

AWARD NUMBER: W81XWH-21-1-0613

TITLE: Using Metabolomic Signatures for Risk-Stratification and Personalized Treatment of Bladder Cancer

PRINCIPAL INVESTIGATOR: Dr. Nagireddy Putluri, Ph.D

CONTRACTING ORGANIZATION: Baylor College of Medicine, Houston, TX

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14. ABSTRACT Approximately 25- 39% of patients with MIBC harbor disease which is not sensitive to chemotherapy. This appreciation that some bladder cancers are more susceptible to chemotherapy supports research of tumor classification to help identify which patients stand to benefit the most from NAC. We have demonstrated in preliminary studies that metabolic characterization into high and low glycolytic tumors may risk-stratify for bladder cancer survival particularly in the more aggressive basal molecular subtype population. We hypothesize use of metabolic characterization of bladder cancer can both predict tumor sensitivity to neoadjuvant chemotherapy as well as characterize treatment response in patients. We have to date in year 1 even despite some delays due to COVID surges and workforce shortages established the human and animal research regulatory infrastructure as well as recruited our first 8 patients to study. The work continues now on pace for good progress and with promising early results presented in this annual review.					
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1. Introduction

Level 1 evidence has demonstrated the utility of neoadjuvant chemotherapy (NAC) prior to radical cystectomy for the treatment of muscle-invasive bladder cancer (MIBC). However, approximately 25- 39% of patients with MIBC harbor disease which is not sensitive to chemotherapy. This appreciation that some bladder cancers are more susceptible to chemotherapy supports research of tumor classification to help identify which patients stand to benefit the most from NAC. Study of The Cancer Genome Atlas (TCGA) initiative data set have led to the identification of two fundamental molecular phenotypes of bladder cancer, luminal and basal molecular subtypes, which are associated with prognosis and chemotherapy sensitivity. Parallel studies in part by our investigators into bladder cancer metabolism shows metabolic characterization can predict tumor behavior and act as an early biomarker for response to chemotherapy. We have demonstrated in preliminary studies that metabolic characterization into high and low glycolytic tumors may risk-stratify for bladder cancer survival particularly in the more aggressive basal molecular subtype population. This has laid the foundation that tissue-level metabolic characterization, as well as non-invasive metabolic MRI using hyperpolarized [1-13C]pyruvate, hold promise to improve the management of bladder cancer. We hypothesize use of metabolic characterization of bladder cancer can both predict tumor sensitivity to neoadjuvant chemotherapy as well as characterize treatment response in patients. In this project, we have set a plan to study 3 aims: To characterize the ability of metabolomic profiles of bladder urothelial cancer to predict therapeutic sensitivity of these tumors to chemotherapy; to investigate the accuracy of Hyperpolarized 13C Metabolic MRI to non-invasively identify early therapeutic real-time responsiveness of tissue to chemotherapy treatment; and to prospectively study in a clinical human translational study the feasibility of Hyperpolarized 13C Metabolic MRI to stage, risk-stratify, and monitor treatment response of muscle-invasive bladder cancer.

2. Keywords

Bladder cancer, metabolomics, MRI, hyperpolarized 13C, molecular subtypes

3. Accomplishments

a. What were the major goals of the project?

The major goals that were laid out for this project in the milestones are included in the table below:

	Timeline Months	Site 1	Site 2	Site 3	Site 4
<i>Milestone(s) Achieved: All necessary IRB approval obtained for tissue procurement phase of study</i>	3				
<i>Milestone(s) Achieved: Recruit first 10 patients in study</i>	8				
<u>Subtask 1.</u> Exposure of organoid cultures to chemotherapeutic treatments	4-30	Siddiqui			Siddiqui
<i>Milestone(s) Achieved: ACURO approval</i>	3				
<u>Subtask 1:</u> Establish baseline imaging protocol.	4-6	Mayer			
<u>Subtask 1:</u> Adapt thin slice culture method for bladder tumors	4-6	Siddiqui			
<u>Subtask 1</u> Complete IRB approvals for hyperpolarized MRI at UMMC and DOD approval.	1-6	Siddiqui / Mayer			
<i>Milestone(s) Achieved: IRB Approval for study</i>					
<u>Subtask 1.</u> Establish baseline imaging protocol	4-6	Mayer			
<u>Subtask 1.</u> Procure tissue at time of cystectomy and perform isotopomer metabolic flux analysis.	7-36	Siddiqui	Putluri		
<u>Subtask 4:</u> Generate organoids for use in Aims 1 and 2	7-36	Siddiqui			

b. What was accomplished under these goals?

We made strong progress majority of our milestones. There were some delays due to regulatory IRB office staffing shortages and backlog in completion of all regulatory materials, however we were able to complete all IRB and HRPO approvals for the project at all sites, as well as all IACUC and ACURO approvals for animal experiments We submitted the IRB on 08/31/2021 at the University of Maryland School of Medicine, which was approved on 11/16/2021. We then started patient recruitment from the University of Maryland Medical Center while submitting documents to the VA Baltimore IRB for review. Final approval was received on 07/14/2022 after a full committee review from the Maryland VA Health Care System Research and Development Committee. **Up to today, we have enrolled 22 bladder cancer patients** from the University of Maryland Medical Center. We established a tissue procurement workflow for efficient distribution of tissues between Siddiqui, Putluri, and McConkey labs.

Organoid generation (Siddiqui and McConkey lab)

Organoid culture technique was learned and culture techniques validated. To establish clinically relevant models for human bladder cancer, we have generated organoid lines. We established bladder cancer organoid lines using fresh patient tissues samples ranging from low-grade non-muscle-invasive disease to high-grade muscle-invasive cancer. Tumor tissues were transported directly from the cystoscopy suite or operating room to the laboratory for processing, where they were divided into pieces for organoid culture, as well as for analysis

of the parental tumor Figure.1 and 2. Our culture conditions are similar to those previously described, which include Matrigel to support three-dimensional culture, hepatocyte medium, charcoal-stripped serum, and ROCK inhibitor to improve the survival of dissociated epithelial cells. We currently were able to generate 8 organoid cell cultures from the 22 patient tumor samples obtained thus far. **Figure 1** demonstrates representative organoids cultured and expanded from tumor and benign urothelial tissue. We have managed to maintain organoids through 4 passages.

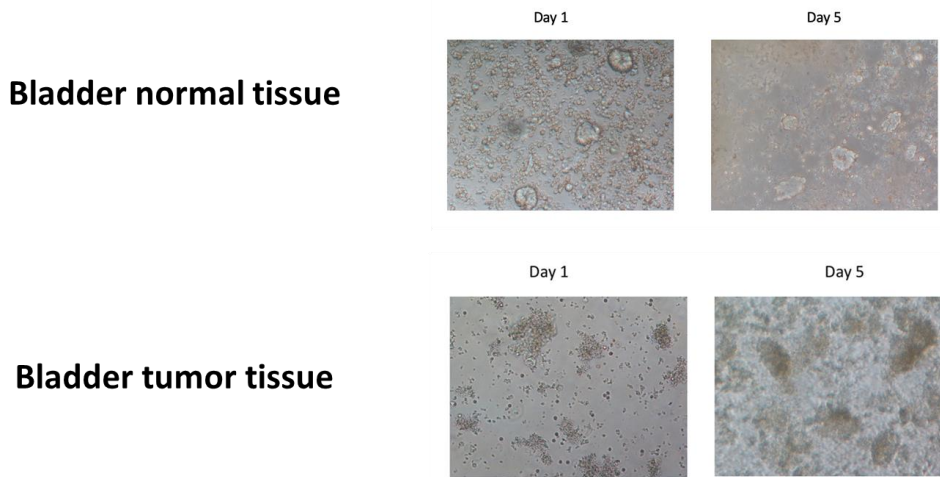


Figure 1: Successful culture and expansion of bladder cancer organoid tissue. Bright-field microscopy images of organoids from normal (A) and tumor tissue (B) on day 1 and day 5

