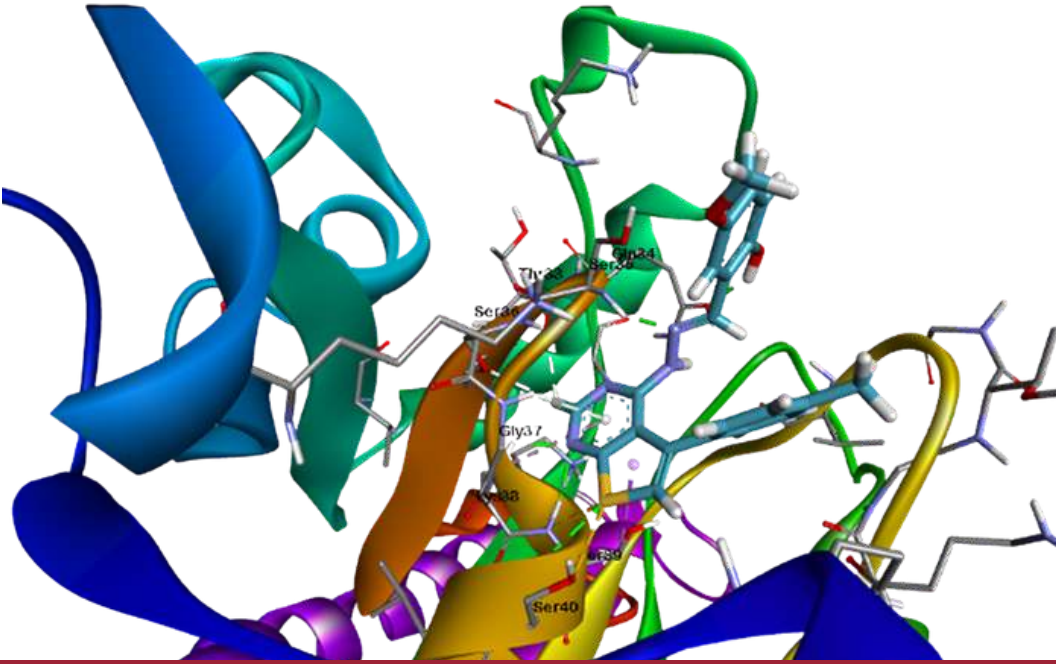
# UAMS SHOWCASE OF MEDICAL DISCOVERIES

# Drug Discovery and Emerging Therapies

## MAY 13, 2026




UAMS
Research & Innovation

A Research & Innovation event featuring UAMS investigators showcasing their research and discoveries.

# Welcome Message

Welcome to the UAMS Showcase of Medical Discoveries. This edition features Drug Discovery and Emerging Therapies! Join us to celebrate groundbreaking work from our researchers across departments including Pharmacology & Toxicology, Biochemistry & Molecular Biology, Pharmaceutical Sciences, Epidemiology, and more.

**Daniel Voth**
*Vice Chancellor for Research & Innovation*

This booklet showcases abstracts highlighting cutting-edge therapeutics—from SIRPα/CD47 neuroprotection and TK-850 for radiation-induced lung fibrosis, to MLKL screening for necroptosis research, novel PROTACs, and other innovative projects. Lab bios feature principal investigators like Alan J. Tackett, PhD, Dan A. Dixon, PhD, and Amit K. Tiwari, PhD.

Discover UAMS's leadership in developing next-generation treatments for cancer, infectious disease, retinal injury, and beyond!

**Amit K. Tiwari, PhD, DABT**
Associate Dean of Research and Graduate Studies
Director of Graduate Programs
Professor of Pharmaceutical Sciences

**1. What is the central mission or focus of your lab?**
Our lab is focused on overcoming one of the biggest barriers in cancer treatment: drug resistance. The lab brings together medicinal chemistry, pharmacology, systems toxicology, and pharmaceutical engineering to develop new therapeutics and delivery strategies that can bypass resistance mechanisms and improve treatment response in therapy-resistant cancers.

**2. What areas of drug discovery or emerging therapies is your lab currently exploring?**
Our lab is exploring several innovative therapeutic approaches aimed at resistant tumors, including targeting mitochondrial fission and tumor bioenergetics to trigger non-apoptotic, immunogenic forms of cancer cell death. Dr. Tiwari's team has also developed first-in-class agents designed to activate pathways such as necroptosis, methuosis, methuophagy, ferroptosis, entosis, and immunogenic cell death, while also advancing macropinocytosis-based delivery platforms to improve intracellular delivery of siRNAs and proteins.

**3. How does your lab's work help move scientific discoveries closer to meaningful clinical or real-world impact?**
Our lab is strongly translational, combining biomimetic microfluidics, high-content imaging, and AI-driven analytics to better predict and overcome chemotherapy failure. That work is paired with patented therapeutic and delivery platforms, federal and foundation support, and broad collaborative activity, helping move discoveries from preclinical innovation toward more effective treatment strategies for patients with resistant cancers.

**Alan J. Tackett, PhD**

Distinguished Professor of Biochemistry and Molecular Biology
Deputy Director of Winthrop P. Rockefeller Cancer Institute
Scharlau Family Endowed Chair for Cancer Research

**1. What is the central mission or focus of your lab?**

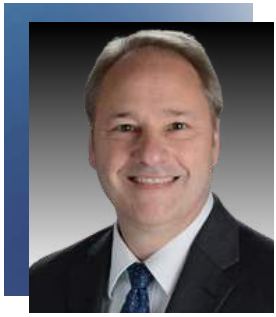
Our lab is focused on discovering new therapeutic strategies for metastatic melanoma and developing next-generation molecular profiling technologies to identify cancer biomarkers. Through this work, we aim to better understand cancer biology and translate those discoveries into more precise and effective treatment approaches.

**2. What areas of drug discovery or emerging therapies is your lab currently exploring?**

Our research team is actively working in cancer therapeutics, with particular emphasis on novel immunotherapeutic strategies and advanced proteomic technologies. In parallel, we are developing innovative molecular and systems biology tools that can uncover actionable biomarkers and support more targeted approaches to cancer treatment. This work spans both basic discovery and translational application, helping move promising ideas toward clinical relevance.

**3. How does your lab's work help move scientific discoveries closer to meaningful clinical or real-world impact?**

Our lab helps bridge discovery and application by identifying therapeutic targets, developing biomarker-driven technologies, and translating promising findings into real-world tools and treatments. This impact is further strengthened through leadership of major NIH-supported research centers, which provide proteomics resources, large-scale data capabilities, and training support to laboratories across the country. In addition, our translational efforts extend into biotechnology through companies focused on advancing novel cancer immunotherapies and delivering proteomics and bioinformatics solutions to the broader biomedical community.



**Dan A. Dixon, PhD**
Professor of Biochemistry and
Molecular Biology

**1. What is the central mission or focus of your lab?**

The Dixon laboratory studies how the loss of post-transcriptional gene regulation contributes to tumorigenesis in colorectal and pancreatic cancer. Our central mission is to better understand the molecular mechanisms that allow cancer-promoting genes to become overexpressed and drive disease progression.

**2. What areas of drug discovery or emerging therapies is your lab currently exploring?**

Our lab focuses on the signaling pathways and regulatory factors involved in controlling oncogenic and inflammation-associated gene expression. Using a range of cellular, molecular, and in vivo approaches, we are working to identify chemoprevention drug targets that could help control oncogenic gene expression in tumors.

**3. How does your lab's work help move scientific discoveries closer to meaningful clinical or real-world impact?**

By studying how normal RNA-binding proteins and microRNAs fail to regulate oncogenic mRNAs in tumor cells, we have identified new pathways and factors involved in cancer development. We aim to translate these discoveries into early cancer-detection blood markers and prevention-focused therapeutic strategies that can improve early detection and patient outcomes.

