them to become more fit and spread. Our research impacts all women with ovarian cancer. Determining the early steps of metastasis and identifying strategies to stop it, can be translated into treatment options and development of prevention strategies.



Specific Aims:

1. To target and inhibit the factors (growth factors, lipid uptake molecules etc.) that create and promote ovarian cancer cell dependency on adipocytes for their sustenance, growth and spread.
2. To measure the exact contribution of adipocyte derived fat to the ovarian cancer cells and determine how these fats (lipids) are transforming the ovarian cancer cell in terms of helping them to grow and spread.

Why This Research Matters:

This research will identify targets to stop the early metastatic spread of ovarian cancer. Identification of therapeutic targets will have a clinical impact by providing treatment options to the oncologist. Understanding the contribution of lipids to ovarian cancer cells will help to define lifestyle modifications that will assist in better patient outcomes.

Funding Needs

1. **2-year Post-Doctoral Fellowship in Ovarian Cancer – *$150K***
Funds the salary of a newly graduated cancer biologist for two years to help start his or her research career. The research produced will form the basis of various grant proposals (NCI)

2. **Animal Work Support – *$200K***
Funds extensive mouse studies based on various genetic and xenograft models to prove hypothesis and test the various therapeutic agents in mice, before allowing for Phase 1 clinical trials.

3. **Biorepository Funds – *$100K***
Allows for collection of patient specimen to validate our laboratory findings

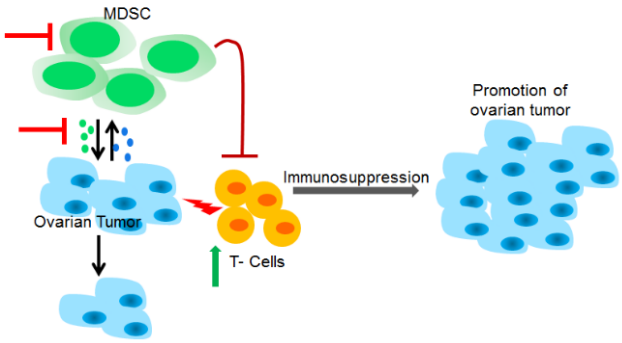
For more information, contact: **Ramandeep Rattan, Ph.D.**, Assistant Scientist, at rrattan1@hfhs.org

Understanding and targeting Immune suppression in Ovarian Cancer

Principal Investigator: Ramandeep Rattan, Ph.D.
Co-Investigators: Adnan Munkarah, M.D & Shailendra Giri, Ph.D.

PROJECT DESCRIPTION:

Studies have confirmed a distinguished role for the host immune system in modifying the clinical process of ovarian cancer. Antitumor immunity is often curbed by immunosuppressive cells prevalent around the tumor. One of the immunosuppressive cells that have been associated with worse outcomes in ovarian cancer are the Myeloid Derived Suppressor Cells (MDSCs). MDSCs deregulate antitumor activity by suppressing the T-cell activity and promoting tumor growth. Prevalence of MDSCs also impedes the effectiveness of various recent immunotherapies. Our aim is to understand what controls and regulates the immunosuppressive ability of MDSCs at the tumor and the host level. Understanding this phenomenon will guide us to precisely target the MDSCs and restore antitumor activity. Our research will help in changing the understanding of antitumor immunity in the field of ovarian cancer, improve antitumor immunity and increase the effectiveness of various immunotherapies currently under clinical trials.



SPECIFIC AIMS:

1. To interrogate the precise role of MDSCs in dysregulating antitumor immunity and promoting ovarian cancer growth.
2. To elucidate the mechanisms of immunosuppressive function of MDSCs to optimize new promising cancer immune-therapeutics.

WHY THIS RESEARCH MATTERS:

Immunotherapy against various cancers has shown promising results, while in ovarian cancer the overall response rates have been markedly low at 10-15%. Our research will target immunosuppression, one of the reasons for these markedly low response rates, to improve the effectiveness of various immunotherapies currently under clinical trials and innate anti-tumor immunity.

FUNDING NEEDS

1. **2-year Post-Doctoral Fellowship in Ovarian Cancer – *$150K***
Funds the salary of a newly graduated cancer biologist for two years to help start his or her research career, allowing for completion of promising studies, publication of results and submission of federal grants for the next phase of studies

2. **Flow Activated Cell Sorter – *$150K***
Funds purchase of a flow activated cell sorter, an essential equipment need to study immune cells.

3. **Biorepository Funds – *$100K***
Allows for collection, storage and annotation of patient specimen to validate our laboratory studies.