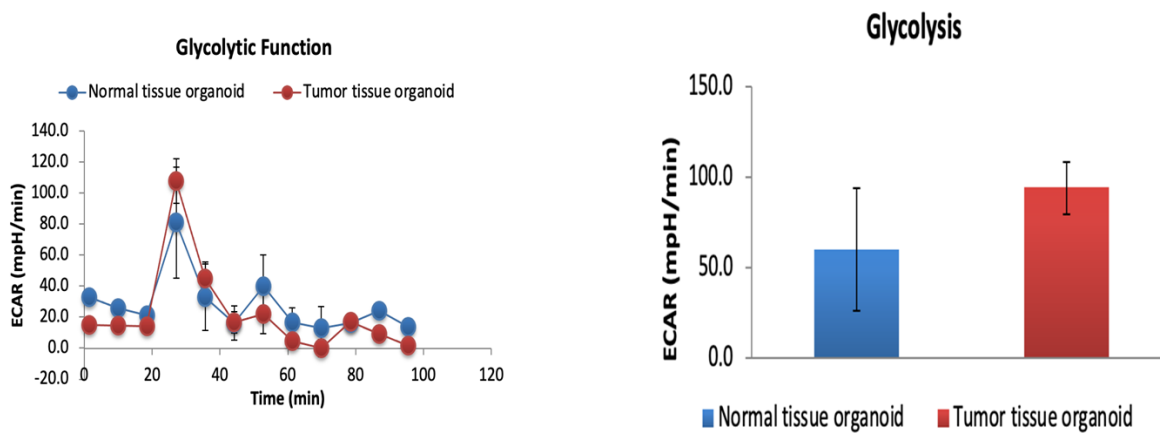


Figure 2; Glycolysis of organoids from normal bladder tissue and tumor tissue. Baseline measurements were performed of ECAR . The organoids from tumor tissue demonstrated a 30% higher glycolysis than the organoids from normal tissue

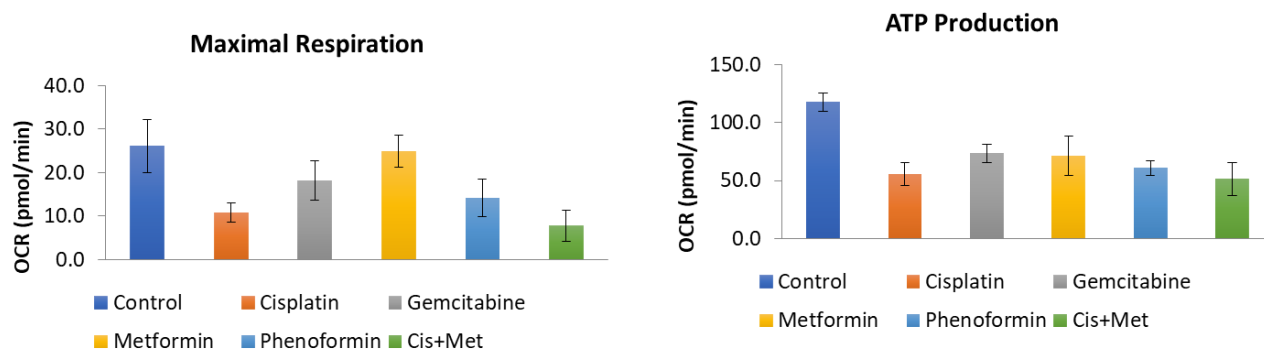


Figure 3; Mitochondrial respiration of organoids after treatment for 6 days. Baseline measurements were performed of OCR by seahorse. Cisplatin reduced respiration by around 55%. Gemcitabine reduced respiration by around 30. Metformin slightly reduced respiration by around 10% Phenformin reduced respiration by around 40%. Co-treatment of cisplatin and metformin reduced respiration by 65%.

Drug Response experiments (Siddiqui Lab)

Chemotherapeutic response experiment protocols have also been established as well as basic metabolic flux measurement protocols. **Figure 2** demonstrates an ability to measure differential glycolytic function between tumor and normal tissue organoid tissues. The effect of chemotherapeutics on organoid tissue metabolism was also evaluated We further performed comparison of chemotherapeutic sensitivity of tumor derived organoids, Mitochondrial respiration of organoids after treatment for 6 days were performed of OCR by seahorse. We found cisplatin reduced respiration by around 55%. Gemcitabine reduced respiration by around 30%. Metformin slightly reduced respiration by around 10%, Phenformin reduced respiration by around 40%. Co-treatment of cisplatin and metformin reduced respiration by 65%.

Metabolic Characterization (Putluri Lab)

Overall, in year 1 we performed the following experiments to address the goals proposed in **Major Task**. Additionally, we have published papers, presented abstracts and had oral presentations which are listed in the publication section.

In collaboration with Dr. Minhaj, we received 15 flash-frozen tissue samples from patients, of which six were healthy and nine were bladder cancer tissue. Five patients received neoadjuvant treatment. Samples were stored at -80 °C until analysis. An equal amount of tissue was homogenized in 1/4 water/methanol (v/v) with internal standards and extracted by sequential addition of ice-cold organic and aqueous solvents (water/methanol/chloroform/water, 1/4/3/1 (v/v) and subsequently vacuum dried. Samples were dissolved and filtered applying Amicon Ultra 3K centrifugal units (MilliporeSigma, Burlington MA) and dried. Finally, samples were reconstituted in 50/50 methanol water (v/v) and analyzed by liquid chromatography-coupled to tandem mass spectrometry (LC-MS/MS). We targeted 241 metabolites by four in-house developed LC-MS/MS methods (A, B, C, D) in selective reaction monitoring. For method A and B, we applied the positive ionization mode using an Xbridge Amide (3.5 μm, 4.6 x 100 mm) column (Waters Corporation, Milford, MA) for separation and 0.1% formic acid in water and 0.1% formic acid in acetonitrile as mobile phases. For method C,

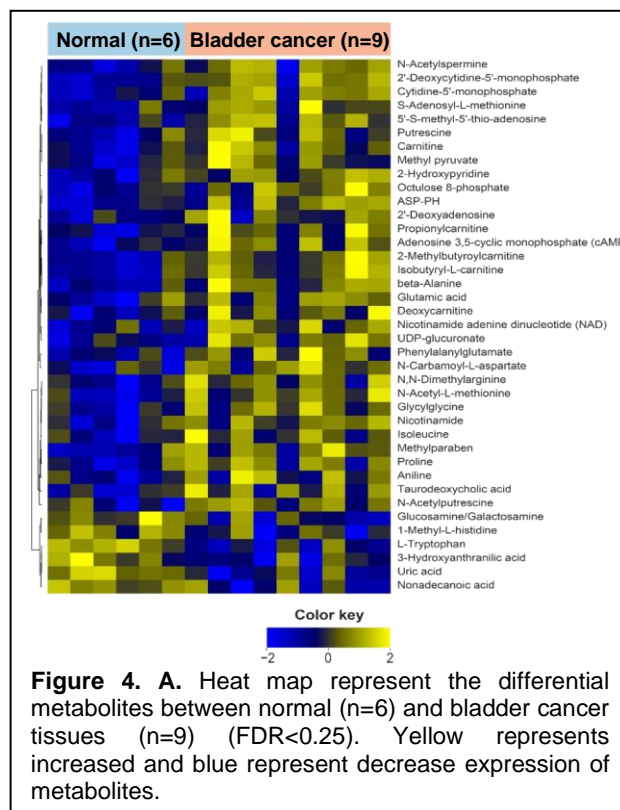


Figure 4. A. Heat map represent the differential metabolites between normal (n=6) and bladder cancer tissues (n=9) (FDR<0.25). Yellow represents increased and blue represent decrease expression of metabolites.

we also used positive ionization mode with a Luna-NH2 (3 μ m, 2x150 mm) column (Phenomenex, Torrance, CA) and 5 mM ammonium acetate in water and acetonitrile as mobile phases. For method D, we applied the negative ionization mode with the Waters XBridge Amide (3.5 μ m, 4.6 x 100 mm) column and 5 mM ammonium acetate in water and acetonitrile as mobile phases.

