AWARD NUMBER: W81XWH-18-1-0309

TITLE: PDE5 inhibitor (Sildenafil) for ameliorating androgen deprivation therapy (ADT)-induced cardiotoxicity

PRINCIPAL INVESTIGATOR:
Dr. Rakesh C. Kukreja

CONTRACTING ORGANIZATION: Virginia Commonwealth University
Richmond, VA 23284

REPORT DATE: August 2019

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE August 2019	**2. REPORT TYPE:** Annual Report	**3. DATES COVERED** 15 July 2018- 14 July 2019

4. TITLE AND SUBTITLE

PDE5 inhibitor (Sildenafil) for ameliorating androgen deprivation therapy (ADT)-induced cardiotoxicity

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-18-1-0309

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S): Surinder K. Batra and Rakesh C. Kukreja

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

Site 1
University of Nebraska Medical Center
Biochemistry and Molecular Biology
985870 Nebraska Medical Center Omaha,
Nebraska – 68198-5870.

Site 2
Virginia commonwealth University
Pauley Heart Center
Richmond, VA 23298-0204, USA

8. PERFORMING ORGANIZATION REPORT

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

U.S. Army Medical Research and Materiel 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

Androgen deprivation therapy (ADT) is the primary systemic therapy for treating locally advanced or metastatic prostate cancer (PCa). Since 1990, the majority of locally advanced and metastatic PCa patients received GnRH agonists as first-line ADT treatment. Despite its positive effect on PCa patient survival, ADT cause various adverse effects, including increased cardiovascular risk factors and cardiotoxicity. Lifespans extension, early use of ADT, and second-line treatment with next-generation androgen receptor pathway inhibitors would further extend the duration of ADT and possibly increase the risk of ADT-induced cardiotoxicity. However, currently no experimental study has reported the detrimental effect of GnRH agonist in cardiac tissue and no therapeutic strategy has been developed or even conceptualized to prevent GnRH agonist-induced cardiac dysfunction. The underlying mechanism and association between GnRH agonists and cardiovascular events is also not clear. In the proposed research, our objective is to determine the protective role and elucidate the molecular mechanisms of sildenafil against cardiotoxicity caused by GnRH agonists in vitro and in vivo. Here, we update our accomplishment with respect to submitted proposal. We have successfully generated and validate the Pten null PCa GEMMs for the project. In addition, we have also established GEMMs derived syngeneic cell lines. Further, our in vitro studies show that GnRH agonists induce cardiac cell death and sildenafil citrate is able to prevent the agonists induced cardiac cell death. Further, the dose dependent escalation pilot study to determine the optimal dose of GnRH agonists in inducing cardiotoxic events and sildenafil citrate in preventing the GnRH effects is ongoing.

15. SUBJECT TERMS: Prostate cancer, Androgen deprivation therapy, GnRH agonists, Cardiotoxicty, PDE5 inhibitor, sildenafil citrate, GEMMs, apoptosis, PDE5/cGMP and NO/GC.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	30	**19b. TELEPHONE NUMBER** *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Androgen deprivation therapy (ADT) is the cornerstone of metastatic prostate cancer (PCa) treatment. ADT is achieved either by surgical or chemical castration. Since 1990, the majority of locally advanced and metastatic PCa are challenged with GnRH agonists as ADT therapeutic regimen. Despite its positive effect on PCa patient survival, ADT cause various adverse effects, including increased cardiovascular risk factors and cardiotoxicity risk [1, 2]. Lifespans extension, early use of ADT, and second-line treatment with next-generation androgen receptor pathway inhibitors would further extend the duration of ADT and possibly increase the risk of ADT-induced cardiotoxicity. With the probability of long-term survival of PCa patients and increased number of survivors, GnRH agonists-mediated cardiovascular events are an emerging problem in cardio-oncology [3]. Until now, no experimental study has reported on the detrimental effects of GnRH agonists on cardiac tissue or on any agents shown to prevent GnRH agonists-induced cardiac dysfunctions. Our extensive work on cardiovascular pathophysiology [4-7] and novel findings of the cardio-protective effect of sildenafil citrate (Viagra) [8-17] form the basis of this proposal. The project will determine the association between GnRH agonist use and cardiovascular risk events. Further, we will scientifically elucidate the functional contribution of these agents to cardiovascular pathophysiology; and we will demonstrate its prevention by sildenafil. The proposed use of in vitro (primary cardiomyocytes) and in vivo animal models (C57BL/6 mouse with intact immune system and transgenic (GEM) PCa animal model) will allow us to determine whether GnRH agonists-induced cardiovascular events, and predict the efficacy of sildenafil in preventing them. Altogether, completion of this project will this study will open up a new avenue to facilitate prevention and improved management of side effects of systemic therapy and increase the quality of life PCa patients.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Prostate cancer, Androgen deprivation therapy, GnRH agonists, Cardiotoxicty, PDE5 inhibitor, sildenafil citrate, GEMMs, apoptosis, PDE5/cGMP and NO/GC.

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

The major goals for the funding period of July 2018-July 2019 are

Virginia Commonwealth University Site; PI: Dr. Kukreja
Major Task 1: Determine the therapeutic effect of sildenafil in improving the GnRH agonists-induced cardiotoxicity in vitro.
Subtask 1: Web based meeting for the experimental planning (Months 1-2).
Subtask 2: Analyze the cardiotoxic effect of GnRH agonists on primary cardiomyocytes in vitro (Months 1-3).

Subtask 3: Analyze the therapeutic impact of sildenafil citrate (Months 5-6).
Major Task 2: Determine the therapeutic beneficial of sildenafil in improving the GnRH agonists-induced cardiotoxicity in vivo.
Subtask 1: Submit documents for IACUC approval (Months 1-3).
Subtask 2: Development of GnRH agonists-induced cardiotoxic potential in C57BL/6J wild-type 12-month old male mice (Months 4-10)
Subtask 3: Determination of cardioprotective effect of sildenafil citrate on GnRH agonists-induced cardiotoxic effects (Months 11-20).

University of Nebraska Medical Center Site; PI: Dr. Batra

Major Task 3: Determine the benefit of sildenafil in improving the GnRH agonists-induced cardiotoxicity in genetically engineered mouse model (GEMM) (Months 1-25).
Subtask 1: Web based meeting for the experimental planning (Months 1-2).
Subtask 2: Submit documents for local IACUC approval (Months 1-3).
Subtask 3: Generation of spontaneous animal model for prostate cancer (Months 3-8).
Subtask 4: Development of GnRH agonists-induced cardiotoxic potential in GEMMs (Months 9-14).

What was accomplished under these goals?

Virginia Commonwealth University Site; PI: Dr. Kukreja

The major accomplishments during the FY 2018-2019 funding period are:

1) Web based meetings between the PIs - Drs. Batra and Kukreja and their research group (Major Task 1, Subtask 1) have been regularly conducted.

