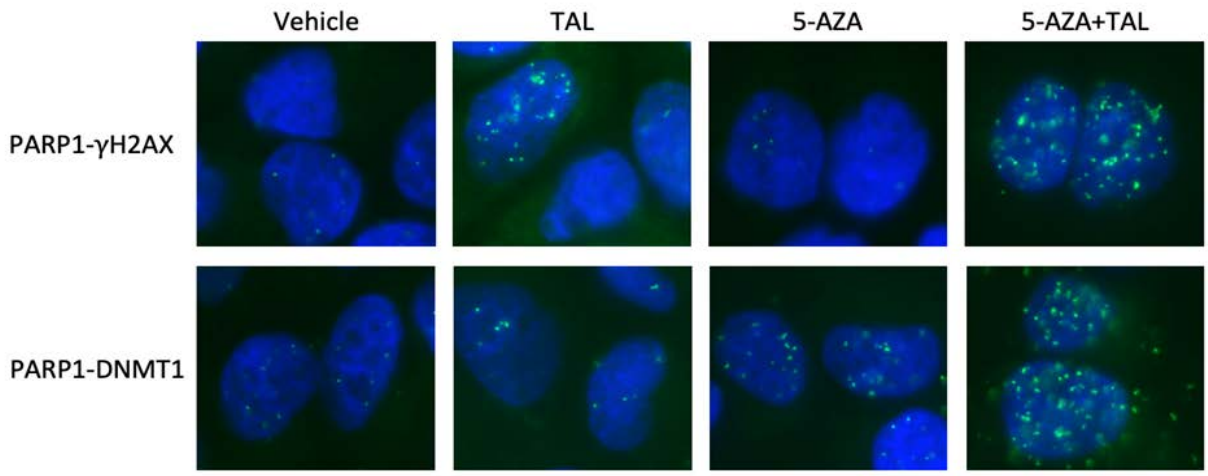
UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM
COMPREHENSIVE CANCER CENTER

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 non-small cell lung cancer (NSCLC) ((PNAS Paper, Abbots et al 2019)

Experimental Therapeutics Program 2020 Annual Retreat

Thursday, October 8, 2020, 1:00 PM – 5:00 PM

Zoom https://umaryland.zoom.us/j/96907771506

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"

1:45 Christian Rolfo, M.D., Ph.D., M.B.A. – "Liquid Biopsy Research in SARS-COV2: a new opportunity"

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

Maria Baer. M.D.

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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 *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

Kapoor S, Natarajan K , Baldwin PR, Doshi KA, Lapidus RG, Mathias TJ, Scarpa M, Trotta R., Davila E, Kraus M, Huszar D, Tron AE, Perrotti D, Baer MR. Concurrent inhibition of Pim and FLT3 kinases enhances apoptosis of FLT3-ITD acute myeloid leukemia cells through increased Mcl-1 proteasomal degradation. Clinical Cancer Research 24:234-247, 2018.

Scarpa M, Singh P, Bailey C, Lee JK, Kapoor S, Lapidus RG, Niyongere S, Sangodkar J, Wang Y, Perrotti D, Narla G, Baer MR. PP2A-activating drugs enhance FLT3 inhibitor efficacy through AKT inhibition-dependent GSK-3b-mediated c-Myc and Pim-1 proteasomal degradation. Under review.

Perl AE, Martinelli G, Cortes JE, Neubauer A, Berman E, Paolini S, Montesinos P, Baer MR, Larson RA, Ustun C, Fabbiano F, Erba HP, Di Stasi A, Stuart R, Olin R, Kasner M, Ciceri F, Chou WC, Podoltsev N, Recher C, Yokoyama H, Hosono N, Yoon SS, Lee JH, Pardee T, Fathi AT, Liu C, Hasabou N, Liu X, Bahceci E, Levis MJ. Gilteritinib or chemotherapy for relapsed/refractory *FLT3*-mutated AML. New England Journal of Medicine 381:1728-40, 2019.

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 (PARPis) 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 PARPis.

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 PARPis in sensitizing NSCLC to IR (DOD submitted)
Role of PARP1 in aging and cancer (RO1/NIEHS)

Publications

Muvarak NE, Chowdhury K, Xia L, Robert C, Choi EY, Cai Y, Bellani M, Zou Y, Singh ZN, Duong VH, Rutherford T, Nagaria P, Bentzen SM, Seidman MM, Baer MR, Lapidus RG, Baylin SB, **Rassool FV**. Enhancing the Cytotoxic Effects of PARP Inhibitors with DNA Demethylating Agents - A Potential Therapy for Cancer. Cancer Cell. 2016 Oct 10;30(4):637-650. doi: 10.1016/j.ccell.2016.09.002.

