Experimental Therapeutics
2020 Program Retreat

Agenda  Program Overview  Themes  Members

Co-Leaders:  Maria Baer, M.D., Feyruz Rassool, Ph.D.

PARP and DNMT1 trapping at DNA double strand breaks with PARP/DNMT inhibitor treatment

Vehicle  TAL  5-AZA  5-AZA+TAL

PARP1-γH2AX

PARP1-DNMT1
1:00 Introductory Remarks – Maria Baer, M.D., Co-Leader, Experimental Therapeutics Program

Theme 1: Target detection and measurement - Diagnostic advances including molecular early detection, liquid biopsy and imaging
1:15 Rena Lapidus, Ph.D. – “Overview of UMGCCC Shared Services”
1:30 Feng Jiang, M.D., Ph.D. – “A Direct Plasma miRNA Assay for the Early Detection of Lung Cancer”

Theme 2: Molecular targeting - Development and preclinical and clinical testing of new cancer therapies based on novel molecular targets
2:00 Ranee Mehra, M.D., and Daria Gaykalova, Ph.D. – “Phase 2 Study of Pembrolizumab and Vavituximab for Progressive Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck – Discussion of Rationale and Correlates”
2:15 Yixing Jiang, B.M., M.D. – “First-in-Human Phase I Study of Cerexa in Advanced Solid Tumors”
2:30 Ashkan Emadi, M.D., Ph.D. – “Venetoclax and pegcrisantaspase for complex karyotype acute myeloid leukemia”

Theme 3: Treatment delivery - Novel delivery strategies, including molecular carriers, nanotechnology, radiation therapy and radiation protection
2:45 Anthony Kim, Ph.D. – “Clinical Translation of Decreased nonspecific adhesivity, receptor-targeted (DART) Nanoparticles”
3:00 Victor Frenkel, Ph.D. - “Pulsed focused ultrasound for enhancing the delivery of anticancer agents in solid tumors: Mechanisms and applications”
3:15 Pranshu Mohindra, M.D., M.B.B.S - “Early Phase combined modality chemoradiation trials”
3:30 Isabel Jackson, Ph.D. - “Tissue sparing effects of ultra-high dose rate proton therapy: translational promise and road to the clinic”

New Investigators: Research updates
3:45 Sandrine Niyongere, M.D. – “Cytokine Expression and Targeting BCL-2 Regulation in CMML”
4:00 Rachel Abbotts, Ph.D. - “Modulation of the DNA damage response by epigenetic therapy in NSCLC”
4:15 Heather Ames, M.D., Ph.D. – “Microtubules and Neurodevelopmental Pathways in Glioblastoma Invasion”

4:30 WRAP UP - Feyruz Rassool, Ph.D., Co-Leader, Experimental Therapeutics Program
The Experimental Therapeutics (ET) Program Overview

A critical mission of the UM Marlene and Stewart Greenebaum Comprehensive Cancer Center is to improve patient outcomes through the development of novel therapies and therapeutic strategies. To that end, the Experimental Therapeutics (ET) Program develops and tests new therapies for solid tumors and hematologic malignancies.

The ET Program consists of members from five schools of the University of Maryland, including the School of Medicine (representing several departments) and the School of Pharmacy. Program members are supported by many individual peer-reviewed grants. The unifying theme of this Program is to build translational clinical trials based on innovative and novel laboratory research projects.
The ET Program's scientific goals are based on three themes:

1. Target detection and measurement - Diagnostic advances including molecular early detection, liquid biopsy and imaging

2. Molecular targeting - Development and preclinical and clinical testing of new cancer therapies based on novel molecular targets

3. Treatment delivery - Novel delivery strategies, including molecular carriers, nanotechnology, radiation therapy and radiation protection
ET Members
Personal Statement
My research focuses on preclinical and clinical investigations in acute myeloid leukemia (AML). My laboratory works on signal transduction pathways in AML with \textit{fms}-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) and preclinical development of novel therapeutic approaches to AML with this common and prognostically unfavorable molecular abnormality. I also collaborate with a number of other investigators on developing and testing novel therapies in preclinical models of AML. Finally, I am extensively involved in clinical trials of FLT3 inhibitors and other agents and therapeutic approaches in AML.

