

## **Pediatric Cancer Research Group Supported by the Nebraska Legislature (LB 417) in collaboration with The Fred and Pamela Buffet Cancer Center & Children's Nebraska**

The State of Nebraska has funded the Pediatric Cancer Research Group (PCRG) since 2013. These resources are being leveraged with key strategy leaders within the University of Nebraska system, the state of Nebraska and Children's Nebraska to change the landscape of pediatric cancer research for generations to come.

This year, the PCRG hosted the sixth annual Pediatric Cancer Research Group Symposium on August 29, 2023. The Symposium, co-sponsored by the Child Health Research Institute, was attended by over 130 participants and included hands on experiences with robotics and virtual reality tools. Participants were also able to browse the nearly 30 scientific posters from trainees, and junior and senior faculty from various disciplines.

The morning featured an opening address by Governor Jim Pillen and a panel discussion with Chancellor Gold, Governor Pillen and Mrs. Chanda Chacón from Children's Nebraska reviewing the intersection of academic institutions, government and private children's hospitals in the distribution of health care to pediatric cancer patients. PCRG member presentations, including a review of implementation science with agricultural producers (Graze-Masters) in Nebraska, were highlighted in the morning session.

Keynote speaker Dr. Austin Brown, Assistant Professor from Baylor College of Medicine, provided a review of epidemiology work for long term survivors of pediatric leukemia. The event concluded with updates from the PCRG affinity research groups: Hematological Malignancies, Central Nervous System Tumors, Drug Development and Epidemiology.

A report of the current composition of the Pediatric Cancer Research Group and an accounting of the usage of the \$1.8 million dollars follows:

### **Current Program Personnel:**

#### *Program Director*

Don Coulter, MD, Professor, Pediatric Hematology/Oncology, University Tower 5117, Lab: 11<sup>th</sup> floor Lied Tower

#### *Research Team Members*

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Alfred Bothwell, PhD, Professor, Pathology/Microbiology

Alan Kolok PhD, Director Center for Environmental Health and Toxicology (University of Idaho)

Amanda Ortmeier, BSN, RN, Nurse, Children's Nebraska

Amanda Whitman, Patient Education Specialist, Children's Nebraska

Amarnath Natarajan, PhD, Professor, Eppley Cancer Institute

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Amritha Kizhake, Postdoctoral Research Associate

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Angie Rizzino, PhD, Professor, Eppley Cancer Institute (Tumor Biology)  
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Anum Akbar, Graduate Assistant  
Anup Pathania, PhD, Instructor  
Arjun Dhir, Graduate Research Assistant  
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Babu Guda, PhD, Professor, Bioinformatics and Systems Biology Core  
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Dong Wang, PhD, Professor, Pharmaceutical Sciences  
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Grace Murray, MD, Pediatric Hematology/Oncology Fellow  
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James Ford, DO  
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Javeed Iqbal, PhD, Professor, Pathology & Microbiology  
Jeff Jeppson, Research Technologist II  
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John Davis, PhD, Professor, Obstetrics and Gynecology  
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Jonathan Vennerstrom, PhD, Professor, Pharmaceutical Sciences  
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Kendra Ratnapradipa, PhD, Assistant Professor, Epidemiology  
Kerrie Weber, PhD, Associate Professor, Biological Sciences and Earth & Atmospheric Sciences  
Kishor Bhakat, PhD, Associate Professor & Research Scientist, GCBA (DNA Repair)  
Kishore Challagundla, PhD, Assistant Professor, Biochemistry and Molecular Biology (Tumor  
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Surinder Batra, PhD, Professor & Chair, Biochemistry & Molecular Biology  
Sutapa Ray, PhD, Assistant Professor  
Taiba Jabeen, Graduate Assistant  
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Wafaa Aldhafiri, Graduate Research Assistant  
Wonmi So, Postdoctoral Research Associate  
Yuxiang Dong, PhD, Research Assistant Professor, Pharmacy

### **New Projects:**

#### **Translational Science Research:**

##### *1. Hematopoietic Stem Cells and Bone Marrow Failure*

In patients with leukemia, malignant cells can exploit the bone marrow to maximize their own growth and harm the normal processes of hematopoiesis (generation of new blood cells). This is particularly a concern for patients with acute myeloid leukemia (AML), who often experience severe deficiencies in red and white blood cells and platelets. Dr. Swenson’s lab proposes that AML cells secrete specific proteins that impair normal hematopoiesis within the bone marrow. The research aims are to test how two of these cytokine proteins affect red blood cell generation and to identify gene networks that become deregulated by AML.

