AWARD NUMBER: W81XWH-20-1-0556

TITLE: Preventing Blood Cancers and Other Malignancies in Military Personnel at Risk Due to Occupational Radiation Exposure

PRINCIPAL INVESTIGATOR: Stephen J. Kron

CONTRACTING ORGANIZATION: The University of Chicago, Chicago, IL

REPORT DATE: July 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
July 2023	Annual	01Jul2022-30Jun2023

4. TITLE

Preventing Blood Cancers and Other Malignancies in Military Personnel at Risk Due to Occupational Radiation Exposure

5a. CONTRACT NUMBER
W81XWH-20-1-0556

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER
0011488298-0001

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER
5E688

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

We are pursuing a project to examine strategies to promote DNA double strand break repair and thereby prevent and mitigate the toxicity of radiation in the bone marrow and other rapidly proliferative tissues, toward reducing both the acute and delayed effects of radiation, including malignancy. During the third year of research, we pivoted to evaluating a new protective agent. Our *in vitro* and *in vivo* studies have established supplementation with oral nicotinamide riboside as a promising means to protect bone marrow from radiation in mice. This approach will be validated during the No Cost Extension.

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	24	19b. TELEPHONE NUMBER *(include area code)*

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1. Introduction

This project is directed at testing a non-toxic intervention as a means to protect individuals at risk of radiation exposures from damaging effects to the bone marrow and other proliferative tissues. Briefly, our work identified a core cellular metabolism pathway, the hexosamine biosynthetic pathway (HBP), as a determinant of radiation tolerance. The HBP incorporates metabolic inputs from glucose and glutamine to form UDP-GlcNAc. Then, O-GlcNAc transferase utilized the UDP-GlcNAc to transfer GlcNAc moieties to protein serines and threonines, leading to altered function, localization, stability and/or expression. Our data suggest that OGT substrates are activated upon O-GlcNAcylation to enhance repair of DNA double strand breaks, promote cell survival, and/or resist cellular senescence after radiation exposure. The impetus for this project is that simply feeding cells the precursor amino sugar N-acetyl glucosamine (GlcNAc) is sufficient to drive the HBP and overall O-GlcNAcylation, leading to enhanced radiation tolerance *in vitro*. Feeding GlcNAc to animals or humans similarly increases O-GlcNAcylation, suggesting that this may be sufficient to enhance radiation tolerance *in vivo*.

A complementary activity that similarly promotes DNA double strand break repair and cell survival and resists senescence is poly-ADP-ribose polymerase 1, PARP1. Upon activation by DNA breaks, PARP1 utilizes nicotinamide adenine dinucleotide (NAD+) as a subtrate to form poly-ADP-ribose (PAR), thereby depleting NAD+ pools. Like OGT with GlcNAc, PARP1 activity can be enhanced, leading to increased DNA damage tolerance, by treating cells with its substrate NAD+ or the precursor nicotinamide dinucleotide (NMN) or nicotinamide riboside (NR). NMN or NR, like GlcNAc, are orally available, suggesting the value of treating with both agents to further increase repair capacity to improve cellular survival after radiation.

Our focus is on bone marrow and decreasing morbidity and mortality due to the acute hematopoietic syndrome and then late effects such as bone marrow failure and hematopoietic malignancies after accidental, occupational or military radiation exposures. Using bone marrow cultures and mouse models, we hoped to explore if increasing O-GlcNAcylation via feeding with GlcNAc prior to and after otherwise lethal whole body irradiation could preserve hematopoiesis at the level of stem cell and precursor survival and proliferation.

2. Keywords

Radiation, bone marrow, metabolism, DNA repair, hematopoiesis, stem cells, precursors

3. Accomplishments

We have listed the tasks that were proposed in the SOW and progress on each:

Major Task 1: Establish bone marrow cultures

Subtask 1: Isolate bone marrow with high culture viability. Progress made in Year 1.

Subtask 2: Optimize culture growth and feeding. Progress made in Years 1 and 2.

Major Task 2: Establish radiation response assays in cultures

Subtask 1: Establish assays of DNA damage and senescence Progress made in Year 1.

Mechanism of OGT in DSB repair Along with progress made in Years 1 and 2, Year 3 studies have reinforced the model that increased O-GlcNAcylation promotes EZH2 activity to enhance NHEJ and protect against single strand resection, thereby limiting HR repair. The net effect protects cells by increasing the speed of DSB repair, insofar as NHEJ is several fold faster than HR, and by preventing resection so that the number of breaks shunted to HR remains below saturation of capacity. The net effect may be higher cell survival at a given radiation dose.

Further, our Year 3 work confirms that PARP1 and OGT function in parallel to promote NHEJ. While OGT appears to enhance the activity of EZH2 in trimethylation of H3 K27, we have yet to resolve how PARP1 promotes NHEJ.

Biomarkers of DNA damage response Along with progress made in Years 1 and 2, Year 3 studies have continued to utilize our emerging methods to interrogate the secretome. Briefly, we adsorb proteins from conditioned growth media onto ProteoMiner dynamic range compression particles and then perform LC-MS/MS to ID proteins and measure their intensity by label-free quantitation. We then filter out bovine proteins and use cat as a decoy proteome to leave only mouse or human proteins. We then examine predicted secreted proteins as a model secretome. Thereby, we compared secretomes of bone marrow cells from mice treated with radiation or not, in the presence or absense of GlcNAc.

Subtask 2: Determine effects of radiation using flow cytometry. Progress made in Years 1 and 2.

Subtask 3: Determine radiation effects on bone marrow cultures with single cell RNA-seq. Not initiated.

Major Task 3: Evaluate effects of increased O-GlcNAcylation on radiation response

Subtask 1: Develop methods to regulate O-GlcNAcylation in bone marrow culture. Progress made in Year 2.

Subtask 2: Evaluate effects of O-GlcNAcylation on bone marrow growth and differentiation. Progress made in Year 2.

Subtask 3: Confirm mechanisms of effects of increased O-GlcNAcylation on DSB repair, proliferation and senescence. Progress made in Year 2.

Major Task 4: Develop bone marrow irradiation model to examine impacts of O-GlcNAcylation

Subtask 1: Identify radiation dose producing <20% mortality within 2 weeks due to H-ARS. We have used 6 Gy whole body irradiation, which appears to be compatible with high viability.

Subtask 2: Obtain baseline data on H-ARS with respect to bone marrow function. We have examined dosing with whole body irradiation to obtain high survival but signicant bone marrow suppression. Our results show that a 6 Gy dose applied to C57BL/6 mice is sufficient to suppress levels of PBMCs to close to the limits of detection by flow cytometry, but the numbers rebound within two weeks.

Subtask 3: Examine irradiation in Cux1 shRNA model. Not initiated.

Major Task 5: Examine impacts of O-GlcNAcylation on early bone marrow response

Subtask 1: Establish gavage treatment to increase bone marrow O-GlcNAc levels before and after irradiation. Beyond Year 2 studies, we found that while 50 mg/ml GlcNAc in drinking water is well-tolerated, we could not document convincing increases in bone marrow O-GlcNAcylation levels.

Subtask 2: Examine effects of O-GlcNAcylation on blood counts after irradiation. Our studies of GlcNAc effects on recovery of bone marrow cells indicated little if any benefit to providing GlcNAc in drinking water.