2) Submission and obtained approval from VCU IACUC and DOD ACURO - PI Dr. Kukreja (Major Task 2, Subtask 1). Since there was very little previous publications available for the in vivo models of GnRH-induced cardiotoxicity, there are several technical and animal health issues potentially involved in the chronic drug treatment with repeated mini-pump implantations for a prolonged duration of 3 months were raised by both VCU IACUC and/or ACURO. Therefore, it took several review and

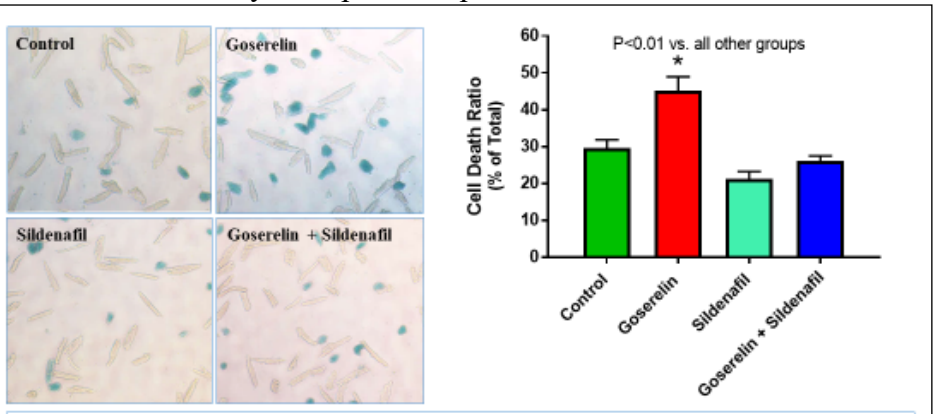

Figure 1. Ventricular cardiomyocytes were freshly isolated from 4-month-old male C57BL/6J mice. The *in vitro* drug treatment experiments were performed in the cardiomyocytes 1 hour after cell isolation. Cell death ratio was determined by trypan blue exclusion 48 hours after the drug additions to the cell culture medium with the contractions of Goserelin 50 nM and Sildenafil 1 µM, respectively. Left panel shows representative images of adult mouse cardiomyocytes after trypan blue staining. Right graph shows the mean values quantified from the 3 wells per treatment and 6-8 images per well. The results clearly indicated Goserelin-induced cytotoxicity in cardiomyocytes and its prevention with co-incubation of phosphodiesterase 5 (PDE5) inhibitor - Sildenafil.

revision processes that withheld the permission to formally start the in vivo experiments in Major Task 2 at VCU. Finally we obtained ACURO approval on May 20, 2019 and we also expect that the VCU IACUC will soon complete their required veterinary observation on the surgical replacement procedure of the implanted mini-pump by mid-July, 2019.

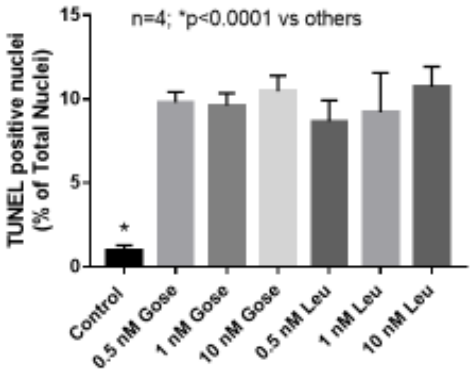

Figure 2. Ventricular cardiomyocytes were freshly isolated from adult male C57BL/6J mice. The *in vitro* drug dose-response experiments were performed and cell apoptosis level was determined by TUNEL assay 48 hours after the drug additions to the cell culture medium in three different contractions (0.5, 1, 10 nM) respectively. The mean results (n=4/group) show that all tested concentrations of GnRH agonists led to a significant increase in cardiomyocyte apoptosis and the higher dose (10 nM) of Goserelin (Gose) or Leuprolide (Leu) did not increase cell apoptosis level further as compared with the drug concentration of 0.1 or 1 nM.

3) We have performed in vitro experiments specified in Major Task 1, Subtask 2 and determined the cardiotoxic effect of GnRH agonist (Geserelin) and its prevention by Sildenafil for the first time in the primary adult mouse cardiomyocytes in vitro. Our results are summarized in **Figure 1**:

4) We further evaluated GnRH-induced cardiomyocyte apoptosis in the in vitro experiments specified in Major Task 1, Subtask 2. As shown in **Figure 2** below, in vitro treatment of GnRH agonists (either Geserelin or Leuprolide) led to significant increase in TUNEL-positive cardiomyocytes from adult C57BL/6J mice and there was no difference among 0.1 to 10 nM doses.

University of Nebraska Medical Center Site; PI: Dr. Batra

The major accomplishments during the FY 2018-2019 funding period are: Web based meeting between the PI's Drs. Batra and Kukreja and their research group (Major task 1&3, sub task 1); Submission and obtained approval from respective institutional IACUC and ACURO PI Dr. Batra (Major task 3, sub task 2); Generation of spontaneous animal model for prostate cancer PI Dr. Batra (Major task 3, sub task 3).

Specific Aim 2: *Determine the therapeutic benefits of PDE5 inhibitor in improving the GnRH agonists-induced cardiotoxicity in murine PCa progression model*.

Major Task 3: Determine the benefit of sildenafil in improving the GnRH agonists-induced cardiotoxicity in genetically engineered mouse model (GEMM).

In the initial two months after approval of the grant both PI (Drs. Batra and Kukreja) and their lab personnel met once in two weeks through skype for the planning and execution of experiments at both ends, as per major task 3, subtask 1 of the SOW. Following the web based discussion, respective PI's submitted IACUC protocol. As we mentioned in the grant application, there was not many studies that has been designed or performed to the extent which we have proposed, it took few revisions, before the IACUC approved experimental protocol on April 19, 2018 and genetically engineered PCa animal model protocol on September 26, 2018. Followed by we submitted our approved IACUC and ACURO application to DoD application which we got approval by end of Jan 2019 (major task 3, Subtask.2).

Generation of spontaneous animal model for prostate cancer (Major task 3 Subtask.3)

We have completed the subtask 3 and brief detail on the experiment performed and data description is as follows.

As per the IACUC and ACURO Animal Ethics Committee approved protocol and guidelines, we have developed a composite strain of Pten conditional knockout (herein referred as Pten cKO) mice model by crossing $Pten^{fl/fl}$ mice with ROSA26-pCAGGs-LSL-Luciferase mice to generate $Pten^{fl/+}$;ROSA26-pCAGGs-LSL-Luciferase mice (F1). Further, we backcrossed the $Pten^{fl/fl}$ mice with $Pten^{fl/+}$;ROSA26-pCAGGs-LSL-Luciferase mice to generate $Pten^{fl/fl}$;ROSA26-pCAGGs-LSL-Luciferase mice (Pten-Rosa26) (F2). Finally, $Pten^{fl/fl}$-$Rosa26^{+}$ mice were crossed with $Pten^{fl/fl}$; PB-$Cre4^{+}$ mice to generate the experimental mice of $Pten^{fl/fl}$; PB-$Cre4^{+}$;ROSA26-pCAGGs-LSL-Luciferase (Pten cKO-Rosa26) genotype mice.