Applying these four methods using targeted metabolomics, a total of 205 metabolites in the tissues were successfully detected. Across the analysis of the samples, we distributed mice liver tissue samples as quality controls and detected a very good mean CV of 5.38% (n=4 quality control samples, all 205 metabolites) with a minimum of 0.17% and a maximum of 17.96% for the respective analytes. For the differential metabolite analysis, data was log₂ transformed and normalized with internal standards on a per-sample, per-method basis. For every metabolite in the normalized dataset, unpaired t-tests were conducted to compare metabolite levels. Differential metabolites were identified by adjusting the p-values for multiple testing at an FDR threshold of <0.25 for heatmap analysis. Unpaired t-tests were performed for the graphical representation as box plots.

When comparing bladder cancer tissue versus normal tissue, we found six metabolites being significantly downregulated in bladder cancer and 33 being significantly upregulated (**Fig. 4**). Pathway analysis using Metaboanalyst 5.0 revealed arginine and proline metabolism as the top pathway ($-\log_{10}(p)=3.88$, impact 0.3), indicating the increased need of amino acids for highly proliferative cancer cells.

In the following analysis, we divided patients into treatment with and without neoadjuvant therapy. We found three metabolites being significantly downregulated during neoadjuvant treatment (Maltose, 5-methylcytosine, maltotetraose), while eight metabolites were upregulated (2'-deoxycytidine-5'-monophosphate, lactic acid, succinic acid, hypoxanthine, butyrylcarnitine, adenine, N-acetylspermine, and cytidine-5'-monophosphate) (**Fig. 5**).

Our data from 15 patient tissue samples provided first valuable insights into the metabolomic response of cancer treatment. Larger sample sizes in the following years, will verify and strengthen these findings.

McConkey lab has similarly performed gene expression profiling of the tumor samples. They also provided extensive support and training to Siddiqui lab as well as troubleshooting for the development of cancer organoid tissues which have ultimately proven to demonstrate early success. We are awaiting the recruitment of further before performing analytic association studies between gene-expression, metabolic profile, and tumor behavior characteristics.

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

Professional development for Postdoctoral Fellow

1) Karthik Reddy Kami Reddy

- Continue expanding network of Biotechnology IP professionals by attending local seminars and events.
- Complete the Career Planning Workshop series arranged by BCM career development center.
- Performing survival surgeries for animal experiments for own project and other collaborations.
- Attending various departmental and institute organized seminars at Baylor College of Medicine.
- Participated in DLDC, AACR symposiums and conferences.
- Published one first author paper in Metabolites (2022)

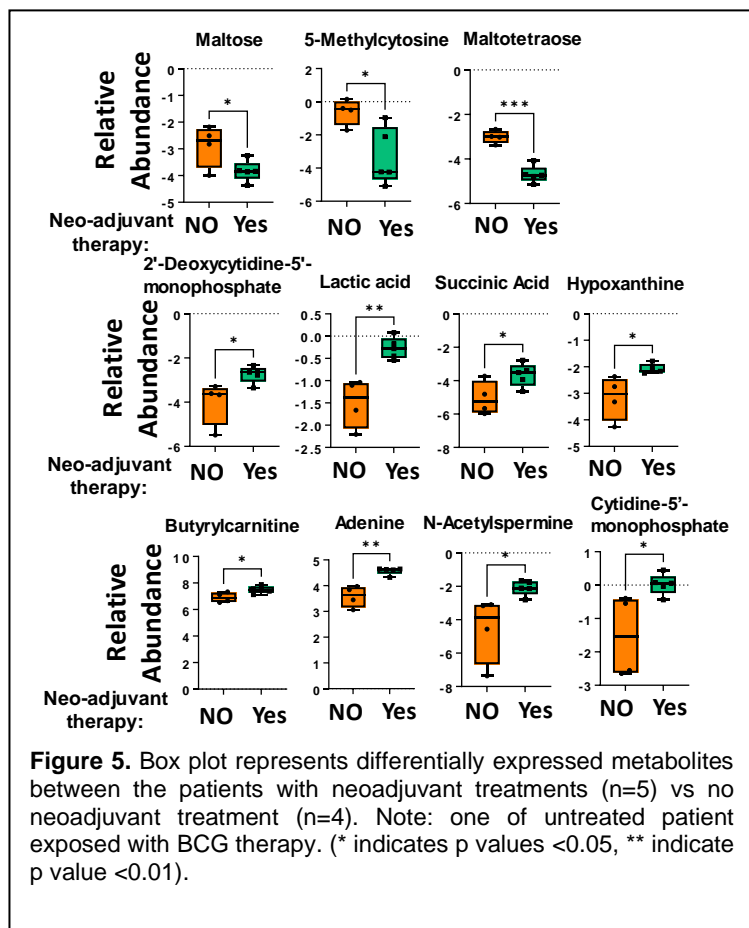


Figure 5. Box plot represents differentially expressed metabolites between the patients with neoadjuvant treatments (n=5) vs no neoadjuvant treatment (n=4). Note: one of untreated patient exposed with BCG therapy. (* indicates p values <0.05, ** indicate p value <0.01).

- One of the co-author manuscripts was under revision in Science Translational Medicine.
- Learning on grant writing and able to write the annual progress report
- Plan to submit the postdoc grant
- Write the IACUC, IRB and IBC reports and ensure these are kept updated
-

How were the results disseminated to communities of interest?

Nothing to report, it is early to disseminate outcomes from this study still in early establishment phases of work.

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

There are a number of goals for this coming year. We will continue to procure tumor samples from our various sites and generate organoids. We will be adapting modifications to organoid protocols that will potentially allow greater expansion of the organoids. This will allow for mouse implantation of the tumors. Siddiqui lab will continue to send samples to McConkey lab which will perform gene expression profiling and Putluri lab to perform metabolic profiling.

During the next funding period, we plan to acquire a larger number of bladder cancer tissue along with normal bladder tissues to validate the metabolic profiling comparing known molecular subtypes of basal and luminal BLCA. We plan to acquire the complete clinical information along with treatment information. We will validate Multi-omic comparative analysis of molecular subtype to metabolic profiles. We completed the in vivo experiment with infusion of ¹³C labeled compounds into mice and perform isotopomer analysis to characterize metabolic pathways. Further we are developing the ex vivo ¹³C isotopomeric labeling in the fresh bladder cancer tissue with thin slice tissue culture to measure the metabolic profiling and analysis. Tumors will be harvested for ex vivo correlation with imaging and analyzed using thin slice culture techniques. Glycolysis and glutamineolysis pathway utilization will be analyzed with exposure to [U-¹³C]glucose and [U-¹³C]glutamine for 4 hours and the therapies of interest. We are developing the mass spectrometry method for measuring the isotopomeric labeled compounds from bladder cancer patient tissues and xenograft tissues. We are generating organoids from bladder cancer patient tissues and will be use these organoids for treatment and analyze the metabolomics. Surgically resected tumor samples will be mechanically dissociated and partially digested with liberase DH. Clusters of cells will be collected and cultured for further therapeutic experiment and metabolic profiling.

4. Impact

Currently nothing to report. We are optimistic that significant aspects of this project are going well. Specifically we have demonstrated proof of concept of tissue procurement, organoid growth, and metabolic + gene expression profiling. This lays the foundation for ultimately deriving “metabolotypes of tumor based on metabolic profiling. Such biologic understanding would open the avenue for new therapeutic targets and biomarker discovery.

