AWARD NUMBER: W81XWH-19-1-0231

TITLE: A novel agent for lung cancer prevention

PRINCIPAL INVESTIGATOR: Sharma, Arun Kumar

RECIPIENT: The Pennsylvania State University

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A novel agent for lung cancer prevention

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5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Arun Kumar Sharma

E-Mail:

5d. PROJECT NUMBER

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The Pennsylvania State University

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13. SUPPLEMENTARY NOTES

14. ABSTRACT: Lung cancer is the leading cause of cancer related deaths in the United States. Despite the identification of several preventive agents and strategies, optimal prevention of lung cancer, especially in smokers and ex-smokers who are at high risk, has not been achieved. More effective agents are therefore required that would safely achieve prevention without drastic side effects. Novel compounds which are rational modifications of well-established chemopreventive agents and follow a similar mechanism of action, but with enhanced potency, reduced toxicity, and lower dose requirement, may be clinically more relevant. We have developed one such agent p-XS-Asp, designed by conjugating two well-known chemopreventive agents i.e. 1,4-phenylenebis(methylene)-selenocyanate (p-XSC) and aspirin, which has shown promising lung cancer preventive properties in our preliminary in vitro and animal studies. The long-term goal of this project is to develop this rationally-designed, effective, and safe agent for the prevention and interception of smoking-related lung cancer. Given the preeminence of tobacco carcinogens in initiating and driving lung cancer, we hypothesize that p-XS-Asp exerts chemopreventive effect at both initiation and post-initiation stages of lung tumorigenesis through (i) inhibition of Phase I carcinogen activation, (ii) induction of Phase II carcinogen detoxification, (iii) suppressing activation of AKT/COX-2 pathways, and (iv) inhibiting proliferation and viability of preneoplastic cells. The specific objectives of this proposal are to (i) test the efficacy of p-XS-Asp for inhibiting lung cancer development at different stages of NNK-induced carcinogenesis using the A/J mouse lung cancer model, (ii) evaluate the pharmacological and biochemical mechanisms by conducting p-XS-Asp metabolism and comparing PK/ bioavailability with p-XSC, and (iii) elucidate mechanisms of action(s) of anti-initiation and anti-progression effects of p-XS-Asp. The specific aims of this project are: (i) To determine the stage-specificity of chemopreventive efficacy of dietary p-XS-Asp in tobacco carcinogen NNK-induced lung adenocarcinogenesis in A/J mice models; and (ii) To elucidate mechanisms of action(s) and biomarkers of chemopreventive effects of p-XS-Asp. These studies will establish the potential of p-XS-Asp as an efficacious lung cancer preventive agent.

15. SUBJECT TERMS

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	15	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. INTRODUCTION:

Lung cancer is the leading cause of cancer related deaths in the United States. Despite the identification of several preventive agents and strategies, optimal prevention of lung cancer, especially in smokers and ex-smokers who are at high risk, has not been achieved. More effective agents are therefore required that would safely achieve prevention without drastic side effects. Novel compounds which are rational modifications of well-established chemopreventive agents and follow a similar mechanism of action, but with enhanced potency, reduced toxicity, and lower dose requirement, may be clinically more relevant. We have developed one such agent p-XS-Asp, designed by conjugating two well-known chemopreventive agents i.e. 1,4-phenylenebis(methylene)-selenocyanate (p-XSC) and aspirin, which has shown promising lung cancer preventive properties in our preliminary in vitro and animal studies. The **long-term goal** of this project is to develop this rationally-designed, effective, and safe agent for the prevention and interception of smoking-related lung cancer.

Given the preeminence of tobacco carcinogens in initiating and driving lung cancer, we **hypothesize** that p-XS-Asp exerts chemopreventive effect at both initiation and post-initiation stages of lung tumorigenesis through (i) inhibition of Phase I carcinogen activation, (ii) induction of Phase II carcinogen detoxification, (iii) suppressing activation of AKT/COX-2 pathways, and (iv) inhibiting proliferation and viability of preneoplastic cells. The **specific objectives** of this proposal are to (i) test the efficacy of p-XS-Asp for inhibiting lung cancer development at different stages of NNK-induced carcinogenesis using the A/J mouse lung cancer model, (ii) evaluate the pharmacological and biochemical mechanisms by conducting p-XS-Asp metabolism and comparing PK/bioavailability with p-XSC, and (iii) elucidate mechanisms of action(s) of anti-initiation and anti-progression effects of p-XS-Asp. The **specific aims** of this project are: (i) To determine the stage-specificity of chemopreventive efficacy of dietary p-XS-Asp in tobacco carcinogen NNK-induced lung adenocarcinogenesis in A/J mice models; and (ii) To elucidate mechanisms of action(s) and biomarkers of chemopreventive effects of p-XS-Asp. These studies will establish the potential of p-XS-Asp as an efficacious lung cancer preventive agent.