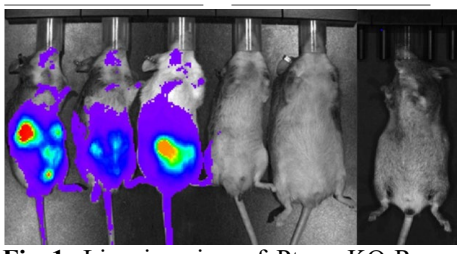

Fig 1. Live imaging of Pten cKO-Rosa 26 mice using IVIS system. Our lab generated $Pten^{-/-}$:Rosa26;PB-$Cre4^{+}$ (left) showed positive tumor imaging as shown by the luciferase expression as compared to $Pten^{-/+}$:Rosa26;PB-$Cre4^{-}$ littermate control mice (right).

Establishment and monitoring prostate cancer (PCa) tumor growth in Pten cKO mice model.

Initially, we wanted to check the tumor growth of Pten cKO-Rosa26 mice using luciferase imaging.

We injected both Pten cKO-Rosa26 and littermate control mice (N=3/group) with luciferin (150 mg Luciferin/kg body weight) intraperitoneally (i/p) to determine the tumor growth. After 10-15 minutes of luciferin administration, the photons emitted from each mouse was imaged using IVIS machine located at our animal facility. As shown in **fig.1**, upon luciferin injection the Pten cKO mice with Rosa26 positive animals exhibit a full-blown tumor whereas the negative animals do not show such tumor growth or luciferase positivity. The imaging was captured at various time points such as 1 sec, 2 sec, 5 sec, 1 and 2 minutes to determine the peak signal intensity and time. Through this preliminary experiment, we were able to locate the PCa tumor at 2 sec and the maximum signal could be observed at 2 minutes. This IVIS imaging will be useful while correlating the tumor reduction and response of the PCa tumor during GnRH agonists treatments. At this end, the animals are ready for the initial dose escalation studies as proposed in the grant.

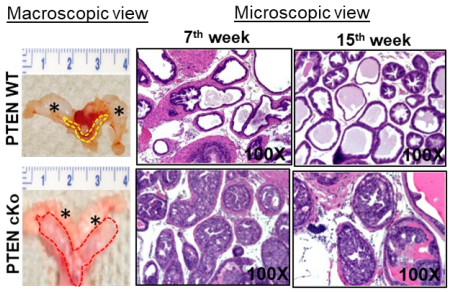

Fig 2. Gross morphology and histology analysis of Pten cKO mouse model and wild type controls. Mouse urogenital organs such as prostate, seminal vesicle along with bladder were excised from 7 and 15 weeks old PTEN cKO and $PTEN^{WT}$ mice. The tissues were examined for gross morphology and histology. Seminal vesicle were shown by asterix symbol followed by the dotted lines representing the normal prostate in $Pten^{wt}$ and full blow tumor and Pten cKO mice (Right). Histological analysis of wild type and Pten cKO mice exhibit initiation of PCa at 7^{th} weeks and adenocarcinoma at 15^{th} weeks old mice (Left). (Seshacharyulu et al., oncogene 2019).

Validation of Pten cKO mice derived PCa tumors and Pten cKO mice derived cell lines for PDE-5 expression.

In our preliminary data section (Fig. 8) of the grant application, we observed that the initiation of PCa at 4 weeks old mice (PIN lesion) followed by the advancement of PCa tumor at 20 weeks. Hence, to confirm the PCa

progression in Pten cKO tissues initially we performed histological analysis in 7th and 15 weeks old mice tissues. We observed that low-grade PIN lesion in the 7 weeks old Pten cKO mice whereas the 15-week old mice exhibited high-grade PINs and adenocarcinoma (**Fig. 2**). This data suggest that the age of the mice which we chose for the proposed experimental studies were appropriate. This data and description of these preliminary results have been included as figures 1B, 1C and supplementary figure 1B in the recent publication (Seshacharyulu et al., Oncogene, 2019[18]).

Since GnRH agonists is used as androgen deprivation therapeutic agent in PCa and we proposed to study the preventive effect of sildenafil citrate in GEMM, we wanted to observe an additional effect of sildenafil citrate in prostate, if any. We examine the sildenafil citrate target, PDE5 expression in the mouse derived prostate tumor and tumor derived syngenic cell lines. We observed that PDE5 transcript levels are elevated in Pten cKO mice tissues as compared to wild-type mice (**Fig.3**), suggesting that PCa could be susceptible upon sildenafil treatment, which targets PDE5. In addition, we evaluated the PDE5 expression in OCT161 ($Pten^{wt}$) and E2, E4, cE1 and cE2 (derived from Pten cKO mouse tumor). We found that PDE5 expression is higher at both protein and transcript levels in the Pten cKO derived cells that correlated with the cell growth (Seshacharyulu et al., Oncogene 2019[18]) as compared to wild-type control cells (**Fig. 4**). These results suggest that the mouse syngenic cell lines can be expanded *in vitro* and can be utilized for the pre-clinical studies and to explore the mechanism behind the synergy of GnRH agonist and sildenafil co-treatment.

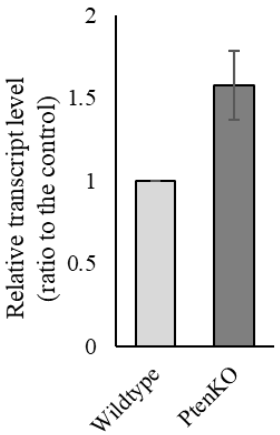

Fig 3. *PDE5* expression in Pten wild-type and Pten cKO mouse tissues. *PDE5* relative mRNA expression was analyzed by qPCR in normal prostate- and PCa tissues from PTEN cKO mouse. The relative fold change of PDE5 is upregulated in conditional knockout mouse tissues as compared to wild-type controls (N=3/group).

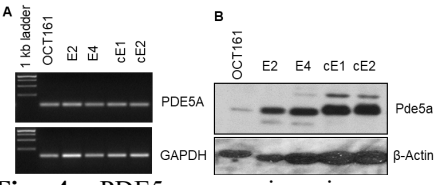

Fig 4. PDE5 expression in mouse syngenic cell lines. PDE5 protein and mRNA expressions are elevated in Pten cKO mouse prostate derived cell lines compared to wild-type mouse derived cell lines.

What opportunities for training and professional development has the project provided?

While working under the mentorship of Dr. Batra, Dr. Muniyan has acquired skill sets and knowledge in the area of identifying the underlying factors and novel therapeutic agents for CRPC. In addition to already acquired skills under the formal mentorship of Dr. Batra, the research area of addressing therapy-induced adverse effects is unique to Dr. Muniyan. This unique expertise gained is largely as a result of the mentorship and the collaborative efforts of Dr. Batra, which helped Dr. Muniyan to get promotion into Assistant Professor in the department of Biochemistry and Molecular Biology.

How were the results disseminated to communities of interest?

a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

Virginia Commonwealth University Site; PI: Dr. Kukreja

For the next 12-month reporting period (July 16, 2019 to July 15, 2020), we plan to primarily focus on Major Task 2, Subtasks 2 and 3 for accomplishing the proposed major goals and objectives, including determination of in vivo dose-dependent cardiotoxic effects of GnRH agonists (Goserelin and Leuprorelin) and the cardioprotective effects of sildenafil co-treatment in elderly male C57BL/6J mice.