5. Changes/Problems

Changes in approach and reasons for change

We are troubleshooting the expansion of organoids with McConkey lab. Currently we have only been able to expand to 4 passages, with the number of organoids falling short of sufficient expansion for animal injection. This has limited the mouse implantation experiments currently. We also currently have an approximately 36% success rate with organoid formation and are troubleshooting how to improve the engraftment rate with similar protocol changes. We are optimistic that new adopted protocols will allow for greater expansion of organoids and thus open up avenues for animal experiments as well. We continue effectively however with in vitro experiments with our current protocols

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

The further development of the human imaging for hyperpolarized ¹³C imaging is currently on hold as there has been no availability this year due to supply-chain issues of the sterile fluid paths required for the imaging

procedure. This is a major issue that is being addressed by all sites using the hyperpolarized ¹³C imager across the world. GE has pledged support and is troubleshooting an alternative. Since the fluid paths are required for the IND, which is required in turn for the IRB submission, this portion of the project is on hold. We have confidence at this stage that once the fluid paths are available we will be able to catch up relatively easily.

Changes that had a significant impact on expenditures

We had a slow startup period due to understaffing in the regulatory review offices that lead to slow review of all protocols. As the project is now full speed on accruals, we expect the allocated funds will be used on originally intended uses of the funds.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
None

6. Products

List of Relevant Scientific Presentation and Publications

Publications:

1. Kami Reddy KR, Piyarathna DWB, Kamal AHM, Putluri V, Ravi SS, Bollag RJ, Terris MK, Lotan Y, Putluri N. Lipidomic Profiling Identifies a Novel Lipid Signature Associated with Ethnicity-Specific Disparity of Bladder Cancer. *Metabolites*. 2022 Jun 14;12(6):544. doi: 10.3390/metabo12060544. PMID: 35736477; PMCID: PMC9230655.

Abstracts presented in conference:

2. Title: **Quantification of Carcinogens in Bladder Cancer Urine using LC-MS/MS**, Abu Hena Mostafa Kamal, Chandra Sekhar Amara, Chandra Shekar R. Ambati, Vasanta Putluri, Karthik Reddy Kami Reddy, Yair Lotan, Nagireddy Putluri, (2021), American Society of Mass Spectrometry (ASMS) November 2021, Philadelphia
3. Title: **Quantification of arachidonic acid (AA) metabolites by LC-MS/MS**, Chandra Shekar Reddy Ambati, Mohammed Khurshidul Hassan Hassan, Abu Hena Mostafa Kamal, Vasanta Putluri, Meghashyam Kavuri, Nagireddy Putluri, (2021), American Society of Mass Spectrometry (ASMS) November 2021, Philadelphia.
4. Title: **Quantification of Carcinogens in Urine from Bladder Cancer using Liquid Chromatography-Mass Spectrometry**, Abu Hena Mostafa Kamal, Chandra Sekhar Amara, Chandra Shekar R. Ambati, Vasanta Putluri, Karthik Reddy Kami Reddy, Mohammed Khurshidul Hassan, Yair Lotan, Arun Sreekumar, Nagireddy Putluri, (2022), American Society of Mass Spectrometry (ASMS) June 2022, Minneapolis.
5. Title: **Mitochondrial metabolism and racial disparity of bladder cancer**, Karthik Reddy Kami Reddy, Jun Hyoung Park, Roni J. Bollag, Allison Bellman, Martha Terris, Seth P. Lerner, Leomar Y. Ballester, Yair Lotan, Benny Abraham Kaiparettu, Nagireddy Putluri. (2022). In: Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; *Cancer Res* 2022;82(12_Suppl):Abstract nr 3771.
6. Title: **Gender-specific metabolome in bladder cancer: Role of EPHX2 in bladder cancer**, Mohammed Khurshidul Hassan, Roshan Borkar, Karthik Reddy Kami Reddy, Danthasinghe Waduge Badrajee Piyarathna, Chandra Shekar Amara, Allison Bellman, Chandra Shekar R. Ambati, Vasanta Putluri, Abu Hena Mostafa Kamal, Roni J. Bollag, Martha K. Terris, Leomar Y. Ballester, Yair Lotan, Cristian Coarfa, Arun Sreekumar, Nagireddy Putluri (2022), In: Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; *Cancer Res* 2022;82(12_Suppl):Abstract nr 2379.
7. Title: **Elucidating the role of SMARCB1 in bladder cancer progression and metastasis**, Chandra Sekhar Amara, Karthik Reddy Reddy, Yuntao Yang, Badrajee Waduge Danthasinghe, Allison Bellman, Andrea B. Apollo, David J. Shih, Leomar Ballester, Pavlos Msaouel, Wenjin J. Zheng, Matthew J. Ellis, Seth P. Lerner, Arun Sreekumar, Shyam M. Kavuri, Nagireddy Putluri (2022), In: Proceedings of the

American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; Cancer Res 2022;82(12_Suppl):Abstract nr 2417.

8. Title: **Metformin concentration is a deciding factor of its pro- or anti-tumor function in triple negative breast cancer**, Jun Hyoung Park, Dongya Jia, Sukjin Yang, Kwang Hwa Jung, Abha Tiwari, Debasmitta Dutta, Meron Ghidry, Nagireddy Putluri, Cristian Coarfa, Chad Creighton, José N. Onuchic, Benny A Kaiparettu (2022), In: Proceedings of the 2021 San Antonio Breast Cancer Symposium; 2021 Dec 7-10; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2022;82(4 Suppl):Abstract nr P5-05-06.

Oral Presentations (major ones listed)

1. **11th Annual Metabolism in Cancer Symposium.**
Title: Molecular Profiling Reveals Unique Metabolic Features in African American Bladder Cancer
 Date: Sep 14th 2022
 Location: MD Anderson Cancer Center, Houston, TX
 Speaker: Nagireddy Putluri
2. **Invited speaker- departmental seminar series.**
Title: Metabolic Detours in Bladder Cancer: Biological and Therapeutic Implications
 Date: Sep 21th 2022
 Location: University of Houston, Houston, TX
 Speaker: Nagireddy Putluri
3. **Invited Speaker - Indian Institute of Chemical Technology**
Title: STAT3 activation is a therapeutic vulnerability in metastatic bladder cancers harboring SMARCB1 loss.
 Date: June 23, 2022
 Location: Indian Institute of Chemical Technology, India
 Speaker: Nagireddy Putluri
4. **Overduckers seminar series**
Title: Metabolic Vulnerabilities in Bladder Cancer Racial Disparity
 Date: January 29, 2022
 Location: online meeting
 Speaker: Karthik Reddy Kami Reddy
5. **Invited speaker -Houston Methodist Cancer Center Cancer Center Work in Progress Meeting.**
Title: Metabolomics as a Tool to Study Disease Progression
 Date: October 28, 2021
 Location: Houston Methodist Hospitals, Houston, TX
 Speaker: Nagireddy Putluri
6. **DLCCC 17th Symposium**
Title: STAT3 activation is a therapeutic vulnerability in metastatic bladder cancers harboring SMARCB1 loss
 Date: September 16, 2021
 Location: DLCCC, Baylor College of Medicine, Houston, TX.
 Speaker: Nagireddy Putluri

7. Participants & Other Collaborating Organizations

The three organizations remain University of Maryland, Biltmore, Baylor College of Medicine, and Johns Hopkins University.

The active staff in this study are:

SNO	Name	Role
1	Mohammad Siddiqui, M.D , University of Maryland,	PI
2	Nagireddy Putluri , Ph.D, Baylor College of Medicine	PI

3	David McConkey, Ph.D, Johns Hopkins	PI
4	Karthik Reddy Kami Reddy Ph.D, Baylor College of Medicine	Key personnel /pos doc
5	Dexue Fu, M.D, Ph.D, University of Maryland,	Key personnel /Staff
6	Ganine Markowitz, M.S, University of Maryland,	Key personnel /Clinical coordinator

There has been no change from intended participants of this project

What individuals have worked on the project?