For more information, contact: **Ramandeep Rattan, Ph.D.**, Assistant Scientist, at rrattan1@hfhs.org

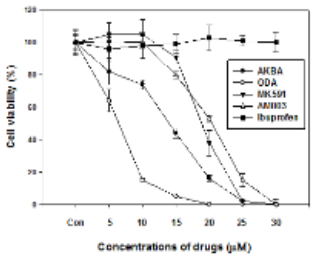
Breast Cancer

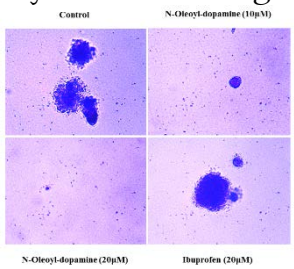
Development of a Novel Therapy against Metastatic Triple-Negative Breast Cancer

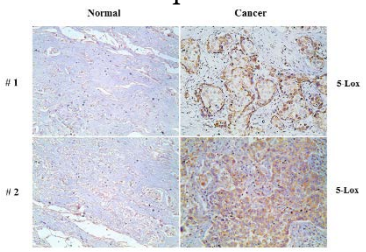
Principal Investigator: Jagadananda Ghosh, Ph.D.
Co-Investigators: Siva Sarveswaran, Ph.D. & Dan Chitale, M.D.

PROJECT DESCRIPTION:

Metastatic triple-negative breast cancer (mTNBC) is an incurable, end-stage disease mainly due to the lack of druggable targets to attack and kill the resistant cancer cells. Aggressive nature of the TNBC cells defy chemotherapy and the resistant cancer cells progress rapidly leading to widespread metastatic tumors causing excruciating pain and suffering highlighting a pressing need for new therapeutic agents. We recently found that a few anti-inflammatory compounds, which block metabolism of arachidonic acid via 5-lipoxygenase (5-Lox), dramatically kill TNBC cells but not normal, non-cancer cells, and that these compounds strongly inhibit the oncogenic c-Myc and CDK4 in TNBC cells. We also found that TNBC cells express high levels of 5-Lox but the expression of 5-Lox in non-cancer cells is undetectable. Thus, suitable 5-Lox-targeting agent(s) may emerge as a new promising therapy for deadly mTNBC. However, details of the mechanism of downregulation of c-Myc, CDK4 and AR by 5-Lox inhibitors in TNBC cells is unknown and these agents need to be tested in vivo for their efficacy to block tumor growth for development of a new therapy against TNBC.







SPECIFIC AIMS:

1. To characterize the molecular mechanisms how N-oleoyl-dopamine (ODA) and acetyl-keto-beta-boswellic acid (AKBA) block c-Myc, CDK4 and AR, and induce apoptotic death in TNBC cells.
2. To determine the *in vivo* effects of ODA and AKBA against TNBC using cell line and patient-derived xenograft (PDX) models.

WHY THIS RESEARCH MATTERS:

Because of the lack of expression of ER, PR and Her2/neu in TNBC cells, there is a serious deficiency in the available treatment options for TNBC. Our new findings of the dramatic killing of TNBC cells by 5-Lox-targeting drugs bring new hope to develop an effective treatment option for TNBC. However, molecular mechanisms of action of these novel drugs are yet to be understood, and proper *in vivo* testing is needed to find suitable compounds for clinical use in TNBC patients.

FUNDING NEEDS

1. **2-year Post-Doctoral Fellowship in Cancer Biology – *$150K***

Funds the salary of a newly graduated cancer biologist for two years to help start his or her research career

2. **Bridge Funding Grant – *$200K***

Funds an additional year of research allowing for completion of promising studies, publication of results and submission of federal grants

3. **Microscope – *$25K***

Allows slide viewing at the highest level of resolution and clarity. It also captures publication-grade images that will facilitate dissemination of the study results

For more information, contact: **Jagadananda Ghosh, Ph.D.**, Associate Scientist, at jghosh1@hfhs.org

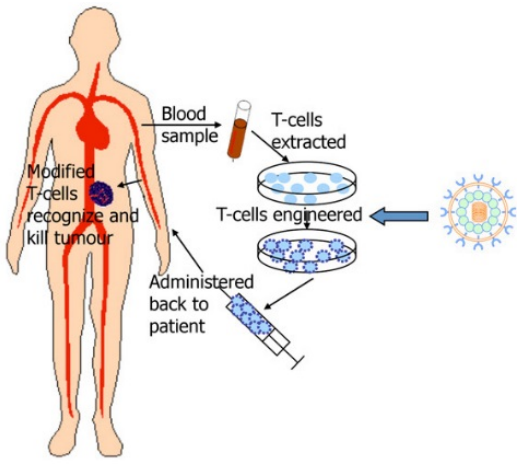
Breast Cancer

A novel chimeric antigen receptor (CAR) T cell-based immunotherapy to address racial disparities in metastatic triple negative breast cancer

Principal Investigator: Maria J. Worsham, Ph.D., FACMG
Co-Investigators: Josena Stephen, M.D & Kang Mei Chen, M.D.