**Yong Zhu, PhD, Professor**
Fay W. Boozman College of Public Health
Associate Director for Population & Translational Sciences
Winthrop P. Rockefeller Cancer Institute

**1. What is the central mission or focus of your lab?**
Our lab focuses on bridging cancer epidemiology, molecular biology, and translational science to identify and develop clinically actionable biomarkers and therapeutic targets. We aim to improve early detection and treatment of cancer by translating population-based discoveries into practical clinical applications.

**2. What areas of drug discovery or emerging therapies is your lab currently exploring?**
We are developing novel therapeutic strategies rooted in our biomarker discoveries, with a particular emphasis on first-in-class piRNA-based cancer therapies. In parallel, we are advancing epigenetic approaches, including next-generation histone deacetylase (HDAC) inhibitors derived from natural compounds, designed to improve efficacy, specificity, and safety in solid tumors.

**3. How does your lab's work help move scientific discoveries closer to meaningful clinical or real-world impact?**
Our research integrates population-based discovery with functional and preclinical validation to accelerate translation into clinical applications. By prioritizing innovative modalities such as piRNA-based therapeutics and optimizing delivery, target specificity, and safety early in development, we aim to move promising discoveries efficiently toward clinical testing and ultimately improve patient outcomes.

## Abdelrahman (Abdel) Y. Fouda, B.Pharm, PhD

Associate Professor of Pharmacology and Toxicology

**1. What is the central mission or focus of your lab?**

Our lab studies how myeloid cells, particularly microglia and macrophages, respond to both acute and chronic injury. Its work focuses on shifting these cells from a pro-inflammatory state toward one that supports repair. By examining how they interact with neurons and the surrounding vasculature, the lab aims to uncover new strategies for neurovascular protection and tissue repair in stroke, diabetic retinopathy, and traumatic optic neuropathy.

**2. What areas of drug discovery or emerging therapies is your lab currently exploring?**

Our lab is exploring several emerging therapeutic strategies aimed at improving immune cell function after injury. Current work includes enhancing efferocytosis to promote the clearance of dead and dying cells and reduce secondary inflammation, including studies of the HDAC3-CD5L-CD36 signaling axis and the use of CD47 or SIRPα neutralizing antibodies to overcome inhibitory "don't eat me" signals. The lab is also investigating metabolic reprogramming through glycolytic enzymes such as HK2 and ENO2 to better understand and influence immune cell behavior. This work is designed to help translate basic discovery into clinically relevant therapeutic approaches.

**3. How does your lab's work help move scientific discoveries closer to meaningful clinical or real-world impact?**

By working with clinical collaborators to study human aqueous and vitreous humor samples, the team is identifying proteomic biomarkers and validating insights from preclinical models. Its close collaboration with ophthalmologists and clinicians at the Jones Eye Institute keeps the research aligned with pressing patient needs, including new approaches to vision recovery after central retinal artery occlusion. The lab is also developing intellectual property, such as neutralizing antibodies for CNS ischemia, to help move new therapies closer to clinical application

**Darin Jones, PhD**

Associate Professor of Pharmaceutical Sciences

**1. What is the central mission or focus of your lab?**

Our primary mission is the identification of novel therapeutics that target diseases of unmet medical need. More specifically, our work is centered in medicinal chemistry and chemical biology, with a strong focus on essential proteins involved in DNA repair.

**2. What areas of drug discovery or emerging therapies is your lab currently exploring?**

We study the structure and mechanism of proteins that respond to DNA damage, including repairing enzymes and signaling proteins. We develop small molecule inhibitors of essential proteins in several DNA repair pathways that are used to probe the regulation and possible crosstalk between pathways responding to damage and repair.

**3. How does your lab's work help move scientific discoveries closer to meaningful clinical or real-world impact?**

The identification and targeting of new protein targets may lead to safer and more efficacious therapies. Our lab helps move discoveries toward real-world impact by focusing on druggable mechanisms involved in DNA repair and chemotherapeutic resistance, which are highly relevant to cancer treatment and other serious diseases. In addition to identifying promising targets, we design and study small-molecule inhibitors that can clarify how these proteins function and help lay the groundwork for more precise and effective therapeutic strategies.

**Tudor Moldoveanu, PhD**

Associate Professor of Biochemistry and Molecular Biology

**1. What is the central mission or focus of your lab?**

Our lab is focused on understanding the molecular mechanisms of programmed cell death and using that knowledge to identify new therapeutic strategies. The lab studies how key cell-death pathways function at a structural and mechanistic level, with the goal of uncovering druggable targets that could ultimately support new treatments for cancer and other serious diseases.

**2. What areas of drug discovery or emerging therapies is your lab currently exploring?**

Our lab uses structural biology and chemical biology approaches to study major cell-death pathways, including apoptosis, necroptosis, and ferroptosis. To do this, the team applies high-resolution methods such as X-ray crystallography, NMR spectroscopy, and cryo-electron microscopy, then uses those mechanistic insights to rationally design small molecules that directly target the molecular machinery controlling these pathways. Key areas of focus include the BCL-2 family of proteins, the necrosome, and other regulatory systems involved in ferroptosis.

**3. How does your lab's work help move scientific discoveries closer to meaningful clinical or real-world impact?**

By linking fundamental structural insight to small-molecule design, Dr. Moldoveanu's lab helps translate basic discoveries into preclinical therapeutic development. The lab's work is positioned to inform next-generation cancer therapies, and its collaborative efforts with investigators at the UAMS Myeloma Center are aimed at characterizing novel biomarkers and regulatory hubs in multiple myeloma that may improve treatment strategies and strengthen the broader cancer research mission at the Winthrop P. Rockefeller Cancer Institute.

**Brendan Frett, PhD**

Assistant Professor of Pharmaceutical Sciences

**1. What is the central mission or focus of your lab?**

The central mission of our laboratory is small molecule drug discovery. We focus on the design, synthesis, and development of drug-like small molecules that modulate disease-relevant biological targets. Our work spans the early stages of the drug discovery pipeline, including medicinal chemistry, structure–activity relationship development, and preclinical evaluation. The overall goal of the lab is to translate fundamental biological discoveries into potential therapeutic candidates.

**2. What areas of drug discovery or emerging therapies is your lab currently exploring?**

Our laboratory works broadly in the areas of oncology, infectious disease, and immunology. We focus on discovering small molecules that target key biological pathways involved in cancer progression, infectious disease, and immune-related disorders. Much of our work involves developing targeted therapies designed to modulate specific proteins or signaling pathways that drive disease, with an emphasis on emerging therapeutic strategies and novel mechanisms of action.

**3. How does your lab's work help move scientific discoveries closer to meaningful clinical or real-world impact?**

Our research is highly translational and focused on moving discoveries from the laboratory toward clinical application. We design and optimize small molecules and evaluate them through pharmacological and preclinical studies. By working at the interface of chemistry, biology, and medicine, our lab helps transform early scientific discoveries into therapeutic candidates that can advance toward clinical development and ultimately improve patient care.

**Mokarram Hossain, PhD**

Assistant Professor of Pharmaceutical Sciences

**1. What is the central mission or focus of your lab?**

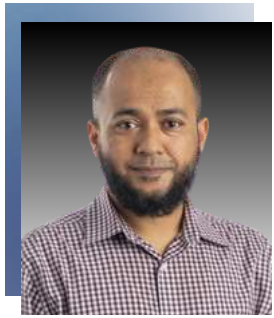
My research explores how myeloid immune cells drive cancer progression and how they can be reprogrammed into powerful tumor-killing effectors. I also study the role of myeloid cells in inflammatory diseases.

**2. What areas of drug discovery or emerging therapies is your lab currently exploring?**

My lab develops bispecific neutrophil engagers to treat solid cancers with limited T cell infiltration and to overcome immunotherapy barriers in these cancers.

**3. How does your lab's work help move scientific discoveries closer to meaningful clinical or real-world impact?**

My work focuses on the design and development of novel bispecific antibodies. We conduct all in vitro testing of our antibodies and develop the necessary mouse models to test these targeted therapies in vivo. The comprehensive data package we generate will help move our products to IND submissions.