Name:	<i>Mohammad Siddiqui (University of Maryland)</i>
Project Role:	<i>PI - CA200996</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0002-4484-6820</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Execute the project, design the experiments, overseas the project.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Nagireddy Putluri (Baylor College of Medicine)</i>
Project Role:	<i>Partnering PI - CA200996P1</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0003-4488-7400</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Execute the project, design the experiments, overseas the project.</i>
Funding Support:	<i>n/a</i>

Name:	<i>David McConkey (Johns Hopkins)</i>
Project Role:	<i>Partnering PI - CA200996P2</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0003-1971-0638</i>
Nearest person month worked:	<i>1</i>

Contribution to Project:	<i>Execute the project, design the experiments, overseas the project.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Dirk Mayer (University of Maryland)</i>
Project Role:	<i>Co-I</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0003-1296-8265</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Oversee design, implementation, regulatory work on hyperpolarized imaging.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Karthik Reddy Kami Reddy (Baylor College of Medicine)</i>
Project Role:	<i>Postdoc Associate</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0002-3288-394X</i>
Nearest person month worked:	<i>5</i>
Contribution to Project:	<i>He is responsible for carrying out experiments under the direction of Dr. Putluri. Dr. Kami Reddy has extensive experience in metabolomics, functional analysis as well as organoids, in vitro and in vivo tumorigenicity experiments. He helped implement the metabolic characterization presented.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Dexue Fu (University of Maryland)</i>
Project Role:	<i>Research Associate</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0002-3968-4871</i>
Nearest person month worked:	<i>9</i>
Contribution to Project:	<i>He is responsible for carrying out experiments under the direction of Dr. Siddiqui. Dr. Fu has extensive experience in cell culture, cancer biology and metabolic characterization.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Ganine Markowitz (University of Maryland)</i>
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Project Role:	<i>Clinical Trial specialist</i>
Researcher Identifier	
Nearest person month worked:	2
Contribution to Project:	<i>She is responsible for regulatory IRB and IND oversight related to the patient recruitment at both UMMC and the VA</i>
Funding Support:	<i>n/a</i>

Name:	<i>Rosy Njonkuo (University of Maryland)</i>
Project Role:	<i>Clinical Trial specialist</i>
Researcher Identifier	
Nearest person month worked:	1
Contribution to Project:	<i>She is responsible for regulatory IRB and IND oversight related to the hyperpolarized MRI. She has extensive experience with hyperpolarized MRI and clinical trial management</i>
Funding Support:	<i>n/a</i>

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

Other support is attached for PIs. No overlapping new support for any of the PIs or key personnel

What other organizations were involved as partners?

Organization Name: University of Maryland

Location of Organization: 29 S Greene St Suite 500, Baltimore MD 21201

Partner's contribution to the project

- *Project oversight, patient recruitment, laboratory experiments, animal work and imaging studies*

Organization Name: Baylor College of Medicine

Location of Organization: One Baylor Plaza, Houston, TX 77030-3411

Partner's contribution to the project (identify one or more)

- *Metabolomic characterization*

Organization Name: Johns Hopkins University

Location of Organization: One Baylor Plaza, Houston, TX 77030-3411

Partner's contribution to the project (identify one or more)

- *Characterization of cellular genetic tumor phenotype, guidance on organoid generation*

8. Special Reporting Requirements

Not applicable

9. Appendices

Attached are Other Support

Active Grants

- 9/1/22-8/30/23 PI, 5% salary support
“Precision Medicine Utilizing Bacillus Calmette–Guérin Vaccine in Non-Muscle Invasive Bladder Cancer”
FDA CERSI Award as part of NIH U01 FD005946-04S4 Polli PI
Total Direct Costs:
- 9/1/21-8/30/24 PI, 20% salary support
“Using Metabolic Signatures for Risk-Stratification and Personalized Treatment of Bladder Cancer”
Department of Defense-Peer Reviewed Cancer Research Program Translational Team Science Award
CA200996
Annual Direct Costs:
Total Direct Costs:
- 6/1/19-5/30/23 Site PI
“Implementing Risk-Aligned Bladder Cancer Surveillance”
VA Merit Award I01 HX002780
Annual Direct Costs:
Total Direct Costs:
- 12/1/16-11/30/25 Site Investigator, 2% salary support
“Diagnosing clinically-significant prostate cancer in African American men: systematic random versus mr-image-fusion guided biopsy
NIH- R01 NCI CA205058-01
Annual Direct Costs:
Total Direct Costs:
- 5/1/21-10/30/22 PI, 0% salary support
“Metabolic Imaging in the Diagnosis and Risk-Stratification of Prostate Cancer”
University of Maryland, Baltimore (UMB), Institute for Clinical & Translational Research (ICTR)/ Clinical Translational Science Award (CTSA) 1UL1TR003098.
Total Direct Costs:

Completed Grants

- 9/1/21-8/30/22 PI, 0% salary support
“National patterns of MRI utilization for prostate cancer diagnosis”
University of Maryland, Baltimore (UMB), Institute for Clinical & Translational Research (ICTR)/ Clinical Translational Science Award (CTSA) 1UL1TR003098.
Total Direct Costs:
- 6/15/20-1/15/22 PI, 5% salary support
“Assessment of Patient Tolerance for Risk Associated with High Intensity Focused Ultrasound (HIFU) for the Ablation of Prostate Tissue”
FDA CERSI Award as part of NIH U01 FD005946-04S4 Polli PI
Total Direct Costs:
- 4/1/21-3/31/22 PI, 2% salary support
“Prioritization of CER/PCOR on Prostate Cancer Active Surveillance: Community Consensus Initiative”
Patient-Centered Outcomes Research Institute (PCORI) EAIN-19842
Total Direct Costs:
- 2/4/16-12/30/16 PI, 0% salary support
“Metabolic characterization of prostate cancer biopsy samples”
American Cancer Society Institutional Research Grant

Annual Direct

Costs:

10/1/16-9/30/17	<p>Total Direct Costs: Co-I "The effects of a ketogenic diet intervention on overweight and obese men undergoing active surveillance for prostate cancer" Nutrition Obesity Research Center (NORC) Annual Direct Costs: Total Direct Costs:</p>
8/1/16-7/30/19	<p>PI, "Using Metabolic Pathways to Improve Diagnosis and Risk Stratification of Prostate Cancer" Department of Defense-Prostate Cancer Idea Development Award PC150408 Annual Direct Costs: Total Direct Costs:</p>
12/1/16-11/30/19	<p>Co-PI, "Hyperpolarized 13C imaging of mitochondrial metabolism for improved characterization of prostate" NIH-R21 NCI CA213020-01 Annual Direct Costs: Total Direct Costs:</p>
8/1/17-1/30/20	<p>PI "Metabolic urinary based signature for bladder cancer detection" Maryland Industrial Partnerships Grant Annual Direct Costs: Total Direct Costs:</p>

Previous/Current/Pending Support

PUTLURI, NAGIREDDY

PREVIOUS SUPPORT (5 years back)

Title:	1127430-RSG-15-105-01-CNE (Putluri) Elucidating the Role of Xenobiotic Metabolism in Bladder Cancer Progression
Effort:	3 calendar
Supporting Agency	American Cancer Society
Grants Officer contact info:	Susanna Greer // sgreer@gsu.edu
Performance Period:	07/01/2015-06/30/19
Funding Amount:	
Project Goals/Aims:	Aims 1. define stage specific profiles of key xenobiotic metabolites in bladder cancer; 2. define the regulation and function of AOX1 in bladder cancer; and 3. develop a prognostic panel of urinary xenobiotic metabolites.
Overlap:	None

Title:	RP120092 Tumor Metabolomics Core Facility
Effort:	effort 3 calendar
Supporting Agency	CPRIT
Grants Officer contact info:	Michael Brown / mbrown@cprit.state.tx.us
Performance Period:	12/01/2011-11/30/2016
Funding Amount:	
Project Goals/Aims:	Goals: 1. establish a cancer metabolomics core facility at Baylor College of Medicine; and 2. support metabolomics studies of investigators at Baylor College of Medicine in the area of Cancer Research.
Overlap:	None