2. KEYWORDS:

Lung cancer, p-XS-Asp, tobacco carcinogen, NNK, chemoprevention

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The major goals of the project are listed below in the format of the original SOW:

Specific Aim 1. To determine the stage-specificity of chemopreventive efficacy of p-XS-Asp in tobacco carcinogen NNK- induced lung adenocarcinogenesis in A/J mice models.

- **Major Task 1**: Evaluation of the chemopreventive efficacy of *p*-XS- Asp in NNK-induced lung cancer in A/J mice (total of 340 mice, 170 male and 170 female):
    - *ACURO approval received – October 21, 2019*
    - Subtask 1: Bulk synthesis of p-XS-Asp - Several batches have been synthesized to meet the requirements of the study as needed.
    - Subtask 2: Preparation of the control and experimental diets
        - Control and experimental diets for p-XS-Asp were prepared- Fresh diets are being prepared every two weeks to ensure no decomposition of the preventive agents takes place
    - Subtask 3: Determine the chemopreventive effects of dietary p-XS-Asp in A/J mice
        - The experiment started on December 3, 2019; NNK was injected on December 17, 2019.
        - A/J mice were divided into seven groups: Five groups (groups 3-7, n=30) were exposed to NNK, and two (groups 1-2, n=10) served as carcinogen free controls. Group 3 served as a carcinogen exposed control group, p-XS-Asp is being fed to Group 4 for the complete duration, Group 5 only during peri-initiation, Group 6 post-initiation, or Group 7 during progression

- Subtask 4: Termination endpoints
  - Termination endpoint 1 (adenomas) was after 26 weeks – *COMPLETED*, June 2020
  - Termination endpoint 2 (adenocarcinomas) will be after 40 weeks - *ONGOING*

- Subtask 5: Collection of lungs for analysis – *COMPLETED* for endpoint 1

- **Major Task 2: Histopathology assessment.**
  - Subtask 1: Prepare and stain transverse sections of lung tissues – *ONGOING* for endpoint 1
  - Subtask 2: Score sections for number of adenomas, adenomas with dysplasia and adenocarcinomas for the NNK-induced lung lesions - *ONGOING* for endpoint 1

Milestone #1*:* Establish the carcinogenesis stage-specificity of chemopreventive efficacy of *p*- XS-Asp.

Specific Aim 2. To elucidate key mechanisms of action(s) of anti- initiation effects of p-XS-Asp and explore cellular processes for its anti-progression effects.

- **Major Task 1**: Comparison of *in vitro* and *in vivo* metabolism and PK/distribution of *p*-XS-Asp and *p*-XSC.
  - Subtask 1: Determination of p-XS-Asp vs. p-XSC in vitro metabolism – *ONGOING*
  - Subtask 2: Evaluation of PK/bio-availability and -distribution to target organ lung following oral administration of *p*-XS-Asp vs. *p*-XSC in A/J mice – *To be done in Year 2*
    - Serum, lung, and liver will be evaluated for formation of metabolites at different time points.

- **Major Task 2**: Evaluation of Phase I Cyp450 and Phase II conjugation enzyme gene expression, protein level changes and activities.
  - Subtask 1: To validate whether the inhibition of NNK-induced DNA adducts by p-XS-Asp is due to inhibition of Phase I Cyp activity/expression and/or induction of Phase II detoxifying enzymes – *To be done in Year 2*

i) We will validate these findings with 6 frozen lung tissues per group from mice exposed to p-XS-Asp vs. p-XSC for 2 weeks.

ii) Western blot analyses for their respective protein abundance and RT-PCR for the mRNA changes.

  - Subtask 2: mRNA expression patterns by RNAseq profiling – *To be done in Year 2*

i) RNAseq and primary data processing

ii) Ingenuity pathway analyses (IPA) will be used to interrogate network and hierarchical connection nodes affected by *p*-XS-Asp, especially Phase I and Phase II drug metabolism genes

Major Task 3: Immunohistochemistry (IHC) for tumor size cellular indices for anti-progression mechanisms (apoptosis, senescence, p53-p21 signaling) – *To be done in Year 2*

Milestone #2: Establish the metabolic and PK profile and get insight into the mechanism of chemopreventive action of *p*-XS-Asp.