**Sayem Miah, PhD**
Assistant Professor
Department of Biochemistry and Molecular Biology

**1. What is the central mission or focus of your lab?**

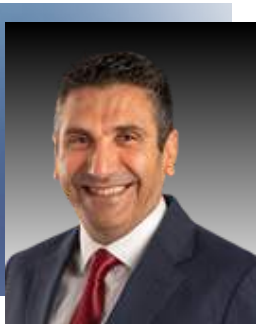
Our laboratory focuses on understanding how dysregulated protein tyrosine kinases, particularly BRK and ALK, drive progression and therapy resistance in triple-negative breast cancer. We investigate how these kinases disrupt tumor suppressor pathways, including SMAD signaling, and reprogram cellular states to promote invasion and metastatic potential.

**2. What areas of drug discovery or emerging therapies is your lab currently exploring?**

Our work integrates targeted protein degradation strategies (PROTACs) with dual BRK–ALK inhibition to overcome compensatory signaling networks. Using proteomics, genomics, and functional models, we define actionable vulnerabilities associated with kinase-driven tumor plasticity.

**3. How does your lab's work help move scientific discoveries closer to meaningful clinical or real-world impact?**

This research advances the development of more effective therapeutic strategies for patients with aggressive and treatment-resistant breast cancers.



**Mohamed Elasri, PhD**
Associate Vice Chancellor for Research
Division of Research and Innovation

**Gyan Sahukhal, PhD**
Assistant Staff Scientist
Department of Microbiology and Immunology

## A First-in-Class Dual-Target Therapeutic Against S. aureus Biofilms in Chronic and Implant-Associated Infections

Biofilm-associated infections caused by Staphylococcus aureus are a major contributor to chronic and recurrent infections across diverse clinical contexts, including wounds, orthopedic implants, and bone. Biofilms protect bacteria from host immunity and antimicrobials, promote persister cell formation, and exacerbate inflammation, making them a major therapeutic challenge. Two global regulators in S. aureus, SarA and MsaB, control biofilm formation, virulence, and persistence. Targeting these regulators represents a novel pathogen-specific anti-biofilm strategy. Using a structure-guided screening approach, we identified small molecules that bind SarA and MsaB, blocking their DNA-binding activity. Lead compound VB917 was chemically optimized for potency and specificity. Its antibiofilm activity was evaluated in USA300 (MRSA) and UAMS-1 (MSSA) clinical strains using microtiter biofilm assays, confocal imaging, and ImageJ analysis.

VB917 cytotoxicity was assessed on RAW 264.7 macrophages. Antibiotic synergy studies were performed with vancomycin and gentamicin. Preliminary in vivo efficacy was assessed in chronic wound infection model. VB917 inhibited biofilm formation with $IC_{50}$ values of 10.6 μM (USA300) and 12.0 μM (UAMS-1) and significantly disrupted established biofilms. Confocal imaging confirmed reduced biofilm biomass, increased bacterial cell death, and structural disintegration. VB917 showed no cytotoxicity up to 200 μM. When combined with vancomycin, its $IC_{50}$ was reduced to 5.46 μM indicating strong synergy. In vivo, VB917 significantly reduced bacterial burden in wounds and promoted wound healing, confirming its antibiofilm activity under physiological conditions. Conclusions: VB917 is a novel, dual-target anti-biofilm compound that disrupts S. *aureus* biofilm regulatory networks by inhibiting SarA and MsaB. It prevents and dismantles biofilms, enhances antibiotic efficacy, and demonstrates strong safety and in vivo performance. VB917 shows high potential as a next-generation therapeutic for treating biofilm-associated chronic infections.

**Tudor Moldoveanu, PhD**
Associate Professor, Department of Biochemistry and Molecular Biology
Director of Screening and Drug Discovery Resource

# High Throughput Screening for MLKL Activators for Necroptosis Research

*Tudor Moldoveanu[1], Elisabeth Ferreira[1], Perry Caviness[1], Ashish Sharma[1], Cristina Guibao[2], Dan McNamara[2], Casey Cai[2], Jonathan Low[2], Taosheng Chen[2], Darin Jones[3], Tudor Moldoveanu[1]*

Necroptosis is a non-apoptotic program cell death form implicated in pathologies including infectious diseases, inflammatory conditions, and cancer. The pathway is executed through plasma membrane rupture by the pseudokinase mixed lineage kinase domain-like, MLKL. MLKL is a fusion protein between an N-terminal pore-forming domain, known as the N-terminal executioner domain (NED), and the C-terminal pseudokinase domain (psKD), which regulates the activation of NED through phosphorylation by the upstream kinase receptor interacting proteins kinase 3 (RIPK3). We characterized the mechanism of activation of MLKL and showed that NED is kept in an inactive state by the autoinhibitory linker that connects it to the psKD. We showed that disrupting the interaction between the autoinhibitory linker potently activates necroptosis and validated this domain as a drug target. Using this domain we performed two pilot high throughput screening (HTS) cell-based assays in necroptosis deficient cells to identify several dozen small molecules among ~17,000 compounds that included bioactive, drug-like, and covalent inhibitors. We validated these as MLKL activators orthogonally in functional, binding, and conformational assays, and determined their mechanism of action using NMR spectroscopy. The compounds serve as useful preclinical tools for necroptosis and cancer research. Our effort supports the need for additional HTS to identify leads that may be chemical elaborated for in vivo use.

[1] UAMS Biochemistry and Molecular Biology, Little Rock, AR
[2] St. Jude Children's Research Hospital, Memphis, TN
[3] UAMS Pharmaceutical Sciences, Little Rock, AR

**Brendan Frett, PhD**
Assistant Professor
Department of Pharmaceutical Sciences

# Tk-850: A Novel Small Molecule Inhibitor for Mitigating Radiation-Induced Lung Fibrosis

Radiation-induced lung fibrosis (RILF) is a serious long-term complication that can develop in thoracic cancer survivors following radiotherapy and can significantly impair lung function and overall quality of life. Radiation exposure initiates a cascade of pro-inflammatory and pro-fibrotic signaling pathways, including the release of key cytokines such as transforming growth factor-β (TGF-β) and tumor necrosis factor-α (TNF-α), which play central roles in driving inflammation and fibrotic tissue remodeling. Targeting these cytokines represents a promising therapeutic strategy to mitigate the development and progression of RILF. In this study, we report the discovery and development of Tk-850, a novel dual anti-cytokine therapeutic designed to simultaneously inhibit TGF-β and TNF-α signaling. By targeting both fibrotic and inflammatory pathways, Tk-850 has the potential to prevent the onset of radiation-induced lung fibrosis and improve long-term pulmonary outcomes in patients undergoing thoracic radiotherapy.

**Alicja Urbaniak, MSc, PhD**
Instructor
Department of Biochemistry and Molecular Biology

# Repositioning Monensin: Enhancing Anti-Cancer Activity and Immune Modulation in Breast Cancer Cells

*Alicja Urbaniak[1], Eric Siegel[2], Marta Jędrzejczyk[3], Greta Klejborowska[3], Natalia Stępczyńska[3], Adam Huczyński[3], Bolni Marius Nagalo[4], Amit K. Tiwari[5], Eric U. Yee[4], Thomas Kelly[4], Steven Post[4], Alan J. Tackett[1]*

Monensin is an FDA-approved drug used in veterinary medicine. Recent studies have highlighted its potent anticancer activity. Because the de novo drug discovery process typically requires 10–15 years and an investment of approximately $1.3–$3 billion, drug repositioning offers an attractive strategy to bypass several stages of development and increase the likelihood of success.