Major Task 6: Examine modulation by O-GlcNAcylation of changes in blood counts after irradiation.

Subtask 1: Optimize whole body irradiation dose to accelerate bone marrow failure and myeloid leukemia in Cux1 shRNA mice. Not initiated.

Subtask 2: Determine if altered O-GlcNAcylation modulates bone marrow failure or leukemia. Not initiated.

Major Task 7: Determine whether O-GlcNAcylation modulates the timeline for onset of malignancy in Cux1 sRNA model .

Subtask 1: Demonstrate long term maintenance of high O-GlcNAcylation in vivo. Not initiated.

Subtask 2: Obtain data on overall survival impact of high O-GlcNAcylation. Not initiated.

Due to the lack of progress with rescuing bone marrow function with feeding mice with GlcNAc as a means to increase O-GlcNAcylation and thereby accelerate NHEJ repair, we examined whether driving the parallel activity PARP1 by increasing NAD levels via feeding mice nicotinamide riboside (NR) in their water might be more successful. This led to three new Tasks that were initiated in Year 3 and are continuing during the No Cost Extension year as follows:

New Task A: Evaluate effects of increased NAD levels on radiation response

Subtask 1: Develop methods to regulate NAD levels in bone marrow culture. We confirmed that NR can be added to tissue culture cells and bone marrow cultures without toxicity. Initial attempts to measure changes in NAD levels using commercial kits were not successful.

Subtask 2: Evaluate effects of increased NAD levels on radiation response in vitro. We examined the response of J774.A monocytic cancer cells to 1 day treatment with 0.5 mM NR, then 6 Gy irradiation, and 6 days recovery in tissue culture. Without radiation, NR had no appreciable effect. After radiation, NR reduced ROS levels and formation of senescent cells based on flow cytometry assays.

Subtask 3: Confirm mechanisms of effects of increased NAD levels on DSB repair, proliferation and senescence. Our in vitro studies of contributions of OGT-dependent O-GlcNAcylation and PARP1-dependent PARylation on DSB repair after irradiation have defined these two pathways as independent determinants limiting single strand resection and thus favor NHEJ over HR repair. We have confirmed that GlcNAc effects are mediated by the histone H3 K27 trimethylation modifier EZH2, a subunit of PRC2. How PARP1 restricts single strand resection and whether increased NAD pools mediate their impact via increasing PARP1 activity has not been determined yet.

New Task B: Examine impacts of NR supplementation on early bone marrow response

Subtask 1: Establish methods to raise NAD levels by feeding with NR in drinking water. We established reliable methods to provide NR to mice in their drinking water. C57BL/6 mice were fed with water containing 0.5 g/l NR and tolerated the treatment well.

Subtask 2: Examine effects of NR feeding on blood counts after irradiation. This work was primarily performed after July 1, 2023 and is reported in the 10/30 quarterly report.

New Task C: Examine modulation by NR supplementation of survival, bone marrow failure and leukemia after irradiation.

Subtask 1: Optimize whole body irradiation dose to accelerate bone marrow failure and myeloid leukemia in leukemia-prone mice. Not initiated yet.

Subtask 2: Determine if feeding with NR in drinking water modulates bone marrow failure or leukemia. Not initiated yet.

4. Impact

Nothing to report.

5. Changes/Problems

We obtained considerable evidence that oral supplementation with N-acetyl glucosamine (GlcNAc) failed to cause a substantial protective effect on bone marrow after irradiation. We could not distinguish among potential mechanisms, but it may be that the supplementation was not increasing O-GlcNAcylation levels in the bone marrow. Whether oral GlcNAc could protect other tissues, such as intestinal epithelium, was not examined.

6. Products

Nothing to report.

7. Participants & Other Collaborating Organizations

Name: Stephen Kron, MD, PhD
Project Role: PI
Research Identifier: 0000-0003-1518-2436
Person Month Worked: 2 CME
Contribution to Project: Dr. Kron has been involved in planning and analysis of experiments and in coordinating activities of the research and technical staff.
Funding Support: See continuation pages.

Name: Megan McNerney, MD, PhD
Project Role: Co-Investigator
Research Identifier: 0000-0002-8260-3598
Person Month Worked: 0.5 CME
Contribution to Project: Dr. McNerney has been available for consulation.
Funding Support: See continuation pages.

Name: Sandeep Gurbuxani, MBBS-PhD
Project Role: Co-Investigator
Research Identifier: 0000-0003-0716-8730
Person Month Worked: 0.5 CME
Contribution to Project: Dr. Gurbuxani has been available for consulation.
Funding Support: See continuation pages.

Name: Elena Efimova, PhD
Project Role: Senior research professional
Research Identifier: None
Person Month Worked: 6.0 CME
Contribution to Project: Dr. Efimova has been studying the mechanism of modulation of DNA damage response and repair by O-GlcNAcylation and PARylation *in vitro*.
Funding Support: NA

Name: Sera Averbek, PhD
Project Role: Postdoctoral research scientist
Research Identifier: None
Person Month Work: 12 CME
Contribution to Project: Dr. Averbeck has has been studying modulation of bone marrow response to radiation by supplementation with GlcNAc and NR.
Funding Support: NA

Name: Camille Johnson
Project Role: Undergraduate research assistant
Research Identifier: None
Person Month Work: 3 CME
Contribution to Project: Assisted Averbek with studies to understand NAD as a potential determinant of radiation response.
Funding Support: NA

Name: Emily Gamboa
Project Role: Undergraduate research assistant
Research Identifier: None
Person Month Work: 4 CME
Contribution to Project: Assisted Efimova studies to examine determinants of single strand resection after DNA damage.
Funding Support: NA

Other Support

Kron, Stephen, PI

PREVIOUS:

Title: *Image-guided radiation-induced permeability (IGRIP) for IGDD*
Supporting Agency: NIH/NCI, R01 CA199663
Project Goals: We intend to leverage image-guided radiation as a means to target nanomedicines to tumors.
Specific Aims:
Aim 1. Optimize and validate image-guided radiation-induced permeability (IIGRIP) and establish IGRIP for image-guided drug delivery (IGDD) to prostate cancer tumors in mice
Aim 2. Towards establishing radiation-guided gene delivery, develop novel nucleic acid vectors for systemic injection and validate these nanocarriers by demonstrating efficient radiofection of mouse PCa tumor models with reporter genes
Aim 3. Toward translation of radiation-guided gene therapy, a) apply mouse models of PCa to demonstrate image-guided radiofection of CD-UPRT, evaluate CD-UPRT/5-FC enzyme prodrug therapy and examine synergy with radiation and b) target oncogenes by radiofection of siRNA for knockdowns and CRISPR for knock outs.
Performance Period: 7/1/15-6/30/2021
Level of Effort: 13%, 1.5 CME
Role: MPI with R. Weichselbaum
Contact: Pushpa Tandon
Tandonp@mail.nih.gov
Overlap: None