- *Overall Project Milestones to be achieved:*

(i) Manuscript(s) submission after the termination at endpoint 2 and the relevant analyses are completed

(ii) *Submit R01 grant application to NCI, to be submitted in February or June 2021*

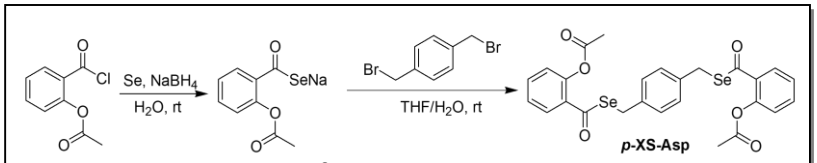
What was accomplished under these goals?
Below are the major results obtained during the reporting period:

Specific Aim 1. To determine the stage-specificity of chemopreventive efficacy of p-XS-Asp in tobacco carcinogen NNK- induced lung adenocarcinogenesis in A/J mice models.
Objective: Evaluate the efficacy of dietary p-XS-Asp administered peri-initiation vs. post-initiation for inhibiting lung adenoma development and progression to adenocarcinoma by the best characterized tobacco carcinogen NNK**.**

Major activities during the first year as per the Statement of Work were directed towards accomplishing Aim 1 of the proposal. The major tasks proposed to determine the stage-specificity of chemopreventive efficacy of p-XS-Asp in tobacco carcinogen NNK-induced lung adenocarcinogenesis in A/J mice models included: (i) bulk synthesis of p-XS-Asp through multiple smaller batches (ii) preparation of the control and experimental diets (iii) evaluate chemopreventive effects of dietary p-XS-Asp in both male and female A/J mice at different stages of NNK induced carcinogenesis. **Major activities and results** are described below:

Major Task 1: Evaluation of the chemopreventive efficacy of *p*-XS- Asp in NNK-induced lung cancer in A/J mice

Synthesis of *p*-XS-Asp (Subtask 1): The synthesis is accomplished in two simple steps as depicted in **Scheme 1**. The final compound obtained from each batch was purified and characterized by NMR and Mass spectrometry before use. Several batches of *p*-XS-Asp were synthesized to keep up with the requirement of the study.



Scheme 1. Synthesis of *p*-XS-Asp

Preparation of the control and experimental diets (Subtask 2)

i) AIN-93M experimental diet for p-XS-Asp was prepared.
ii) Fresh diets were prepared every two weeks to ensure no decomposition of the preventive agents takes place

Determination of stability of p-XS-Asp in chemopreventive test diet: The stability of *p*-XS-Asp, when incorporated in AIN-93M diet, was determined prior to the initiation of bioassay to ensure that the compound is not decomposed over time. Briefly, 2.0 g of test diet, containing *p*-XS-Asp, was extracted by stirring with ethyl acetate (200 ml) for 1 hour at room temperature. The reaction mixture was filtered, ethyl acetate was evaporated under reduced pressure and re-dissolved in 500 µl of THF. 50 µl of this solution was then analyzed by reverse phase high performance liquid chromatography (HPLC). The *p*-XS-Asp peak was identified by comparing with the corresponding standard and the peak area were determined. The process was repeated weekly and the peak area was compared with the freshly prepared diet to access the decomposition. P-XS-Asp was found stable in diet stored at 4ºC for up to 1-month time. However, to avoid any possibility of decomposition, the test diet was prepared biweekly for this study.

Evaluation of the chemopreventive efficacy of *p*-XS-Asp in NNK-induced lung cancer in A/J mice (Task 3-5). A/J mice (5-6 weeks of age) were ordered from Jackson Laboratories, Bar Harbor, ME and quarantined for one week. After 1-week acclimation period, 340 mice were weighed and randomized into groups based on weight (n=30 per group for NNK Groups 3-7, and n=10 for control Groups1,2; half male, half female) for two separate experiments i.e. 26 week and 40 week endpoints (170 mice each). For those mice involved in carcinogen exposure (Groups 3-7), each received a single IP injection of 10 µmol (100 mg/kg) of NNK (0.1 ml saline) to induce lung tumors as illustrated in **Fig 1**. The NNK was injected on Dec. 17, 2019. Two separate control groups (Groups 1 & 2) without NNK, each with 10 mice, were maintained to provide long term toxicity/ safety and lung tissues for spontaneous adenoma count data.

Termination endpoint 1. The 170 mice for 26-week endpoint were sacrificed in the first week of June, 2020. At