Monensin and several of its novel analogs demonstrated potent activity against human and mouse breast cancer cell lines. Furthermore, these compounds induced apoptotic cell death, as evidenced by Annexin V/PI assays, downregulation of Bcl-2, and upregulation of Bak in MDA-MB-231 cells. Proteomic analysis revealed significant alterations in several molecular pathways associated with MHC class I and II antigen presentation following treatment with these compounds. Additionally, monensin and its analogs significantly increased the expression of MHC

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[2]Department of Biostatistics, University of Arkansas for Medical Sciences
[3]Department of Medical Chemistry, Adam Mickiewicz University
[4]Department of Pathology, University of Arkansas for Medical Sciences
[5]Department of Pharmaceutical Sciences, University of Arkansas for Medical Sciences

class I and II molecules. Our studies also showed that these compounds increased surface calreticulin levels. Treatment of MDA-MB-231 cells with monensin and its analogs also resulted in increased expression of p62 and LC3-II, suggesting disruption of the autophagic process.

Collectively, these findings indicate that monensin and its analogs not only exhibit potent anti–breast cancer activity but also modulate immune-related pathways. By disrupting autophagy and enhancing surface calreticulin levels, these compounds may potentiate antitumor immune responses, providing a promising avenue for drug repositioning in cancer therapy.

**Funding**
This work was supported by the UAMS Translational Research Institute, through grant TRI K12 TR004924 and UM1 TR004909 from the NIH National Center for Advancing Translational Sciences, as well as the Arkansas Breast Cancer Research Program. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

**Perry Caviness, PhD**
Associate Staff Scientist
Department of Biochemistry & Molecular Biology

## Screening and Drug Discovery Resource

*Perry Caviness, Ashish Sharma, Amit Tiwari, John Imig, Darin Jones, Tudor Moldoveanu*

The Screening and Drug Discovery Resource (SDDR) at the Winthrop P. Rockefeller cancer institute (WPRCI) enables cost-effective access to early-stage small molecule drug discovery infrastructure and expertise for the UAMS community. SDDR is staffed by two scientists with expertise in assay development, high throughput screening (HTS), and synthetic and medicinal chemistry. The resource has: 1) A growing library of >85,000 compounds categorized into a dozen of focused sets (e.g., targeting certain classes of proteins including helicases and kinases), a diversity set, as well as the Federal Drug Administration (FDA)-approved drugs set; 2) Contemporary compound management capabilities including registration and storage; 3) Liquid handling instrumentation; 4) Instrumentation for assay development and HTS using cells or purified targets; 5) Access to the latest software packages used in drug discovery including in silico structure activity relationship, data visualization and collaboration; and 6) Robust standard operating procedures to enable cross-institute collaborations in academic drug discovery. The primary goal of SDDR is to boost the impact of research at WPRCI and UAMS through publications and funding, which aligns with UAMS 2029 vision to obtain WPRCI NCI designation.

**Qin Qin, PhD**
Associate Staff Scientist
Department of Epidemiology

# PiRNA as a Novel Therapeutic in Hepatocellular Carcinoma: Insights from Population Screening

*Qin Qin[1*], Rui Han[2], Ran Liu[2], Tiansu Wu[2], Yaya Guo[2], Peyton Cook[1], Kinsey Garofalo[1], Yujuan Guo[1], Bolni M Nagalo[3] and Yong Zhu[1]*

Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality worldwide and the fastest-growing cause of cancer-related deaths in the United States. Current therapies are largely ineffective in advanced HCC due to tumor resistance and adverse effects, and 80–85% of patients fail to respond to immunotherapies. These challenges highlight the urgent need for novel therapeutic strategies. Small non-coding RNAs (ncRNAs), particularly piwi-interacting RNAs (piRNAs), represent a promising yet underexplored approach for cancer treatment. In this study, we identified a candidate piRNA and evaluated its therapeutic potential in HCC. piRNA profiling of 12 paired HCC and normal liver tissues revealed significant downregulation of piRNAs, including piR-37213, which was further validated in TCGA data (N=331 HCC; N=48 normal). Lipid nanoparticles (LNPs) were used to deliver piR-37213 in functional assays. Restoration of piR-37213 significantly inhibited tumor growth in vitro ($P<0.01$) and reduced tumor burden by 90% in vivo ($P<0.001$), with improved survival ($P<0.05$) in treated mice (N=44). Mechanistically, genome-wide expression analysis showed downregulation of genes involved in cell cycle progression, DNA replication, and repair. These findings demonstrate that piR-37213 functions as a tumor suppressor and provide proof of concept for piRNA-based therapeutics in HCC. Further studies are warranted to advance this innovative approach toward clinical application.

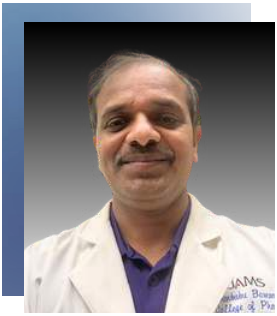
[1] Department of Epidemiology, College of Public Health, UAMS; [2] Department of Environmental Health Sciences, School of Public Health, Yale University; [3] Department of Pathology, College of Medicine, UAMS

**Ashish Sharma, PhD**
Associate Staff Scientist
Department of Biochemistry & Molecular Biology

## Rational Design and Optimization of BAK Activators for Apoptosis and Cancer Research

*Ashish Sharma, Perry Caviness, Elisabeth Ferreira, Darin Jones, Tudor Moldoveanu*

Mitochondrial apoptosis is essential for maintaining cellular homeostasis through elimination of damaged or abnormal cells. A critical step in this pathway is mitochondrial outer membrane permeabilization (MOMP), which is regulated by members of the BCL-2 family proteins. The pore-forming BCL-2 family proteins BAK and BAX execute MOMP upon activation by pro-death initiator BH3-only proteins such as BIM and PUMA, leading to cytochrome c release and activation of caspases that drive programmed cell death. Dysregulation of this pathway is commonly observed in cancer through upregulation of pro-survival BCL-2 proteins, which antagonize the pro-death counterparts, but also by downregulation of the initiators together leading to apoptosis resistance and tumor progression. To design selective small-molecule activators of BAK that promote apoptosis in cancer, we previously discovered and validated a benzothiazole derivative, SJ572946, as a weak BAK activator. Here we performed two rounds of structure activity relationship to 1) improve physico-chemical properties of BAK activators and 2) elaborate them to target features of the activation groove of BAK. We profiled a total of ~60 molecules to identify several leads that were orthogonal validated as BAK activators in biochemical and functional in vitro and cell-based assays and used NMR spectroscopy and in silico modeling to determine their mechanism of action. The improved BAK activators small molecules serve as useful chemical probes for mechanistic studies in apoptosis and preclinical cancer research.



**Shobanbabu Bommagani, PhD**
Assistant Staff Scientist
Department of Pharmaceutical Sciences

# Design and Synthesis of Novel RIPK3 PROTACS and Biological Evaluation

*Shobanbabu Bommagani[1], Perry Caviness[2], Elzabete Ferreira[2], Ashish Sharma[1,2], Tudor Moldoveanu[2], Darin E. Jones[1]*

Programmed cell death is a type of cellular demise or regulated cell death that is made possible by specialized molecular machineries. Necroptosis, which combines elements of both necrosis and apoptosis, is one of the most notable forms in cell death from a range of disease states, including ischemia reperfusion injury, neurodegenerative diseases, pancreatic cancer, and autoimmune diseases like inflammatory bowel disease (IBD). One of the kinases shown to be crucial to this necroptosis pathway is RIPK3. If the death receptors are involved, caspase 8 is involved; otherwise, necrosome-mediated cell death occurs. RIPK3 is a protein kinase that produces inflammation in necroptosis by associating RIPK1 and MLKL, all three of which form the necrosome. The groundbreaking discoveries have been made since the mid-2000s to identify RIPK1, RIPK3 and MLKL, encoded in the genome of mammals, moreover the complexity and growing number of distinct cell death modalities being identified can be explained by the role of several cellular homeostatic processes in mediating cell survival. The challenging complexity of necroptosis gained our attention to design and synthesis of novel PROTACS to target the RIPK3, RIPK2 and RIPK1 inhibition, and study their biological evaluations.