Title: *Nanoscale metal-organic frameworks for light triggered and X-ray induced photodynamic therapy of head and neck cancers*
Supporting Agency: NIH/NCI, U01 CA198989 (W. Lin, R. Weichselbaum MPIs)
Project Goals: Radiation-activated nanoparticle cancer therapy technology
Specific Aims:
Aim 1: Synthesis and characterization of nanoscale metal-organic frameworks (NMOFs) for NIR triggered and X-ray induced PDT.
Aim 2: Evaluation of NIR triggered PDT efficacy in experimental head and neck cancers.
Aim 3: Evaluation of X-ray induced PDT efficacy in experimental head and neck cancers.
Performance Period: 9/1/15-8/31/20
Level of Effort: 9%, 1.0 CME
Role: Co-I
Contact: Wenbin Lin PhD
wenbinlin@uchicago.edu
Overlap: None

Title: *Probing impact of cellular senescence on intestinal crypt function using organoid models*
Pilot & Feasibility grant; NIH, UChicago DDRCC Pilot
Project Goals: Examining aging in intestinal organoids using single cell methods.
Specific Aims:
Aim 1: Establish organoid formation defects associated with cellular senescence from models of intestinal epithelial aging including naturally aged mice, irradiated mice and mice lacking telomerase.
Aim 2: Examine effects of eliminating senescent cells on rescuing organoid formation by depleting senescent cells using genetic or chemical ablation.
Aim 3: Evaluate effects of genetic or chemical ablation of senescent cells on intestinal epithelial aging in vivo.
Period of Performance: 12/1/19-11/30/20

Level of Effort: 2%, 0.2 CME
Role: PI
Contact: Kailee Zingler
kzingler@bsd.uchicago.edu
Overlap: None

Title: *Tag-ChIP-MS for analysis of chromatin-level regulation of DNA repair*
Supporting Agency: NIH/NCI, R21 CA213247
Project Goals: We will leverage advanced tools for genome editing, protein tagging, chromatin enrichment and LC-MS/MS analysis to establish a new approach to chromatin proteomics
Specific Aims:
Aim 1. Establish split MPLUM tagging to visualize proteins involved in IRIF formation and resolution
Aim 2. Leverage split MPLUM tagging for TAG-CHIP-MS to dissect chromatin dynamics at IRF
Performance Period: 3/1/17-2/29/20 (NCE 2/28/21)
Level of Effort: 2%, 0.2 CME
Role: PI
Contact: John Knowlton
Jk339o@nih.gov
Overlap: None

Title: *Targeting Cancer Metabolism as a Novel Synthetic Lethality Strategy For BRCA Deficient Breast Cancers*
Funding Agency: NIH/NCI, F32 CA250347
Project Goals: NRSA to Tamica Collins PhD, a post-doctoral fellow in the Kron laboratory.
Specific Aims:
Aim 1. Assess effects of modulating O-GlcNAcylation in BRCA breast cancer in vitro and in vivo
Aim 2. Evaluate OGT inhibitors as PARPi sensitizers in BRCA breast cancer in vitro and in vivo
Aim 3. Define gene expression signatures for activation of O-GlcNAcylation in BRCA breast cancer
Period of Performance: 6/1/20-5/31/22 (Early Termination)
Level of effort: 0
Role: Mentor and Sponsor
Contact: Sonia B. Jakowlew PhD
jakowles@mail.nih.gov
Overlap: None

Title: *Veliparib interactions with genotoxic and immuno-therapy: Therapy-induced senescence and anti-tumor immunity*
Supporting Agency: AbbVie/UChicago collaboration grant
Project Goals: Exploring determinants of response to PARP inhibition including potentiating immunotherapy
Specific Aims:
Aim 1 Examine responses to Veliparib combined with a platinum agent or radiation in NSCLC PDX models in immunodeficient NSG mice.
Aim 2(A) Examine responses to Veliparib combined with genotoxic agents in NSCLC PDX models in CD34+ HSC humanized NSG mice and (B) Examine responses to Veliparib combined with genotoxic agents in i) CT26 tumor spheroids co-cultured with BALB/c mouse splenocytes and in ii) CT26 and 4T1 tumors in immunocompetent BALB/c mice.
Aim 3 Examine potentiation of Veliparib effects by PD-1/PD-L1 immune checkpoint blockade in i) CT26 tumor spheroids co-cultured with BALB/c mouse splenocytes and in ii) CT26 and 4T1 tumors in immunocompetent BALB/c mice.
Performance Period: 10/1/16-12/31/21
Level of Effort: 9%, 1.0 CME
Role: PI

Contact: Eric Johnson
Eric.f.johnson@abbvie.com
Overlap: None

Title: *Probing breast cancer immune infiltrates to monitor checkpoint blockade response*
Funding Agency: NCI, UCCCC Pilot
Project Goals: T3 and single cell analysis of TNBC biopsies to track response to immune checkpoint blockade.
Specific Aims:
Aim 1. Apply single cell RNA sequencing to discover biomarkers of response to immune checkpoint blockade (ICB) antibody therapy.
Aim 2. Establish workflow that applies T3 for rapid and reproducible 3D analysis in core needle biopsies from TNBC patients.
Aim 3. Validate candidate biomarkers of response to ICB therapy using T3 for analysis of TNBC core needle biopsy tissue
Period of Performance: 2/2/20-8/31/21
Level of effort: 2%, 0.2 CME
Role: PI
Contact: Toni Cipriano-Steffens
tciprian@medicine.bsd.uchicago.edu
Overlap: None

Title: *Leveraging DNA repair to enhance CRISPR genome editing*
Funding Agency: Chicago Biomedical Consortium, Catalyst Award
Project Goals: Examining novel strategy to increase HDR by CRISPR for site-directed mutagenesis based on recruiting DNA repair activities.
Specific Aims:
Aim 1: Examine the ability of DNA repair enzymes linked to resolution of DNA-protein crosslinks to detect and resolve stable Cas9-DSB complexes in vitro.
Aim 2: Evaluate the efficiency of Cas9-mediated homology-directed repair using donor DNAs that incorporate specific forms of DNA damage (DNA-repair beacons) to target DNA repair to the Cas9-DSB complex
Period of Performance: 3/1/19-11/30/22
Level of effort: 2%, 0.2 CME
Role: MPI with L. Hanakahi, UIC
Contact: Karen R. Snapp, DDS, PhD
ksnapp@northwestern.edu
Overlap: None

Title: *Single cell analysis of tumor immune infiltrates to track breast cancer immunotherapy*
Supporting Agency: NCI, UCCCC Pilot
Project Goals: Evaluate scRNA-seq analysis of the immune repertoire and apply this approach to documenting response to immune checkpoint blockade.
Specific Aims:
Aim 1 Modeling anti-PD-1/PD-L1 checkpoint blockade in mouse models of breast cancer to develop and validate scRNA-seq as an assay for anti-tumor immune activation
Aim 2 Applying scRNA-seq to analysis of on-treatment biopsies from breast cancer patients receiving anti-PD-1/PD-L1 therapy
Performance Period 12/1/17-11/30/22
Level of Effort: 2%, 0.2 CME
Role: PI
Contact: Robyn Egan
regan@bsd.uchicago.edu
Overlap: None