Title:	P30 CA125123 (Osborne) Title: Baylor College of Medicine Cancer Center
Effort:	2.4 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	SHAFIK, HASNAA; email: shafikh@mail.nih.gov
Performance Period:	07/01/2015-06/30/2020
Funding Amount:	
Project Goals/Aims:	Goal: The purpose of this shared resource is to provide investigators with cost effective, state-of-the-art instrumentation and specialized expertise for analysis of metabolomics with the goal to identify novel metabolic biomarkers and pathways with application in prevention, diagnosis and treatment of cancer
Overlap:	none

Title:	RP150451 SRC-2 driven “metabolic switch” in metastatic prostate cancer- prognostic and therapeutic implications
Effort:	0.6 calendar
Supporting Agency	CPRIT
Grants Officer contact info:	Grant Specialist: Michael Brown / mbrown@cprit.state.tx.us
Performance Period:	03/01/15 - 02/31/18
Funding Amount:	
Project Goals/Aims:	Goals: To define the metabolic alterations associated with SRC2 action in Castrate Resistant Prostate Cancer.
Overlap:	None

Title:	5 U01 CA167234-03 Metabolomic profiling and biologic basis of racial disparity in prostate cancer
Effort:	0.6 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Grant Specialist: Rosemary Ward / / wardros@mail.nih.gov
Performance Period:	08/01/12 – 07/31/17
Funding Amount:	
Project Goals/Aims:	Goals: definitively define and compare the PCa metabolome of AA and EA men and uncover the biological mechanism in an ancestry-verified subset of AA and EA prostate cancers. To functionally characterize the race-associated metabolic pathways and evaluate the pathway-associated metabolites in urine specimens from AA and EA men with prostate cancer
Overlap:	None

Title:	U01 CA179674-01A1 Delineating racially distinct metabolic pathways in triple negative breast cancer
Effort:	1 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Grant Specialist: Bryann E Benton / / bentonb@mail.nih.gov
Performance Period:	09/01/14 – 08/31/19
Funding Amount:	
Project Goals/Aims:	Aim 1: Validate elevated levels of unsaturated fatty acids and lipids in AA TN BCa. Aim 2: Functionally characterize the pathways leading to accumulation of 2-OHG and arachidonic acid in AA TN BCa using in vitro and in vivo models. Aim 3: Measure the serum levels of metabolites in tryptophan, unsaturated fatty acids (including arachidonic acid) and 2-HG pathway in AA TN BCa.
Overlap:	None

ENDED – no longer on project

Title:	1R01CA227904-01A1 (Zhang/ Sreekumar) Title: Rewired Metabolism Regulates Vessel Normalization and Immunosuppression
Effort:	0.12 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Program Official Information: Dr. NEERAJA SATHYAMOORTHY, email: ns61r@nih.gov
Performance Period:	09/01/2019 – 08/31/2024
Funding Amount:	
Project Goals/Aims:	Goals: Determine how AADAT promotes metastasis via regulating the HIF1 α -VN axis in TN BCa; Determine the tumor-intrinsic role of AADAT in regulating HIF1 α signaling, bioenergetics and Metastasis; Determine to what extent genetic knockdown or pharmacological inhibition of AADAT can reduce metastasis in conjunction with chemotherapies Role: Co-Principal Investigator
Overlap:	None

CURRENT SUPPORT

Title:	1R01CA227559-03 (Sreekumar/ Palapattu) Metabolic Rewiring Promotes AA PCa by Regulating Stromal-Epithelial
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	Interaction
Effort:	0.12 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Program Official Information: Dr. NEERAJA SATHYAMOORTHY, email: ns61r@nih.gov
Performance Period:	07/01/2019-06/30/2024
Funding Amount:	
Project Goals/Aims:	Goals: Determine the biochemical mechanism leading to inosine accumulation in AA PCa; Evaluate the role of inosine in modulating AA tumor epithelial-stromal interactions; Evaluate ratio of pre-treatment inosine to adenosine (surrogate for ADA) in plasma as a predictive marker for biochemical recurrence (BCr) in <i>ancestry-verified</i> AA men with PCa. Role: Co-Investigator
Overlap:	None

RENEWED

Title:	RP210227 (Edwards) Renewal of RP170005 Title: Proteomics and Metabolomics Core Facility
Effort:	1.20 calendar
Supporting Agency	CPRIT
Grants Officer contact info:	Dr. Michael Brown / mbrown@cprit.state.tx.us
Performance Period:	08/31/2021 – 08/30/2026
Funding Amount:	
Project Goals/Aims:	Goals: Establish the workflow and conduct new services for multi-omics characterization of human tumors from mouse patient-derived xenograft (PDX) models and clinical investigational studies.. To support metabolomics studies of investigators at Baylor College of Medicine in the area of Cancer Research
Overlap:	None

Title:	5R01CA220297-05 NCE (Putluri) Title: Racial disparity in bladder cancer and identification of altered metabolism in African American compare to European American bladder cancer
Effort:	0.6 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Dr. WILLIS, KRISTINE AMALEE; email: kristine.willis@nih.gov
Performance Period:	06/05/17 – 05/31/2023 (NCE)
Funding Amount:	
Project Goals/Aims:	Goals: 1) characterize the mitochondrial associated metabolites in AA and EA BCa 2) Verify the D-2HG and associated enzymes (GLS, ADHFE1, and IDH1/2) in BCa patients and establish a therapeutically targeted deregulation pathway for glutamine metabolism in AA BCa. 3) Assess the levels of lyso PC and PC and the function of their metabolizing enzymes PLA1A and LRAT in AA BCa
Overlap:	None

Title:	5R01CA216426-04 (Putluri/El-Zein) Title: Identify the DNA adduct and associated metabolic alterations in bladder cancer of smokers
Effort:	1.5 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Program Official Information: Dr. WENDY WANG,, email: ww70q@nih.gov
Performance Period:	04/01/2018 – 03/31/2023
Funding Amount:	
Project Goals/Aims:	Goals: 1) Verify elevated level of DNA adducts, xenobiotic and methylated metabolites and, their pathways in smokers with BCa 2) To determine the interplay between smoke-induced alteration in methylation and DNA repair in promoting BCa 3) Quantify levels of smoke-associated DNA adducts,

	methylated and xenobiotic metabolites in urine of BCa patients with a longer term goal of developing a first-generation non-invasive panel of markers for BCa risk assessment among smokers.
Overlap:	None

Title:	U01CA214263 (Sen/Killary) Title: Circulating Biomarkers and Imaging for Early Detection of Pancreatic Cancer
Effort:	0.36 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Program Official Information: Dr. SHARMISTHA GHOSH-JANJIGIAN,, email: ghoshjanjigias@mail.nih.gov
Performance Period:	08/07/2018 – 07/31/2023
Funding Amount:	
Project Goals/Aims:	Goals: Development and validation of incipient early stage PDAC associated biomarker signatures. Development and validation of PDAC early precursor lesion associated biomarker signatures. Development and validation of high resolution early detection imaging tools to be integrated with circulating markers.
Overlap:	None

Title:	5P01DK113954-04 (O'Malley) Title: Nuclear Receptors and Their Coactivators as Mediators Of Systems Metabolism. Core B (Metabolomics Component).
Effort:	1.2 calendar
Supporting Agency	NIH
Grants Officer contact info:	Program Official Information: Dr. CORINNE M SILVA,; email: silvacm@mail.nih.gov
Performance Period:	07/01/2018 – 04/30/2023
Funding Amount:	
Project Goals/Aims:	Goals: The core will provide expertise in measurement of steady state levels of metabolites and their flux in cell lines and in tissue extracts isolated from a variety of genetically engineered mouse models. The metabolomics core will also provide assistance with downstream data analysis and interpretation in the context of pathways, as well as support the development and implementation of innovative methods to integrate OMICS-based datasets
Overlap:	None