University of Nebraska Medical Center Site; PI: Dr. Batra

In the upcoming funding period, with reference to the approved SOW subtask 4 under major task 3, we will set GnRH agonists dose concentration that will induce cardiotoxicity in prostate cancer animal model. Followed by dose escalation study, we will determine the therapeutic beneficial of sildenafil in improving the GnRH agonists-induced cardiotoxicity in Genetically engineered mouse models (GEMM).
Since we have generated and validated the double transgenic animal model of Pten cKO with ROSA, we hope that we will achieve our subtask 4 and 5 in the coming funding period.
By completion of these two subtask of main task 3, we can able to achieve an experimental set up to show ADT-induced cardiotoxicity in animal model and we can see if sildenafil citrate able to prevent the AT-induced cardiotoxicity.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Combined Impact of Virginia Commonwealth University Site; PI: Dr. Kukreja and University of Nebraska Medical Center Site; PI: Dr. Batra

Considering two facts that cardiovascular-related death is number one killer among prostate cancer patients and number of prostate cancer survivors are more than any other cancer among men, our project will have a major impact on prostate cancer patients. In this project, we are just beginning our work to test whether sildenafil citrate could be therapeutic agent to reduce or prevent ADT induced cardiotoxicity. Since there were not many preclinical or no clinical studies on this aspect, the project will take some more time to give an impact. However, because sildenafil citrate is already clinically approved with known toxicity profile and drug pharmacokinetics, this drug will move from bench to bedside quicker than traditional drug discovery

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

5. CHANGES/PROBLEMS:
Changes in approach and reasons for change

a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

Changes that had a significant impact on expenditures

a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Significant changes in use or care of human subjects

a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

Significant changes in use or care of vertebrate animals

a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

Significant changes in use of biohazards and/or select agents

a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications.

1. Seshacharyulu P, Rachagani S, Muniyan S, Siddiqui JA, Cruz E, Sharma S, Krishnan R, Killips BJ, Sheinin Y, Lele SM, Smith LM, Talmon GA, Ponnusamy MP, Datta K, **Batra SK**. FDPS cooperates with PTEN loss to promote prostate cancer progression through modulation of small GTPases/AKT axis. Oncogene. 2019Jun;38(26):5265-5280. doi: 10.1038/s41388-019-0791-9. Epub 2019 Mar 26. PubMedPMID: 30914801; PubMed Central PMCID: PMC6597298. *(Published)*
2. Muniyan S, Xi L, Datta K, Das A, Teply BA, **Kukreja RC, Batra SK.** Androgen deprivation therapy and cardiovascular risk in prostate cancer patients: Potential therapeutic role of PDE5 inhibition. *(Near submission)*
3. Samidurai S, Xi L, Salloum FN, Das A, **Kukreja RC.** PDE5 inhibitor sildenafil attenuates cardiac microRNA 214 upregulation and pro-apoptotic signaling after chronic alcohol ingestion in mice. *(Submitted to "Alcoholism: Clinical and Experimental Research" and currently under revision)*
4. Koka S, Xi L, **Kukreja RC**. Chronic inhibition of phosphodiesterase 5 (PDE5) with tadalafil protects against cardiac diastolic dysfunction and ischemia/reperfusion injury in a mouse model of metabolic syndrome. *(Under preparation)*

Books or other non-periodical, one-time publications.

1. Muniyan S, Siddiqui JA and **Batra S.K**. Therapeutic options for prostate cancer: A contemporary update [Chapter] In: Gene Regulation & Therapeutics Ed: SURINDER K. BATRA & MOORTHY P. PONNUSAMY, Pubs: *SCIENCE PUBLISHERS (CRC Press/ Taylor & Francis Group-In press).*

Other publications, conference papers and presentations.

1. Muniyan S**,** Nimmakayala RK, Karmakar S, Rachagani S, Siddiqui JA, Seshacharyulu P, Lin MF, Datta K, Ponnusamy MP, **Batra SK**. Role of polymerase II associated factor 1, PAF1, in docetaxel resistant prostate cancer cells poster [abstract]. Department of Biochemistry and Molecular Biology Annual symposium August 2018. Poster presentation.
2. Ridwan Islam, Zhengdong Hong, Navatha S Polavaram, Tyler Gilbreath, Sanjana Eyunni, Kaustubh Datta and Samikshan Dutta. "NRP2 axis, a potential target for neuroendocrine-like therapy resistant prostate cancer". Oral Presentation in Midwest Student Biomedical Research Forum, February 2019.
3. Ridwan Islam, Zhengdong Hong, Navatha S Polavaram, Tyler Gilbreath, Kaustubh Datta and Samikshan Dutta. "NRP2 axis, a potential target for neuroendocrine-like therapy resistant prostate cancer". Poster Presentation in the conference of Society for Redox Biology and Medicine, SfRBM, June 2018.
4. Ridwan Islam, Zhengdong Hong, Navatha S Polavaram, Tyler Gilbreath, Kaustubh Datta and Samikshan Dutta. "NRP2 axis, a potential target for neuroendocrine-like therapy resistant prostate cancer". Poster Presentation in Annual Research Symposium, Department of Biochemistry and Molecular Biology, July 2018.
5. Presented 'Role of Polymerase II associated factor 1, PAF1, in docetaxel-resistant prostate cancer' at GU Oncology Focus Group Meeting at UNMC, January 17, 2019. (Oral presentation by Dr. Muniyan)

- **Website(s) or other Internet site(s)**

  a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

  b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

- **Technologies or techniques**

  a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

  b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

- **Inventions, patent applications, and/or licenses**

  a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

  b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

- **Other Products**

  a. Virginia Commonwealth University Site; PI: Dr. Kukreja: Nothing to report

  b. University of Nebraska Medical Center Site; PI: Dr. Batra: Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Surinder K. Batra Ph.D
Project Role:	PI (UNMC)
Researcher Identifier (eRA commons):	SBATRA (eRA commons)
Nearest person month worked:	0.48 months
Contribution to Project:	Dr. Batra is the initiating PI and convene the monthly meeting between the groups, oversee the activities related to the project and Give guidance to Dr. Muniyan and Mr. Ridwan related to the project and on their career.
Funding Support:	This Grant

Name:	Rakesh C. Kukreja Ph.D
Project Role:	PI (VCU)
Researcher Identifier (eRA commons):	OMGANESH (eRA commons)
Nearest person month worked:	1.2 months
Contribution to Project:	Dr. Kukreja is the partnering PI and responsible to convene the monthly meeting and oversee the activities from the other institution. Further, he guides Dr. Kraskauska on day to day research activities.
Funding Support:	This Grant

Name:	Sakthivel Muniyan Ph.D
Project Role:	Postodctoral fellow/Project personal (UNMC)
Researcher Identifier (eRA commons):	muniyan.sakthivel (eRA commons)
Nearest person month worked:	6.0 months
Contribution to Project:	With the guidance of Dr. Batra, Dr. Muniyan is responsible for the continuous maintenance and establishment of additional transgenic prostate cancer animal model related to the project.
Funding Support:	This Grant

Name:	Donatas Kraskauskas D.V.M
Project Role:	Research technician/project personal (VCU)
Researcher Identifier (e.g. ORCID ID):	(eRA commons)
Nearest person month worked:	3.6 months
Contribution to Project:	With the guidance of Dr. Kukreja, Dr. Kraskauskas is responsible for all the in vitro and in vivo experiments proposed on this grant.