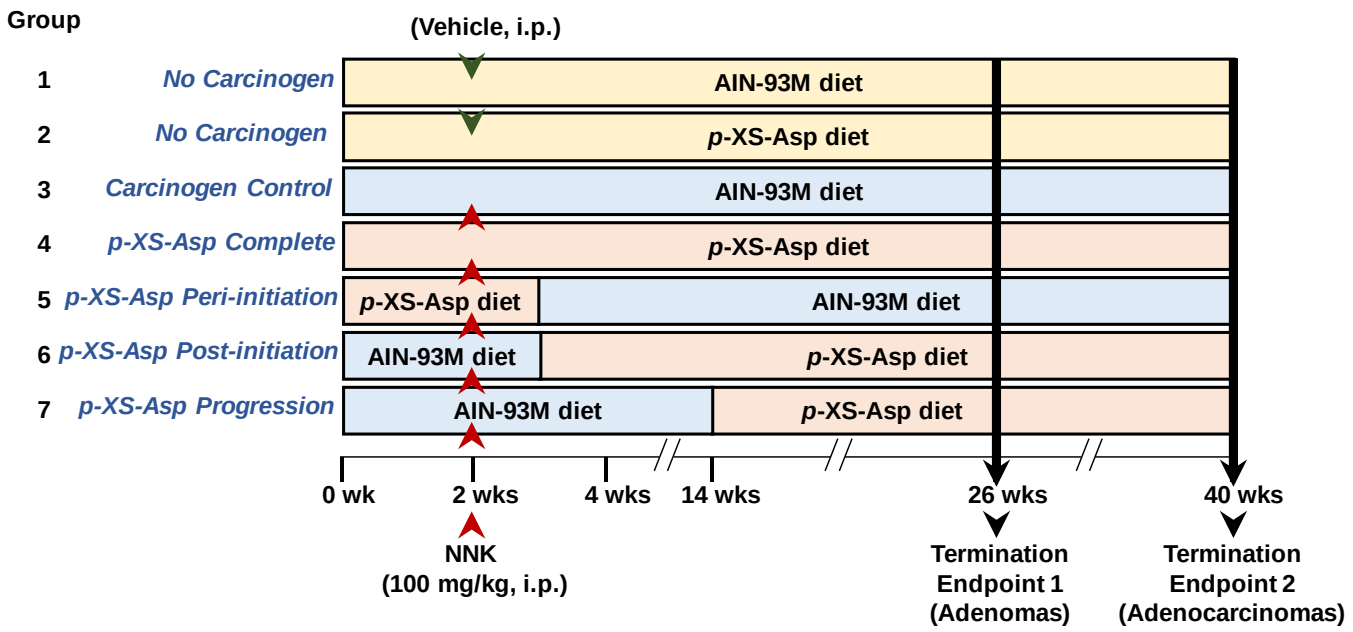


Fig 1. Experimental design evaluating the stage specificity of chemopreventive efficacy of *p*-XS-Asp in A/J mice. *p*-XS-Asp (15 ppm as Se, 50% of MTD) was fed to Group 3 for the complete duration, Group 4 only during peri-initiation (2 weeks prior to carcinogen and 1week post), Group 5 post-initiation (1week post carcinogen), or Group 6 during progression (12 weeks post carcinogen). Number of mice for adenoma and adenocarcinoma count metric: Groups 3-7: n=30; Groups 1-2: n= 10.

the end of the study 24 weeks after NNK injection, the animals were euthanized by CO2 asphyxiation and blood and tissues were collected. Blood was taken by cardiac puncture from 3 mice each group for blood chemistry evaluation. Necropsy was performed to collect the lungs, liver and kidneys. All the lungs were fixed in formalin and 5 randomly selected lungs from each group were cut and snap frozen. Lung nodules were enumerated by Mr. Aliaga, blinded to sample identifiers. Tumor incidence and multiplicity were calculated for each group by averaging the individual count of the reader's number per mouse (**Fig. 2**). Cryopreserved lungs will be used for biochemical analyses (e.g., Phase I Cyp and Phase II conjugating enzyme activities, Western blot, RNAseq) or for *p*-XS-Asp and metabolite measurements (for Aim 2). Liver and kidneys were collected from 5 randomly selected mice from each group for toxicity evaluation.

Results

The lung nodules count showed p-XS-Asp to be equally effective in the complete (Group 4) and peri-initiation (Group 5) stages (see **Fig. 1** for details diet schedule in each group) in both the male and female animals both in tumor multiplicity (**Fig. 2A**) and incidence (**Fig. 2B**). **Fig. 2C** shows scatter plot of the lung nodules count for all the mice. There was about 70-90% inhibition in tumor incidence in both the groups with ~25-30% lower tumor incidence as compared to NNK control. P-XS-Asp was relatively less effective in post-initiation stages (Group 6) with about 20-25% inhibition in tumor multiplicity, and tumor incidence similar to NNK control.

Toxicity/safety parameters were monitored for mice in each group. Notably, body weights (**Fig. 2D**) and blood chemistry analysis (**Fig. 3**) showed no apparent signs of systemic toxicity on 26-week dietary feeding of p-XS-Asp.