Title: *Mechanisms determining local and systemic anti-tumor immune response after metastasis-directed image-guided radiation combined with PD-1/PD-L1 checkpoint blockade*
Funding Agency: METAVivor, Research Award
Project Goals: Mouse model studies of radiation to potentiate immune checkpoint blockade in breast cancer.
Specific Aims:
Aim 1. Validate radiation-targeted delivery of anti-PD-L1 to both primary and metastatic murine mammary tumors.
Aim 2. Examine determinants of synergy of anti-PD-L1 with radiation
Aim 3. Explore requirements for systemic anti-tumor immune response targeting distant metastases
Period of Performance: 2/1/20-12/31/22
Level of Effort: 9%, 1 CME
Role: PI
Contact: Sonya Negley
Sonya@metavivor.org
Overlap: None

Title: *Targets of Reactive Lipid Species regulating DNA damage response and cell senescence*
Supporting Agency: NIH/NCI, R01 CA217182
Project Goals: To establish a new mechanism of action for etoposide and related chemotherapy agents
Specific Aims:
Aim 1A) Examine the effects of lipid peroxidation and reactive lipid species on Top2 poisoning and cell senescence, and B) Examine modification of Top2 by 4-HNE and other reactive lipid species and mutate reactive sites to examine functional significance.
Aim 2 Directly test whether DNA damage is sufficient to induce accelerated senescence and examine if 4-HNE and DNA damage interact additively (same pathway) or synergistically (distinct pathways).
Aim 3A) Apply proteomics to identify targets of RLS in etoposide-treated cells, and B) Examine Top2 as a signal transducer mediating the adaptive response to oxidative stress and ionizing radiation.
Performance Period: 7/1/17-6/30/23
Level of Effort: 4%, 0.48 CME
Role: PI
Contact: Paul Okano PhD
Po8k@nih.gov
Overlap: None

ACTIVE:

Title: *Chemotherapy delivery with nanoparticles for targeted induction of immunogenic cell death*
Funding Agency: NIH/NCI, R01 CA232419
Project Goals: Studies are directed at targeting nanoparticles bearing immune checkpoint antagonists to tumors.
Specific Aims:
Aim 1. To develop ICD-inducing NPs and evaluate their ability to promote an anti-tumor immune response.
Aim 2. To evaluate the anti-cancer effect of ICD-inducing NPs in combination with local ionizing radiation.
Aim 3. To investigate the contribution of ICD-inducing NPs to ICB therapy.
Period of Performance: 4/1/18-3/31/24 (NCE)
Level of effort: 4%, 0.48 CME
Role: Co-Investigator (Y. Yeo, PI)
Contact: Yoon Yeo PhD
yyeo@purdue.edu
Overlap: None

Title: *Systemic delivery of short nucleic acid by anionic flexible carriers for cancer immunogene therapy*

Funding Agency: NIH (Yoon Yeo, Purdue)
Project Goals: *Studies of a soft nanocapsule as a gene carrier.*
Specific Aims:
Aim 1. To optimize design and production of Nanosac for multigene targeting
Aim 2. To define toxicity, pharmacokinetics (PK), biodistribution (BD), and pharmacodynamics of Nanosac
Aim 3. To leverage systemic delivery of Nanosac and tumor targeting by image-guided radiation
Period of Performance: 04/2021-03/2025
Level of effort: 10%; 0.96 CME
Role: PI (with Y. Yeo)
Contact: Yoon Yeo PhD
yyeo@purdue.edu
Overlap: None

Title: *Bioinspired chemical probe approach targeting telomerase reverse transcriptase*
Funding Agency: NIH/NCI R01 CA254047
Project Goals: Subcontract for biological studies to further develop covalent TERT inhibitors to probe telomere and non-canonical roles of TERT.
Specific Aims:
Aim 1. Advance chrolactomycin analogs to inhibit htert in cells.
Aim 2. Explore selectivity and define extra-telomeric roles for htert catalytic activity with chrologs.
Aim 3. Investigate effects of chrologs on radiation sensitivity, tumor formation, recurrence and metastasis in the CT26 mouse colon carcinoma model.
Period of Performance: 7/1/20-6/30/25
Level of Effort: 8%, 0.96 CME
Role: PI (with K. Scheidt)
Contact: Sharad Verma PhD
sharad.verma@nih.gov
Overlap: None

Title: *Lipid signaling in cellular senescence and tissue aging*
Funding Agency: NIH/NIA R01 AG069865
Project Goals: Study to examine role for lipid peroxidation and accelerated senescence in pulmonary fibrosis.
Specific Aims:
Aim 1. Characterize the lipidomic changes in pulmonary cell senescence in vitro and in vivo
Aim 2. Examine impacts of modulating sphingolipid, ceramide and other lipid pathways on senescence
Aim 3. Target lipid metabolism to block senescence and delay pulmonary fibrosis
Period of Performance: 9/1/20-8/31/25
Level of Effort: 8%, 0.96 CME
Role: PI
Contacts: Yih-Woei Fridell PhD
Yih-Woei.fridell@nih.gov
Overlap: None

Title: *Nanoscale Metal-Organic Frameworks Enable Radiotherapy-Radiodynamic Therapy and Deliver CpG Oligodeoxynucleotides to Generate Tumor Vaccines and Potentiate Immunotherapy of Head and Neck Cancers*
Funding Agency: NIH/NCI
Project Goals: This project examines cancer therapy with MOFs as nanomedicines for immunotherapy.
Specific Aims:
Aim 1: Elucidate the cellular mechanisms of nMOF-mediated RT-RDT and CpG oligonucleotides.
Aim 2: Profile tumor microenvironment and extracellular matrix after treatment with RT-RDT.
Aim 3: Investigate the anticancer efficacy and adaptive immune response of nMOF/CpGmediated RT-RDT and immunotherapy

Aim 4: Determine novel immunotherapy combinations that are potentiated by RT-RDT in HNSCC models resistant to PD-1/PD-L1 blockade.
Period of Performance: 7/1/20-6/30/25
Level of Effort: 5%, 0.60 CME
Role: Co-I (W. Lin and R. Weichselbaum, PIs)
Contact: Jennifer Couch PhD
couchj@mail.nih.gov
Overlap: None

Title: *Enabling T3 imaging cytometry of the tumor immune microenvironment in formalin fixed paraffin embedded (FFPE) biopsy tissue*
Funding Agency: Duckworth Foundation; (University of Chicago Cancer Center)
Project Goals: Studies to accelerate translation of 3D imaging to its potential commercial applications.
Specific Aims:
Aim 1: Adapt T3 to enable 3D imaging cytometry in FFPE, using 20-50 μm thick macrosections cut from archival head and neck cancer tissue samples to examine immune microenvironment.
Aim 2: Validate 3D cytometry in FFPE macrosections by comparing T3 analysis of immune microenvironment on fresh tissue and fixed and embedded thick sections from individual head and neck cancers.
Aim 3: Demonstrate higher sensitivity, specificity and quantitative resolution of T3 3D cytometry in FFPE thick sections over conventional multiplex IHC in thin sections.
Performance Period: 5/20-12/22 (NCE to 12/23)
Level of Effort: 2% 0.24 CME
Role: PI
Contact: Robyn Egan
regan@bsd.uchicago.edu
Overlap: None