Projects
Enhancing FLT3 inhibitor efficacy in acute myeloid leukemia with FLT3-ITD.
Developing and testing novel therapies in preclinical models of acute myeloid leukemia.
Clinical trials in acute myeloid leukemia.

Publications


Feyruz Rassool, Ph.D.
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Personal Statement
I have spent more than 20 years studying the contribution of DNA damage/repair and altered repair of DNA double strand breaks (DSBs) to genomic instability that leads to the progression of cancers and leukemias to more aggressive forms of disease and/or resistance to standard therapies. Error-free DNA repair also breaks down in cells as part of the aging process, leading to repair by error-prone salvage repair pathways, predisposing to genomic instability and cancer.

Repair of DNA damage is also essential for cancer cell survival and this vulnerability can be exploited. Our recent work has been focused on therapeutic strategies involving targeting DNA repair factors in cancer. PARP expression is upregulated in several cancers, in particular those that are therapy-resistant. Recently we have shown that PARP inhibitors (PARPi) in combination with DNA methyltransferase inhibitors (DNMTi) cause synergistic cytotoxicity by trapping PARP in DNA. Additionally, DNMTis reprogram the DSB repair response in BRCA proficient cancers, sensitizing to PARPi.

Projects
Epigenetic and PARPi induction of innate immune signaling directly drives homologous recombination deficiency. (Adelson Foundation, VAI-SU2C funding and SPORE submitted)
Role of DNMTis and PARPi in sensitizing NSCLC to IR (DOD submitted)
Role of PARPi1 in aging and cancer (RO1/NIEHS)

Publications
Personal Statement
My main research focus is brain-specific invasion programs in glioblastoma. Glioblastoma is the highest-grade diffuse glioma and the most common primary malignant brain tumor in adults. Diffuse gliomas have a unique ability among both primary and metastatic brain tumors to travel along white matter tracts, namely the corpus callosum, to establish bilateral, unresectable disease. Because of the ability of glioblastoma tumor cells to sparsely infiltrate normal brain, it is particularly difficult to identify the furthest extent of glioblastoma spread at both the gross and microscopic level. These tumors are therefore often recurrent, with only one-third of patients surviving for more than 5 years. The over-arching goals of my research are to identify and clinically target those biological pathways that allow high grade gliomas to traverse and colonize the unique microenvironments present in the brain.

Projects
“Transient expression of neurodevelopmental migratory cues in glioblastoma invasion.”
Passano Foundation Clinician Investigator Award (2020)

“Profiling hidden cells: Detection and transcriptional analysis of glioblastoma invading the corpus callosum.”
American Cancer Society Internal Research Grant (2019)

Publications


Curt Civin, M.D.
Professor of Pediatrics and Physiology
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Personal Statement/Projects
Next Generation 2-Carbon-Linked Artemisinin Dimers for AML Treatment
Artemisinins are in worldwide clinical use as orally active antimalarial drugs with low/absent human toxicity. Artemisinins have promising antileukemic activity, even against cancer cells resistant to current antineoplastic drugs, via reducing MCL1 levels in addition to increasing cellular reactive oxygen species levels via their endoperoxide pharmacophores. We found that ARTs synergize strongly with kinase inhibitors (e.g. sorafenib) and BCL2 family member inhibitors (e.g. venetoclax) to reduce established AML xenografts to undetectable levels for months.

Current clinical artemisinins are susceptible to rapid metabolism and excretion, limiting their in vivo efficacy, especially for cancer treatment where prolonged high drug levels are desired. Since structure-activity relationship analyses suggested that dimers (artemisinin monomers tethered together via a short linker) are the most active artemisinin derivatives, we began to evaluate a panel of 2-carbon-linked artemisinin dimeric analogs (2C-ARTs) designed to resist metabolic degradation and deliver 2 endoperoxide pharmacophore payloads per molecule. We selected for study a set of 26 of these next generation 2C-ART dimers, based on their published in vivo antimalarial activity and tolerability, and we initially screened 2 of these for efficacy against human AML cell lines and for pharmacological parameters. One of these two 2C-ART analogs, ART714, demonstrated nM in vitro antileukemic activity and acceptable preliminary pharmacology. Our novel sorafenib+ART+venetoclax (“SAV”) regimen was tolerable and induced long remissions -- potential cures -- in human AML xenograft models.