##### *2. The Role of HMGB3 in Acute Myeloid Leukemia*

A protein called HMGB3 is involved in the promotion of multiple types of malignancies, and in Dr. Swenson’s lab, its role in acute myeloid leukemia (AML) is being explored. The team is working on generating various experimental models, including cultured cell systems to evaluate how HMGB3 regulates cell proliferation, cell death, and colony formation, and experimental mice to evaluate how it affects survival. These steps to understanding how HMGB3 functions in the disease biology of AML will be crucial to securing extramural funding for longer-term translational research to achieve much-needed new treatments.

3. *Development Of A Permeability-Limited Pulmonary Physiological-Based Pharmacokinetic (PBPK) Model To Improve MO-OH-Nap Dosing And Pulmonary Delivery For Treatment And Prevention Of Metastatic Osteosarcoma*

Osteosarcoma (OS) is a common bone tumor in children and adolescents, and it often spreads to the lungs. The current treatments have limitations and can cause serious side effects and poor response. Our research aims to develop a new treatment approach for OS using a novel compound called Tropolone MO-OH-Nap (MO-OH-Nap). However, MO-OH-Nap has poor solubility, which hampers its drug development. To overcome this challenge, PhD Candidate and Research Assistant, Wafaa Aldhafiri, and team will develop a special formulation of MO-OH-Nap that can target the lungs. The lab will use a computational model to guide the dosing of MO-OH-Nap to achieve optimal drug delivery to the lungs. This model will take into account various factors such as the physical and chemical properties of MO-OH-Nap and the structure of the lungs. By developing this precision dosing strategy, the aim is to improve the delivery of MO-OH-Nap to the lungs and enhance its effectiveness and safety in treating pediatric patients with pulmonary metastatic OS.

4. *Role of TME in Refractory Pediatric ALL: Is NOTCH Signaling a Viable Target for ALL Therapy*

Although most pediatric acute lymphoblastic leukemias (ALL) are treatable with chemotherapies to induce remission, infant ALLs are very aggressive. Developing an effective treatment strategy for infant ALLs requires understanding how molecular and cellular features of the tumor microenvironment regulate ALL progression. More specifically, Dr. Joshi is interested in how signaling proteins of the NOTCH pathway are activated in the ALL tumor microenvironment, and how drugs could target those proteins to treat ALL. Research aims include measuring the expression of key members of the NOTCH pathway in patients' cells and tissues and evaluating the therapeutic value of NOTCH inhibitor drugs in cultured ALL cell lines and in mice bearing ALL.

5. *Improving the Immunologic and Therapeutic Effect of Chemotherapy in Neuroblastoma with Nano-CCL21*

High-risk neuroblastoma is often resistant to standard treatments, and therefore patients can experience toxic side effects yet potentially limited therapeutic benefit. Dr. Solheim's lab is working on the development of new immunotherapies (such as nano-CCL21), which is a vital strategy for targeting neuroblastoma with less toxicity and better long-range efficacy for pediatric patients.

6. *Development of Tumor-targeted Peripherally Cross-linked Polymer Micelles to Improve the Systemic Treatment of Solid Pediatric and Adult Tumors with PROTACs Drugs*

PROTACs are a novel class of small molecule drugs that catalytically target cellular proteins for degradation, in contrast to a conventional drug that only inhibits its target protein for as long as it stays bound to it. The promise of PROTACs as targeted anticancer therapies is limited by poor water solubility,

wide tissue distribution, and the potential for toxic properties. Drs. Vetro and Natarajan propose to address these drawbacks by a broadly applicable strategy of encapsulating PROTACs in core-shell polymer micelles, with the goal of improving the treatment of solid pediatric and adult tumors. Aims of this project include employing chemistry techniques to improve the potency of an encapsulated PROTAC in cultured human cancer cells and to improve its potency/toxicity profile in several experimental tumor models in mice.