RENEWED

Title:	P30 CA125123-15 (Heslop) Title: Baylor College of Medicine Cancer Center
Effort:	1.2 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Program Official Information: Dr. SHAFIK, HASNAA; Email: shafikh@mail.nih.gov
Performance Period:	08/14/2020 - 06/30/2025
Funding Amount:	
Project Goals/Aims:	Goal: The purpose of this shared resource is to provide investigators with cost effective, state-of-the-art instrumentation and specialized expertise for analysis of metabolomics with the goal to identify novel metabolic biomarkers and pathways with application in prevention, diagnosis and treatment of cancer
Overlap:	none

Title:	R01 HL148217-01 (Zachariah) Title: Causal Mechanisms of Adolescent Aortic Stiffness
Effort:	0.36 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Program Official Information: Dr. MCDONALD, CHERYL; Email: mcdonalc@mail.nih.gov
Performance Period:	09/01/2019 – 08/31/2024
Funding Amount:	
Project Goals/Aims:	Goals: This randomized, placebo controlled, double blind trial examines the role of a dietary supplement on adolescent arterial stiffness.

Overlap:	none
Title:	1P30ES030285 (Walker) Title: Gulf Coast Center for Precision Environmental Health
Effort:	0.3 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Program Official Information: Dr. THOMPSON, CLAUDIA L; Email: thomps14@niehs.nih.gov
Performance Period:	05/15/2019 - 03/31/2024
Funding Amount:	
Project Goals/Aims:	Goals: The major goal is to support environmental exposure research at BCM, UT Health Science Center, UT San Antonio, UTMB Galveston
Overlap:	none

NEW

Title:	1P42ES027725 (Moorthy) Title: Polycyclic aromatic hydrocarbons; Ultrasensitive detection, early life exposures-clinical outcomes (preterm births, chronic lung disease, and neurocognitive deficits), prevention and remediation
Effort:	0.6 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Program Official Information: Dr. CARLIN, DANIELLE J; Email: danielle.carlin@nih.gov
Performance Period:	02/28/2020 – 01/31/2025
Funding Amount:	
Project Goals/Aims:	Goals: The major goal is detection and remediation of PAHs at the Houston Superfund site; assess health effects in lung exposures and preterm birth.
Overlap:	none

NEW

Title:	1R01-HL153320-01 (Sun) Title: Cardiac Circadian Clock and Dilated Cardiomyopathy
Effort:	0.6 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Program Official Information: Dr. BALIJEPALLI, RAVI C; Email: ravi.balijepalli@nih.gov
Performance Period:	09/01/2020-05/31/2024
Funding Amount:	
Project Goals/Aims:	Goals: Using a new mouse model, a novel phase-restricted re-expression technique, and integrative multi-omics approaches, we aim to provide new insights into how the circadian clock regulates gene expression and “housekeeping” functions such as energy metabolism in cardiomyocytes in the pathobiology of heart failure, which can potentially lay an intellectual groundwork for novel chronotherapy strategies of dilated cardiomyopathy.
Overlap:	none

THIS AWARD

Grant name/#:	W81XWH-21-1-0613 CA200996P1 (Putluri)
Project Title:	Using metabolomic signatures for risk-stratification and personalized treatment of bladder cancer
Effort:	1.2 calendar to be reduced to 0.96 as of 9/1/22
Supporting Agency	Department of Defense
Grants Officer contact info:	Science Officer (SO): Dr. AMIE D. BUNKER, Ph.D, email: amie.d.bunker.CIV@mail.mil
Performance Period:	09/01/21 – 08/31/24
Funding Amount:	
Project Goals/Aims:	Aim 1. To characterize the ability of metabolomic profiles of bladder urothelial cancer to predict therapeutic sensitivity of these tumors to chemotherapy. Aim 2. To investigate the accuracy of Hyperpolarized 13C Metabolic MRI to non-invasively identify early therapeutic real-time responsiveness of tissue to chemotherapy treatment. Aim 3. To prospectively study the feasibility of Hyperpolarized 13C Metabolic MRI to stage, risk-stratify, and monitor treatment response of muscle-invasive bladder cancer in a clinical human translational study
Overlap:	none

Title:	R01-CA222224 (Barbieri) Title: TOWARDS NOVEL DIFFERENTIATION THERAPIES FOR NEUROBLASTOMA
Effort:	0.24 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Amy R Bartosch, email: amy.bartosch@nih.gov, Ph:
Performance Period:	05/01/19 – 04/30/25
Funding Amount:	
Project Goals/Aims:	1) The contribution of CHAF1A to NB resistance to differentiation therapy, 2) the molecular mechanisms through which CHAF1A blocks NB differentiation and reprograms tumor metabolism, and 3) how CHAF1A metabolic reprogramming alters NB tumorigenesis and response to differentiation therapy.
Overlap:	None

NEW

Title:	22RDM002 (Ripley) Title: Patient-Derived Organoids Predict Mitochondrial Resistance in Apoptosis in Esophageal Adenocarcinoma
Effort:	0.36 calendar (effort only)
Supporting Agency	MACDONALD RESEARCH FUND-ST. LUKE'S HOSP
Grants Officer contact info:	Herbert L. DuPont, Chair, MacDonald Fund Committee
Performance Period:	04/01/22 – 03/31/23
Funding Amount:	
Project Goals/Aims:	Aim 1: Determine whether DBP and metabolite secretion differ in PDOs from pre-therapy biopsies in patients who achieve a pCR versus those without a response. Aim 2: Develop a training set, clin-omics model by merging the transcriptomic and metabolomic data in conjunction with our clinically annotated data to create a deep learning model to predict pCR. Our short-term goals are 1) to determine whether PDOs from pre-therapy biopsies differ between patients who achieve a pCR versus those who do not, and 2) whether the molecular data from PDOs can be combined with the patient clinical data to develop a deep-learning, clin-omics training set. The long-term goal of these projects is to identify and disrupt the tumor mitochondria to overcome therapeutic resistance.
Overlap:	None

NEW

Title:	R01-DK114356 (Hartig) Title: Metabolic impacts of type II interferon signals in obesity
Effort:	0.36 calendar
Supporting Agency	NIH/NIDDK
Grants Officer contact info:	Mary K. Rosenberg, Ph: , email: mary.rosenberg@nih.gov
Performance Period:	7/15/22 – 6/30/27
Funding Amount:	
Project Goals/Aims:	The major goal of this project is to define ways WAT inflammation causes insulin.
Overlap:	None

NEW

Title:	R01 DK129579-01A1 (Wooton-Kee) Title: Nuclear Receptor Dysfunction Reprograms Metabolism and Cellular Proliferation in Wilson's Disease
Effort:	0.24 calendar
Supporting Agency	NIH/NIDDK
Grants Officer contact info:	Karin Johnson, Email: karen.johnson3@nih.gov , Ph:

Performance Period:	7/18/22 – 5/31/27
Funding Amount:	Total award:
Project Goals/Aims:	This project will explore how nuclear receptors interface with copper metabolism in the liver.
Overlap:	None

PENDING SUPPORT

Grant name/#:	CA220731 (Putluri)
Project Title:	STAT3 ACTIVATION IS A THERAPEUTIC VULNERABILITY IN SMARCB1 DEFICIENT METASTATIC BLADDER CANCER
Effort:	1.2 calendar
Supporting Agency	DOD
Grants Officer contact info:	Not yet assigned
Performance Period:	09/01/23 – 08/31/27
Funding Amount:	Total award:
Project Goals/Aims:	Aim. 1. To investigate the prevalence, early stratification of SMARCB1 deficient and STAT3 activation in BLCA patients and correlate to treatment response and patient outcome. Aim. 2. To investigate the preclinical efficacy and acquired resistance mechanisms to STAT3 inhibition on BLCA progression.
Overlap:	none