PROJECT DESCRIPTION:

Triple negative breast cancer (TNBC) is an aggressive histological subtype with frequent metastases, poor prognosis and limited treatment options. Our goal is to develop a novel CAR T cell-based immunotherapy to re-engineer the patients T-cells, the immune cells, to recognize and attack surface antigens on the cancer cell. The tumor antigen selected as a target is the membrane-bound chondroitin sulphate proteoglycan (CSPG) 4, which is expressed on TNBC cells, but has a restricted distribution in normal tissues, therefore minimizing the side effects caused by targeting normal cells. Surprisingly, this molecule does not appear to be expressed in TNBC tumors from African American (AA) women, making them ineligible for currently available CAR T cell-therapy developed against CSPG4. To counteract this racial disparity, we plan to investigate the mechanisms underlying the lack of CSPG4 expression in AA women's TNBC tumors with emphasis on epigenetic mechanisms. This information will be used to design strategies to restore CSPG4 expression in AA women's TNBC tumors. Should this approach fail, we will develop CAR T cell immunotherapy for TNBC in AA women utilizing a different target (B7-H3) that we have already found to be expressed in AA women's TNBC tumors.



SPECIFIC AIMS:

1. Investigation of the mechanism(s) underlying lack of CSPG4 expression in AA women's tumors with special emphasis on the analysis of epigenetic mechanisms and utilize this information to develop strategies to restore CSPG4 expression on TNBC cells from AA women.
2. Assessment of the ability of B7-H3 to mediate lysis by CAR T cells of TNBC from AA women.

WHY THIS RESEARCH MATTERS:

This research will contribute to our understanding of the mechanisms underlying the racial disparity in CSPG4 expression to impact the application of CAR T cell therapy for TNBC in AA women. Given the high potential of CAR T for malignancies, its use may have a major impact on the treatment of metastatic TNBC.

FUNDING NEEDS

1. **Bridge Funding Grant – *$200K***
   Funds an additional year of research allowing for completion of studies, publication of results and submission of federal grants for the next phase of studies
2. **Expression and methylation assays – *$55K***
   Funds for expression of CSPG4 and B7-H3; methylation studies for CSPG4
3. **Co-culture assays – *$25K***
   Will support assessment of the anti-tumor activity of B7-H3 CAR T cells

For more information, contact: **Maria J. Worsham, Ph.D.**, Senior Scientist, at mworsha1@hfhs.org

Biomarkers of progression to breast cancer from benign breast disease

Principal Investigator: Maria J Worsham, Ph.D., FACMG
Co-Investigators: Dhananjay Chitale, M.D., George Divine, Ph.D. & Lisa Newman M.D.

PROJECT DESCRIPTION:

The goal of our research is to characterize the pattern of methylation markers in tissues of patients with benign breast disease (BBD) who did or did not go on to develop invasive breast cancer (BC) in order to develop biomarkers that distinguish high risk from low risk BBD. These candidate markers will then be examined in blood plasma, serum, and in saliva of BC patients with potential to serve as minimally invasive, early detection biomarkers in diagnostic tests.

SPECIFIC AIMS:

1. Identify and confirm a BBD specific panel of genes whose methylation status is associated with progression to primary BC.
2. Validate the candidate gene panel from Aim 1 as potential predictors of progression to primary BC in BBD tissue.
3. Investigate the 20 gene panel's potential to serve as minimally invasive, early detection markers for BC in blood plasma, serum, and in saliva

WHY THIS RESEARCH MATTERS:

Non-malignant benign breast lesions are often treated vigorously because of the possibility that they are likely to adopt aggressive behaviors with time. A putative diagnostic, prognostic, and predictive biomarker panel would provide additive value as a minimally invasive screening test, given the limitations of screening mammography. Administered at the time of mammography, or prior to biopsy as in the case of a suspicious mammogram, it could be particularly applicable for women with BBD, a characteristic associated with an increased breast cancer risk and reduced sensitivity of mammography.