Collaborators: Michelle Rudek PhD/PharmD, Johns Hopkins University, Soren Bentzen PhD/DMSc, UMSOM

Publications


Kevin Cullen, M.D.
Professor, Medicine
Director, Program in Oncology
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Director, Marlene and Steward Greenebaum Comprehensive Cancer Center (UMGCCC)
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Personal Statement
Research interests include Cisplatin action and resistance in head and neck cancer; prognostic and predictive biomarkers in head and neck cancer; disparities in head and neck cancer; human papillomavirus in head and neck cancer and other malignancies.

Projects
Major focus: Director, NCI P30 Cancer Center Support Grant
The Cancer Center Support Grant provides the resources and infrastructure to facilitate the coordination of interdisciplinary programs across a broad spectrum of research from basic laboratory research to clinical investigation to population science. Active admin supplements include CURE, and NADC.

Publications


Victor Frenkel, Ph.D.
Associate Professor and Director of Translational Focused Ultrasound Research, Dept. of Diagnostic Radiology and Nuclear Medicine
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Personal Statement
For more than 20 years, my research in the field of focused ultrasound (FUS) has been centered on investigating the mechanisms of interaction of ultrasound with biological tissues. By elucidating these mechanisms, and the bioeffects that they produce, my colleagues and I have proposed and developed novel applications in the fields of oncology, cardiovascular disease, cellular therapy and neurological disease. Working with physicists, engineers, biologists, and clinicians, my research utilizes a variety of techniques and methodologies including mathematical modeling and computer simulations, the development of novel in vitro/ex vivo model systems, and translationally oriented in vivo studies using advanced animal and disease models. I also employ a range of imaging modalities from electron and fluorescent microscopy to diagnostic ultrasound, PET-CT, and MRI.

Projects
DARPA SBIR Phase II SB173-001 (Restaino) as subcontract PI:
“Wearable ultrasound for imaging and modulation” This study will develop a prototype ultrasound device for noninvasive treatment of sleep apnea.

NIMH/ NIH 1R01MH121402-01A1 (Gendelman) as subcontract PI:
“HIV Theranostics” This study will employ theranostic nanoparticles for both bioimaging of antiretroviral drugs to track their distribution and simultaneously attenuate viral infection in tissue reservoirs within and outside the CNS.

Greenebaum Comprehensive Cancer Center (Frenkel, Kim, Winkles)
“Pulsed Focused Ultrasound and Tumor-penetrating, Fn14-targeted Nanotherapeutics for the treatment of Head and Neck Squamous Cell Carcinoma” This study investigates the potential of combining pulsed focused ultrasound exposures with targeted nanoparticles for improving the delivery and treatment of head and neck tumors.

Publications


Alonso Heredia, Ph.D.
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Personal Statement
Thanks to antiretroviral therapy (ART), HIV-infected patients are living longer. Older HIV-infected patients often develop cancer, necessitating treatment with both ART and anticancer therapy. Unfortunately, cancer treatment rates in HIV-infected cancer patients are lower than in uninfected individuals. This disparity in cancer treatment is due in part to the exclusion of HIV-infected patients from most cancer clinical trials. As a result, the optimal cancer treatments for those infected with HIV are not known. A main reason for the exclusion of HIV-infected patients from cancer clinical trials is toxicity from drug-drug interactions between cancer drugs and ART. Our laboratory is investigating drug interactions between ART and cancer therapies, assessing their impact on control of both HIV and malignancy.

Projects
NCI 1R01CA233441-01A1 (PI)
Impact of concomitant chemotherapy on HIV resistance to cART and reservoir size.

NCI 3P30CA134274-13S2 (Co-Leader)
PI: Kevin Cullen, MD Replacement of cART with broadly neutralizing antibodies to enable effective lung cancer immunotherapy in HIV infected patients

Publications
Personal Statement
At University of Maryland, I am a member of the Experimental Therapeutics program in Oncology in my capacity as collaborator in the many clinical trials underway at the comprehensive cancer center. Some of the more exciting work currently underway has to do with the CAR-T cell treatment of refractory diffuse large B-cell lymphoma. I am involved in characterizing the patients’ disease status as well as characterizing the complications we have been seeing in some of these patients, including CD19-negative relapses. Other work has been in relation to our experience with using specific treatment regimens in acute lymphoblastic leukemias and acute myeloid leukemias. We have also contributed several unique leukemia and lymphoma cases to the literature to further expand our knowledge of the genetic and immunophenotypic characteristics of these malignancies.