Title: Roswell Park Ovarian Cancer SPORE (Kron RDP: *Targeting telomerase reverse transcriptase to improve treatment of advanced ovarian cancer)*
Funding Agency: NIH/NCI; Roswell Cancer Center; University of Chicago Comprehensive Cancer Center
Project Goals: Examine TERT as a target to enhance ovarian cancer treatment.
Specific Aims:
Aim 1: Confirm that NU-1 and NU-PROTAC-1 inhibit/degrade TERT and sensitize human and mouse OvCa cell lines as monolayers and spheroids to genotoxic chemotherapy and targeted agents in vitro.
Aim 2: Determine effectiveness of NU-1 and NU-PROTAC-1 in targeting TERT in xenograft, PDX and syngeneic models of OvCa peritoneal carcinomatosis.
Aim 3: Examine NU-1 and NU-PROTAC-1 as sensitizers A) to systemic and/or intraperitoneal chemotherapy in xenograft models and B) to chemotherapy and/or immunotherapy in the ID8 syngeneic OvCa model.
Performance Period: 2/1/2022-12/31/2023 (NCE)
Level of Effort: 2% 0.24 CME
Role: PI
Contact: Robyn Egan
regan@bsd.uchicago.edu
Overlap: None

Title: *Targeting TET2 to block adaptive resistance to radiation*
Funding Agency: The University of Chicago Comprehensive Cancer Center
Project Goals Targeting the ability of interferon gamma to induce expression of immunosuppressive factors by blocking demethylation and activation of promoters.
Specific Aims:
Aim 1: Validate TET2 as a critical mediator of adaptive resistance to radiation
Aim 2: Examine small molecule approaches to targeting TET2 to overcome adaptive resistance

Performance Period 6/1/2022-5/31/2024 (NCE)
Level of Effort: 2% 0.24 CME
Role: PI
Contact: Robyn Egan
regan@bsd.uchicago.edu
Overlap: None

Title: *ChicAgo Center for Health and EnvironmenT (CACHET)*
Funding Agency: NIH/NIEHS
Project Goals: CACHET will continue to promote multidisciplinary environmental health research among clinician, laboratory and population scientists from two Chicago area universities with complementary strengths and structure to understand, evaluate and ultimately reduce environmental health related disparities among residents of the region and beyond.
Performance Period 06/01/2022-03/31/2027
Level of Performance: 3% 0.36 CME
Role: Co-I, Co-leader, Career Development (H. Ahsan, G. Prins, PIs)
Contact: H. Ahsan, The University of Chicago
habib@uchicago.edu
Overlap: None

Title: *PAIRS: Validating telomerase reverse transcriptase (TERT) as an intrinsic vulnerability toward sensitizing cancer to radiation*
Funding Agency: NIH/NCI R01 CA282781
Project Goals: Examining TERT as a pan-cancer vulnerability that can be targeted to overcome intrinsic radiation resistance in cancer.
Specific Aims:
Aim 1: Dissect functions of TERT in DSB repair and adaptive response to radiation
Aim 2: A) Advance pharmaceutical properties of chrolog telomerase inhibitors and B) Optimize combination treatment to drive abscopal response and suppress metastasis
Performance Period: 7/1/2023-6/30/2028
Level of Effort: 10% 1.2 CME
Role: MPI with K. Scheidt
Contact: Pat Prassana
patajeprasanna@mail.nih.gov
Overlap: None

PENDING:

Title: *Targeting telomerase reverse transcriptase to overcome therapy resistance in blood cancer*
Funding Agency: LLS
Project Goals: Evaluate telomerase reverse transcriptase as a determinant of resistance to conventional and targeted therapies for acute myeloid leukemia.
Specific Aims:
Aim 1: Validate NU-1 and other chrologs as hTERT inhibitors in human AML cell lines in vitro and as xenografts and confirm role for hTERT in chemoresistance in vitro.
Aim 2: Characterize mechanisms by which hTERT can influence intrinsic therapy resistance in AML and identify additional vulnerabilities.
Aim 3: Model incorporating chrologs into treatment of human leukemia xenografts, transduced bone marrow transplant models and leukemia-prone models in mice.Performance Period:
Level of Effort: 0.6 CME
Role: PI
Contact: Melissa Roccuzzo

ResearchPrograms@LLS.org
Overlap: None

Title*: Molecular determinants of immunogenicity in therapy-induced senescence*
Funding Agency: NIH/NCI R01 CA289678
Project Goals: Examine immunogenic senescence to enhance the efficacy of therapy for colon cancer.
Specific Aims:
Aim 1 Characterize immunogenic senescence in syngeneic models for colorectal cancer.
Aim 2 Examine response to immunogenic SnC injection in vivo and formation in situ.
Aim 3 Evaluate combining immunogenic senescence and one-two punch senolytic therapy.
Performance Period: 4/1/2024-3/31/2029
Level of Effort: 15% 1.8 CME
Role: PI
Contact: Anju Singh
anju.singh@nih.gov
Overlap: None.

Title: *Senescent tumor cell loaded dendritic cell vaccine to reduce recurrence and metastasis in lung cancer*
Funding Agency: CDMRP LCRP Idea Development Award
Project Goals: Examine immunogenic senescence and DC vaccines to enhance the efficacy of therapy for lung cancer.
Specific Aims:
Aim 1: Establish LLC1 SnC-loaded DC vaccines and confirm CTL-dependent suppression of LLC1 engraftment and tumor growth.
Aim 2: Model SnC-loaded DCs as adjuvant therapy by examining suppression of LLC1 spontaneous metastasis after tumor excision.
Performance Period: 10/1/24-9/30/27
Level of Effort: 13% 1.56 CME
Role: PI
Contact: Stephen Kron
skron@uchicago.edu
Overlap: None.

Title*: PARP1 as a target for immunogenic radiosensitization in breast cancer*
Funding Agency: CDMRP BCRP Breakthrough Level II
Project Goals: Examine how PARP1 protects tumors from the anti-tumor response to radiation.
Specific Aims:
Aim 1 Reexamine mechanisms by which PARP1 promotes NHEJ over HR repair.
Aim 2 Characterize adaptive resistance and define the effects of veliparib treatment on the anti-tumor immune response following radiation.
Aim 3 Define mechanisms by which PARP1 mediates PD-L1 expression and evaluate targeting the TET2 cytosine demethylase to disrupt adaptive resistance.
Performance Period: 9/30/2024-9/29/2027
Level of Effort: 15% 1.8 CME
Role: PI
Contact: Stephen Kron
skron@uchicago.edu
Overlap: None.

Title*: Personalized immunogenic senescent tumor cell pulsed dendritic cell vaccines to treat advanced and metastatic colorectal cancer*
Funding Agency: CDMRP PRCRP Impact

Project Goals: Model personalized dendritic cell vaccines for colon cancer using mouse models.
Specific Aims:
Aim 1 Enhance activity of SnC-pulsed DC vaccines and confirm CTL-dependent suppression of CT26 or MC38 engraftment and tumor growth.
Aim 2 Model SnC-pulsed DCs as adjuvant therapy in suppression of CT26 and MC38 peritoneal metastasis and liver metastasis from spleen injection or orthotopic cecal tumors.
Performance Period: 10/1/2024-9/30/2027
Level of Effort: 15% 1.8 CME
Role: PI
Contact: Stephen Kron
skron@uchicago.edu
Overlap: None.