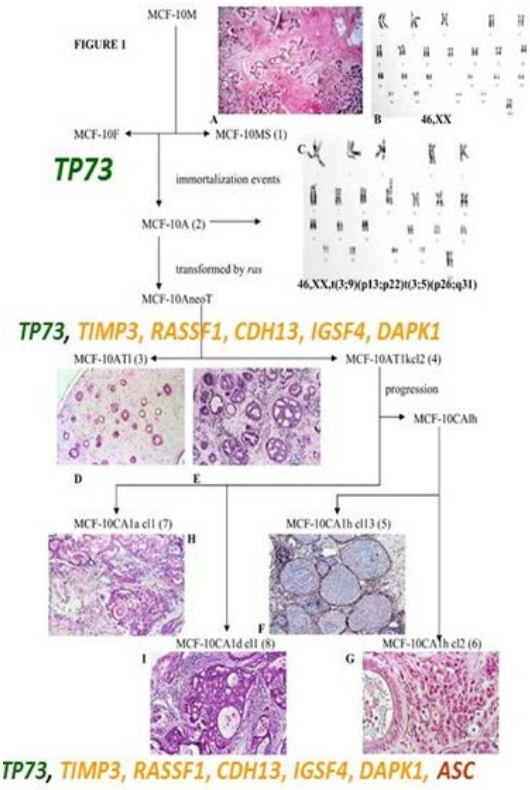


Figure: Methylation markers associated with immortalization, transformation, and progression of breast cancer in the MCF10 model. *TP73* was observed in all 7 cell lines

FUNDING NEEDS

1. **Bridge Funding Grant – *$200K***
   Funds an additional year of research allowing for completion of studies, publication of results and submission of federal grants for the next phase of studies
2. **Methylation profiling – *$ 200K***
   Will support comprehensive methylation profiling and validation of methylation targets
3. **Evaluation of target panel in blood plasma, serum, and in saliva – *$50K***
   Will support development and implementation of minimally invasive BBD diagnostics

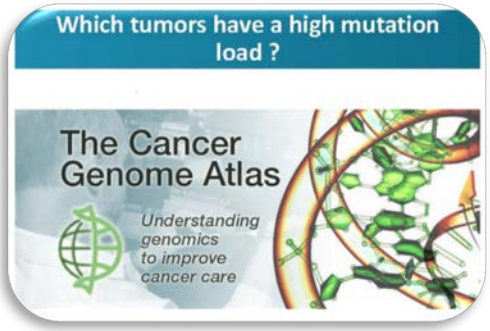
For more information, contact: **Maria J. Worsham, Ph.D.**, Senior Scientist, at mworsha1@hfhs.org

Mining New Determinants of Immunotherapy Response to Inflammatory Breast Cancer

Principal Investigator: Maria J Worsham, Ph.D., FACMG
Co-Investigators: Dhananjay Chitale M.D., Josena Stephen M.D., Kang Mei Chen, M.D. & George Divine Ph.D.

PROJECT DESCRIPTION:

The goal of this proposal is to perform comprehensive genomic profiling to predict tumor mutational load to guide the use of immunotherapies in inflammatory breast cancer (IBC).



Recent studies suggest the importance of immune cells in the progression and treatment of cancer. Immunotherapy with immune checkpoint-specific monoclonal antibodies (mAbs) have conclusively shown that this immunotherapeutic strategy can be effective, however, not all patients are responsive to this therapy. For instance, only about 20% of patients with TNBC respond to immunotherapy with the anti-PD-1 mAbs. Very little is known about the mechanisms of resistance to immunotherapy with immune checkpoint-specific mAbs. As immunotherapy has rapidly gained ground in the oncology community, research has accelerated in tandem to identify molecular markers or signatures that can best predict which patients may benefit. This proposal will comprehensively characterize both, the immunologic landscape of IBC (400 immune genes) and IBC tumor mutational burden (409 genes) using next generation sequencing to predict tumor mutational load to guide the use of immunotherapies.

SPECIFIC AIMS:

1. Determine tumor mutation burden using the Ion AmpliSeq™ Comprehensive Cancer Panel (409 key cancer tumor suppressor genes and oncogenes most frequently cited and most frequently mutated.) and measure the expression of genes involved in tumor-immune interactions (400 genes relevant to oncology and immune therapy response research).
2. Correlate mutations enriched in IBC whose tumors have high mutation-burden with immune cell expression profiles to assess how these mutations could impact immune response to guide the use of immunotherapies in IBC.

WHY THIS RESEARCH MATTERS:

IBC with its clinical and biological characteristics of rapid proliferation, is the most aggressive form of breast cancer. About 20% to 40% of IBC cases are triple-negative breast cancer (TNBC) which is associated with a more-aggressive clinical course and decreased overall and breast cancer-specific survival. Because current treatments do not result in long-term eradication of disease, there is an urgent need to define the biology of IBC to develop therapies that may prove more effective.

FUNDING NEEDS

1. **Bridge Funding Grant – *$200K***
   Funds an additional year of research allowing for completion of studies, publication of results and submission of federal grants for the next phase of studies.

2. **Next generation sequencing for tumor mutational burden and immune cell profiling – *$250K***
   Will support comprehensive mutation detection for 409 cancer genes and 400 immune genes.

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