University of Nebraska Medical Center

Children's HOSPITAL & MEDICAL CENTER

CHILD HEALTH RESEARCH INSTITUTE

December 29, 2019

Mr. Patrick J. O'Donnell
Clerk of the Legislature
State Capitol, Room 2018
Lincoln, Nebraska 68509

Dear Mr. O'Donnell:

In 2019 LB294 continued appropriations originally described by LB 417 (2015) from the General Fund to support pediatric cancer research at the University of Nebraska Medical Center. The original bill required electronic communication outlining the utilization of these resources be sent to the Legislature by December 31. Attached please find the report for the Pediatric Cancer Research Group created by these funds.

If I can provide any further information please feel free to contact me.

Sincerely,

Don Coulter M.D.
Director, Pediatric Cancer Research Group
Associate Professor, Pediatrics
Pediatric Hematology, Oncology & Stem Cell Transplant
University of Nebraska Medical Center
Children's Hospital and Medical Center

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

This year, the Pediatric Cancer Research Group hosted the second annual Pediatric Cancer Research Group Symposium on August 27, 2019. The Symposium, co-sponsored by the Child Health Research Institute and the Nebraska Coalition to End Childhood Cancer, was attended by over 120 participants. The agenda of the Symposium is included as Appendix A. Furthermore, the Pediatric Cancer Research Group continued to develop the capabilities of its Core Lab, which is available to all members of the group. This included purchases of vital equipment that will assist in the translation of basic science findings into future novel therapies. The core lab provides a vital collaborative tool to investigators throughout the group as they move their projects from the bench to the bedside.

Finally, the Pediatric Cancer Research Group is combining financial resources with the Child Health Research Institute to augment the ability of Children's Hospital and Medical Center and the University of Nebraska Medical Center to offer clinical trials of the latest discoveries to Nebraska families and children. By recruiting qualified Certified Research Administrator and Data Managers to focus on pediatric cancer, we will ensure the necessary infrastructure is in place to provide new treatments to the children of Nebraska.

A report of the current composition of the Pediatric Cancer Research Group and an accounting of the utilization of the 1.8 million dollars transferred from the General Fund for pediatric cancer research infrastructure at the University of Nebraska follows:

Current Program Personnel:

Program Director
Don Coulter, M.D., University Tower 5117, Lab: Wittson Hall 4027

Research Team Members
Janina Baranowska-Kortylewicz, Ph.D., Radiation Oncology, Lab: Epp. Science 10025 (Radiation Biology)
Shantaram Joshi, Ph.D., Genetics, Cell Biology and Anatomy, Lab: Wittson Hall 2010A (Tumor biology/Immunology)
Tim McGuire, D.Pharm, Pharmacy Practice, COP 4044, Wittson Hall 4057, 4059 (Tumor Biology/Pharmacology)
Christopher Shaffer, D.Pharm, Pharmacy Practice, Lab: COP 4050 (Pharmacology)
J. Graham Sharp, Ph.D., Genetics, Cell Biology and Anatomy, Lab: Wittson Hall 4027 (Tumor Biology)
Joyce Solheim, Ph.D., Eppley Institute, Lab: Eppley Science Hall 8006 (Immunology)
Jon Vennerstrom, Ph.D., Pharmaceutical Sciences, COP 3042
(Drug synthesis/Discovery)

Kishore Challagundla, Ph.D., Biochemistry and Molecular Biology, DRC 1 7032 (Tumor biology/Experimental Therapeutics)