Projects
- Consultant and DeCODE panelist, Child Health and Mortality Prevention Surveillance (CHAMPS) Study, Mali, Africa section (PI: Karen Kotloff)
- Bill and Melinda Gates Foundation
- Member, DeCODE panel, which ascertains cause of death of each child in the study
- Pathology Residency Program Director
- Core educator, University of Maryland School of Medicine
- Course Director, Blood and Host Defense, Renaissance curriculum

Publications
Soleimani A, Koka M, Singh ZN, Kesari V, Badros A. Biologic Implications of t(11;14) in multiple myeloma explained with a case of refractory disease sensitive to ventoclax. Clinical Lymphoma, Myeloma and Leukemia. 2020 Jun 14:S2152-2650(20)30287-1. PMID: 32653454


Personal Statement
My research focuses on the development of MRI-based imaging techniques for the noninvasive investigation of metabolic processes under both normal and pathologic conditions that can be applied in preclinical and clinical settings. In particular, my research interests have centered on the use of dynamic nuclear polarization to increase the MR signal of metabolically active, $^{13}$C-labeled compounds for in vivo metabolic imaging. Specific areas of research include optimized acquisition and reconstruction techniques, kinetic modeling for quantitative analysis, and new probe development. At this time, I am exploring the application in tumor diagnosis and treatment monitoring, and in the study of cardiovascular and liver pathologies, inflammatory diseases, and brain metabolism.

Projects
NIH R01 DK106395 “Metabolic Imaging of nonalcoholic fatty liver disease”
The goal of this project is to develop novel metabolic imaging biomarkers for the improved diagnosis and treatment monitoring of nonalcoholic steatohepatitis.

NIH R21 CA213020 “Hyperpolarized $^{13}$C imaging of mitochondrial metabolism for improved characterization of prostate cancer”
The goal of this project is to develop novel metabolic imaging tools for the improved characterization of prostate cancer.

R21 EB029083 “Enzyme-enabled hyperpolarized $^{13}$C MRI for antibody-targeted imaging”
The goal of this project is to develop a novel MRI-based approach to antibody-targeted imaging for breast cancer.

Publications


Ranee Mehra, M.D.
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**Personal Statement**
My research focus is to develop and conduct clinical trials for upper aerodigestive malignancies, and in particular head and neck cancers. My background includes experience in the development of targeted therapies and immunotherapy for these disease. In addition, in conjunction with experimental therapeutics, I have an interest in biomarker development related to treatment selection.

**Projects**
Phase 2 study of pembrolizumab and bavituximab
Clinical collaboration with Rania Younis and her work related to semaforinD as a biomarker for immunotherapy response
Phase 2 study of ADU-S100 plus pembrolizumab for SCCHN

**Publications**
*Abstract PO-017: Evaluating the impact of the coronavirus (COVID-19) pandemic on treatment paradigms in head and neck cancer at a tertiary care hospital*


*Concurrent Definitive Immunoradiotherapy for Patients with Stage III–IV Head and Neck Cancer and Cisplatin Contraindication* Clinical Cancer Research 2020
Robert C. Miller, M.D.
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Personal Statement
Interested in normal tissue radiation injury mitigation science
FLASH radiotherapy for cancer
Microbiome of the oral cavity during radiation therapy

Projects
FLASH radiotherapy pre-clinical grant
A Translational Approach to Implement FLASH Radiotherapy in Non-Small Cell Lung Cancer
Microbiome genetic changes during proton radiotherapy for Head and Neck cancer

Publications


Abraham Schneider, D.D.S., Ph.D.
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Personal Statement
The Schneider laboratory is gaining insight into the potential repurposing of metformin, a first line low-cost anti-diabetic drug and well-known activator of the AMP-activated protein kinase (AMPK) signaling pathway in oral and craniofacial conditions. We are collaborating with investigators at the UMB School of Dentistry to formulate novel metformin-loaded nanomineral bioscaffolds to enhance dental pulp stem cell-based craniofacial vascularized bone regeneration, and the first metformin-containing bioactive dental cement to enhance dentin repair. Through cross-disciplinary collaboration with members of the Greenebaum Comprehensive Cancer Center’s Experimental Therapeutics Group, we are also developing metformin-loaded nanotherapeutic platforms to control oral cancer progression. In particular, we are interested in the role played by the AMPK signaling pathway in these processes.