[1]Department of Pharmaceutical Sciences, University of Arkansas for Medical Sciences, Little Rock, AR 72205; [2]Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock, AR 72205.

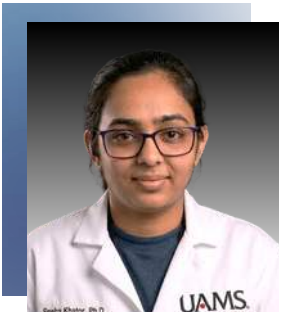
**Rami A. Shahror, MSc, M. Med., PhD**
Senior Postdoctoral Fellow
Department of Pharmacology and Toxicology

## Novel Therapeutic Potential of CD5L in Ischemic Retinal Injury and Ocular Disease

*Rami A. Shahror, Abdelrahman Y. Fouda*

Ischemic retinopathies, including diabetic retinopathy (DR), retinopathy of prematurity (ROP), and retinal vascular occlusions, are leading causes of vision loss and place a significant burden on healthcare systems. These conditions arise from impaired retinal blood flow, resulting in oxygen and nutrient deprivation and subsequent retinal cell damage. Despite available treatments, clinical outcomes remain limited, highlighting the need for novel therapeutic strategies.

Recently, we identified histone deacetylase 3 (HDAC3) as a negative regulator of efferocytosis, a reparative process in which myeloid cells clear apoptotic cells following ischemic injury. We demonstrate that CD5L, a protein upregulated in HDAC3-deficient macrophages, functions as a pro-efferocytic factor in the retina. Mechanistically, HDAC3 suppresses CD5L expression via an LXRα-dependent pathway. Using CD5L knockout mice and recombinant CD5L treatment, we show that CD5L exerts a protective effect against retinal ischemic damage. Furthermore, CD36, a receptor for CD5L, is upregulated in retinal myeloid cells after injury, and in vitro studies confirm that CD5L promotes efferocytosis through CD36 signaling. Importantly, therapeutic administration of CD5L preserves retinal function following ischemic insult, suggesting its potential as a novel treatment for ischemic retinal diseases.




**Sneha Khator, PhD**
Post Doctoral Fellow
Department of Biochemistry & Molecular Biology

# A PROTAC R-919 Degrader Suppresses the Oncogenic Functions of BRK

*Sneha Khator[1*], Md Asaduzzaman[1], Baku Acharya[2], Brendan Frett[2], Sayem Miah[1]*

Metastatic triple-negative breast cancer (TNBC) remains a highly aggressive disease with limited therapeutic options and a five-year survival rate of approximately 12%. Protein tyrosine kinase 6 (PTK6/BRK), a non-receptor tyrosine kinase overexpressed across breast cancer subtypes, promotes tumor growth, survival, and metastasis and is associated with poor clinical outcomes. Notably, BRK exhibits both kinase-dependent and kinase-independent oncogenic functions, limiting the efficacy of conventional kinase inhibitors.

Here, we evaluate a BRK-targeting proteolysis-targeting chimera (PROTAC), R-919, as a strategy to eliminate BRK protein and suppress oncogenic signaling. Triple-negative breast cancer cell lines, including MDA-MB-231and MDA-MB-468, were treated with increasing concentrations of R-919 for 24 hours, and BRK protein levels were assessed by western blot analysis. R-919 induced robust, proteasome-mediated degradation of BRK with nanomolar potency across multiple breast cancer models, while sparing non-transformed cells. BRK degradation suppressed cancer cell growth and viability and induced apoptosis, accompanied by increased expression of pro-apoptotic proteins. In contrast, BRK kinase inhibition failed to fully recapitulate these effects, although both approaches impaired cell migration.

These findings highlight BRK-directed PROTACs as a promising therapeutic strategy for targeting both BRK's kinase-dependent and kinase-independent functions in metastatic TNBC.

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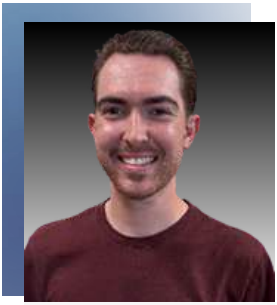

**Peyton Cook**
Research Assistant
Department of Epidemiology

# N-hydroxyhexanamide (NHH) as a Next-Generation HDAC-Targeted Therapy for Hepatocellular Carcinoma

*Peyton Cook[1*], Qin Qin[1], Kinsey Garofalo[1], Yujuan Guo[1], Amit Tiwari[2], Sean Taverna[3] and Yong Zhu[1]*

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with limited effective therapies for advanced disease. Histone deacetylases (HDACs) are promising therapeutic targets, yet currently approved HDAC inhibitors show limited efficacy in solid tumors and are often associated with toxicity. Building on prior work demonstrating that valeric acid (VA) functions as a novel HDAC inhibitor, we developed chemically modified VA derivatives to improve potency and safety. Among three candidates, N-hydroxyhexanamide (NHH) emerged as the lead compound. NHH demonstrated enhanced anti-tumor activity across multiple HCC cell lines and reduced cytotoxicity in normal liver cells. Comparative analyses showed that NHH achieved HDAC inhibition and anti-cancer efficacy comparable to the FDA-approved inhibitor belinostat, with improved cancer selectivity. Molecular docking and biochemical assays confirmed strong binding of NHH to multiple HDAC isoforms (HDAC2, 3, 6, and 8). Functionally, NHH significantly inhibited cell proliferation, colony formation, migration, invasion, and 3D spheroid growth in vitro. Mechanistic analyses suggest modulation of HDAC-regulated pathways, including p21/CDKN1A, E-cadherin, and NF-κB signaling. These findings identify NHH as a promising next-generation HDAC inhibitor and support the development of valeric acid derivatives as novel epigenetic therapies for HCC.

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**Mohammad J. Rahman, MS**
Research Assistant
Department of Pharmaceutical Sciences

# Harnessing Neutrophils to Eliminate Enhertu-Resistant HER2+ Breast Cancer

*Mohammad J. Rahman[1], Rezwan Ali1, Khandoker U. Ferdous1, Nishank Jain[2], and Mokarram Hossain[1]*

**Background:** Trastuzumab deruxtecan (Enhertu), an antibody–drug conjugate (ADC), has greatly improved outcomes in HER2-positive breast cancer; however, acquired resistance is a major challenge. Notably, most resistant tumors continue to express HER2, suggesting that resistance is often due to payload-related mechanisms rather than loss of the target, highlighting a critical unmet therapeutic need.

**Methods:** We developed HER2-expressing, deruxtecan-resistant breast cancer cell lines to model clinically relevant resistance. We tested a HER2-targeting bispecific neutrophil engager (NE) that binds HER2 on tumor cells and CD89 on neutrophils, promoting targeted neutrophil activation and tumor cell killing. Neutrophil-mediated destruction was evaluated using in vitro co-culture assays.

**Results:** Deruxtecan-resistant cell lines maintained HER2 expression but were refractory to deruxtecan-mediated cytotoxicity. In contrast, engaging neutrophils with the HER2-targeting NE resulted in robust and efficient killing of resistant tumor cells. These findings demonstrate that NE is a novel and promising therapeutic approach to target Enhertu-resistant breast cancer.

**Conclusions:** A HER2-directed bispecific neutrophil engager effectively redirects neutrophils to eliminate Enhertu-resistant, HER2-positive breast cancer cells. This approach overcomes resistance mechanisms that are independent of HER2 expression and highlights the therapeutic potential of harnessing innate immunity in refractory breast cancer.