Funding Support:	This Grant

Name:	Ridwan Islam M.S
Project Role:	Graduate Student (UNMC)
Researcher Identifier (e.g. ORCID ID):	(eRA commons)
Nearest person month worked:	12 months
Contribution to Project:	With the guidance of Dr. Batra, Mr. Islam is closely working with Dr. Muniyan in maintaining the genetically engineered PCa animal model and performing the experiments involved in GnRH agonists induced cardiac effects.
Funding Support:	This Grant

Name:	Lei Xi M.D
Project Role:	Co-investigator (VCU)
Researcher Identifier (eRA commons):	LEIXIMD
Nearest person month worked:	2.4 months
Contribution to Project:	With his expertise on drug-induced cardiotoxicty, he Is closely working with Dr. Kukreja to give suggestions and experimental guidance to Dr. Kraskauskas in performing in vitro and in vivo experiments related to GnRH agonists induced cardiotoxicity
Funding Support:	This Grant

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

There are two changes in the Graduate Student (UNMC) and Postdoctoral Fellow (VCU).

Since Ms. Sundandini Sharma (UNMC) chose Gastro intestinal cancer program for her graduate studies from prostate cancer, the Investigator's team selected Mr. Ridwan Islam to work on this project and ultimately to train in prostate cancer.

Dr. Rui Wang (VCU) has resigned as Postdoctoral Fellow from our lab and took a new position as Research Associate in the Department of Microbiology and Immunology at VCU, the Investigator's team has replaced Dr. Wang's role with an experienced senior Research Technician – Dr. Donatas Kraskauskas to continue the proposed research projects.

Updated other support is attached in an Appendix.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Except the initiating PI and partnering PI's respective institution, no other organization is directly or indirectly involved in the project.

Virginia Commonwealth University Site; PI: Dr. Kukreja
Nothing to report
University of Nebraska Medical Center Site; PI: Dr. Batra
Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

The project was a collaborative Idea Award –partnering PI options. Hence this report was jointly prepared by two PI's. The goals, accomplishments and plan for next funding period is clearly marked for each site with site and PIs' Name

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. **APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

References

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PHS 398/2590 Other Support

Batra, Surinder K.

ACTIVE

1P01CA217798 (Batra) 06/08/2018 - 05/31/2023 2.40 calendar
DHHS/NIH $1,079,000
Pancreatic Cancer Metastasis
The overall objective of this PO1 is to investigate implications of MUC16 for metastasis in pancreatic cancer.
Role: PI

1R01CA228524 (Singh) 04/01/2018 - 03/31/2023 0.91 calendar
DHHS/NIH $318,040
Targeting CXCR2 axis in Pancreatic Cancer
Altogether, the results from this proposed study will provide a mechanism for Kras-dependent expression of CXCR2 ligands, delineate their role in PC pathobiology and determine their potential as therapeutic targets.
Role: Co. PI

U01CA210240 (Hollingsworth) 05/01/2017 - 04/30/2022 0.48 calendar
DHHS/NIH $253,795
Pancreatic Cancer Detection Consortium
To assemble a unique and robust collection of early lesions and blood samples from patients at risk and those with lesions representing early stages of pancreatic cancer and to undertake a series of biomarker discovery and prevalidation projects proposed within this application.
Role: Co. Investigator

R01CA210637 (Ponnusamy) 03/06/2017 - 02/28/2022 0.91 calendar
DHHS/NIH $249,000
Role of PD2/Paf1 in Pancreatic Acinar to Ductal Metaplasia
The overall goal of this study is to define the role of PD2/Paf1 in trans-differentiation of acinar cells to ductal cells during PDAC progression through self-renewing pancreatic CSC population.
Role: Co. PI

2P30CA036727 (Cowan) 08/01/2016 - 07/31/2021 0.12 calendar
DHHS/NIH/NCI $1,400,000
Fred and Pamela Buffett Cancer Center Support Grant
The mission is to coordinate basic research and clinical cancer research, patient care and educational programs, to facilitate application of new knowledge about the etiology, diagnosis, treatment and prevention of cancer and to improve health and quality of life.
Role: Co.I. Education and training program

PC170891 (Batra & Kukreja) 07/01/2018 - 06/30/2021 0.48 calendar
U.S. Army/USAMRAA/CDMRP $150,000
PDE5 inhibitor (Sildenafil) for ameliorating androgen deprivation therapy (ADT)-induced cardiotoxicity. The overall objective of the proposed studies is to understand the molecular mechanisms and develop strategies to counter ADT-induced cardiotoxicity
Role: PI

R01CA206444 (Ouellette) 05/01/2016 - 04/30/2021 0.91 calendar
DHHS/NIH/NCI $249,000
RAC1 GTPase in tumorigenesis and progression of pancreatic cancer
Role: Co. PI
The objective of this proposal is to elucidate the underlying mechanisms of Rac1-induced transformation and its cooperation with the MAPK pathway.

5R01CA195586 (Batra) 07/17/2015 - 06/30/2020 0.91 calendar
DHHS/NIH/NCI $290,503
Targeted Radiation Therapy for Pancreatic Cancer

The overall objective of the proposed studies is to determine the utility of targeting pancreatic cancer with novel radiolabeled anti-MUC4 antibodies in combination with rationally selected specific modulators of tumor microenvironment (TME)
Others: Co. PI: Maneesh Jain

U01CA185148 (Batra) 05/01/2015 - 04/30/2020 0.72 calendar
DHHS/NIH/NCI $228,250
MIC-1 and its functional partners in prostate cancer racial disparity
The overall objective of this proposal is to establish the functions of macrophage inhibitory cytokine-1 (MIC-1) and its cooperative interactions with epidermal growth factor receptor (EGFR) and CXC chemokine receptor 4 (CXCR4) in prostate cancer (PC) pathogenesis and in the racial disparity between black and white men.
Role: PI

U01CA200466 (Brand) 05/17/2016 - 03/31/2020 1.20 calendar
University of Pittsburgh $261,545
Validation of Biomarkers for Early Diagnosis and Risk Prediction of Pancreatic Neoplasms
The overall objective of this CVC proposal is to demonstrate the ability of the aforementioned biomarkers to distinguish pancreatic adenocarcinoma (PC) patients from healthy controls, patients with benign biliary obstruction and chronic pancreatitis (CP), and to identify those cysts with high malignant potential.
Role: Co. PI

5R01CA183459 (Batra) 09/19/2014 - 08/31/2019 0.69 calendar
DHHS/NIH/NCI $207,841
Targeting Mucin and EGFR Axis in Pancreatic Cancer
The overall objective of the proposed study is to test and develop a novel combination therapy against lethal pancreatic cancer by combining the canertinib (CI 1033) and cytotoxic agent gemcitabine.
Role: PI

5P50CA127297 (Hollingsworth) 09/23/2014 - 08/31/2019 0.91 calendar
DHHS/NIH/NCI $1,437,283
SPORE in Pancreatic Cancer
Role Project Co. Leaders (Batra and Lin): Project 2
The overall objective of this project is to identify and characterize pathway(s) contributing to radioresistance (RR) in pancreatic cancer (PC) that can be explored as novel targets for radiosensitization (RS).
Role: Project Leader

PENDING

(Batra) 12/01/2019 – 11/30/2024 0.84 calendar
DHHS/NIH – sub with UC San Diego $250,000
Molecular Biomarkers and Imaging Probes for Early Detection of Pancreatic Neoplasms

(Batra/Singh) 12/01/2019 – 11/30/2024 0.84 calendar
DHHS/NIH $350,000
Mechanistic and Prognostic Implications of NGAL in Severe Acute Pancreatitis

OVERLAP: There is no overlap of the currently considered grant application with funded or submitted grant applications. Should any of the pending projects be funded, changes in effort on currently funded grants will be made to maintain < 12 calendar months.