Abbotts R, Topper MJ, Biondi C, Fontaine D, Goswami R, Stojanovic L, Choi EY, McLaughlin L, Kogan AA, Xia L, Lapidus R, Mahmood J, Baylin SB, **Rassool FV**. DNA methyltransferase inhibitors induce a BRCAness phenotype that sensitizes NSCLC to PARP inhibitor and ionizing radiation. Proc Natl Acad Sci U S A. 2019 Nov 5;116(45):22609-22618. doi: 10.1073/pnas.1903765116.

McLaughlin LJ, Stojanovic L, Kogan AA, Rutherford JL, Choi EY, Chui Yen R-W, Xia L, Zou Y, Lapidus R, Baylin SB, Topper MJ, **Rassool FV**. Pharmacologic induction of innate immune signaling directly drives homologous recombination deficiency. *Proc Nat Acad Sci USA.* 2020 Jul 6. Online ahead of print.

Heather Ames, M.D., Ph.D.

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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)

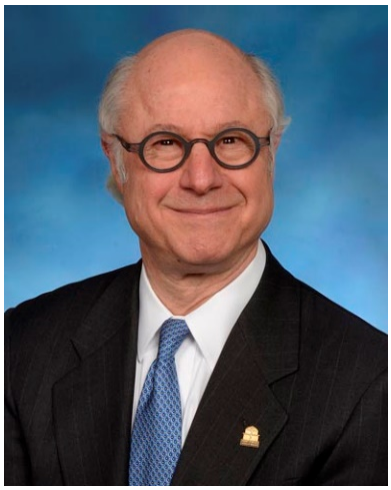
"Profiling hidden cells: Detection and transcriptional analysis of glioblastoma invading the corpus callosum."
American Cancer Society Internal Research Grant (2019)

Publications

Ames HM, Rooper LM, Laterra JJ, Eberhart CG, Rodriguez FJ. 2018. INSM1 expression is frequent in primary central nervous system neoplasms but not in the adult brain parenchyma. *J Neuropathol Exp Neurol*. 77: 374-382.

Ames HM, Yuan M, Vizcaino MA, Yu W, Rodriguez FJ. 2017. MicroRNA profiling of low-grade glial and glioneuronal tumors shows an independent role for cluster 14q32.31 member miR-487b. *Mod Pathol*. 30: 204-216.

Voss DM, Sloan A, Spina R, Ames HM, Bar EE. The Alternative Splicing Factor MBNL1 Inhibits Glioblastoma Tumor Initiation and Progression by Reducing Hypoxia-Induced Stemness. Cancer Res. 2020 Sep 14.



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

Campos-González R., Skelley A.M., Gandhi K., Inglis D.W., Sturm J.C., **Civin C.I.**, Ward T. Deterministic Lateral Displacement: The Next Generation CAR T-Cell Processing? SLAS Technol 1-14, 2018. PMID: 29361868

Creed M., Baldeosingh R., Eberly C.L., Schlee C.S., Kim M.J., Cutler J.A., Pandey A., **Civin C.I.**, **Fossett N.G., Kingsbury T.J.** PAX-SIX-EYA-DACH Network modulates GATA-FOG function in fly hematopoiesis and human erythropoiesis. Development 2020, 147. PMID: 31806659

Fox JM, Moynihan JR, Mott BT, Mazzone JR, Anders NM, Brown PA, Rudek MA, Liu JO, Arav-Boger R, Posner GH, **Civin CI, Chen X.** Artemisinin-derived dimer ART-838 potently inhibited human acute leukemias, persisted in vivo, and synergized with antileukemic drugs. Oncotarget. 2016 Feb 9;7(6):7268-79. PubMed PMID: 26771236

Kevin Cullen, M.D.

Professor, Medicine
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Director, Marlene and Steward Greenebaum
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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

Settle K, Posner MR, Schumaker LM, Tan M, Suntharalingam M, Goloubeva O, Strome SE, Haddad RI, Patel SS, Cambell EV 3rd, Sarlis N, Lorch J, Cullen KJ. Racial survival disparity in head and neck cancer results from low prevalence of human papillomavirus infection in black oropharyngeal cancer patients. Cancer Prev Res (Phila). 2009 Sep;2(9):776-81. PubMed PMID: 19641042; PubMed Central PMCID: PMC4459126.

Ambulos NP Jr, Schumaker LM, Mathias TJ, White R, Troyer J, Wells D, Cullen KJ. Next-generation sequencing-based HPV genotyping assay validated in formalin-fixed, paraffin-embedded oropharyngeal and cervical cancer specimens. J Biomol Tech. 2016 Jul;27(2):46–52. PubMed PMID: 27006646; PubMed Central PMCID: PMC4802743.