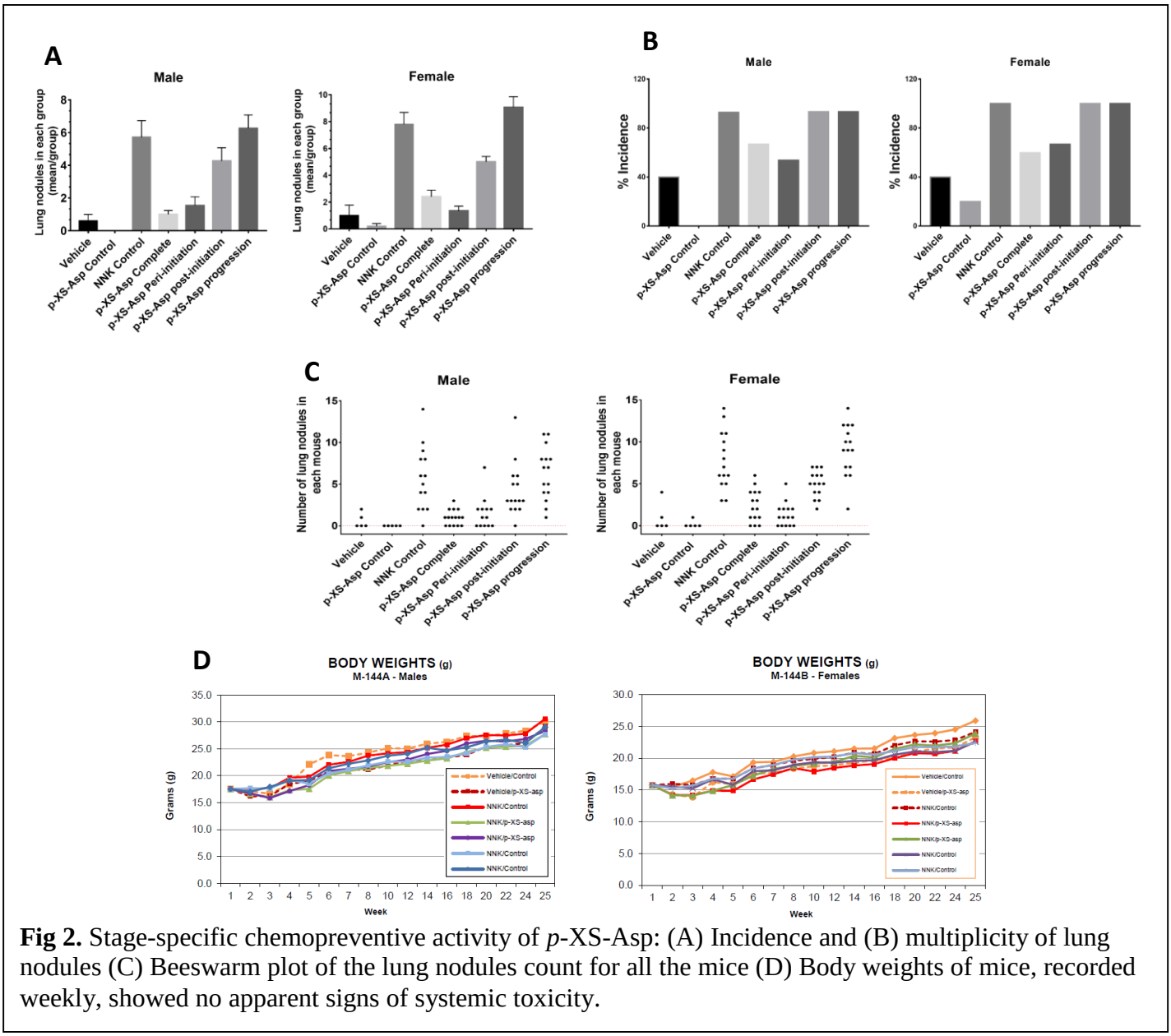


Fig 2. Stage-specific chemopreventive activity of *p*-XS-Asp: (A) Incidence and (B) multiplicity of lung nodules (C) Beeswarm plot of the lung nodules count for all the mice (D) Body weights of mice, recorded weekly, showed no apparent signs of systemic toxicity.

Termination endpoint 2: The experiment with the remaining 170 mice in all 7 groups is continued. These mice will be sacrificed after completing 40-weeks time, for termination endpoint 2, approximately in the second week of September.

Stated goals not met: We have been generally on track with experiments based on our Tasks of the SOW. Delays are however are experienced in getting histopathology assessment of the lung tissues (Major Task 2, Aim 1) obtained from A/J mice because of partial closures due to COVID-19 pandemic.

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

- The postdoc, Dr. Asif Raza, has acquired a wide new skill set in the fields of lung cancer and chemoprevention during this award period. Furhter, he has been trained in techniques such as handling and sacrificing mice, mouse dissection and blood extraction, preparing test diets, safely handling chemical carcinogen NNK, and preparing slides for histopathology analysis, in addition to strengthening his experience in regular lab techniques. He has been regularly meeting with Dr. Sharma, who has mentored Dr. Raza throughout the grant period. Dr Raza has also benefitted from discussions with Drs. Junxuan Lu and Shantu Amin, co-investigators on the project, and has taken advantage of career

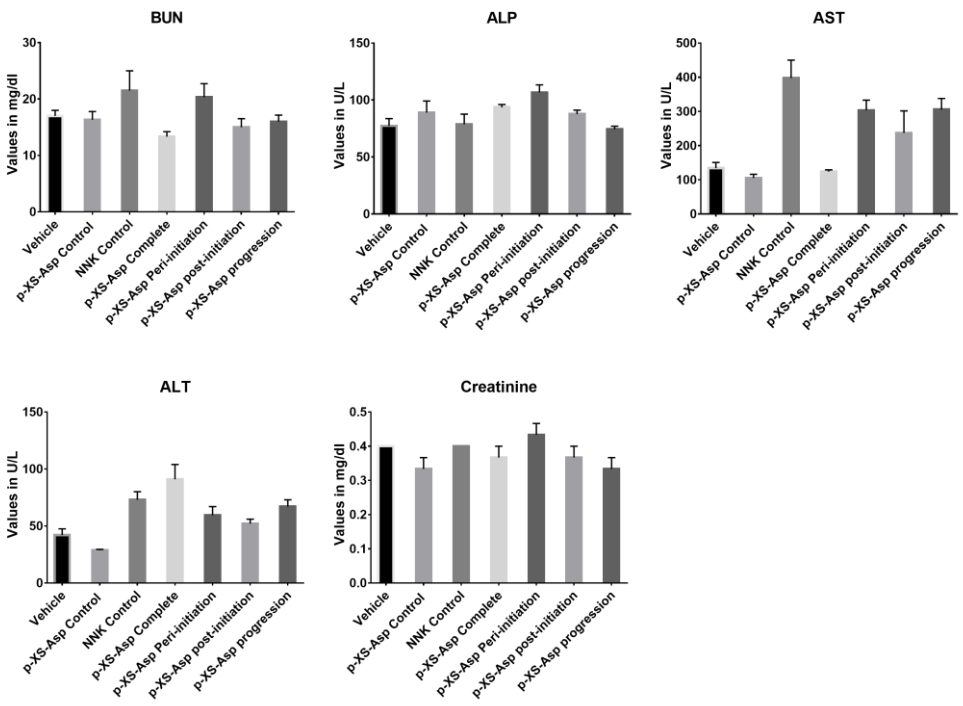


Fig 3. Serum chemistry analysis revealed no significant changes in liver function or other molecular markers related to kidney toxicity with chronic feeding of p-XS-Asp.

development seminars through the Penn State Cancer Institute and Penn State College of Medicine, Hershey.

- The PI, Dr. Arun Sharma, and postdoc, Dr. Raza, attended virtual AACR Annual meeting in June 2020. The meeting was held online due to cancellation of in-person meeting scheduled to be held at San Diego due to COVID-19 pandemic.

How were the results disseminated to communities of interest?

- Preliminary data used in this proposal has been presented at AACR annual meeting previously. Results from the current study will be presented in similar meetings and published once the study is completed.

What do you plan to do during the next reporting period to accomplish the goals?
We will address the remaining goals of our proposal as outlined in the SOW.

Specific Aim 1. To determine the stage-specificity of chemopreventive efficacy of p-XS-Asp in tobacco carcinogen NNK- induced lung adenocarcinogenesis in A/J mice models.

- Complete the experiment to evaluate chemopreventive effects of dietary p-XS-Asp in A/J mice (Subtask 3) by sacrificing A/J mice for termination endpoint 2 (40 weeks) which is scheduled for around the second week of September 2020 (Subtask 4), and the tissues collected will be analyzed (Subtask 5).
- Histopathology assessment to score sections for number of adenomas, adenomas with dysplasia and adenocarcinomas for the NNK-induced lung lesions (Major Task 2).

Specific Aim 2. To elucidate key mechanisms of action(s) of anti- initiation effects of p-XS-Asp and explore cellular processes for its anti-progression effects.

- All the studies proposed in Aim 2 will be completed in Year 2 of the grant period.
  - For Major Task 1 i.e. Comparison of in vitro and in vivo metabolism and PK/distribution of p-XS-Asp and p-XSC:
    - we have initiated in vitro metabolism studies (Subtask 1)
    - We have also carried out a pilot PK study (Subtask 2). p-XS-Asp (10 mg/kg) was administered to A/J mice by oral gavage and the mice were sacrificed after 0h, 2h, 4h, 8h, and 16h time points. 4 mice/group (2 males and 2 females) were used for this pilot study. Serum, lung, and liver were collected and will be evaluated for p-XS-Asp or its metabolites at different time points and for presence of selenium content.

- Studies proposed under Major Task 2 i.e. evaluation of Phase I Cyp450 and Phase II conjugation enzyme gene expression, protein level changes and activities; and the Major Task 3 i.e. immunohistochemistry (IHC) for tumor size cellular indices for anti-progression mechanisms will be carried out in year 2.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Initial results from our ongoing animal studies have demonstrated that p-XS-Asp is extremely effective at preventing lung cancer development at the peri-initiation stages (70-90% inhibition) and also to some extent (25-30%) in the post-initiation stages of NNK induced carcinogenesis, without any apparent systemic toxicity. A similar trend is observed in both male and female mice. These results suggest p-XS-Asp may be a promising lung cancer preventive for smokers who are continuously exposed to tobacco carcinogens.

What was the impact on other disciplines?

p-XS-Asp is designed by conjugating two well-known chemopreventive agents i.e. 1,4-phenylenebis(methylene)-selenocyanate (p-XSC) and aspirin. Our results indicate that the design of Se-aspirinyl prodrug strategy is an efficient innovative way to design novel potent and safe prodrug candidates and will have impact in the field of medicinal chemistry and drug discovery. In addition, data emanating from this work has opened new research avenues for the investigation of p-XS-Asp as a preventive agent in other cancers, particularly those known to be induced by cigarette smoking.

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to Report

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

Institutional closures and restrictions in ordering animals due to COVID-19 pandemic caused a delay in the analysis of tissue samples obtained after animal sacrifice as well as performing a compete PK experiments.

Changes that had a significant impact on expenditures

Nothing to Report

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

Nothing to Report

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals.

Nothing to Report

Significant changes in use of biohazards and/or select agents

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.

  Nothing to Report

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

  Nothing to Report

  Other publications, conference papers, and presentations.

  Nothing to Report

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

  Nothing to Report

- **Technologies or techniques**

  Nothing to Report

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

  Nothing to Report

- **Other Products**

  Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Arun Sharma
Project Role:	P.I.

Researcher Identifier:	orcid.org/0000-0002-7679-7779
Nearest person month worked:	3
Contribution to Project:	**From Budget Justification:** will devote 3.0 calendar months (25% effort) to the project. Dr. Sharma is an Associate Professor in the Department of Pharmacology and is Co-director of the Penn State Cancer Institute Organic Synthesis Core. He is an accomplished bioorganic and medicinal chemist with track record for the synthesis, metabolism, and DNA binding studies, *in vitro* and *in vivo* evaluation of cancer chemopreventive and chemotherapeutic agents, and analytical techniques. Dr. Sharma has been involved extensively in the development, efficacy determination, mechanism evaluation, and pharmacokinetics of small anti-cancer compounds. He has developed several drug-like small molecules, including *p*-XS-Asp, which has shown promising potential as a lung cancer chemopreventive agent. Dr. Sharma will be responsible for planning and supervising execution of the overall project and submit annual and final reports, and manuscripts for publications.
Name:	Mahammad A Raza
Project Role:	Postdoctoral Scholar
Researcher Identifier:	orcid.org/0000-0002-5716-7202
Nearest person month worked:	12
Contribution to Project:	**From Budget Justification:** (12 calendar months, 100% effort) Dr. Raza is a postdoctoral scholar in the laboratory of Dr. Sharma and has experience in molecular biology techniques, pharmacological assays and animal models of cancer chemoprevention. He will carry out the majority of research experiments proposed including A/J mouse chemoprevention experiments and pharmacological assays.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes. Drs. Sharma, Lu and Amin all had changes in their active other support. Please see below.

PROJECT FUNDED SINCE LAST REPORT – Sharma, Arun

1S10 OD028589-01 (Yannawar, Neela H.) 7/01/2020-7/09/2021 0.00 calendar months
NIH $600,000 DC/Yr
Contracting Officer: Karen Brummett
Title: Modification of Existing MicroMax-007Hf X-ray Diffraction System
Goals: With the new state-of-the-art Rigaku components upgrade, our goal is to enhance the Penn State University X-ray crystallography facilitiy's capacity to coninute to excel in chemical crystallography, macromolecular crystallography and solution small angle x-ray scattering.

Specific Aims:
Role: Faculty

5R21CA234681-02 (Sharma, Arun K.) 12/01/2019-11/30/2020 2.20 calendar months
NIH $97,875 DC/Yr
Contrating Officer: Chelsea Simone Daly
Title: A promising small molecule for pancreatic cancer therapy
Goals: Successful outcomes are expected to identify novel orally bioavailable agent that could be used alone or in combination with Gem or other standard of care (SOC) to treat PDAC and will provide a solid rationale to evaluate in depth mechanism, efficacy studies and eventually clinical trial in PDAC patients.
Specific Aims: 1) Optimize the treatment regimen n which AS-10 and its combination with Gem gives maximum efficacy to inhibi umor growth and metastasis with minimal toxicity in PDAC xenograft mouse models.
2) To elucidate mechanisms of action(s)accounting fo therapeutic effects of AS-10.
Role: PI

5R01CA233844-02 (Yang, Shengyu) 12/1/2019-11/30/2020 0.60 calendar months
NIH $236,016 DC/Yr
Contracting Officer: Taneshia Knight Shelton
Title: A novel role of fascin in cancer metastasis
Goals: Out long-terms goals are to define the molecluar mechanisms by which fascin controls cancer metastasis and progression,
Specific Aims: Aim 1) We will biuld on these exciting preliminary findings to investigate the functional role of fascin-mediated remodling of mitochondrial actin filaments.
Aim 2) We will then definte the role of the AMPK-AP/TAZ pathway in fascin-mediated augmentation of cancer cell stemness.
Aim 3) We will determne the novel mitochondrial role of fascin and mitochondrial actin filaments in fascin-mediated NSCLC metastasis, and will explore the feasibility to inhibit cancer cell stemness and metastatic recurrence by targeting fascin.
Role: Co-Investigator

PROJECTS ENDED SINCE LAST REPORT – Sharma, Arun:

445654-EXT 01/04/208-05/31/2020
University of Arizona $59,540 DC/Yr
Contracting Officer: Kandie Stanton;
Title: Cationic Bolaamphiphiels (CAB) and Phosphorothioate Gapmers as Antisense Therapy for C. Difficile
Goal: Dr. Sharma's laboratory will perform the desin, synthesis, purification, characterization, and purity detemrination of variety of functionally diverse novel ationic bola-amphiphiles (CABs) required for studies proposed in this grant application.
Role: Consortium PI

PROJECTS FUNDED SINCE LAST REPORT – Amin, Shantu

1U01 DK119702-01 9/23/2019-6/31/2024 0.36 calendar months
NIH $27,160 DC/Yr
Contracting Officer: Kevin Reeves
Title: R01: FXR and he Gut Microbiome as Modulators of Non-Alcoholic Fatty Liver Disease
Goal: Our team propses to investigate the novel concept that intestine-selective FXR antagonism has the potential to prevent or reverse NAFLD/NASH.

Specific Aims:
Role: Co-Investigator

1R01CA24138-01A1 4/15/2020-03/31/2021 01.50 calendar months
NIH $405,054 DC/Yr
Contracting Officer: Chelsea Simone Daly
Title: Targeting Aldehyde Dehydrogenase for Cancer Prevention
Goal: Over the long-term, this significant and innovative research will determine the effiacy of targeting the ALDH protein and increasing effector CD8 to inhibit recurrent resistant disease development mediated by cancer stem cells and improve the efficacy of chckpoint antibody immunotherapy to increase the numbe of melanoma patients responding
Specific Aims: 1) Determine the mechanism through which a non-toxic broad-spectrum ALDH drug can inhibit the high ALDH activity occurring in plastic CSCs to elminate this cell subpopulation and prevent recurrent resistant disease developmetn mediated by these cells
2) Determine whether a non-toxic boradpspectrum ALDH inhibitor (naoKS100) can create a melanoma tumor immune microenvironment (TIME) that is more responsive to immunotherapy by decresaing Tregs and increasing effector CD8 T-cell activity,
Role: Multi-PI

PROJECTS ENDED SINCE LAST REPORT – Lu, Junxuan

5R01CA172169-06-EXT 04/01/2018-03/31/2020 01.49 calendar months
NIH $131,635 DC/Yr
Contracting Officer: Leslie Hickman
Title: Prevention of Prostate Carcinogenesis by Next-Generation Selenium
Goal: The results are expected to reveal the in vivo significance of the p53-p21-senecence pathway to mediate the efficacy of MSeA/C in these models and the new paradigm of harnessing irreversible cell cycle arrest (senescence) of early lesions for prevention in contrast to previous studies focusing on apoptosis.
Specific Aims: Aim 1: To contrast the in vivo preventive efficacy of MSeA and MSeC with (the lack thereof) SeMet against Pten loss driven prostate carcinogenesis utilizing condition Pten knockout (KO) mouse model, and to critically assess the contribution fo the P53-p21-mediated cellular senescence to their efficacy using Pten and p53 double KO prostate mouse models.
Aim 2: To contrast the in vivo preventive efficacy of MSeA and MSeC with the lack thereof by Se Met against chemically-induced, androgen-promoted prostate carcinogenesis in rates and to determine whether p53-p21 senescence activation is involved in mediating their preventive efficacy in this model (Year 1-4).
Aim 3: To identify proteomic signatures and molecular targets in the prostate gland and prostate carcinomas from studies of Aims 1 and 2 of MSeA and MSeC in addition to delineating the upstream signaling mechanisms of the P53-p21 senescene pathway and validate identified key targets.
Role: PI

What other organizations were involved as partners?

Nothing to Report (N/A)

8. SPECIAL REPORTING REQUIREMENTS

N/A

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating 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.

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.