Other Support (Kukreja, RC)

ACTIVE

5R01HL134366-04 07/01/2018 – 06/30/2020
NIH/NHLBI Kukreja (PI) and Das (PI) $338,449
Cardioprotection with mTOR inhibition
The major goals of this project are to examine the role of rapamycin in cardioprotection against ischemia/reperfusion injury in type-2 diabetic mice and rabbits and to investigate the involvement of STAT3 and microRNA-17/20.
Role: PI
Effort: 3.0 months
OVERLAP
None

1R01CA221813-01A1 01/01/2018 - 12/31/2019
NIH/NCI Singla (PI) and Kukreja (PI) $143,006
University of Central Florida
Amelioration of Doxorubicin-induced Muscle Dysfunction with Embryonic Stem Cells-Derived Exosomes
The goal of this project is to investigate the effect of embryonic stem cells derived exosomes on improvement of muscle dysfunction following doxorubicin treatment of mice.
Role: PI
Effort: 1.8 months
OVERLAP
None

1R01DK120866-01 01/19/2018 - 08/31/2019
NIH/NIDDK Singla (PI) and Kukreja (PI) $150,691
University of Central Florida
BMP-7 Modulates Inflammation induced cell death in Diabetic Cardiac and Skeletal Muscle
The major goal is to study the role of BMP-7 on anti-inflammatory effects of M2 macrophages and IL-10 cytokine in improving cardiac and smooth muscle function in diabetes.
Role: PI
Effort: 2.4 months
OVERLAP
None

2R01HL057244-20 02/05/2018 - 01/31/2020
NIH/NHLBI Li (PI) $52,273
Lysosome Regulation of Exosome Release and Function in Arterial Smooth Muscle
The main goal of this project is to understand the role of ceramide signaling and activation of the mTORC1 pathway in calcification of coronary arterials smooth muscle.
Role: Co-Investigator
Effort: 1.2 months
OVERLAP
None

PENDING

1R01DK124099-01 09/01/2019 - 08/31/2024
NIH/NIDDK Kukreja (PI) and Tipparaju (PI) $165,000
University of South Florida
NAD Basis for Inflammation and Metabolism in the Muscle
The goals of this project are to investigate the mechanistic information on the fundamental role of NAD in inflammation and diabetes, discover molecular pathways in causing skeletal and cardiac muscle injury, and identify new therapeutic targets for protection
Role: PI
Effort: 1.2 months
OVERLAP
None

Other Support

Datta, Kaustubh

ACTIVE

5R01CA182435-05 (Datta) 02/01/2015 - 01/31/2020 5.40 calendar
DHHS/NIH/NCI $221,887
Neuropilin-2 Axis in Docetaxel Resistance and Prostate Cancer Bone Metastasis
The long term objective of this proposal is to understand the potential of Neuropilin-2 (NRP-2) inhibitors as novel therapies against metastatic prostate cancer (PCa). We will specifically investigate how NRP-2 axis promotes PCa bone metastasis and confers therapy resistance to cancer cells.

W81XWH1810308 (Batra) 07/15/2018 - 07/14/2021 0.48 calendar
U.S. Army/USAMRAA/CDMRP $500,000
PDE5 inhibitor (Sildenafil) for ameliorating androgen deprivation therapy (ADT)-induced cardiotoxicity
PDE5 inhibitor (Sildenafil) for ameliorating androgen deprivation therapy (ADT)-induced cardiotoxicityThe major goal of this study is to determine the therapeutic potential and the novel mechanism of a PDE5 inhibitor, sildenafil citrate, on GnRH agonist (ADT)-induced cardiotoxicity in prostate cancer.

5U01CA185148-05 (Batra) 05/01/2015 - 04/30/2020 0.36 calendar
DHHS/NIH/NCI $222,029
MIC-1 and its functional partners in prostate cancer racial disparity
The overall objective of this proposal is to establish the functions of macrophage inhibitory cytokine-1 (MIC-1) and its cooperative interactions with epidermal growth factor receptor (EGFR) and CXC chemokine receptor 4 (CXCR4) in prostate cancer (PC) pathogenesis and their involvement in the racial disparity between black and white men.

(Datta) 01/22/2019 - 01/21/2020 0.12 calendar
aTYR Pharma INC $118,622
Elucidation of the Role of NRP2 and iMOD in Myeloid Cell Biology

PENDING

(Datta) 12/01/2019 - 11/30/2024 3.00 calendar
DHHS/NIH $250,000
Nuclear Neuropilin2: a novel molecular mediator for aggressive Prostate Cancer
Altogether, our proposal will determine how nuclear NRP2 promotes PCa and thus can be an effective biomarker for aggressive PCa.

(Garrison) 12/01/2019 - 11/30/2020 0.60 calendar
AdductNE, LLC $98,361
Development of a GRPR-targeted Peptide Based Radiotherapeutic for Prostate Cancer

OVERLAP: None

PHS 398/2590 Other Support

Lin, Ming-Fong

ACTIVE

5U01CA185148-04 (Batra) 05/01/2015 - 04/30/2020 0.36 calendar
DHHS/NIH/NCI $228,250
MIC-1 and its functional partners in prostate cancer racial disparity
The overall objective of this proposal is to establish the functions of macrophage inhibitory cytokine-1 (MIC-1) and its cooperative interactions with epidermal growth factor receptor (EGFR) and CXC chemokine receptor 4 (CXCR4) in prostate cancer (PC) pathogenesis and their involvement in the racial disparity between black and white men.

W81XWH1810308 (Batra) 07/15/2018 - 07/14/2021 0.24 calendar
U.S. Army/USAMRAA/CDMRP $500,000
PDE5 inhibitor (Sildenafil) for ameliorating androgen deprivation therapy (ADT)-induced cardiotoxicity
PDE5 inhibitor (Sildenafil) for ameliorating androgen deprivation therapy (ADT)-induced cardiotoxicityThe major goal of this study is to determine the therapeutic potential and the novel mechanism of a PDE5 inhibitor, sildenafil citrate, on GnRH agonist (ADT)-induced cardiotoxicity in prostate cancer.

P30 CA036727 Buffet Cancer Center Pilot Project (Lin) 01/01/2019 – 01/31/2019 0.6 calendar
p66Shc oxidase as a biomarker for prostate cancer disparity $50,000
The objective is to analyze p66Shc protein levels in PCa archival specimens from African American vs. Caucasian patients to investigate if p66Shc plays a role in PCa disparity.