Grant name/#:	U54 CA274321 (Myers)
Project Title:	THE HOUSTON CENTER FOR ACQUIRED RESISTANCE RESEARCH
Effort:	0.48 calendar
Supporting Agency	NIH/NCI
Grants Officer contact info:	Not yet assigned
Performance Period:	09/01/22 – 08/31/27
Funding Amount:	Total award: (sub Sandulache)
Project Goals/Aims:	Aim 1. Is the shift toward amino acid (AA) production designed to generate glutathione, required and sufficient for acquired cisplatin resistance? Aim 2. How are glutathione synthesis and utilization transcriptionally coordinated? Aim 3. Are metabolic shifts associated with resistance directly or indirectly regulating TIME?
Overlap:	none

Grant name/#:	BC22154P1 (Echeverria)
Project Title:	TARGETING INTRA-TUMOR HETEROGENEITY IN RESPONSE TO HER2 ONCOGENIC MUTATIONS IN METASTATIC ER+ BREAST CANCER
Effort:	0.6 calendar
Supporting Agency	DOD
Grants Officer contact info:	Not yet assigned
Performance Period:	01/01/23 – 12/31/26
Funding Amount:	Total award:
Project Goals/Aims:	Our proposed research has two potentially high-impact outcomes. 1) It will provide evidence that FTL activation can predict endocrine therapy and neratinib resistance and organ-specific metastasis for the 6-10% of ER+ mBCs harboring HER2 mutations. 2) We will include FTL-high as a predictive resistance biomarker in our ongoing ER+ HER2-mutant phase II clinical trials of neratinib (NCT01670877), and stratify patients based on the FTL expression, who can respond to neratinib treatment versus non-responders. 3). Based on the preclinical efficacy of poziotinib, we are initiating phase II clinical trials with our clinical collaborators to evaluate clinical efficacy of poziotinib and test whether FTL-high can predict poziotinib response in ER+ HER2-mutant mBC. If our project is successful, we will be a step closer to the goal of achieving complete regression of breast tumors, thereby reducing the chances of metastatic relapse for patients living with ER+ non-HER2-amplified breast cancer.
Overlap:	none

Grant name/#:	R01CA278842 (Putluri/Gao)
Project Title:	EXAMINE THE ROLE OF EPHX2 LOSS ASSOCIATED BLADDER CANCER PROGRESSION

Effort:	1.2 calendar
Supporting Agency	NIH
Grants Officer contact info:	Not yet assigned
Performance Period:	04/01/2023 – 03/30/2028
Funding Amount:	Total award:
Project Goals/Aims:	Aim 1. Determine the mechanisms by which EPHX2 promotes tumor progression in bladder cancer. Aim 2. Determine the clinical significance and therapeutic implications of EPHX2 loss in bladder cancer
Overlap:	none

Grant name/#:	R01ES035076 (Sen/Putluri)
Project Title:	Environmental Carcinogen Associated Biomarkers for Risk Stratification of Bladder Cancer
Effort:	1.2 calendar
Supporting Agency	NIH
Grants Officer contact info:	Not yet assigned
Performance Period:	04/01/2023 – 03/30/2028
Funding Amount	Total award:
Project Goals/Aims:	Aim 1. Validation of metabolome, methylome, miRnome and proteomic biomarkers in urine and serum (liquid biopsy) associated with xenobiotic metabolites and deregulated pathways in NMIBC (Phase 2 of PRoBE design). Aim 2. Blinded validation of liquid biopsy biomarkers in retrospective pre-diagnostic samples from individuals developing BC (Phase 3 of PRoBE design). Aim 3. Screening of the biomarker assays in liquid biopsies for predicting risk of disease in individuals with various exposures and hematuria (Phase 4 of PRoBE design).
Overlap:	none

Grant name/#:	RP230097 - Sen (MDACC)
Project Title:	RISK STRATIFICATION AND EARLY DETECTION OF BLADDER CANCER
Effort:	1.2 calendar
Supporting Agency	CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS (CPRIT)
Grants Officer contact info:	Not yet assigned
Performance Period:	03/01/2023 – 02/28/2028
Funding Amount:	Total award:
Project Goals/Aims:	Aim 1. Validation of metabolome, methylome, miRnome and mutant DNA in urine and serum (liquid biopsy) associated with xenobiotic metabolites and deregulated pathways in NMIBC (Phase 2 of PRoBE design). Aim 2. Monitor early-stage liquid biopsy biomarker signatures using metabolic imaging with longitudinal samples from mouse models with progressive stages of BC and utilize Deep Learning (DL) algorithm (Artificial Intelligence) to detect and monitor BC in the two mouse models (Phase 1 of PRoBE design). Aim 3. Blinded validation of liquid biopsy biomarkers in retrospective pre-diagnostic samples from individuals developing bladder cancer (Phase 3 of PRoBE design). Aim 4. Screening of the biomarker assays in liquid biopsies for predicting risk individuals with various exposures and hematuria (Phase 4 of PRoBE design).
Overlap:	none

Grant name/#:	Not yet assigned (Sandulache)
Project Title:	METABOLIC ADAPTATION ENABLES CISPLATIN RESISTANCE AND INHIBITS TUMOR IMMUNITY
Effort:	0.84 calendar
Supporting Agency	NIH
Grants Officer contact info:	Not yet assigned
Performance Period:	04/01/23 – 03/31/28
Funding Amount:	Total award:
Project Goals/Aims:	We will first define the critical metabolic steps required for generation of an enhanced reductive state that supports cisplatin resistance in Aim 1. In Aim 2 we will determine how GS synthesis and utilization (by GPX2 and non GPX means) are coordinated transcriptionally at least in part through Nrf2 in order to support cisplatin resistance. In Aim 3 we will test the impact of GS metabolism via canonical (e.g. NF-kB) and metabolic paracrine signaling on development of a suppressive TIME.

Overlap:	none
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Grant name/#:	Not yet assigned (Wang)
Project Title:	DECIPHER AND TARGET THE METABOLIC SYMBIOSIS IN PROSTATE CANCER BONE METASTASIS
Effort:	0.6 calendar
Supporting Agency	NIH
Grants Officer contact info:	Not yet assigned
Performance Period:	07/01/23 – 6/30/28
Funding Amount:	Total award: (subaward)
Project Goals/Aims:	the measurement of intracellular metabolites in co-culture experiments
Overlap:	none

Grant name/#:	R01MD018407 (Salim)
Project Title:	MENTAL STRESS AND BREAST CANCER RISK AMONG HOUSTON-BASED AFGHAN AND SYRIAN REFUGEE WOMEN
Effort:	1.2 calendar
Supporting Agency	NIH
Grants Officer contact info:	dagaduhe@csr.nih.gov
Performance Period:	04/01/2023 – 03/31/2028
Funding Amount:	(subaward)
Project Goals/Aims:	Refine the Refugee Breast Cancer Outreach and Prevention Program (RBCOPP) for delivery with Houston-based Afghan and Syrian refugee women Examine general health behavior, mental health status, perceived stress, and breast cancer awareness in Syrian and Afghan refugee women re-settled in Houston, TX.
Overlap:	none

Grant name/#:	Not yet assigned (Dasgupta)
Project Title:	DECODING METABOLIC DEPENDENCIES IN THE TUMOR MICROENVIRONMENT DRIVING METASTATIC BREAST CANCER
Effort:	0.36 calendar
Supporting Agency	Department of Defense
Grants Officer contact info:	Not yet assigned
Performance Period:	12/01/2022 – 11/30/2026
Funding Amount	(Subaward)
Project Goals/Aims:	to identify the metabolic rewiring in tumor microenvironment in Breast cancer metastatic.
Overlap:	none

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award and accept the obligation to comply with Section 223(a) of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Signature:

Date: