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TITLE: Mesoscale Nanotechnology: A Novel Therapeutic Strategy in Polycystic Kidney Disease

PRINCIPAL INVESTIGATOR: Edgar A. Jaimes

CONTRACTING ORGANIZATION: Sloan Kettering Institute for Cancer Research, New York, NY

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14. ABSTRACT The <i>central hypothesis</i> of this proposal is that the <u>targeted tubular delivery of novel therapeutic agents is an effective strategy for the treatment of polycystic kidney disease.</u> Aim 1. Evaluate therapeutic efficacy of nanoparticle-targeted mTOR inhibition in a rat model of PKD Mesoscale nanoparticles will be synthesized to encapsulate an ASO against mTOR. We will use the PCK- <i>Pkhd1</i> ^{pck} rat model of PKD that closely mimics ADPKD in humans. Efficacy will be evaluated by longitudinal serial live imaging via MRI, as well as post-mortem phenotypic surrogate markers of renal cystogenesis. Aim 2. Evaluate therapeutic efficacy of nanoparticle-targeted miR-17 inhibition in a rat model of PKD Mesoscale nanoparticles will be synthesized to encapsulate an oligonucleotide against miR-17. Just like in Aim 1 we will use the Pkhd1pck/pck rat model of PKD that closely mimics ADPKD in humans. Efficacy will be evaluated by longitudinal serial live imaging via MRI, as well as post-mortem phenotypic surrogate markers of renal cystogenesis.					
15. SUBJECT TERMS None listed.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. INTRODUCTION

In this project we are developing novel therapeutic strategies for adult polycystic kidney disease (ADPKD) utilizing newly-developed mesoscale nanoparticles encapsulating an anti sense oligonucleotide against mTOR or an oligonucleotide against miR-17. These studies are being performed in the *Pkhd1*^{PCK/PCK} rat which closely resembles ADPKD in humans and was the pre-clinical model of ADPKD used in the studies that led to the clinical trials with tolvaptan, the only drug currently approved for the treatment of ADPKD. The investigators will employ mesoscale nanoparticles to target an ASO against mTOR or an oligonucleotide against miR-17 specifically to site of injury in order to slow cystogenesis without triggering dose-limiting toxicities. We expect that the effect of one injection will last for up to two months, providing a prolonged therapeutic benefit.

2. KEYWORDS

Polycystic kidney disease
Mammalian target of rapamycin
Kidney
Renal Function
Nanoparticles
Chronic Kidney Disease

3. ACCOMPLISHMENTS

- What are the major goals of the project?

Major Task 1: Mesoscale Nanoparticle synthesis: 1-4 months (partially completed)

Major Task 2: In Vivo Efficacy of ASO against mTOR: 6-13 months (partially completed)

Major Task 3: Efficacy of oligonucleotides against miR-17: 15-23 months (not completed)

- What was accomplished under these goals?

Mesoscale nanoparticles (MNP) have been synthesized and encapsulated with the mTOR inhibitor sirolimus. Encapsulation with oligonucleotides against mTOR has shown to be more challenging than anticipated and as result we are trying a different nanoparticle formulation that has high affinity against galectin and that we hope will be easier to encapsulate with oligonucleotides.

Since we had difficulties encapsulating oligonucleotides, we did perform in vivo experiments in PCK-*Pkhd1*^{pck} rats utilizing nanoparticles encapsulated with the mTOR inhibitor sirolimus. These studies showed that the particles were safe and well tolerated and resulted in a significant reduction in cyst formation as assessed by MRI.

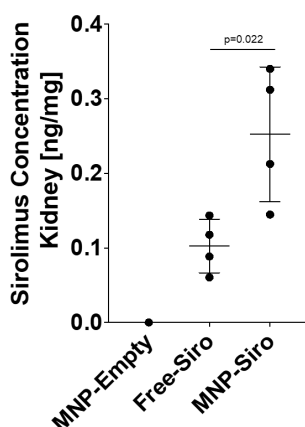


Figure 1. MNP sirolimus-encapsulated (MNP-Siro) target to kidneys more efficiently vs free sirolimus (Free-Siro) after an intravenous administration to *Pkhd1*^{PCK/PCK} rats. The sirolimus (rapamycin) concentration in kidneys was determined with mass spectrometry. Empty MNPs without sirolimus (MNP-Empty) were used as negative control.

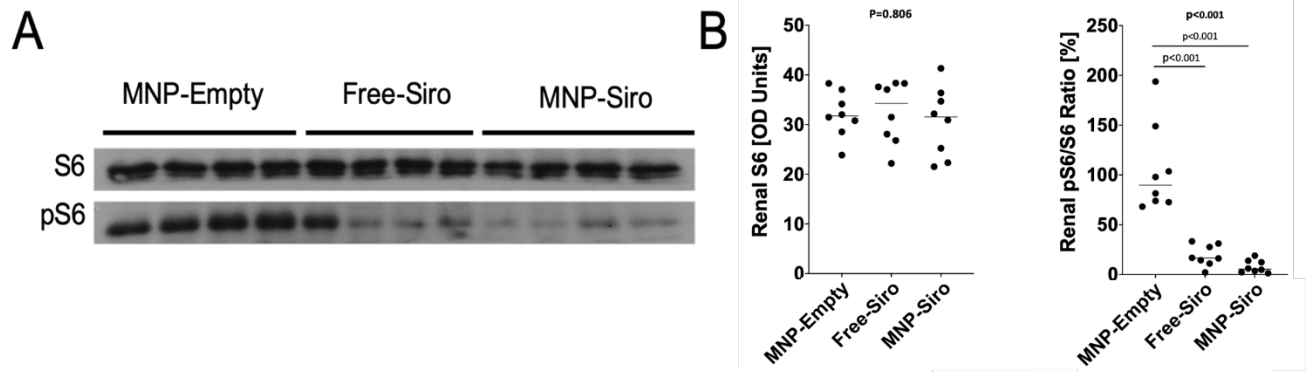


Figure 2. MNP sirolimus-encapsulated (MNP-Siro) inhibits mTOR pathway activity in *Pkhd1*^{PCK/PCK} rat kidneys. **Panel a:** Representative example of an immunoblot of S6 and pS6 comparing the renal effect of MNP-Siro vs free sirolimus (Free-Siro) vs MNPs without sirolimus (MNP-Empty) administration. **Panel b:** While the S6 levels did not change (left panel), the pS6 levels and the pS6/S6 ratios the averages were reduced more efficiently by the MNP-Siro (vs Free-Siro) administration.

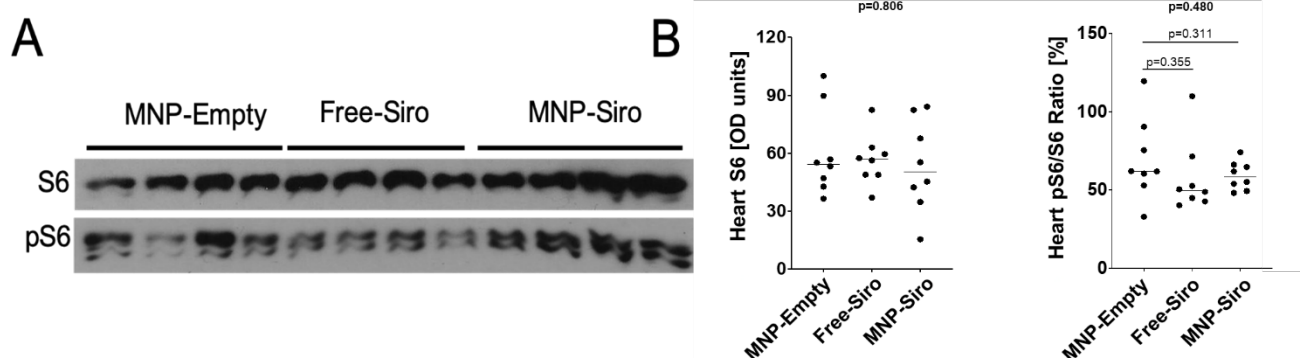


Figure 3. MNP sirolimus-encapsulated (MNP-Siro) effects on mTOR pathway activity in *Pkhd1*^{PCK/PCK} rat hearts are similar to those of MNPs without sirolimus (MNP-Empty). We examined the cardiac mTOR activity because free sirolimus (Free-Siro) administration was associated with focal myocardia necrosis in outbred Sprague-Dawley rats (PMID: 1871790). **Panel a:** Representative example of an immunoblot of S6 and pS6 comparing the effect of MNP-Siro vs Free-Siro vs MNP-Empty. **Panel b:** The mean pS6 levels and the pS6/S6 ratios are similar after MNP-Siro and MNP-Empty administration; however, they are numerically lower after Free-Siro (pointing to a protective effect of MNP-Siro encapsulation).

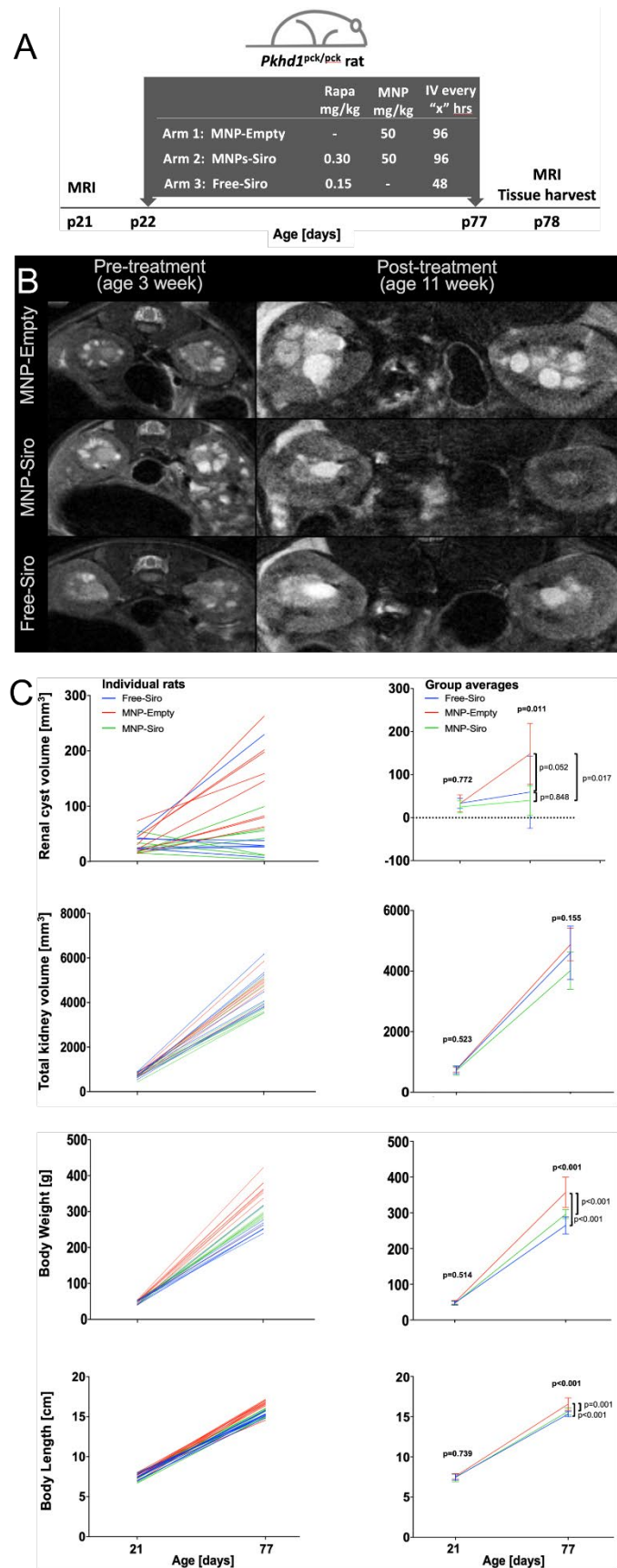


Figure 4. MNP-Siro (green lines) has stronger renal cystogenesis-inhibiting effects in *Pkhd1*^{PCK/PCK} rat and lower adverse effects when compared to Free-Siro (blue lines); MNP-Empty was used as a control. Panel a: Experiment design. **Panel b:** Representative MRI images in an individual rat from each treatment arm before treatment at postnatal day 21 (3 weeks) and after treatment at postnatal day 77 (11 weeks). **Panel c:** Effects of MNP-Siro (vs MNP-Empty and Free-Siro) on renal cyst and total kidney volumes, body weights and body lengths.

Based on these, we concluded:

1. MNP-Sirolimus particles target the kidneys more efficiently vs free Sirolimus
2. MNP-Sirolimus particles inhibit renal mTOR activation and potentially less so in hearts
3. MNP-Sirolimus renal cystogenic-inhibiting effects are stronger vs free-Siro but did not reach statistical significance
4. MNP-Sirolimus side effects are less prominent as compared to free-Sirolimus

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

Nothing to report

- **How were the results reported to communities of interest?**

A poster with the above results was presented at the 2021 Kidney Week Meeting of the American Society of Nephrology

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

We will continue the optimization of particles to allow efficient loading of oligonucleotides and perform experiments utilizing particles loaded with oligonucleotides against mTOR and miR-17. Our studies so far have shown that our system effectively blocks mTOR activation and reduces cyst formation as compared to free drug and therefore the main focus of the second year will be on blockade of miR-17 once we have the particle formulation to allow the efficient loading of oligonucleotides.

4. IMPACT

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

We anticipate that results from these studies will have a significant impact in the treatment of polycystic kidney disease and we expect that after full completion of this study clinical trials utilizing our technology will be planned and executed.

- **What was the impact on other disciplines?**

Nothing to report

- **What was the impact on technology transfer?**

A start-up company called named Goldilocks Therapeutics, Inc was founded by Drs Edgar Jaimes (CMO), Daniel Heller (CSO) and Mr. Arthur Klausner (CEO)

- **What was the impact on society beyond science and technology?**

Nothing to report

5. CHANGES/PROBLEMS

- **Changes in approach and reasons for change**

We had technical difficulties encapsulating oligonucleotides in our nanoparticles and therefore we used the small molecule mTOR inhibitor sirolimus as a payload. The scope of the study however remains unchanged. We are optimizing our particles to allow the use of oligonucleotides as a payload that we expect to accomplish during the second year of funding.

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

We had delays in the approval of our IACUC protocol which delayed the start of our studies.

- **Changes that had a significant impact on expenditures**

The changes we had to implement had no significant impact on expenditures

- **Significant changes in use or care of human subjects**

Not applicable

- **Significant changes in use or care of vertebrate animals.**

No changes

- **Significant changes in use of biohazards and/or select agents**

Not applicable

6. PRODUCTS:

- **Publications, conference papers, and presentations**

- **Journal publications.**

Nothing to report

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

Nothing to report

- **Other publications, conference papers, and presentations**

- Poster presentation at ASN Kidney Week 2021: Efficacy and Adverse Effects of a Novel Mesoscale Nanoparticle-Guided Sirolimus Delivery Strategy in a *Pkhd1*^{PCK} Rat Model. Michal Mrug, Chintan H. Kapadia, Phillip Chumley, Gabriel Rezonzew, Janki Shah, Sean Mullen, Ronald Royce, Juling Zhou, Arthur Klausner, Daniel Heller, Edgar A. Jaimes.

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

Nothing to report

- **Technologies or techniques**

Nothing to report

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

Nothing to report

- **Other Products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- What individuals have worked on the project?