Title*: Senescent cell-loaded dendritic cell vaccines to target pulmonary fibrosis*
Funding Agency: Longevity Impetus Grant
Project Goals: Examine senescent cells as a vaccine to prevent or treat idiopathic pulmonary fibrosis.
Performance Period: 4/1/2024-3/30/2026
Level of Effort: 10% 1.2 CME
Role: PI
Contact: Stephen Kron
skron@uchicago.edu
Overlap: None.

Title*: Modulating biomolecular condensates to reduce stress-induced premature senescence*
Funding Agency: Hevolution
Project Goals: Explore the role of biomolecular condensates in mediating DNA damage response and other signaling pathways impacting cellular senescence.
Specific Aims:
Aim 1 Genetically perturb BMCs and assess the consequences on senescence induction
Aim 2 Reveal BMCs proteome-wide in proliferating and senescent cells
Aim 3 Engineer synthetic condensate surfactants to enhance BMC liquidity
Performance Period: 12/1/2023-11/30/2028
Level of Effort: 12.5% 1.5 CME
Role: PI (with D. Pincus)
Contact: Stephen Kron
skron@uchicago.edu
Overlap: None.

Title*: Senescent tumor cell-pulsed dendritic cell vaccine for colorectal cancer*
Funding Agency: NIH NCI R21 CA292279
Project Goals: Establish a practical methodology to form patient-specific dendritic cell vaccines for cancer immunotherapy.
Specific Aims:
Aim 1 Advance methods to induce SnC immunogenicity that promote an effective DC vaccine
Aim 2 Apply conditional reprogramming to culture patient CRC tumor cells, induce immunogenic senescence, pulse monocyte-derived DCs, and examine DC maturation and priming of CTLs.
Performance Period: 7/1/2025-6/30/2026
Level of Effort: 5% 0.6 CME
Role: PI
Contact: Stephen Kron
skron@uchicago.edu
Overlap: None.

Title*: Senescence as a link between lipids and breast cancer metastatic progression*
Funding Agency: NIH NCI U01 CA293475
Project Goals: Pursue an interdisciplinary investigation of whether dietary fats may drive senescence to potentiate metastasis in breast cancer patients.
Specific Aims:
Aim 1 Evaluate deregulated lipid metabolism in driving lung cell senescence and inflammatory SASP in vitro and senescent-dependent lung metastasis in a mouse model of metastatic BC.
Aim 2 Investigate whether mechanistic risk factors for metastasis are associated with cellular senescence and other markers of biological aging in women with BC.
Aim 3 Characterize clinically relevant mechanisms of cellular senescence and other markers biological aging in women with BC to identify intervention targets.
Performance Period: 7/1/2024-6/30/2029
Level of Effort: 15% 1.8 CME
Role: PI (with P. Sheean)
Contact: Stephen Kron
skron@uchicago.edu
Overlap: None.

Sandeep Gurbuxani

Previous, Current, and Pending Support

PREVIOUS

- Title: **Regulation of hematopoiesis by CUX1 (McNerney)**
- Agency: NIH/NCI - 5R01HL142782-05
- Project Goals: The overall objective is to determine the transcriptional role for CUX1 in normal HSPCs and erythroid progenitors and the pathways downstream of CUX1 haploinsufficiency that block erythroid differentiation.
- Specific Aims: Aim 1: Overall hypothesis – CUX1 is a transcriptional regulator of HSPC homeostasis conserved in mice and humans. Aim 2: Overall hypothesis – CUX1 promotes erythroblast cell cycle exit necessary for terminal differentiation by suppressing PI3K signaling.
- Performance Period: 7/15/18 – 6/30/23
- Level of Funding:
- Effort: 0.24 CM (2%)
- Contracting/Grants Officer: C Brian Bai
    - Contact Information: Email: brian.bai@nih.gov

Overlap with the Proposed Project: None

- Title: **The impact of chromosome 7q deletions in juvenile mylelomonocytic leukemia (McNerney)**
- Agency: NIH/NCI - 5R01 CA231880-04
- Project Goals: The long-term goal of this proposal is to understand the molecular pathogenesis of -7/ del(7q) and to reveal new therapeutic targets for JMML patients.
- Specific Aims: Aim 1: Identify the cellular and molecular mechanisms by which Cux1 knockdown and Ras cooperate in JMML. Aim 2: Define the pathogenesis of combinatorial dosage imbalance of 7q genes in JMML.
- Performance Period: 9/20/18-8/31/2023
- Level of Funding:
- Effort: 0.24 CM (2%)
- Contracting/Grants Officer: Chamelli Jhappan
    - Contact Information: Email: jhappanc@mail.nih.gov

Overlap with the Proposed Project: None

CURRENT - None

SUBMITTED/PENDING

None

Megan McNerney

PREVIOUS

- Title: **Determining the role of CUX1 in myeloid neoplasia (McNerney)**
- Agency: NIH/NCI - 5K08CA181254-05
- Project Goals: The overall objective of the current application is to identify these biological functions and the molecular pathways regulated by CUX1, and how CUX1 haploinsufficiency alters these programs.
- Specific Aims: Aim 1: Identify the aberrant CUX1 transcription targets in acute myeloid leukemia. Aim 2: Identify the mechanisms of human CUX1 tumor suppressor activity.
- Performance Period: 9/16/14 - 8/31/19
- Effort: 50%
- Contracting/Grants Officer: Susan E Lim
    - Contact Information: Email: lims@mail.nih.gov

- Title: **Synergistic Role of the Microenvironment and MDS Stem Cells: A Model for the Pathogenesis and Treatment of MDS (LeBeau)**
- Agency: Edward P. Evans Foundation
- Project Goals: The overarching goal of our project is to integrate studies of the marrow microenvironment and hematopoietic stem cells (HSCs) to examine the novel hypothesis that deregulation of WNT signaling in the stroma is an early event that leads to the acquisition of mutations in HSCs, leading to myelodysplastic syndrome, and that mitigation of WNT signaling is a viable therapeutic target.
- Specific Aims: 1. To identify the molecular targets of altered WNT signaling in MSCs and HSCs derived from our MDS mouse model, and from MDS patients, particularly those with a del(5q); and 2. To extend our studies evaluating whether the microenvironment is a viable target in MDS for treatment or prevention of progression, and whether inhibition of aberrant WNT signaling in the niche in combination with standard or investigational therapy is a viable therapeutic approach using humanized mouse models, and by extending studies of our mouse models.
- Performance Period: 9/1/17 – 8/31/19
- Effort: 0.60 CM (5%)
- Contracting/Grants Officer: Michael Lewis, Ph.D.
    - Contact Information Email: grants@epefoundation.org

- Title: **Establishing a genetically accurate preclinical model of high-risk myeloid malignancy (McNerney)**
- Agency: The Brinson Foundation
- Project Goals: The overall objective of the project funded by the Brinson Foundation is to determine the combined impact of Cux1 insufficiency and oncogenic Ras in cancer development.
- Specific Aims: Aims of Year 1 of the project were to: 1) determine the malignant myeloid phenotype in shCux1 x NrasG12D mice, and 2) identify the molecular mechanism(s) by which combinatorial loss drives disease. The specific Aims for Year 2 of this proposal are to 1) determine the role for oncogenic Nras and Cux1 knockdown in myeloid transformation through increased hematopoietic stem cell survival and self- renewal; and 2) inhibit a pathway induced in Cux1lowxNrasG12D mice, such as PI3K, to block the malignant phenotype.
- Performance Period: 12/1/17 – 11/30/19
- Effort: .24 CM (2%)
- Contracting/Grants Officer: Jamie B. Bender
    - Contact Information: Email: Jamie.bender@brinsonfoundaiton.org