Zandberg DP, Cullen K, Bentzen SM, Goloubeva OG. Definitive radiation with concurrent cetuximab vs. radiation with or without concurrent cytotoxic chemotherapy in older patients with squamous cell carcinoma of the head and neck: Analysis of the SEER-medicare linked database. Oral Oncol. 2018 Nov;86:132–40. PubMed PMID: 30409293; PubMed Central PMCID: PMC6532223.

Victor Frenkel, Ph.D.

Associate Pr**of**essor 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

Shen, WB, Anastasiadis PA, Nguyen BA, Yarnell D, Yarowsky PJ, **Frenkel V**, Fishman PS. Magnetic enhancement of stem cell-targeted delivery into the brain following MR-guided focused ultrasound for opening the blood-brain barrier. ***Cell Transplantation*** 2017;26(7):1235-46. PMC5657739

Hersh DS, Nguyen BA, Dancy JG, Adapa AR, Winkles JA, Woodworth GF, Kim AJ, **Frenkel V**. Pulsed ultrasound expands the extracellular and perivascular spaces of the brain. ***Brain Res*earch** 2016;1646:543-50. PMC5499235

Mohammadabadi A, Huynh RN, Wadajkar AS, Lapidus RG, Kim AJ, Raub CB, **Frenkel V.** Pulsed focused ultrasound lowers interstitial fluid pressure and increases nanoparticle delivery and penetration in head and neck squamous cell carcinoma xenograft tumors. ***Physics in Medicine and Biology*** 2020;65:125017. PMID32460260

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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

Medina-Moreno, S., J. C. Zapata, M. L. Cottrell, N. M. Le, S. Tao, J. Bryant, **E. Sausville**, R. F. Schinazi, A. D. Kashuba, R. R. Redfield, and **A. Heredia**. 2018. Disparate effects of cytotoxic chemotherapy on the antiviral activity of antiretroviral therapy: implications for treatments of HIV-infected cancer patients. *Antivir Ther*. 2019; 24(3): 177–186. PMCID: PMC6779049

Madhurima Koka, MD, PhD
Associate Pr**of**essor, Pathology
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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

Kallen ME, **Koka, R**, Singh Z, Sanchez-Petito G, Yared JA, Duong VH. Teenage Mutant Neutrophilic Precursors: Leukemia Cutis with IDH2 Mutation on Enasidenib Therapy. Leukemia Research. Leuk Res. 2020 Jun 25;96:106406. PMID: 32604058

Sanchez-Petitto G, Holtzman NG, Bukhari A, Brown M, Morales MK, **Koka M**, Yared JA, Dahiya S, Rapoport AP, Hardy NM. Toxoplasma-induced hemophagocytic lymphohistiocytosis after haploidentical allogeneic stem cell transplantation. Transpl Infect Dis. 2020 Apr;22(2):e13242. Epub 2020 Feb 6. PMID. 31895492

Dirk Mayer, Dr. rer. nat.

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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 13C 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 13C 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

J.M. Park, L. Recht, S. Josan, M. Merchant, T. Jang, Y.-F. Yen, R. Hurd, D. Spielman, D. Mayer “Metabolic Response of Glioma to Dichloroacetate Measured *in vivo* by Hyperpolarized ^{13}C Magnetic Resonance Spectroscopic Imaging”, Neuro-Oncology, 5:433-441, 2013. (PMC3607261)

J.M. Park, D.M. Spielman, S. Josan, T. Jang, M. Merchant, R.E. Hurd, D. Mayer, L. Recht “Hyperpolarized ^{13}C-lactate to ^{13}C-bicarbonate ratio as a biomarker for monitoring the acute response of anti-vascular endothelial growth factor (anti-VEGF) treatment”, NMR Biomed., 29:650-659, 2016. (PMC4833516)

S.J. DeVience, X. Lu, J. Proctor, P. Rangghran, J. Medina, E.R. Melhem, R. Gullapalli, G. Fiskum, D. Mayer “Metabolic imaging of energy metabolism in traumatic brain injury using hyperpolarized [1-^{13}C]pyruvate”, Scientific Reports, 15;7(1):1907, 2017. (PMC5432492)

Ranee Mehra, M.D.

Professor of Medicine
University of Maryland School of Medicine
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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
Joshua A. Thompson, Reju Joy, Joshua E. Lubek, Ranee Mehra, Jason K. Molitoris, Rodney J. Taylor, Jeffrey S. Wolf, Matthew E. Witek and Kyle M. Hatten AACR Cancer and Covid Conference

A novel surgeon credentialing and quality assurance process using transoral surgery for oropharyngeal cancer in ECOG-ACRIN Cancer Research Group Trial E3311 Oral Oncology 2020

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.