7. *Co-Targeting IGF-1R and Glutaminase in Ewing Sarcoma*

Ewing sarcoma is the second most common bone-associated cancer among children and young adults. While survival of patients with loco-regional disease has improved, current management is beset with enormous morbidities and life-long disabilities, with high rate of recurrence. Outcomes of metastatic disease remain poor, with only 39% 5-year survival rate. The need for newer therapeutic avenues is urgent. Hyperactivity of a protein called IGF-1R helps promote Ewing sarcoma tumor growth, spread and resistance to current therapies. When IGF-1R is combined with glutaminase inhibitor drug candidates that have been found safe in clinical trials, the combination most profoundly inhibits the growth and spreading behavior of Ewing sarcoma tumor cells in the lab compared to individual drugs. Dr. Band's lab will test if a combination of these two drug candidates can provide a more effective approach to treat Ewing sarcoma. Given their safety in clinical trials, the novel combination could move into clinical trials quickly. The combination of IGF-1R and glutaminase inhibitors is a novel approach never tested previously.

8. *Targeting B7-H3 for Fluorescence-guided Surgery of Extracranial Pediatric Tumors*

Amongst many clinical challenges with childhood malignancies, late diagnosis of the cancer is often associated with poor survival rates. To improve diagnosis and surgery procedures, Fluorescence-guided Surgery (FGS) utilizes pre- and intra-operative imaging to guide the surgery. Dr. Mohs's lab is exploring utilizing fluorescent probes that specifically target biomarkers upregulated in tumors cells to help surgeons in complete resection of any residual tumor.

9. *A Novel Gene Signature Predicting High-risk and Survival Outcome in Pediatric Neuroblastoma Racial Disparities*

Dr. Challagundla's research aims to find new genes that can predict how children with neuroblastoma respond to treatment. Neuroblastoma is a difficult-to-treat cancer, especially in high-risk cases. Currently, doctors use a factor called MYCN amplification status to assess the risk, but it only works for some cases, leaving many unexplained. This lack of predictive tools delays the right treatment and leads to poor outcomes. The team has identified nine genes that accurately determine risk, disease progression, and survival outcomes. One gene, SAP30, showed promising results and may predict response to a chemotherapy drug. The goals are to study how this gene signature works in different races and predict high-risk cases, and to assess survival outcomes in patients of different sexes and

ances. This information will help doctors personalize treatment strategies for different patients, improving their chances of beating the cancer.

## **Neuro-Oncology Research:**

### *1. Pediatric Oncology Translational Therapeutics and Drug Development for Assessment of Novel CNS Penetrants*

The treatment of pediatric brain tumors remains challenging, resulting in the high death rate, even though these tumors only account for about 25% of all childhood cancers. In addition, current treatments have significant toxicities associated with them. The development of safe and effective cancer therapies for children with brain tumors is critical to improve outcomes. One major challenge in the development of new therapies for brain tumors is the ability of drugs to move from the plasma and get to the brain and effectively treat brain tumors. To address this problem, Dr. Murry's team will use bench top methods (in vitro studies), mouse studies (in vivo studies) and computer modeling to identify novel compounds that can effectively cross this barrier. A total of six novel compounds with activity against brain tumors will be evaluated. Based on study results, these novel compounds will then be prioritized for further evaluation in brain tumor models.

### *2. Elucidating Mitochondrial Iron Transporter Mediated Ferroptosis in Group3 Medulloblastoma*

Medulloblastoma (MB) is a leading cause of cancer-related child mortality, and even for survivors the existing treatments often cause long-term side effects. The search for new potential drug targets by which to treat MB has led Dr. Kanchan and team to a protein called ABCB7, which appears to protect multiplying tumor cells against mechanisms that would normally kill them. The proposed studies will test whether inhibiting ABCB7 is an effective way to reduce tumor virulence that could translate to more safe and effective therapies for patients with MB.

### *3. Targeting DNA G-quadruplex Structures and FACT Complex to Prevent Medulloblastoma Recurrence*

After surgery, higher doses of chemotherapies and radiation are required to control and prevent medulloblastoma (MB) recurrence. Unfortunately, these treatments cause multiple side effects leading to devastating consequences on the quality of life of pediatric cancer survivors. Therefore, development of new therapeutic agents to prevent tumor recurrence is crucial. However, efficient delivery of systemic therapies to the brain is a major hurdle due to blood brain barrier and low targeted delivery of drugs to tumor cells. Dr. Bhakat will develop and characterize a novel drug delivery system loaded with small molecules which can cross the blood brain barrier and preferentially target therapy resistant MB and sensitize therapy resistant MB cells to radiation and chemotherapies. Further, the lab will test if this novel strategy prevents tumor recurrence.