R03CA230950 (Lin) 07/05/2018 - 06/30/2020 1.20 calendar
DHHS/NIH/NCI $50,000
Cadherin-catenin Complex and YAP1 in Prostate Cancer

PENDING

(Lin) 12/01/2019 - 11/30/2021 1.80 calendar
DHHS/NIH $125,000
HO-1 collaborating with p66Shc in support of CR PCa Progression

(Lin) 12/01/2018 - 11/30/2023 0.60 calendar
City of Hope National Medical Center $27,869
DNA repair gene mutations and prostate cancer

OVERLAP: None

Other Support

Smith, (Hock) Lynette M.

Active Research Support:

5 P50 CA127297-10 (Hollingsworth) 10/01/14 – 08/30/19 1.20 calendar
DHHS/NIH/NCI $1,528,998
SPORE Biostatistics

This application is for a Specialized Program of Research Excellence in Gastronintestinal (Pancreatic Cancer) will focus on translational studies that address basic and clinical issues of importance to improving the outcome of patients with pancreatic cancer.

2-SRA-2016-288-S-B (Sarvetnick) 09/01/16-08/31/19 0.60 calendar
Juvenile Diabetes Research Foundation International $224,993
Anti-Bacterial Factors as Biomarkers for Predicating T1D in At-Risk Population

Project Goals: In this application, we seek to validate 2 new biomarkers for prediction of T1D development in autoantibody positive subjects. We will test the hypothesis that CD8α+ CD27- MAIT cells and endoCab IgA levels are increased in pre-diabetic at-risk subjects during the disease process. To test our hypothesis, we will evaluate MAIT cells and other immune cell populations in samples obtained from the TrialNet Pathway to Prevention study.

U01CA200466 (Brand & Batra) 09/01/16 – 08/31/20 0.60 calendar
University of Pittsburgh $186,504
Validation of biomarkers for early diagnosis and risk prediction of pancreatic neoplasms

The overall objective of this CVC proposal is to demonstrate the ability of the forementioned biomarkers to distinguish pancreatic adenocarcinoma (PC) patients from healthy controls, patients with benign biliary obstruction and chronic pancreatitis (CP), and to identify those cysts with high malignant potential.

5U54GM115458-03 (Rizzo) 09/01/16-6/30/21 0.24 calendar
NIH/DHHS $2,829,635
Great Plains IDeA-CTR

The aim of the RIISCC model is to reduce readmissions and emergency room visits in high-risk, high-utilization, and high severity diabetic patients; thus improving quality of care and reducing cost. This program will focus on Innovation Category Four- to improve the health of populations through better prevention efforts, and will have a specific focus on underserved populations. The purpose is to develop and test a new care delivery and payment model utilizing telehealth strategies for targeted case management.

5R01CA210637-02 (Ponnusamy) 03/06/17 - 02/28/22 0.60 calendar
DHHS/NIH $241,693
Role of PD2/Paf1 in Pancreatic Acinar to Ductal Metaplasia

The overall goal of this study is to define the role of PD2/Paf1 in trans-differentiation of acinar cells to ductal cells during PDAC progression through self-renewing pancreatic CSC population.

5U01AI130841-02 (Sarvetnick) 07/01/17 - 06/30/22 0.60 calendar
DHHS/NIH/NIAID $395,748
Uncovering pathogenic anti-bacterial defense mechanisms to identify novel targets for prevention of T1D

5 P30 CA036727-32 (Cowan) 08/01/17-07/31/21 0.60 calendar
DHHS/NIH/NCI $1,378,761
Cancer Center Support Grant

The goal of the Biostatistics Shared Resource of the UNMC Eppley Cancer Center is to participate in the research mission of the institution by making the expertise and experience of its personnel available to Cancer Center members for planning, conducting and reporting of basic, translational, clinical, and population-based research projects.

5R21AA026428-02 (Kumar) 09/22/17 - 08/31/19 0.24 calendar
DHHS/NIH/NIAAA $143,782
Alcohol and smoking concurrently aggravate chronic pancreatitis

AIM 1: Identification and correlation of aldehyde-adducts with pathobiology of CP using murine models.
AIM 2: Investigate the mechanistic contributions of aldehyde-adducts during CP using 3D co-culture system.

01100674 (Lin) 12/01/17 - 11/30/19 0.36 calendar
Glebe Medical Research Foundation - NU Foundation $94,000
A Phase I Trail for Patients with Anal Cancer treated with chemoradiation and BMX-001

The primary objective is To determine the maximum tolerated dose (MTD) of BMX-001 in ASCC patients receiving RT and concurrent 5FU/mitomycin chemotherapy.

5R21CA216746-02 (Dhawan) 03/01/18 - 02/28/20 0.12 calendar
DHHS/NIH $126,585
Mastl, a novel therapeutic target in Colon Cancer

Outcome from studies in this grant proposal will help establish a novel oncogenic role of Mastl in colon carcinogenesis and provide preclinical evidence for the efficacy of targeting Mastl for combinational therapies (chemotherapy) to improve therapy and survival outcome.

7474 UNMC (Jain) 03/01/18 - 04/30/20 0.60 calendar
Sanguine Diagnostic and Therapeutics, Inc. $189,240
MUC4/16 assay for the early diagnosis and management of benign and malignant pancreatic diseases

Endoscopic Ultrasound (EUS) based Fine Needle Aspirates (FNAs) represent a valuable pre-surgical diagnostic material for confirming the presence or risk malignant lesions in the pancreas; however their diagnostic utility is limited due to the poor sensitivity of cytological analysis particularly in cases exhibiting atypical epithelial cells. Accurate diagnosis of malignant lesions of the pancreas can provide opportunity for intervention at a curable stage and reduce the risk of surgery associate morbidity in patients harboring benign lesions. The proposed studies will validate if MUC4 and MUC16 staining in EUS-FNAs can predict the risk of malignant lesions and help in appropriate patient selection for surgical resection.

1P01CA217798-01A1 (Batra) 07/01/18 - 05/31/23 0.48 calendar
DHHS/NIH/NCI $1,078,411
Pancreatic Cancer Metastasis

The overall objective of this P01 program is to define the mechanistic role of MUC16 in facilitating pancreatic

cancer metastasis. Specifically, the program aims to determine the molecular mechanisms by which MUC16-Cter mediated signaling and gene regulation, cancer-specific mutations in MUC16, and MUC16 induced alterations in cellular metabolism contribute to PC metastasis. The three projects and three cores are highly integrated to achieve the stated objectives and will provide a comprehensive understanding of MUC16-mediated molecular mechanism for PC metastasis.

W81XWH1810308 (Batra) 08/01/18-07/14/21 0.36 calendar
U.S.Army/USAMRAA/CDMRP $125,000
PDE5 Inhibitor (Sildenafil) for ameliorating androgen deprivation therapy (ADT)-induced cardiotoxicity

The major goal of this study is to determine the potential of PDE5 inhibitor (sildenafil citrate) in preventing ADT (GnRH agonist)-induced cardiotoxicity in PC and identify the underlying molecular mechanism of injury and protection.

1R01CA218545-01A1 (Nasser) 09/01/18-06/30/23 0.48 calendar
DHHS/NIH/NCI $377,443
Novel approach to attenuate small cell lung cancer growth and metastasis

The proposed studies will establish the clinical utility of PCX-miR-1 NPs as a novel therapeutic strategy for the treatment of SCLC patients who are difficult to treat due to their advanced disease stage and/or development of drug resistance and recurrence.