Projects
NIH/NIDCR R21 DE029611 (MPI with Huakun Xu)
“A novel metformin-nanomineral scaffold as enhancer of craniofacial bone regeneration and angiogenesis via dental pulp stem cells”

UMB Institute for Clinical & Translational Research, Accelerated Translational Incubator Pilot (ATIP) program
MPI with Anthony Kim, Jeffrey Winkles
“Repurposing metformin using DART nanoparticle technology for treatment of head and neck squamous cell carcinoma”

Publications


Personal Statement
As the director of the Brain Tumor Treatment and Research Center at the University of Maryland Medical Center and an active member of the UM Greenebaum Cancer Center, I provide leadership and surgical care within a multidisciplinary team of radiologists, medical oncologists, radiation oncologists, neurosurgeons and pathologists treating brain tumor patients and developing new brain tumor treatments. I also take special interest in benign and malignant tumors of the brain and spine, pituitary tumors, Chiari malformation and degenerative conditions of the cervical spine.

Projects
My long-standing goal in treating glioblastoma (GB) is to link tumor-specific features with effective anti-tumor therapies to generate long-term treatment responses to potentially cure GB.

Publications
Repurposing platinum-based chemotherapies for multi-modal treatment of glioblastoma.

Developments in Blood-Brain Barrier Penetrance and Drug Repurposing for Improved Treatment of Glioblastoma.

Emerging Applications of Therapeutic Ultrasound in Neuro-oncology: Moving Beyond Tumor Ablation.
Pan Zheng, M.D., Ph.D.
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Personal Statement
My research interests are tumor immunology, cancer biology and signal transduction in hematopoietic stem cells (HSC) and cancer stem cells. My laboratory has been working on TSC-mTOR signaling in rejuvenation of hematopoietic stem cells (HSC) and immunity. Our collaboration with Dr. Yang Liu’s laboratory identified CD24-Siglec signaling pathway in regulating host defense to tissue damage induced inflammation. The pre-clinical and clinical studies have demonstrated that CD24-Siglec pathway is critical in pathogenesis of COVID-19, autoimmune diseases, metabolic syndrome, non-alcoholic steatohepatitis (NASH), HIV chronic inflammation, and immunotherapy related adverse events (irAE).

Projects
Melanoma Research Alliances MRA Team Science Award #559400 (MPI: Zheng, Liu, Hu-Lieskovan)
DAMPening immunotherapy adverse events in melanoma
This grant supports the final pre-clinical testing and IND filing to initiate a Phase I/II clinical trial for CD24Fc in prevention and reduction of immune related adverse events in melanoma patients treated with Ipilimumab and Nivolumab.

NCI R01CA227671-01A1 (PI: Zheng)
A Mouse Model to Assess Long Term Immunotherapy-related Adverse Effects in Children.
The focus of this grant is to use a mouse model that faithfully recapitulates the irAEs reported in anti-CTLA 4 and anti-PD-1 immunotherapy clinical trials to characterize and predict the long term effects in pediatric cancer patients. We will examine the role of DAMPs-binding protein CD24 and Siglecs in irAE pathogenesis.

Publications


Additional ET Members
Rachel Abbotts, MBChB, PhD, Dept. of Radiation Oncology, UM SOM
Ashraf Badros, MB, ChB, Dept. of Medicine, UM SOM
Eli Bar, PhD, Dept. of Pathology, UM SOM
Soren Bentzen, PhD, DMSc, Dept. of Radiation Oncology; Epidemiology & Public Health UM SOM
Yu Chen, PhD, Dept. of Bioengineering, UMCP
Vu Duong, MD, Dept. of Medicine, UM SOM
Joseph Friedberg, MD, Dept. of Surgery, UM SOM
Lyle Isaacs, PhD, Dep. of Chemistry & Biochemistry, UMCP
Isabel Jackson, PhD, Dept. of Radiation Oncology, UM SOM
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