#### 4. *Targeting JMJD6 in Group 3 Medulloblastoma*

One of the most severe forms of brain cancer in children is Group 3 Medulloblastoma (MB). One trait of these tumors is that cells contain large amounts of the protein MYC. This causes cells to grow and multiply at an unhealthy rate. New treatments that kill Group 3 MB tumors with fewer side effects are needed in order to help save lives and preserve quality of life for survivors. Past studies showed it is not practical to attack MYC protein with drugs. This led researchers to consider other "partner" proteins that interact with MYC as possible targets. Recently, Dr. Chaturvedi's lab has studied a MYC partner protein known as JMJD6 and found that patients with high JMJD6 tend to have poor outcomes. The lab grew Group 3 MB cells and inhibited their JMJD6 protein, and saw signs that this stopped tumor cell growth. The team proposes that the strategy of inhibiting JMJD6 could help cure Group 3 MB patients. The study will provide vital insight on a strategy that could improve survival and quality of life for children with Group 3 MB.

#### 5. *Delivery of PLK1 Inhibitor Loaded Solid Lipid Nanoparticles and Radiation Therapy Synergistically Treat Medulloblastoma (MB)*

Radiation therapy is a desirable option for patients with medulloblastoma (MB) because it causes less damage to healthy cells than the existing drug therapies, and thus, fewer side effects. However, MB tumors often develop resistance to radiation over time, so this project explores a strategy that combines radiation with a drug candidate called volasertib, which may prevent tumor cells from gaining resistance to the radiation. Dr. Mahato proposes to encapsulate volasertib in nanoparticles to ensure it can reach the brain without requiring dangerously high doses. The research aims are to assess the effects of volasertib on MB cell growth when used in combination with radiation, both in cell cultures and in mice implanted with MB tumors.

### **Clinical Research:**

#### 1. *Advanced Machine Learning for Identifying Subtypes of B-Cell Acute Lymphoblastic Leukemia based on Transcriptomic Profiling*

B-cell acute lymphoblastic leukemia (B-ALL) is one of the common pediatric malignancies. Current testing methods for diagnosing and classifying the multiple subtypes of B-ALL are expensive and laborious. Dr. Wan seeks to develop reliable and cost-effective machine learning methods to differentiate all of the B-ALL subtypes based on the gene expression profiles of patient specimens. A rapid, reliable, and cost-effective diagnostic approach to identifying B-ALL subtypes will be an important contribution to delivering optimal patient care.

### **Population Research:**

#### 1. *Impact of Social and Environmental Factors on Pediatric Cancer Survival*

While pediatric cancer survival rates have improved over the last few decades, significant differences in survival rates exist by cancer type, sex, race and



ethnicity, and socioeconomic status. The goal of this project by PhD Candidate and Graduate Assistant, Emma Hymel, is to examine social and environmental predictors of pediatric cancer survival, including neighborhood deprivation, rurality, and travel burden in the United States.

2. *Financial Hardship among Caregivers of Pediatric Cancer Patients: Survey Pilot Study*  
Cancer is one of the most expensive conditions to treat. In 2019, in the United States, cancer treatment was associated with a net patient economic burden of \$21.1 billion. There is a dearth of research on financial hardship affecting the pediatric cancer population. In this cross-sectional pilot study, PhD Candidate and Graduate Assistant, Josiane Kabayundo, will collect data from primary caregivers of pediatric cancer patients diagnosed within the past five years. The study will develop an instrument that will assess financial hardship in primary caregivers of pediatric cancer patients. The study's significance lies in understanding the burden and predictors of financial hardship among caregivers, which will serve as a basis for developing interventions that address financial hardship and improve the quality of life among pediatric cancer patients and their families.
3. *Development of Patient Engagement Training Program to Promote Participation of Pediatric Cancer Patients and their Caregivers in Clinical Translational Research*  
While there are many grassroots organizations being developed to advocate to improve the lives of pediatric cancer patients and caregivers, there is dearth of research to understand how best to engage pediatric cancer patients and caregivers to participate in research processes. Dr. Watanabe-Galloway and team are creating an advisory board of caregivers of pediatric cancer patients to review existing training materials and provide feedback. The research team will work to tailor the materials to the pediatric cancer population and test the materials among the target audience. The project has an implication to improve the process and outcomes of research studies which incorporate input from the affected populations. Also, the project may be extended for other pediatric health conditions.

### **Continued Projects:**

#### **Translational Science Research:**

1. *Role of FBXO21 as an Oncogene in AML*  
Acute myeloid leukemia has a poor prognosis in pediatric patients, and a better understanding of the transformation of normal myeloid cells to leukemia cells could lead to new treatment modalities. Drs. Hyde, Natarajan and Buckley are investigating FBXO21, a potential oncogene thought to play a role in the transformation and progression of these cells. Their early studies could further promote FBXO21 as a potential therapeutic target in this disease.
2. *Targeting Epigenetic Alterations in Pediatric Cancer – Proof of Principle using FLT3 – ITD Driven AML*

Dr. Hamid Band and his team of investigators are developing an integrated experimental and bioinformatics platform that will be available to all investigators within the PCRG. They will use FLT3 driven AML, a specific type of myeloid leukemia with a very low survival rate, as a proof of principle to show that an epigenetics-targeted inhibitor library of compounds can be evaluated for potential therapeutic use. The information provided by testing this library may lead to a number of potential targets for future investigation in leukemia and other pediatric malignancies.

3. *Targeting NK Cell Tolerance to Enhance GD2-targeted Immunotherapy in Neuroblastoma*

While inclusion of dinutuximab in neuroblastoma care has improved outcomes, <50% 5-year survival rates in high-risk patients support the need to enhance its effectiveness. Notably, neuroblastomas exhibit an immunosuppressive tumor microenvironment that specifies poor outcomes. The CBL-family of ubiquitin ligases (CBL, CBL-B and CBL-C) are key negative regulators of immune cell activation. This immunosuppression can impact the ability of therapeutic antibodies, such as GD2 targeted antibodies in neuroblastoma, to have a positive impact for patients. This proposal from Dr. Band aims to complete genetic deletion or chemical inhibition of CBL-B in NK cells and relieve them of immune suppression in the tumor microenvironment to enhance ADCC-mediated neuroblastoma tumor killing by anti-GD2 antibody therapy.

4. *Data-driven Identification of the Regulatory Networks involving Non-coding RNAs in Neuroblastoma*

This study aims to develop an integrative framework for constructing a comprehensive regulatory network involving non-coding for Neuroblastoma (NB). NB is the most common extracranial solid malignancy in children, and most children ultimately die from this disease. Despite intense treatment regimens, the prognosis for high-risk pediatric NB patients remains poor with less than 40% survival due to high expression of several driver transcription factors, epigenetic factors and non-coding RNAs. Dr. Challagundla's lab explores the data-driven identification of driver transcription factors (regulators/regulons) that can explain/predict NB tumor risk, their progression, and the drug resistance and poor survival of the subjects. Most bioinformatic workflows identify correlating factors (passenger markers) that have a low influence on tumorigenicity. Identifying causal factors has been the holy grail of the artificial intelligence (AI)/machine learning (ML) domain and is also an area of active interest in cancer biology research.

## **Neuro-Oncology Research:**

1. *Targeting Chemoresistance in Medulloblastoma using a Hedgehog Signaling Pathway Inhibitor*

Cisplatin is a potent chemotherapeutic agent, but its use to treat medulloblastoma is limited by severe systemic toxicity and inefficient penetration of the blood-

brain barrier. This proposal seeks to combine Hedgehog signaling inhibition with a Cisplatin analogue as therapy for patients with medulloblastoma. The two agents will be encapsulated by Dr. Mahato and his team into a nanoparticle in an attempt to decrease the toxicity of Cisplatin. The combination will be tested in mice with medulloblastoma in hopes of continuing the development of these drugs.

2. *The Creation of the Regional Pediatric Brain Tumor Tissue Bank*

One of the great needs for investigative teams within the PCRG are functioning tumor banks which can provide samples of pediatric tumors for evaluation and research. Dr. Mahapatra is leading a multi-disciplinary team of oncologists, neurosurgeons, pathologists and clinical researchers to develop the necessary infrastructure and protocols to launch the first pediatric brain tumor biobank in Nebraska.

**Clinical Research:**

1. *Implementation of Screening and Virtual Reality-Based Exposure Therapy for Claustrophobia that Interferes with Radiology Care*

Children undergoing MRI and radiotherapy frequently experience fear/anxiety related to these procedures. VR can efficaciously treat claustrophobia and can reduce pain and anxiety for pediatric patients. Dr. Weeks, psychologist, designed this project to improve identification of patients who experience medically-relevant claustrophobia and examine whether treatment via VR exposures to MRI and radiotherapy results in significant reductions in indices of claustrophobia (measured with BE CALMeD scores). Ultimately, the project hopes to help pediatric patients reduce anxiety and improve quality of life.

2. *Metabolic Bone Health in Childhood Cancer Survivors*

While 80% of children will survive their pediatric cancer, 75% of survivors go on to have chronic medical conditions. Among the most common of these are impacts on the health of bones. Dr. Acquazzino, the Director of the Survivorship clinic at Children's Nebraska, has assembled a research team to investigate the impact of exercise on the overall bone health of survivors of pediatric tumors.

**Population Research:**

1. *Impact of Symptom Clusters on Health-related Quality of Life in Pediatric Cancer Survivors after Treatment Completion*

Traditional cancer survivorship research often focus on a single symptom. However, cancer patients rarely exhibit an isolated symptom, but rather experience multiple interrelated symptoms known as symptom clusters. Compared with a single symptom, symptom clusters have a synergistic effect greater than an additive effect of individual symptoms on health outcomes, such as health-related quality of life (HRQoL) among cancer patients. However, there is a knowledge gap on symptom clusters prevalent among pediatric cancer

survivors after treatment completion and the association between symptom clusters and HRQoL. This study by PhD candidate Kristee Napit seeks to increase knowledge of the underlying causes of symptom clusters. Understanding symptom clusters will provide the evidence for symptom assessment and to develop symptom management interventions by targeting the set of symptoms with a single treatment approach and ultimately improving HRQoL.

### **Successful Extramural Funding:**

1. NIH R01 (CA263504): Mechanisms underlying USP1-mediated bypass of EWS-FLI1 oncogene-induced replication stress in Ewing sarcoma. Principal Investigator: Gargi Ghosal, PhD
2. NIH R01 (NS128336-01) Lipid nanomedicine targeting multiple signaling pathways of medulloblastoma. Principal Investigator: Ram Mahato, PhD
3. NIH R01 (NS116037) Overcoming resistance mechanisms in Hedgehog and Myc-amplified Medulloblastoma. Principal Investigators: Ram Mahato, PhD and Don Coulter MD

### **Published Manuscripts:**

1. Ahmad A, Khan P, Rehman AU, Batra SK, Nasser MW. Immunotherapy: an emerging modality to checkmate brain metastasis. *Molecular Cancer*. 2023;22(1).
2. Bala V, Chhonker YS, Morales GA, Maddeboina K, Pal D, Durden DL, Murry DJ. LC-MS/MS method for the quantitation of a dual PI3K/BRD4 inhibitor SF2523 in mouse plasma: Application to plasma protein binding and metabolism studies. *Biomedical Chromatography*. 2023;37(8).
3. Baranowska-Kortylewicz J, Kortylewicz ZP, McIntyre EM, Sharp JG, Coulter DW. Interactions of Butyrylcholinesterase with Neuroblastoma-associated Oncoproteins. *Current Enzyme Inhibition*. 2023;19(2):109-24.
4. Chakraborty S, Bhat AM, Mushtaq I, Luan H, Kalluchi A, Mirza S, Storck MD, Chaturvedi N, Lopez-Guerrero JA, Llombart-Bosch A, Machado I, Scotlandi K, Meza JL, Ghosal G, Coulter DW, Jordan Rowley M, Band V, Mohapatra BC, Band H. EHD1-dependent traffic of IGF-1 receptor to the cell surface is essential for Ewing sarcoma tumorigenesis and metastasis. *Communications Biology*. 2023;6(1).
5. Dasgupta A, Kurenbekova L, Patel TD, Rajapakshe K, Ghosal G, Nirala B, Coarfa C, Yustein J. Modeling Ewing Sarcoma Lung Metastasis. *Current Protocols*. 2023;3(2).
6. Dobish KK, Wittorf KJ, Swenson SA, Bean DC, Gavile CM, Woods NT, Ghosal G, Hyde RK, Buckley SM. FBXO21 mediated degradation of p85 $\alpha$  regulates proliferation and survival of acute myeloid leukemia. *Leukemia*. 2023;37(11):2197-208.
7. Fraser K, Kuhn M, Swanson R, Coulter DW, Copeland C, Zuniga JM. Low Motor Dexterity and Significant Behaviors Following Hospitalized Isolation in Children. *Children*. 2023;10(8).
8. Haney SL, Feng D, Chhonker YS, Varney ML, Williams JT, Smith LM, Ford JB, Murry DJ, Holstein SA. Evaluation of geranylgeranyl diphosphate synthase inhibition as a novel strategy