Research Team Members (continued):
Rhongshi Li, Ph.D., Pharmaceutical Sciences, COP , ESH 8009
(Drug synthesis/discovery)
Joseph Vetro, Ph.D., Pharmaceutical Sciences, COP 3033 (Drug delivery)
Guangshun (Gus) Wang, Ph.D., Pathology and Microbiology, Wittson 4005
(Drug Development)
Erin McIntyre, M.S., Lab Manager, PCRP Lab: Wittson 4057, 4059
Gracey Alexander, M.S., Research Technologist, PCRP Lab: Wittson 4057, 4059
Nagendra Chaturvedi, Ph.D., Senior Postdoctoral Research Associate, Lab: Wittson 2010A
Sutapa Ray, Ph.D. Assistant Professor, Lab: Wittson Hall 4027
Daryl Murry, Pharm D, College of Pharmacy (Drug Development/Analysis)
Angie Rizzino, Ph.D. Professor, Eppley Cancer Institute (Tumor Biology)
Sidharth Mahapatra, MD, Ph.D. Assistant Professor, Pediatrics (Brain tumors)
Shinobu Watanabe-Galloway PhD., Associate Professor, College of Public Health
(Epidemiology)
Hamid Band Ph.D., Professor, Eppley Cancer Institute (Tumor Biology)
Gargi Ghosal Ph.D., Assistant Professor, Genetics, Cell Biology and Anatomy
(Tumor Biology)
Ram Mahato Ph.D., Professor and Chair, Department of Pharmaceutical Sciences
(Drug Development)
So-Youn Kim, Ph.D., Assistant Professor, Department of OB/GYN (Fertility Preservation)
Alan Kolok Ph.D., Director Center for Environmental Health and Toxicology (University of Idaho)
Kate Hyde Ph.D., Assistant Professor, Eppley Cancer Institute, BCC 6.12321 (Leukemia)
Shannon Buckley, Ph.D., Assistant Professor, GCBA, BCC 10.12397 (Leukemia)
David Oupicky, Ph.D., Pharmaceutical Sciences, DRC1 (1009) (Drug Delivery)
Corey Hopkins, Ph.D., Pharmaceutical Sciences, COP3015 (Drug synthesis/Discovery)
Kishor Bhakat, Ph.D., GCBA, BCC.1012392 (DNA Repair)

<u>New Projects:</u>

Population Research:

1. *Impact of watersheds on the incidence of pediatric cancer in Nebraska*
   The University of Nebraska College of Public Health and the Center for Environmental Health and Toxicology have previously evaluated the incidence of pediatric cancer and birth defects in areas surrounding multiple watersheds that exist within the State, and identified a number of watersheds with increased incidence. This collaborative effort led by Dr. Eli Rogan and Dr. Shannon Bartelt – Hunt will evaluate the ground water composition in watersheds with an

increased incidence of pediatric cancer and compare these results to ground water in watersheds with a lower incidence of disease.

Translational Science Research:

1. *Exosomes secreted under Hypoxia Enhance Aggressiveness in Ewing's Sarcoma*

This project led by Dr. Shantaram Joshi will continue investigations into the molecular mechanisms by which low oxygen tension leads to increased resistance and metastasis in Ewing's Sarcoma cells. Under these hypoxic condition, Dr. Joshi and his team have identified that Ewing's Sarcoma cells excrete small pockets of cellular information called exosomes. These exosomes are then able to change the microenvironment surrounding the cancer cell into a more suitable environment for growth and metastasis. A better understanding of the contents and function of these exosomes may lead to further clarity regarding resistance mechanisms in Ewing's Sarcoma.

2. *Deciphering the role of mitochondrial electron transfer flavoproteins in AML*

When compared to patients with Acute Lymphocytic Leukemia, patients with Acute Myeloid Leukemia experience relapses 50 % of the time and overall lower survival rates. A better understanding of the proteins within these cancer cells is necessary to allow for higher remission rates. Dr. Buckley and her team have identified a set of proteins differentially expressed in AML cells, specifically ETFA and ETFB. A further investigation of these proteins and their role in tumor initiation and progression may lead to novel therapeutic targets for these patients.

3. *NET targeted RNAi therapy in high risk Neuroblastoma*

Neuroblastoma is the most common extra-cranial solid tumor in children and requires multimodal therapy with surgery, chemotherapy, radiation therapy and immunotherapy. Still overall survival for patients with High Risk Disease approaches 60 %, and that survival comes with a number of long-term impacts. Dr. Vetro is continuing his investigations into interfering RNA that is packaged into a nano-particle and attached to MABG, an analog of MIBG which is a protein avidly absorbed by neuroblastoma cells.