- Title: **Molecular mechanisms of myeloid suppressor genes on chromosome 5 (LeBeau)**
- Agency: NIH/NCI - R01 CA190372-05
- Project Goals: The overall goal of this project is to identify cooperating mutations and genetic pathways leading to alkylating agent-induced t-MN with a del(5q).
- Specific Aims: Aim 1. To identify the molecular mechanisms of transformation by EGR1 by: a. Identifying the transcriptional targets of, and cellular pathways regulated by, EGR1 in normal hematopoietic stem cells (HSCs), and t-MNs with a del(5q); b. Examining the mechanism by which cell intrinsic loss of Egr1 and Apc cooperate with Tp53 loss in a mouse model of t-MN; and c. Examining the relationship of transcriptional regulatory pathways of the CUX1 transcription factor (a myeloid TSG on 7q22.1) and EGR1, and the mechanism by which lesions on 5q and 7q cooperate. Aim 2. To identify genetic mutations that cooperate with haploinsufficiency of EGR1 and/or APC in the pathogenesis of myeloid neoplasms by: a. Characterizing the genomic pattern of myeloid leukemias arising in mice with haploinsufficiency for Egr1, Apc, and Tp53; b. Expanding upon our studies showing that Egr1 haploinsufficiency cooperates with mutations induced by alkylating agents (ENU) to induce myeloid neoplasms by conducting genomic analysis of myeloid neoplasms arising in ENU-treated Egr1+/- mice; and c. Evaluating the cooperative role of candidate myeloid suppressor genes on 5q, e.g., CSNK1A1 (5q32, plays a critical role in hematopoiesis), SPRY4 (5q31.3, shown by S. Lowe to cooperate with Tp53 loss to promote AML), and a lysine-specific demethylase gene, KDM3B (5q31.2
- Performance Period: 2/1/15 - 1/31/20
- Effort: 0.36 CM (3%)
- Contracting/Grants Officer: Ian M Fingerman
    - Contact Information: Email: fingerma@mail.nih.gov

- Title: **The role of CUX1 in human myelopoiesis (McNerney)**
- Agency: American Society of Hematology
- Project Goals: The objective of this proposal is to identify the role for CUX1 in human HSCs and the molecular pathways downstream of CUX1 haploinsufficiency that lead to malignant hematopoiesis.
- Specific Aims: Aim 1: Hypothesis —CUX1 transcriptionally regulates proliferation and differentiation genes in HSPCs. This will be tested by innovative functional genomic analyses including differential chromatin accessibility and gene expression due to CUX1 haploinsufficiency. Aim 2: Hypothesis — CUX1 suppresses human HSPC proliferation, blocks myelomonocytic differentiation, and is required for megakaryocyte and erythroid differentiation. This hypothesis will be tested by assays including cell-cycle, self-renewal, and myeloid/erythroid differentiation of cord-blood derived human HSCs with and without CUX1 haploinsufficiency.
- Performance Period: 7/1/18 – 6/30/20
- Effort: 0.6 CM (5%)
- Contracting/Grants Officer: Patricia Frustace
    - Contact Information: Email: awards@hematology.org

- Title: **Tag-ChIP-MS for analysis of chromatin-level regulation of DNA repair (Kron)**
- Agency: NIH/NCI - R21CA213247-03
- Project Goals: The aim of this project is to establish Tag-ChIP-MS as an innovative technology for imaging-and-capture tagging to advance analysis of chromatin dynamics by microscopy and proteomics.
- Specific Aims: Aim 1. Establish split MPLUM tagging to visualize proteins involved in IRIF formation and resolution, Aim 2. Leverage split MPLUM tagging for TAG-CHIP-MS to dissect chromatin dynamics at IRF
- Performance Period: 3/1/17-2/29/21
- Effort: 0.24 CM (2%)

- Contracting/Grants Officer: John R Knowlton
    - Contact Information: Email: jk339o@nih.gov

Overlap with the Proposed Project: None

- Title: **The genetic and environmental etiology of therapy-related myeloid neoplasms (McNerney)**
- Agency: American Cancer Society - #132457-RSG-18-171-01-LIB
- Project Goals: The overall objective of the current application is to identify the mechanism by which CUX1 deficiency drives t-MN.
- Specific Aims: Aim 1: Hypothesis – PI3K inhibition blocks the genetic interaction of CUX1-loss and RAS signaling in myeloid transformation. Aim 2: Hypothesis – Insufficient CUX1 causes increased HSC 'fitness' in response chemotherapy due to increased PI3K activity leading to clonal expansion and t-MN.
- Performance Period: 01/01/19 - 12/31/22
- Level of Funding:
- Effort: 0.6 CM (5%)
- Contracting/Grants Officer: Janet Meadows-Harriss
    - Contact Information: Email: janet.harris@cancer.org;

Overlap with the Proposed Project: None

- Title: **Regulation of hematopoiesis by CUX1 (McNerney)**
- Agency: NIH/NCI - 5R01HL142782-05
- Project Goals: The overall objective is to determine the transcriptional role for CUX1 in normal HSPCs and erythroid progenitors and the pathways downstream of CUX1 haploinsufficiency that block erythroid differentiation.
- Specific Aims: Aim 1: Overall hypothesis – CUX1 is a transcriptional regulator of HSPC homeostasis conserved in mice and humans. Aim 2: Overall hypothesis – CUX1 promotes erythroblast cell cycle exit necessary for terminal differentiation by suppressing PI3K signaling.
- Performance Period: 7/15/18 – 6/30/23
- Level of Funding:
- Effort: 1.38 CM (11.5%)
- Contracting/Grants Officer: C Brian Bai
    - Contact Information: Email: brian.bai@nih.gov

Overlap with the Proposed Project: None

- Title: **Preventing Blood Cancers and Other Malignancies in Military Personnel at Risk Due to Occupational Radiation Exposure (Kron)**
- Agency: DoD, W81XWH-20-1-0556
- Project Goals: This study examines metabolic strategies to mitigate radiation exposure.
- Specific Aims: Aim 1 Examine impacts of hexosamine biosynthetic pathway modulation on repair of double strand breaks, survival, proliferation, senescence and differentiation in bone marrow cultures.
  Aim 2 Examine effects of modulation of the hexosamine biosynthetic pathway on repair of double strand breaks and bone marrow integrity and function after total body irradiation.
  Aim 3 Examine whether modulation of the hexosamine biosynthetic pathway can alter kinetics of bone marrow failure and myeloid neoplasms in Cux1 knockdown mice.
- Performance period: 07/01/2020 – 06/30/2023
- Level of Funding:
- Time Commitments: 0.48 CM (4%)
- Contracting/Grants Officer: Jamie A. Shortall
    - Contact Information: Email: jamie.a.shortall.civ@mail.mil

Overlap with the Proposed Project: None

CURRENT

- Title: **The impact of chromosome 7q deletions in juvenile mylelomonocytic leukemia (McNerney)**
- Agency: NIH/NCI - 5R01CA231880-05
- Project Goals: The long-term goal of this proposal is to understand the molecular pathogenesis of -7/ del(7q) and to reveal new therapeutic targets for JMML patients.
- Specific Aims: Aim 1: Identify the cellular and molecular mechanisms by which Cux1 knockdown and Ras cooperate in JMML. Aim 2: Define the pathogenesis of combinatorial dosage imbalance of 7q genes in JMML.
- Performance Period: 9/20/18-8/31/2024
- Level of Funding:
- Effort: 0.6 CM (5%)
- Contracting/Grants Officer: Chamelli Jhappan
    - Contact Information: Email: jhappanc@mail.nih.gov

Overlap with the Proposed Project: None

- Title: ***Cancer Center Support Grant - Molecular Mechanisms of Cancer Core*** **(PI: Odunsi)**
- Agency: NIH/NCI, 5P30CA014599-48
- Project Goals The overall goal of the University of Chicago Medicine Comprehensive Cancer Center is to discover and translate new cancer-specific knowledge to prevent, detect, and treat cancer.
- Performance period: 5/22/18 - 3/31/24
- Level of Funding:
- Time Commitments: 0.6 CM, (5%)
- Contracting/Grants Officer Contact: David G Ransom david.ransom@nih.gov

Overlap with the Proposed Project: None

- Title: **Genomic interrogation of high-risk myeloid neoplasms to identify new therapies (McNerney)**
- Supporting Agency: Leukemia & Lymphoma Society
- Performance period: 7/1/22 – 6/30/27
- Level of Funding:
- Time Commitments: 0.6 CM, (5%), This is a Career Development award which only provides salary support. It is acceptable that that there is overlap between other active/pending research support.
- Project Goals: Over 50,000 people are diagnosed with a myeloid neoplasm every year in the U.S. alone. A high-risk subset of patients is unresponsive to treatment and their survival is less than a year. The long-term goal of my lab is to improve the outcome for these patients. To this end, our research focuses on understanding the underlying genomic abnormalities in high-risk myeloid neoplasms, to identify new treatment avenues.
- Specific Aims:
- Contracting/Grants Officer Contact: researchprograms@lls.org

Overlap with the Proposed Project: None

- Title: **Uncovering drug resistance mechanisms in AML (McNerney)**
- Supporting Agency: Cancer Research Foundation/Fletcher Scholar Award
- Performance period: 10/14/2022 – 10/13/24
- Level of Funding:
- Time Commitments: .24 CM (2%)

- Project Goals: The overall objective of this proposal is to determine the coordinated role of CUX1, EZH2, KMT2C, and KMT2E in the epigenetic regulation of drug sensitivity.

Specific Aims: Aim 1: Overall hypothesis Loss of 7q epigenetic regulators disrupts the DDR. Aim 2: Overall hypothesis – Combinatorial loss of 7q genes disrupts the epigenetic regulation of the DNA damage response

.Contracting/Grants Officer Contact: Matthew Moy Johnson
mjohnson@cancerresearchfdn.orf

Overlap with the Proposed Project: None

- Title: **Establishing CUX1 as a determinant of hematopoietic stem cell fate (McNerney)**
- Supporting Agency: NIH, 1 R01HL166184-01
- Performance period: 12/1/22 – 11/30/2026
- Level of Funding:
- Time Commitments: 2.4 Calendar, (20%)
- Project Goals: We aim to understand the mechanism by which CUX1 levels regulate hematopoietic development with the goal of informing new terventions to improve the quality of life for patients with these genetic changes.
- Specific Aims: **Aim 1*:*** To quantify CUX1 protein at the single-cell level, we have generated a novel CUX1mCherry-reporter mouse with endogenous CUX1 tagged with an in-frame mCherry fluorochrome. **Aim 2:** To determine how CUX1 regulates chromatin remodeling and enhancer poising and activation, we will leverage cutting-edge functional genomics approaches and single-cell methodologies in primary HSCs using our CUX1-reporter and -knockdown mice.
- Contracting/Grants Officer Contact: Brian D. Bai
Brian.bai@nih.gov

Overlap with the Proposed Project: None

- Title: **Restoring CUX1 levels in myeloid malignancies of childhood (McNerney)**
- Supporting Agency: V Foundation, # AST2023-002
- Performance period: 03/1/2023– 03/1/2028
- Level of Funding:
- Time Commitments: 0.6 Calendar (5%)
- Project Goals: The overall objectives of this proposal are to (i) identify druggable regulators of CUX1 expression and (ii) restore CUX1 as a form of differentiation therapy.
- Specific Aims: Aim 1: Define the molecular mechanisms by which CUX1 levels are regulated., Aim 2: Drive normal differentiation of -7/del(7q) myeloid disease through therapeutic restoration of CUX1.
- Contracting/Grants Officer Contact: Carole Wegner
info@v.org

Overlap with the Proposed Project: None

PENDING

- Title: **The role of CUX1 in intestinal epithelium homeostasis (McNerney)**
- Supporting Agency: DOD, #PR230426
- Performance period: 9/1/2024 – 8/31/2028
- Level of Funding:
- Time Commitments: 1.8 CM (15%)

- Project Goals: The overall objective of the current proposal is to determine the dose-dependent transcriptional role for CUX1 in intestinal homeostasis.
- Specific Aims: Aim 1: Overall hypothesis – CUX1 has a conserved role in intestinal stem cell differentiation to secretory epi thelial cells; Aim 2: Overall hypothesis – CUX1 dosage transcriptionally controls genes associated with proliferation and differentiation.
- Contracting/Grants Officer: TBD
- Overlap with the Proposed Project: None

- Title: **Cancer Center Support Grant (PI: Odunsi)**
- Supporting Agency: NIH, 2P30CA014599-48
- Performance period: 04/1/2024- 03/31/2029
- Level of Funding: **Molecular Mechanisms of Cancer**
- Time Commitments: 0.6 CM (5%)
- Project Goals: The overall goal of the University of Chicago Medicine Comprehensive Cancer Center is to discover and translate new cancer-specific knowledge to prevent, detect, and treat cancer. Our objectives are: 1) to conduct innovative and collaborative research to discover the determinants of cancer; 2) to discover and develop novel therapies for cancer; 3) to discover and develop new technology useful in addressing the problem of cancer; 4) to discover and develop new approaches to prevent cancer, and 5) to reduce the burden of cancer in our catchment area and beyond.
- Specific Aims: **Aim 1**: Catalyze and conduct innovative, collaborative cancer research comprehensively across the spectrum of basic, translational, clinical, cancer control and population sciences to improve cancer outcomes and quality of life for patients and survivors in our CA and beyond. **Aim 2:** Reduce the cancer burden and disparities in our CA through community engagement, impactful research, education, and outreach, and accelerate health equity especially in historically underserved populations. **Aim 3**: Translate discovery into clinical investigations and new therapeutic approaches for cancer. **Aim 4**: Enhance and coordinate education, training, and mentorship of the next generation of diverse cancer scientists and practitioners by integrating cancer education and training across the research spectrum and career continuum. **Aim 5**: Integrate diversity, equity, and inclusion throughout the fabric of the UCCCC to promote a climate that advances inclusive excellence in workforce development and leadership.
- Contracting/Grants Officer Contact: Shafik, Hasnaa
  shafikh@mail.nih.gov

- Overlap with the Proposed Project: None