for the treatment of osteosarcoma and Ewing sarcoma. *Drug Development Research*. 2023;84(1):62-74.

9. Haney SL, Feng D, Kollala SS, Chhonker YS, Varney ML, Williams JT, Ford JB, Murry DJ, Holstein SA. Investigation of the activity of a novel tropolone in osteosarcoma. *Drug Development Research*. 2023.
10. Hymel E, Degarege A, Fritch J, Farazi E, Napit K, Coulter D, Schmidt C, Watanabe-Galloway S. Agricultural exposures and risk of childhood neuroblastoma: a systematic review and meta-analysis. *Environmental Science and Pollution Research*. 2023;30(53):113193-204.
11. Katta SS, Nagati V, Paturi ASV, Murakonda SP, Murakonda AB, Pandey MK, Gupta SC, Pasupulati AK, Challagundla KB. Neuroblastoma: Emerging trends in pathogenesis, diagnosis, and therapeutic targets. *Journal of Controlled Release*. 2023;357:444-59.
12. Liu Y, Klein J, Bajpai R, Dong L, Tran Q, Kolekar P, Smith JL, Ries RE, Huang BJ, Wang YC, Alonzo TA, Tian L, Mulder HL, Shaw TI, Ma J, Walsh MP, Song G, Westover T, Autry RJ, Gout AM, Wheeler DA, Wan S, Wu G, Yang JJ, Evans WE, Loh M, Easton J, Zhang J, Klco JM, Meshinchi S, Brown PA, Pruett-Miller SM, Ma X. Etiology of oncogenic fusions in 5,190 childhood cancers and its clinical and therapeutic implication. *Nature Communications*. 2023;14(1).
13. Lyons K, Tibbits M, Schmid KK, Ratnapradipa KL, Watanabe-Galloway S. Prevalence and measurement of adverse childhood experiences (ACE) among children and adolescents in the U.S.: A scoping review. *Children and Youth Services Review*. 2023;153.
14. Malik JR, Podany AT, Khan P, Shaffer CL, Siddiqui JA, Baranowska-Kortylewicz J, Le J, Fletcher CV, Ether SA, Avedissian SN. Chemotherapy in pediatric brain tumor and the challenge of the blood–brain barrier. *Cancer Medicine*. 2023.
15. Mallard HJ, Wan S, Nidhi P, Hanscom-Trofy YD, Mohapatra B, Woods NT, Lopez-Guerrero JA, Llombart-Bosch A, Machado I, Scotlandi K, Kreiling NF, Perry MC, Mirza S, Coulter DW, Band V, Band H, Ghosal G. USP1 Expression Driven by EWS::FLI1 Transcription Factor Stabilizes Survivin and Mitigates Replication Stress in Ewing Sarcoma. *Molecular Cancer Research*. 2023;21(11):1186-204.
16. McAndrew NS, Erickson J, Hetland B, Guttormson J, Patel J, Wallace L, Visotcky A, Banerjee A, Applebaum AJ. A Mixed-Methods Feasibility Study: Eliciting ICU Experiences and Measuring Outcomes of Family Caregivers of Patients Who Have Undergone Hematopoietic Stem Cell Transplantation. *Journal of Family Nursing*. 2023;29(3):227-47.
17. Pathania AS. Crosstalk between Noncoding RNAs and the Epigenetics Machinery in Pediatric Tumors and Their Microenvironment. *Cancers*. 2023;15(10).
18. Ray S. Tumorsphere Formation Assay: A Cancer Stem-Like Cell Characterization in Pediatric Brain Cancer Medulloblastoma. *Methods in Molecular Biology*. 27012023. p. 253-9.
19. Rohrer KA, Song H, Akbar A, Chen Y, Pramanik S, Wilder PJ, McIntyre EM, Chaturvedi NK, Bhakat KK, Rizzino A, Coulter DW, Ray S. STAT3 Inhibition Attenuates MYC Expression by Modulating Co-Activator Recruitment and Suppresses Medulloblastoma Tumor Growth by Augmenting Cisplatin Efficacy In Vivo. *Cancers*. 2023;15(8).
20. Sethi B, Kumar V, Jayasinghe TD, Dong Y, Ronning DR, Zhong HA, Coulter DW, Mahato RI. Targeting BRD4 and PI3K signaling pathways for the treatment of medulloblastoma. *Journal of Controlled Release*. 2023;354:80-90.

## PCRG FY2023 Expenditures

### Current Research Personnel

Don Coulter, MD (PCRG Director, COG PI UNMC)	86,098
Jill Beck, MD (COG PI)	25,036
Sutapa Ray, PhD (Research Scientist)	84,830
Nagendra Chaturvedi, PhD (Research Scientist)	82,783
Erin McIntyre (Lab Manager)	64,936
Grace Alexander (Research Technologist)	50,442
Hillary Stevenson (Research Nurse Coordinator)	70,699
Angie Boettner (Research Nurse Coordinator)	14,002
Sharissa Bohlken (Clinical Study Coordinator)	9,510
Benefits	<u>144,350</u>
 Current Personnel Subtotal	 632,686

### Core Lab Operational Costs

Supplies, Scientific Services, Publication Costs, etc.	87,330
Travel	0
Capital	<u>179,963</u>
 Operational Costs Subtotal	 <u>267,293</u>

**TOTAL RESEARCH PERSONNEL AND CORE LAB FY2022** **\$899,979**

### Awarded Projects FY2023

Targeting Epigenetic Alterations	Band	100,000
Developing Regional Medulloblastoma Core	Mahapatra	100,000
Data-driven Identification of Regulatory Networks	Challagundla	75,000
Role of FBXO21 as an Oncogene in AML	Hyde/Natarajan/Buckley.	150,000
Development of Tumor-Targeted Peripherally	Vetro	100,000
Targeting Chemoresistance in Medulloblastoma	Mahato	75,000
Implementation of Screening and VR	Weeks	50,000
Hematological Malignancies Affinity Group	Hyde	100,000
Patient Engagement Training Program	Watanabe-Galloway	35,000
Financial Hardship among Caregivers	Kabayundo	16,500
Impact of Social & Environmental Factors	Hymel	16,500
Elucidating Mitochondrial Iron Transporter	Kanchan/Mahapatra	50,000
Advanced Machine Learning	Wan	50,000
Role of HMGB3 in Acute Myeloid Leukemia	Swenson	50,000
Immunologic and Therapeutic Effect of Chemo	Solheim	50,000
Delivery of PLK1 Inhibitor Loaded Solid Lipid	Mahato	75,000
Hematopoietic Stem Cells and Bone Marrow	Losole	12,000

Targeting DNA G-quadruplex and FACT	Bhakat	50,000
PBPK Model to Improve MO-OH-Nap Dosing	Aldhafiri	15,000
Start-up Package for Dr. Nagendra Chaturvedi	Chaturvedi	<u>49,350</u>

**TOTAL AWARDED FY2023** **\$1,219,350**

**Planned Funding FY2024**

Development of Tumor-Targeted Peripherally	Vetro/Natarajan	100,000
Pediatric Oncology Translational Therapeutics	Murry	100,000
Novel Gene Signature Predicting High Risk	Challagundla	50,000
Tole of TME in Refractory Pediatric ALL	Joshi	50,000
Targeting B7-H3 for Fluorescenceguided Surgery	Mohs	78,000
Co-Targeting IGF-1R and Glutaminase	Band	100,000
Immersive Exposure Therapy for Trypanophobia	Weeks	10,000
Targeting JMJD6 in Group 3 Medulloblastoma	Chaturvedi	<u>50,000</u>

**TOTAL PLANNED FUNDING TO DATE FY2024** **\$538,000**

TOTAL PLANNED FUTURE FUNDING FY2024 150,000  
(Includes Fred & Pamela Buffett Cancer Center Projects)

**TOTAL PROJECTS FUNDED FY2023 – FY2024** **\$1,907,350**