Pr**of**essor, Radiation Oncology
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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

Sio T, Le-Rademacher J, Leenstra J, Loprinzi C, Rine G, Curtis A, Singh A, Martenson J, Novotny P, Tan A, Qin R, Reiter P, **Miller R.** A Phase III Randomized, Double-Blind Study of Doxepin Rinse versus Diphenhydramine-Lidocaine-Antacid (DLA) Mouthwash versus Placebo in the Treatment of Acute Oral Mucositis Pain for Patients Receiving Head and Neck Radiotherapy with or without Chemotherapy (Alliance A221304). JAMA. 2019; 321(15):1481–1490. doi:10.1001/jama.2019.3504.

Ma DJ, Price KA, Moore EJ, Patel SH, Hinni ML, Garcia JJ, Graner DE, Foster NR, Ginos B, Neben-Wittich M, Garces YI, Chintakuntlawar AV, Price DL, Olsen KD, Van Abel KM, Kasperbauer JL, Janus JR, Waddle M, **Miller R**, Shiraishi S, Foote RL. Phase II Evaluation of Aggressive Dose De-Escalation for Adjuvant Chemoradiotherapy in Human Papillomavirus–Associated Oropharynx Squamous Cell Carcinoma Journal of Clinical Oncology 2019 37:22, 1909-1918. PMID: 31163012 DOI: 10.1200/JCO.19.00463.

Waddle, M. R., Stross, W. C., Vallow, L. A., Naessens, J. M., White, L., Meier, S., Spaulding, A. C., Buskirk, S. J., Trifiletti, D. M., Keole, S. R., Ma, D. J., Bajaj, G. K., Laack, N. N., & **Miller, R. C.** (2020). Impact of Patient Stage and Disease Characteristics on the proposed Radiation Oncology Alternative Payment Model (RO-APM). International journal of radiation oncology, biology, physics, 106(5), 905–911. https://doi.org/10.1016/j.ijrobp.2019.12.012

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

Wang S, Y Xia, T Ma, MD Weir, K Ren, MA Reynolds, Y Shu, L Cheng, **A Schneider***, Hockin H. K. Xu. Novel metformin-containing resin promotes odontogenic differentiation and mineral synthesis of dental pulp stem cells. Drug Delivery and Translational Research 9(1): 85-96, 2019. *Co-senior corresponding author.

Qin W, J-Y Chen, J Guo, T Ma, MD Weir, D Guo, Y Shu, Z-M Lin, **A Schneider*** and HHK Xu. Novel calcium phosphate cement with metformin-loaded chitosan for odontogenic differentiation of human dental pulp cells. Stem Cells Int, 2018: 7173481. *Co-senior corresponding author.

Schneider A. Mouse Models to Study Metformin Effects in Carcinogenesis. In: Berger NA (ed) Murine Models, Energy Balance and Cancer. Energy Balance and Cancer 10: 271-292, 2015. Springer International Publishing, Switzerland.

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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.
Roberts NB, Wadajkar AS, Winkles JA, Davila E, Kim AJ, Woodworth GF.
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Developments in Blood-Brain Barrier Penetrance and Drug Repurposing for Improved Treatment of Glioblastoma.
Harder BG, Blomquist MR, Wang J, Kim AJ, Woodworth GF, Winkles JA, Loftus JC, Tran NL.
Front Oncol. 2018 Oct 23;8:462. doi: 10.3389/fonc.2018.00462. eCollection 2018.
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Emerging Applications of Therapeutic Ultrasound in Neuro-oncology: Moving Beyond Tumor Ablation.
Hersh DS, Kim AJ, Winkles JA, Eisenberg HM, Woodworth GF, Frenkel V.
Neurosurgery. 2016 Nov;79(5):643-654. doi: 10.1227/NEU.0000000000001399.
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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

Tian, R., Zhang, M., Liu, M. Fang, XF., Li, DL., Zhang, LG., Zheng, P., Zheng, YT., Liu, Y. CD24Fc protects against viral pneumonia in simian immunodeficiency virus-infected Chinese rhesus monkeys. *Cell Mol Immunol* (2020). 17:887-8.

Liu Y, Zheng P. Preserving the CTLA-4 checkpoint for safer and more effective cancer immunotherapy. *Trends Pharmacol Sci* (2020). 41 (1):4-12.

Zhang Y, Du X, Liu M, Tang F, Zhang P, Ai C, Fields JK, Sundberg EJ, Latinovic OS, Devenport M, Zheng P, Liu Y. Hijacking antibody-induced CTLA-4 lysosomal degradation for safer and more effective cancer immunotherapy. *Cell Res* (2019). 29(8):609-627.

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