No project number (Kaur) 09/01/18 - 08/31/19 0.60 calendar
Sanguine Diagnostics And Therapeutics, Inc. $175,785
Seromic Mucin Signature for the Early Diagnosis of Pancreatic Cancer

We hypothesize that the mucin core proteins (MUC5AC and MUC4) in combination with CA19-9 create a PC-specific biomarker panel for early detection of pancreatic cancer.

NMC-245947 (Iqbal) 09/01/18-08/31/23 0.36 calendar
Mayo Clinic $337,121
Molecular Pathogenesis and genetic etiology of newly defined subgroups of PTCL-NOS

The goal is to define two novel disease subgroups within PTLC-NOS.

304790 (Sarvetnick) 01/01/19 - 05/31/19 0.12 calendar
Cincinnati Children's Hospital Medical Center $86,972
Gene Regulation as a Foundation for Autoimmune Disease Prevention

Pending – Submitted

No project number (Nasser) 07/01/19-06/30/24 0.60 calendar
DHHS/NIH $364,625
MUC5AC modulates cMet/CD44v6 axis in brain metastasis in breast cancer

The successful completion of this proposal will establish the MUC5AC as novel biomarker for early detection of brain metastasis for TN and ErbB2+ BC patients. Furthermore, blocking ErbB and cMET/FAK/MUC5AC axis with proposed FDA approved drugs will prevent BC brain metastasis in TN and ErbB2+ BC patients.

1R01CA243034-01 (Solheim) 07/01/19 - 06/30/24 0.36 calendar
DHHS/NIH $450,000
Nanomedicine CCL21 Immunotherapy Strategy

The central hypothesis to be tested in this project is that nano-CCL21 persists in neuroblastoma tumors after its administration, that its stabilization and regimen can be optimized, and that it is a superior treatment for neuroblastoma, especially when used with standard and molecular therapies.

No project number (Viswanathan) 07/01/19 - 06/30/24 0.30 calendar
DHHS/NIH $270,049
The Role of TP-R on Obesity-linked Metabolic Disorders

1R01CA234171-01A1 (Holstein) 07/01/19 - 06/30/24 0.36 calendar
DHHS/NIH $433,462
Development of geranylgeranyl diphosphate synthase inhibitor therapy for multiple myeloma

No project number (Fu) 07/01/19 - 06/30/22 0.36 calendar
Leukemia & Lymphoma Society $180,018
Targeting PLK-1 for treating MYC-driven lymphomas

The current proposal aims to determine the rationality and practicability of targeting PLK-1 as a promising therapeutic strategy for treating MYC-driven lymphomas.

No project number (Iqbal) 09/01/19 - 08/31/23 0.60 calendar
U.S. Department of Defense $103,000
Molecular Prognostication and Novel Therapy Targets in Angioimmunoblastic T-Cell Lymphoma

Specific Aim 1: To perform in-depth analysis of the tumor microenvironment (TME) in AITL
Specific Aim 2: To identify vulnerabilities that can be exploited in AITL with IDH2R172 mutation
Specific Aim 3: To target oncogenic mimics of the proximal T cell receptor (TCR) signaling cascade in PTCL.

(Yan) 12/01/2019 - 11/30/2024 0.24 calendar
DHHS/NIH $300,000
PR55-alpha regulated PP2A signaling in pancreatic cancer

(Batra) 12/01/2019 - 11/30/2024 0.36 calendar
University of California - San Diego $250,000
Molecular Biomarkers and Imaging Probes for Early Detection of Pancreatic Neoplasms

(Fu) 12/01/2019 - 11/30/2021 0.36 calendar
DHHS/NIH $167,004
Synthetic rocaglates as promising therapeutic agents for aggressive hematological malignancies

(Kumar) 04/01/2020 - 03/31/2025 0.48 calendar
DHHS/NIH/NCI $350,000
Nanotherapeutics targeting pancreatic cancer microenvironment

Overlap
New awards of pending grants which cause Dr. Smith's FTE to exceed 100% will be transferred to other UNMC biostatisticians.

PHS 398/2590 Other Support

Teply, Benjamin

ACTIVE

ESR-16-12079 (Teply) 01/16/2018 - 01/15/2020 0.07 calendar
Johns Hopkins University $76,005
Phase II Study of Olaparib in Men with High-Risk Biochemically-Recurrent Prostate Cancer Following Radical Prostatectomy, with Integrated Biomarker Analysis

UCa-001 (Teply) 05/01/2019 - 04/30/2021 0.07 calendar
Inovio Pharmaceuticals, Inc. $141,953
An Open-Label, Multi-Center Trial of INO-5401 + INO-9012 in Combination with Atezolizumab in Subjects with Locally Advanced Unresectable or Metastatic/Recurrent Urothelial Carcinoma

W81XWH1810308 (Batra) 07/15/2018 - 07/14/2021 0.07 calendar
U.S. Army/USAMRAA/CDMRP $500,000
PDE5 inhibitor (Sildenafil) for ameliorating androgen deprivation therapy (ADT)-induced cardiotoxicity
PDE5 inhibitor (Sildenafil) for ameliorating androgen deprivation therapy (ADT)-induced cardiotoxicityThe major goal of this study is to determine the therapeutic potential and the novel mechanism of a PDE5 inhibitor, sildenafil citrate, on GnRH agonist (ADT)-induced cardiotoxicity in prostate cancer.

PENDING

(Teply) 01/01/2019 - 09/30/2021 0.07 calendar
Calidum, Inc $79,365
Clinical Development of RISAD-P Dual Targeted Radiotheranostic Technology

OVERLAP: None

Other Support (Xi, L)

ACTIVE

1R01CA221813-01A1 01/01/2018 - 12/31/2019
NIH/NCI Singla (PI) and Kukreja (PI) $143,006
University of Central Florida
Amelioration of Doxorubicin-induced Muscle Dysfunction with Embryonic Stem Cells-Derived Exosomes
The goal of this project is to investigate the effect of embryonic stem cells derived exosomes on improvement of muscle dysfunction following doxorubicin treatment of mice.
Role: Co-Investigator
Effort: 5.4 months
OVERLAP
None

5R01HL134366-04 07/01/2018 - 06/30/2019
NIH/NHLBI Kukreja (PI) and Das (PI) $338,449
Cardioprotection with mTOR inhibition
The major goals of this project are to examine the role of rapamycin in cardioprotection against ischemia/reperfusion injury in type-2 diabetic mice and rabbits and to investigate the involvement of STAT3 and microRNA-17/20.
Role: Co-Investigator
Effort: 1.2 months
OVERLAP
None

PENDING

R01DK124099-01 09/01/2019 - 08/31/2024
NIH/NIDDK Kukreja (PI) and Tipparaju (PI) $165,000
University of South Florida
NAD Basis for Inflammation and Metabolism in the Muscle
The goals of this project are to investigate the mechanistic information on the fundamental role of NAD in inflammation and diabetes, discover molecular pathways in causing skeletal and cardiac muscle injury, and identify new therapeutic targets for protection.
Role: Co-Investigator
Effort: 0.6 month
OVERLAP
None