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**Mohamed Abdelhamed, B.Pharm., M.Pharm.**
PhD Student and Graduate Research Assistant in Dr. Fouda's Lab

# SIRPα/CD47 Inhibition Is Neuroprotective in Ischemic Retinopathy and Enhances Efferocytic Function Under High-Fat Diet

*Mohamed Abdelhamed, M.Pharm; Rami Shahror, PhD; Abdelrahman Y. Fouda, PhD*

**Purpose**
Efferocytosis, the reparative process by which phagocytes clear apoptotic cells (AC), is impaired in diabetes and ischemic retinopathy, causing ACs accumulation. Lingering AC undergo secondary necrosis, releasing inflammatory factors that worsen retinal neurovascular damage. We hypothesized that the SIRPα/CD47 axis suppresses efferocytosis in diabetes and ischemic retinopathies, and that inhibiting this pathway restores phagocytic clearance. Using a retinal ischemia–reperfusion (IR) model and high-fat diet (HFD) mouse model of diabetes, we investigated how targeting SIRPα/CD47 affects efferocytosis and neuronal survival in the ischemic retina.

**Methods**
Retinal IR injury was induced by elevating intraocular pressure for 1 h followed by reperfusion, with the contralateral eye serving as sham control. Retinal SIRPα expression and AC–CD47 colocalization were analyzed 48 h post-IR (n=3–4/group). Intravitreal anti-SIRPα (1 µL, 5.47 mg/mL), anti-CD47 (1 µL, 8.31 mg/mL) or anti-IgG as control were administered 1 h post-IR (n=8–9/group). Retinal thickness (OCT), neuronal survival (NeuN), and leukocytes (CD45) were evaluated 1 week post-IR. Bone marrow–derived macrophages (BMDMs) were isolated from mice fed HFD for 16 weeks or standard chow for quantification of efferocytosis in vitro after treatment with anti-CD47 neutralizing antibody (10 µg/mL) or anti-IgG as control (n=4/group). SIRPα levels were measured in BMDMs subjected to 6 h oxygen-glucose deprivation followed by 18 h of reoxygenation (OGD/R) to mimic IR in vitro (n=7–8/group).

**Results**

IR injury upregulated retinal SIRPα by 141% at 48 h ($p<0.01$) and CD47 colocalized with TUNEL$^+$ AC. Both anti-SIRPα and anti-CD47 treatments improved neuronal survival (NeuN: 1.46-fold for anti-SIRPα, 1.48-fold for anti-CD47, $p<0.01$) with no change in CD45$^+$ cells, compared to IgG group. The treatments had no effects in sham eyes. BMDMs from HFD mice showed reduced efferocytosis by 37% ($p<0.05$) and upregulated SIRPα expression after OGD/R by 1.41-fold ($p<0.05$). CD47 neutralization increased the efferocytic ability of the HFD-BMDM by 2.32-fold ($p<0.01$).

**Conclusions**

IR injury upregulates the SIRPα/CD47 axis in the retina. Antibody neutralization of SIRPα or CD47 ameliorates retinal neurodegeneration after IR with no adverse effect in sham eyes. In HFD macrophages, elevated SIRPα suppresses their efferocytic capacity, and anti-CD47 treatment restores it. Collectively, our study suggests that inhibiting the SIRPα/CD47 axis is a promising therapeutic strategy for ischemic and diabetic retinopathies.

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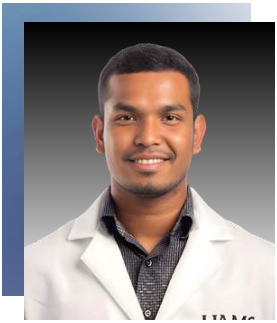

**Sanjay Adhikary, DVM, MSc**
PhD Student in Interdisciplinary Biomedical Science
Graduate Research Assistant

# Characterizing ATF6-dependent Mechanism Improving the Efficacy of Immune Checkpoint Blockade Therapy in Melanoma

*Sanjay Adhikary, Jacob L. Edmondson, Daniel Fil, Megan R. Reed, Billie Heflin, Katie Bronson, Duah Alkam, Katie Wallis, Sydnye L. Shuttleworth, Nathan Avaritt, Sean Taverna, Brian Koss*, Alan J. Tackett**

Advanced melanoma is the deadliest form of skin cancer. Conventional therapeutic interventions including chemotherapy and targeted therapy have poor prognosis due to aggressive nature of advanced melanoma and the nature of oncogenic mutations. Immune checkpoint blockade (ICB) therapy significantly improves the clinical outcome of advanced melanoma patients. However, the response of ICB therapy is limited to a subset of advanced melanoma patients and the cause of ICB non-responsiveness is multifactorial. Very recently, we found activating transcription factor 6 (ATF6) as a regulator of the response of ICB therapy. Literature has reported that ATF6 binds to the promoter region of ER stress responsive genes and controls the expression of ER stress responsive genes. In addition to ER stress response, our findings indicate that ATF6 binds to the promoter region of immunogenic cell death (ICD) inducing genes and transcriptionally controls the expression of ICD inducing genes. We found that ATF6 activation promotes T cell mediated killing in coculture assay and activates the hallmarks of ICD in coculture. ATF6 activation improved the efficacy of ICB therapy in multiple preclinical mouse melanoma models including subcutaneous and metastatic as evidenced through inhibition of tumor growth and prolonged the overall survival of mice. Our laboratory findings lead us to conclude that ATF6 is a novel regulator of ICD and thereby promotes ICB response in preclinical mouse melanoma models.

**Derin Akdeniz**
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# Rab27B Drives Tumor Progression and Represents a Novel Therapeutic Target in MSI-High Colorectal Cancer

*Derin Akdeniz[1], Sahida Afroz[1], Yang Ou[1], Dan A. Dixon[1]*

Colorectal cancer (CRC) progression is strongly influenced by post-transcriptional gene regulation and tumor microenvironment–mediated signaling. Rab27B, a small GTPase that regulates multivesicular body trafficking and extracellular vesicle (EV) secretion, has emerged as a potential mediator of tumor–stroma communication; however, its clinical relevance and therapeutic potential in CRC remain incompletely defined.

Analysis of TCGA datasets revealed that Rab27B is transcriptionally overexpressed in CRC tissues, with significantly higher expression in microsatellite instability–high (MSI-H) tumors compared to microsatellite-stable (MSS) tumors. Mismatch repair (MMR) deficiency, characteristic of MSI-H tumors, is positively correlated with Rab27B overexpression. Immunohistochemical analysis of colon adenocarcinoma tissues confirmed elevated Rab27B protein levels in MMR-deficient tumors relative to MMR-proficient and adjacent normal tissues.

Importantly, Kaplan–Meier survival analysis demonstrated that elevated Rab27B expression is associated with significantly poorer overall survival in MSI patients. Functional studies in the MSI-H CRC cell line HCT116 further demonstrated that Rab27B suppression disrupts vesicle biogenesis, enhances autophagic flux, and significantly inhibits xenograft tumor growth in vivo.

Collectively, these findings identify Rab27B as a therapeutically actionable regulator of vesicle trafficking, autophagy, and tumor progression in CRC, particularly in MSI disease. Given the enhanced responsiveness of MSI tumors to immune checkpoint blockade, pharmacologic inhibition of Rab27B may represent a novel strategy to further potentiate antitumor responses. Ongoing studies are evaluating small-molecule Rab27B inhibitors in MSI (HCT116) and MSS (SW480) models, both as monotherapy and in combination with immune checkpoint inhibitors and autophagy-modulating agents, to define rational combination therapies for CRC.

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**Rezwan Ali, M. Pharm.**
Graduate Assistant
Department of Pharmaceutical Sciences

# Arming Neutrophils to Overcome Immunotherapy Barriers in Pancreatic Cancer

*Mohammad J. Rahman[1], Rezwan Ali[1], Khandoker U. Ferdous[1], Nishank Jain[2], and Mokarram Hossain[1]*

**Background:** Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy with poor response to current immunotherapies. This resistance is driven by an immunosuppressive tumor microenvironment (TME) and a dense extracellular matrix (ECM)–rich stroma that limits cytotoxic T cell infiltration. Neutrophils are abundant in PDAC and possess intrinsic ECM-degrading and cytotoxic capabilities; however, they are not naturally programmed to recognize tumor cells and can instead promote tumor progression.

**Methods:** We developed a bispecific antibody–based neutrophil engager (NE) that targets HER2 on tumor cells and CD89 on neutrophils to induce tumor-specific neutrophil activation. Binding specificity was assessed by bio-layer interferometry. Neutrophil activation and function were evaluated using flow cytometry–based assays, ECM degradation assays, and functional assays of migration, phagocytosis, and NET formation.

**Results:** The NE bound specifically to both HER2 and CD89 and induced neutrophil activation only in the presence of HER2-positive tumor cells. NE-activated neutrophils efficiently degraded ECM components, including collagen and gelatin, indicating their capacity to disrupt stromal barriers. Importantly, NE treatment preserved neutrophil migration and bacterial phagocytosis and did not significantly increase neutrophil extracellular trap (NET) formation.

**Conclusions:** Bispecific neutrophil engagers selectively activate neutrophils within the PDAC TME, enhancing anti-tumor functions while minimizing pro-tumor and off-target effects.

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**Rana Elbishbishy, B. Pharm, MSc.**
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# Discovery and Characterization of Host-Directed Triptan-Derived Antivirals against Hantaviruses

*Rana M. Elbishbishy[1], Maria N. Cajimat[2], Ju-Hyeon Lee[3], Joseph Oleniczak[4], Robert C. Chin[4], Mark Hickman[5], Dennis A. Bente[2,6], Kevin N. Dalby[3] and Tamer S. Kaoud[1,7]*

**Introduction:** Hantaviruses are rodent-borne RNA viruses within the Hantaviridae family that cause severe infections, including hemorrhagic fever with renal syndrome and hantavirus cardiopulmonary syndrome, threatening over 200,000 individuals worldwide. Despite their significant health impact, no approved mechanism-defined antiviral therapies exist. In this study, we identified a series of triptan derivatives that potently block the entry of multiple hantavirus strains. We evaluated their antiviral activity, selectivity, and mechanism of action in physiologically relevant and authentic virus systems. Our results support a host-directed mechanism rather than a direct targeting of the virus.

**Methods:** Compounds 44 and 45 were initially tested in patient-derived colon and lung organoids using HIV particles pseudotyped with Andes orthohantavirus or Hantaan virus glycoproteins to assess inhibition of viral entry and organoid viability. They were also examined against authentic hantavirus infection using plaque-reduction assays in Vero E6 cells. Mechanistic studies employed label-free and fluorescence-based assays to distinguish effects on viral binding, fusion, lysosomal pH, and endosomal trafficking. Preclinical evaluation, including pharmacokinetic, toxicity, and efficacy studies, is being conducted in Syrian golden hamsters.

**Results:** Compounds 44 and 45 significantly reduced entry of Andes- and Hantaan-glycoprotein-pseudotyped particles into both colon and lung organoids without affecting organoid viability, supporting a favorable therapeutic index in tissue-like models. In assays with authentic viruses, both compounds inhibited multiple hantaviruses, including Andes virus, Hantaan virus, and Seoul virus, with nanomolar $IC_{50}$ values for several strains. Mechanistic studies demonstrated that neither compound prevented receptor binding, spike-mediated cell–cell fusion, or neutralized endosomal pH. Instead, compound 45 induced a moderate, time-dependent delay in viral trafficking to acidic compartments, suggesting impaired endosomal trafficking, escape, or early-to-late endosomal maturation. PK and toxicity studies indicated that compounds 44 and 45 exhibited favorable pharmacokinetic parameters and were non-toxic in hamsters at doses up to 100 mg/kg.

**Conclusions:** Triptan-derived compounds 44 and 45 are promising host-directed antiviral candidates against hantaviruses. Their mechanism likely involves a post-attachment step. These observations motivate further target-identification studies focused on host endocytic trafficking pathways.

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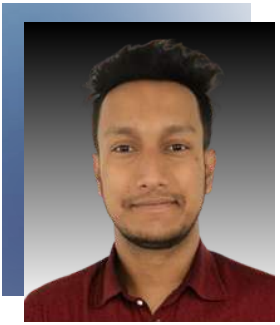
**Joyeeta T. Khan**
Graduate Assistant
Department of Pharmaceutical Sciences

# Endolysosomal Trafficking Disruption via PIKfyve Inhibition Enhances Radiotherapeutic Vulnerability in Glioblastoma

*Joyeeta Tahseen Khan, Veronica Piedra, Prabhash N Tripathi, Karthikeyan Chandrabose, Nukhet Aykin-Burns, Amit K Tiwari*

*Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR*

Glioblastoma (GBM) is an aggressive, grade IV primary brain tumor with poor prognosis and a five-year survival rate of less than 10%. Standard therapy includes surgical resection followed by radiotherapy (RT) with temozolomide, yet GBM frequently develops profound radioresistance driven by enhanced DNA damage repair and cytoprotective autophagy. We investigated whether pharmacological inhibition of PIKfyve, a lipid kinase regulating endolysosomal trafficking and autophagic flux, could disrupt these survival mechanisms and enhance radiosensitivity. PSG-6, a novel PIKfyve inhibitor derived from the MOMIPP and BAPT chemical series, demonstrated a favorable safety profile across GBM cells and normal astrocytes while maintaining potent kinase inhibition ($IC_{50}$ = 20.5 nM, ADP-Glo assay). PSG-6 induced transient vacuolization without significant cytotoxicity and markedly enhanced radiation sensitivity in clonogenic assays, achieving approximately five-fold greater suppression of survival fraction compared with a standard PIKfyve inhibitor and the conventional GBM therapy temozolomide. Drug–radiation interaction analysis using the Highest Single Agent model yielded a synergy score of 13.071, confirming synergistic activity. Mechanistically, PSG-6 increased intracellular and mitochondrial reactive oxygen species, disrupted endolysosomal homeostasis with elevated LAMP1 expression, and impaired late endosomal recycling characterized by reduced RAB9A expression. PSG-6 also blocked autophagic flux, evidenced by LC3B-II accumulation and punctate p62 retention under irradiation. Importantly, PSG-6 potentiated radiation-induced DNA damage, with persistent γH2AX foci observed at 24 and 48 hours after irradiation. Collectively, these findings identify PIKfyve inhibition as a mechanistically grounded radiosensitization strategy that disrupts survival pathways supporting DNA repair in GBM.



**Rajiv Pathak**
Graduate Assistant

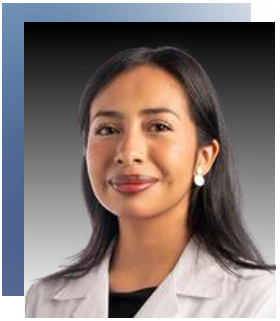
# Targeting Endolysosomal Trafficking to Overcome Paclitaxel Resistance in Triple-Negative Breast Cancer

*Rajiv Pathak, Prabhash N Tripathi, Karthikeyan Chandrabose, Amit K. Tiwari*

Taxane therapy remains the standard treatment for triple-negative breast cancer (TNBC), yet acquired resistance to Paclitaxel occurs in more than 90% of metastatic cases, leaving patients with limited therapeutic options and a 5-year survival below 30%. Resistant TNBC cells adapt by upregulating complementary endolysosomal survival pathways, including macropinocytosis to scavenge nutrients and protective autophagy to sequester or degrade paclitaxel. Both processes depend on the lipid kinase PIKFYVE and its product $PI(3,5)P_2$.

We developed low-nanomolar PIKfyve inhibitors that exploit this vulnerability by simultaneously enhancing macropinocytic drug uptake while blocking protective autophagy. Paclitaxel-resistant SUM159PT/PAC200 cells (PTX $IC_{50}$ >1000 nM) were treated with inhibitors ± paclitaxel. Macropinocytosis was quantified using 70 kDa FITC-dextran uptake and confirmed using the macropinocytosis inhibitor EIPA. Autophagy inhibition was confirmed by increased MAP1LC3B (LC3B-II) and accumulation of SQSTM1 (p62) detected by western blot and proteomics. Sustained autophagic flux blockade was further validated by time-dependent accumulation of p62 by western blot and immunofluorescence, showing pronounced p62 puncta in treated cells. Increased intracellular drug accumulation was validated using the Rhodamine-123 fluorescence accumulation assay, which demonstrated enhanced dye retention despite unchanged levels of the drug efflux transporter ABCB1 (P-glycoprotein) confirmed by western blot and immunofluorescence.

Lead inhibitors (PSG-06 and PSG-09) induced >3-fold macropinocytosis while blocking protective autophagy, resulting in significantly enhanced intracellular paclitaxel accumulation and restored drug sensitivity. Combination treatment produced strong synergy (combination index as low as 0.64), >50% reduction in cell viability, cell-cycle arrest, and apoptosis at clinically relevant paclitaxel concentrations (5–20 nM). The macropinocytosis inhibitor EIPA completely abolished resensitization, confirming an on-target mechanism. Importantly, PSG-06 combined with paclitaxel induced dose-dependent apoptosis in paclitaxel-resistant SUM159PT/PAC200 3D organoids, validated by cleaved PARP detection. Together, these findings demonstrate that PIKfyve inhibition creates a synthetic-lethal vulnerability in resistant TNBC by simultaneously driving macropinocytic paclitaxel uptake and blocking protective autophagy, thereby bypassing ABCB1-mediated drug efflux and overcoming paclitaxel resistance.



**Veronica Piedra, BSc**
Bioinformatics PhD Student

# Macropinocytosis-Inducing Small Molecule PSG-06 Enhances Macromolecule Uptake and Endosomal Leakage in Cancer Cell Lines Through PIKfyve Inhibition

Delivery of macromolecular therapeutics is often constrained by limited cellular uptake and endosomal trapping. We propose to use macropinocytosis, a non-selective fluid-phase uptake mechanism, to deliver large molecules inside cancer cells through PIKfyve inhibition. Macropinocytosis-inducing small molecules (MPIs) may provide a safe strategy to increase internalization and promote access beyond endosomes.

We screened a series of candidate MPIs to identify a lead compound based on (i) minimal cytotoxicity and (ii) robust vacuolization phenotypes in cancer cell models, and (iii) PIKfyve inhibition. Lead selection and characterization included $IC_{50}$ measurements, time-course proliferation curves, and quantitative morphology/phenotype scoring, and led us to identify PSG-06. Macropinocytosis and cargo uptake mediated by PSG-06 were evaluated using FITC-dextran (70 kDa), Lucifer Yellow, and FITC-albumin internalization. Endosomal membrane permeability/escape potential was assessed via a calcein leakage assay, and downstream endolysosomal consequences were profiled using lysosomal activity readouts. Mechanistic support for macropinocytosis and pathway engagement was provided by qPCR and immunoblotting of macropinocytosis and endolysosomal markers, alongside pharmacological inhibitor studies to test pathway dependence of vacuolization and uptake phenotypes.

PSG-06 reproducibly induced prominent vacuolization in cancer cells while maintaining comparatively low cytotoxicity across effective concentrations. Functional assays showed increased internalization of dextran, Lucifer Yellow, and albumin versus controls, indicating enhanced fluid-phase and macromolecular-cargo uptake. Calcein leakage patterns were consistent with increased endosomal membrane permeability, supporting improved potential for cargo release from vesicular compartments. Lysosomal activity measurements revealed compound-dependent modulation of endolysosomal function. Inhibitor studies attenuated key phenotypes (vacuolization and/or uptake), and molecular readouts from western blotting and qPCR further supported macropinocytosis-associated pathway engagement.

These findings position PSG-06 as a potential drug delivery agent, with high macropinocytic uptake capabilities at non cytotoxic concentrations. These results support continued development of this chemotype as a small-molecule platform to enhance intracellular delivery of macromolecular cargo.

**Saloni Sood, M.Tech**
Graduate Assistant
Department of Pharmaceutical Sciences

# Discovery of CAST-D4 as a Small Molecule that Couples Ferroptotic Stress with Entotic Cell-in-Cell Death in Colorectal Cancer Cells

*Saloni Sood[1], Prabhash N. Tripathi [1], Rajiv Pathak, Joyeeta T. Khan, Karthikeyan Chandrabose[1], Amit K. Tiwari[1]*

Apoptosis resistance is a major determinant of therapeutic failure in colorectal cancer (CRC), creating a need for strategies that bypass apoptotic signaling and engage alternative cell death mechanisms. Here we report the discovery of CAST-D4, a hybrid thienopyrimidine-benzoxazole small molecule that induces a dual non-apoptotic cell death program integrating ferroptotic stress with entosis. CAST-D4 potently suppressed proliferation of CRC cells, including HCT-116, with an $IC_{50}$ of approximately 1.5 μM while relatively sparing non-malignant cells, indicating tumor-selective activity. At low micromolar concentrations (2-8 μM), CAST-D4 rapidly induced the formation of cell-in-cell structures characteristic of entosis and produced morphological features distinct from classical apoptotic cell death. Pharmacological inhibition of caspases using the pan-caspase inhibitor z-VAD-fmk failed to rescue cell viability, confirming that CAST-D4-mediated cytotoxicity proceeds independently of apoptotic signaling. Mechanistically, CAST-D4 triggered pronounced lipid peroxidation accompanied by suppression of the ferroptosis regulator GPX4 and induction of oxidative stress-responsive genes including HMOX1, consistent with activation of ferroptotic stress pathways. Proteomic and transcriptional analyses further revealed extensive cytoskeletal remodeling and extracellular matrix reprogramming, including elevated expression of vitronectin, clusterin, and TIMP1, together with activation of the RhoA-ROCK signaling pathway and upregulation of the contractility marker MYL9. These molecular changes promoted actomyosin-driven cell engulfment and entotic cell-in-cell structures. Collectively, these findings identify CAST-D4 as a first-in-class small molecule that bypasses apoptotic resistance by simultaneously activating ferroptosis stress and entosis, revealing a therapeutically exploitable non-apoptotic vulnerability in CRC.

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**Daniel Stuckey, B.S. in Chemistry**
Graduate Student and PhD Candidate
Department of Pharmaceutical Sciences

# Discovery of Small Molecules That Target the Protein-Protein Interface of the Grb2 Dimer

*Daniel Stuckey[1], Zamal Amed[2], Mahfuzul Hasan[1], John A. Tainer[2], Darin E. Jones[1*]*

The growth factor receptor tyrosine kinase (RTK) family is a potent inducer of cellular growth. Ligand binding to cognate receptors on plasma membrane induces receptor dimerization and activation, which in turn recruits intracellular molecules for downstream signal transduction. A key signaling pathway activated by GF receptors is the Ras signaling cascade that ultimately leads to cell proliferation. Activation of RTKs leads to the recruitment of Growth Factor Receptor Bound Protein 2 (Grb2), which is constitutively bound to the mammalian homologue of drosophila son of sevenless (SOS), and a guanine exchange factor (GEF) for Ras. The recruitment of Grb2-SOS complex by activated RTK places the GEF in proximity to Ras and exchange of Ras-GDP to Ras-GTP and the initiation of the mitogen-activated protein (MAP) kinase cascade. All RTKs recruit Grb2 either directly or indirectly to their early signaling complex to activate Ras-MAP kinase signaling. Virtual drug screening has identified several dimer interface binding drug-like molecules bridging the two Grb2 protomers which break the link to SOS that is critical to Ras/MAP kinase activation. The design and synthesis of novel analogues to improve binding and stabilization of dimeric Grb2 is presented.

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## Thank you!

The Division of Research & Innovation sincerely thanks all presenters, researchers, students and trainees, faculty, and staff for their contributions to advancing research and innovation at the University of Arkansas for Medical Sciences.

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