4. *Pharmacokinetic evaluation of MP1 alone and combined with Temsirolimus in balb-c mice*

MP1 is a derivative of Marino pyrroles, a group of natural products modified in the laboratory of Dr. Rongshi Li. Preliminary work has shown that MP1 has anti-tumor activity against Neuroblastoma cells in culture. This study, combining the expertise of Dr. Li with Dr. DJ Murry, will continue the evaluation of this exciting compound developed at UNMC by investigating its pharmacokinetic

properties in mice when compared to Temsirolimus. The data will provide further information which could lead to an early phase trial in patients.

Clinical Research Focus:

1. *A pilot study of 'Immersive Education' Utilizing Virtual Reality Software for Children Undergoing Radiation Therapy and MRI*

Children receiving radiation therapy or imaging with MRI are expected to hold still for extended periods of time. Often the age of the child inhibits their ability to be compliant and sedation is required to complete the therapy. Pediatric sedation is a process with inherit risk, and increasing the proportion of children who can participate in procedures without sedation would decrease cost and increase quality. This project led by Rebecca Swanson DNP, utilizes virtual reality and an education session with a child life specialist in an attempt to decrease the number of children who require sedation for their treatment.

Neuro-Oncology Focus:

1. *Genetic and Pharmacologic targeting of STAT3 in Medulloblastoma*

Medulloblastoma is the most common brain tumor in childhood, and treatment currently involves surgical resection, chemotherapy and radiation therapy. These modalities can have long term impacts for the 60 – 70 % of children who will survive the disease. Dr. Sutapa Ray is investigating STAT3, and its role in maintaining medulloblastoma growth. By inhibiting STAT3 with both genetic and pharmacologic approaches, Dr. Ray hopes to develop therapies that will sensitize Medulloblastoma cells to our current treatment approaches, thereby improving outcomes and the quality of life for these patients.

2. *SOX2 Regulation of Sonic Hedgehog driven Medulloblastoma*

Dr. Rizzino and his team of investigators have previously identified SOX2 as a regulator gene responsible for quiescence in medulloblastoma cells, which is one established mechanism by which cancer cells avoid the toxic impact of chemotherapy. An existing grant is evaluating inhibitors of SOX2 as possible adjuvant therapeutic options for patients with medulloblastoma, and this project seeks to further understand the downstream impacts of SOX2, which may lead to other novel therapeutics for patients with medulloblastoma.

<u>Continuing Research:</u>

Translational Science Research:

1. *Study of the effects of BCHE deletion on tumorigenic potential of neuroblastoma cells*

Previous work by Dr. Janina Baranowska-Kortylewicz has identified butyrylcholinesterase (BChE) as a biomarker in high risk neuroblastoma. These findings were published in the Journal of Pediatric Hematology and Oncology. This project seeks to further elucidate the role of BChE as a proliferation switch in neuroblastoma, which may provide more information regarding the biology of the disease, and potential therapeutic interventions.

2. *Regulation of PD-L1 by MYCN in Neuroblastoma*

Neuroblastoma is the most common extra-cranial solid tumor in children, and has a varied clinical presentation. Patients with amplification of the oncogene MYCN require more toxic therapy and have worse overall outcomes. This project led by Dr. Challagundla seeks to understand the interplay between PD-L1 and MYCN in the hopes of identifying novel drug targets for intervention.

2. *Repurposing the STK10-inhibitory activity of Erlotinib for Ewing Sarcoma Therapy*

The treatment of metastatic Ewing Sarcoma continues to be difficult, and novel therapeutics are urgently needed. The serine threonine kinase 10 (STK10) has been identified as a potential target. This multi-investigator project led by Dr. Hamid Band seeks to evaluate the high STK-10 inhibitory activity of the clinically used EGFR inhibitor Erlotinib in Ewing Sarcoma cell lines and mouse models.

Neuro-Oncology Focus:

1. *The use of Sox 2 inhibitors as novel therapy for medulloblastoma*

Medulloblastoma is the most common brain tumor of childhood, and new therapeutics which can cross the blood brain barrier are needed for the treatment of this disease. This project led by Dr. Rizzino seeks to develop a category of drugs that target Sox 2, a molecule important in the development of therapy resistance in medulloblastoma cells.

2. *Identification of tumor suppressor genes on chromosome 17p13.3 in non SHH/WNT subgroup medulloblastoma*

Dr. Sidharth Mahapatra is elucidating the impact of tumor suppressor genes on chromosome 17 on the development of medulloblastoma using a combination of *in silico* (RNA sequencing), *ex vivo* (patient samples), and *in vitro* (established cell lines) techniques. This research has the potential to identify novel therapeutic targets that could then be administered using nano technology developed by fellow Pediatric Cancer Research Group member Dr. Joe Vetro.

Successful Extramural Funding:

1. NIH RO1: Mechanism of premature ovarian insufficiency in females receiving chemotherapy. Principal Investigator: So-Youn Kim, PhD

Published Manuscripts:

1. Song H, Bhajat R, Kling MJ, Coulter DW, Chaturvedi NK, Ray S, Joshi SS. Targeting cyclin-dependent kinase 9 sensitizes medulloblastoma cells to chemotherapy. Biochem Biopys Res Commun. 2019 Oct 5.

2. Kortylewicz ZP, Coulter DW, Baranowska – Kortylewicz J. In vitro and in vivo evaluation of radiolabeled methyl N-5[5-(3'-halobenzoyl)-1H-benzimidazol-2-yl] carbamate for cancer radiotherapy. Drug Dev Res. 2019 Oct 8.

3. McGuire TR, Coulter DW, Bai D, Sughroue JA, Li J, Zang Z, Qiao Z, Liu Y, Murry DJ, Chhonker YS, McIntyre EM, Alexander G, Sharp JG, Li R. Effects on novel pyrrolomycin MP1 in MYCN amplified chemoresistant neuroblastoma cell lines alone and combined with Temsirolimus. BMC Cancer. 2019 Aug 27;19(1):837.

4. Kortylewicz ZP, Coulter DW, Han G, Baranowska – Kortylewicz J. Norepinephrine-Transporter-Targeted and DNA-Co-Targeted Theranostic Guidelines. J Med Chem. 2019 Jul 3.

5. Chava S, Reynolds PC, Pathania AS, Gorantla S, Poluektova LY, Coulter DW, Gupta SC, Pandey MK, Challagundla KB. miR-15a-5p, miR-15b-5p, and miR-16-5p inhibit tumor progression by directly targeting MYCN in neuroblastoma. Mol Onc. 2019 Oct 21

6. Chaturvedi NK, Mahapatra S, Kesherwani V, Kling MJ, Shukla M, Ray S, Kanchan R, Perumal N, McGuire TR, Sharp JG, Joshi SS, Coulter DW. Role of protein arginine methyltransferase 5 in group 3 (MYC-driven) Medulloblastoma. BMC Cancer. 2019 Nov 6;19(1).

7. Kortylewicz ZP, Coulter DW, Baranowska-Kortylewicz J. Biological Evaluation of a potential anticancer agent Methyl *N*-[5-(3'-Iodobenzoyl)-1*H*-Benzimidazol-2-yl]Carbamate. Cancer Biother Radiopharm. 2019 Nov 5.

PCRG FY2019 Expenditures

Core Lab Current Personnel	
Graham J Sharp, PhD (Assistant Program Director)	41,172
Tim McGuire, D. Pharm (Assistant Program Director)	31,326
Dr. Sutapa Ray, PhD	75,744
Nagendra Chaturvedi, PhD	68,930
Zhen Ye (Graduate Research Assistant)	22,458
Balkissa Ouattara (Graduate Research Assistant)	8,500
Erin McIntyre (Lab Manager)	56,601
Grace Alexander (Research Technologist)	45,596
Jason Sughroue (Research Technologist)	32,354
Benefits	98,523
Current Personnel Subtotal	**481,204**
Core Lab Operational Costs	
Operating Expenses	24,607
Supplies, Scientific Services, Publication Costs, etc.	50,497
Travel	3,186
Capital	7,831
Operational Costs Subtotal	**86,121**

TOTAL CORE LAB FY2019		**567,325**

Funded Studies & Startup FY2019

Precision Medicine Startup Lab	Durden	800,481
Regulation of Metabolic pathways in T cells for effective immunotherapy in medulloblastoma	Mahato	85,798
SOX2 cell cycle control in MB	Rizzino #1	29,864
Examination of chemo resistance in pedi solid tumors	Ford	7,256
Targeting of dormant MB with CQ	Rizzino #2	24,117
Use of novel polymers to inhibit RUNX1 in AML	Hyde	43,202
Total Funded FY2019		**990,718**
GRAND TOTAL FY2019		**1,558,043**

PCRG Projected FY2020 Expenditures

Current Funded Studies FY2020

Impact of watersheds in Nebraska	Rogan	74,340
Exosomes secreted in Ewing's Sarcoma	Joshi	50,000
Flavoproteins in AML	Buckley	50,000
Virtual Reality Software to decrease sedation	Swanson	9,961
Targeted RNAi therapy in Neuroblastoma	Vetro	100,000
Genetic / Pharmacological targeting of STAT3	Ray	50,000
SOX2 in SHH Medulloblastoma	Rizzino	50,000
MP1 evaluation in mice	Li / Murry	73,089
Current Funded Studies Subtotal		**457,390**
Planned funding of Buffett Cancer Center Projects		**150,000**
TOTAL FY2020 Projected as of 12/1/2019		**607,390**

APPENDIX A:

Pediatric Cancer Research Symposium: Tuesday August 27, 2019
Truhlsen Event Center
University of Nebraska Medical Center, Children's Hospital and Medical Center, Fred and Pamela Buffet Cancer Center and Children's Health Research Institute

Support provided by Nebraska Coalition to End Childhood Cancer

8:00	Coffee and Poster Review
8:30	Introduction of Symposium - Don Coulter
9:00 – 10:00	**Keynote by Dr. Brenda Weigel** Pediatric Drug Development: The Changing Landscape
10:00 – 11:30	Epidemiology of Pediatric Cancer in Nebraska – Update Dr. Shannon Bartelt – Hunt Ph. D., UNL

Occurrence of agrichemicals in Nebraska water as detected by citizen science
Dr. Eleanor Rogan Ph.D., College of Public Health
Possible association of higher incidence of pediatric cancers in Nebraska with areas of more intensive agricultural activities

11:30 – 11:45	Break and set up lunch
11:45 – 12:30	Lunch
12:45 – 1:30	DJ Murry, Pharm D., Associate Professor, College of Pharmacy Pediatric clinical pharmacology and personalized therapeutics, Implications for drug development
1:30 – 2:15	Shannon Buckley, Ph.D., Assistant Professor, College of Medicine Exploring the role of Fbox proteins in leukemogenesis
2:15 – 3:00	Gargi Ghosal, Ph.D., Assistant Professor, College of Medicine Novel mechanisms of Ewing Sarcoma oncogenesis and metastasis
3:00 – 3:15	Break
3:15 – 4:00	Joe Vetro, Ph.D., Associate Professor, College of Pharmacy Targeted Chol-RNAi Molecule Polyplexes of PLL-PEG to Improve the RNAi Treatment of Pediatric Tumors
4:00 – 4:45	Ram Mahato:, Ph.D., Chair and Professor of Pharmaceutical Sciences Delivery and Targeting of Small Molecules and miRNA for treating medulloblastoma in Orthotopic Mouse Models
4:45 – 5:30	Nina Baranowska – Kortylewicz, Ph.D., Professor, College of Medicine Making Better Drugs for Children with Cancer
5:30	Closing Remarks