Name:	<i>Edgar A. Jaimes</i>
Project Role:	<i>PI</i>
Researcher Identifier:	
Nearest person month worked:	<i>1.0</i>
Contribution to project:	<i>Dr. Jaimes is in charge of the overall direction and supervision of this project</i>
Funding Support:	<i>Dr. Jaimes is funded by DOD and NIH.</i>

Name:	<i>Daniel Heller</i>
Project Role:	<i>Co-Investigator</i>
Researcher Identifier:	
Nearest person month worked:	<i>1.0</i>
Contribution to project:	<i>Dr. Heller is in charge of the design and supervision related to the nanoparticle formulations utilized in this project</i>
Funding Support:	

Name:	<i>Janki Shah</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier:	
Nearest person month worked:	<i>1.0</i>
Contribution to project:	<i>Mrs. Shah is in charge of the preparation and manufacture of the different formulations used in this study.</i>
Funding Support:	

Name:	<i>Michal Mrug</i>
Project Role:	<i>Co-Investigator</i>

Researcher Identifier:	
Nearest person month worked:	1.0
Contribution to project:	<i>Dr. Mrug is in charge of supervision of the experiments done at the PKD Core at the U of Alabama at Birmingham.</i>
Funding Support:	

- **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. See Other Supports attached.

- **What other organizations were involved as partners?**

- **Organization Name:** University of Alabama at Birmingham
- **Location of Organization:** Birmingham, Alabama
- **Partner's contribution to the project**
 - **Facilities** The Cystic Diseases Core at UAB is used for the execution of the animal studies in this project
 - **Collaboration** Personnel from UAB works in collaboration with the MSKCC team in the execution of the experiments included in this study

8. SPECIAL REPORTING REQUIREMENTS

Not applicable

9. APPENDICES

JAIMES, EDGAR

PREVIOUS/CURRENT/PENDING SUPPORT

PREVIOUS

Title: Discovery of tissue biomarkers of CKD progression in RCC patients

*Major Goals: To lead to tissue biomarkers which can be assessed at nephrectomy (total or partial) to stratify patients into those whose CKD will progress significantly versus those that will not

Status of Support: Completed

Name of PD/PI: Jaimes, E

Source of Support: NIDDK

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 7/1/2017-06/30/2018

*Total Award Amount (including Indirect Costs):

Grants Officer: Christine Maric-Bilkan

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2018	0.24 calendar

Title: Renal tubule specific nanotherapeutics for acute kidney injury

*Major Goals: We propose to develop a method to address the problem of the poor pharmacokinetics and resulting low efficacy of experimental therapies for acute kidney injury (AKI).

In Aim 1 of the proposal, we will characterize the route of nanoparticle uptake in the renal interstitium and tubules. In Aim 2, we will assess the pharmacologic parameters of kidney-targeted ROS inhibitors. In Aim 3, we will assess the efficacy and therapeutic mechanism of tubule-specific ROS inhibitor therapy.

Outcomes: These studies will address the unmet need for new methods to improve drug PK in the kidneys for the treatment of AKI by investigating mesoscale nanoparticle technology. We will determine the route of localization of this new drug delivery vehicle to the kidneys, its ability to modulate drug PK, and its potential to improve therapeutic index of drugs for the treatment of AKI in patients.

Status of Support: Completed

Project Number: R01 DK114321

Name of PD/PI: Heller, D, Jaimes, E

Source of Support: NIDDK

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 08/01/18-07/31/21

*Total Award Amount (including Indirect Costs):

Grants Officer: GOSSETT, DANIEL ROBERT; daniel.gossett@nih.gov

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2019	0.60 calendar
2. 2020	0.60 calendar
3. 2021	0.60 calendar

Title: Investigation of the Effects of Electronic Cigarettes on Vascular Health

*Major Goals: Abstract Electronic cigarettes (EC) have gained significant popularity in the US since their introduction on the market eight years ago. Currently, ECs are not regulated by the FDA, partly because their effects on health have not been well characterized. Aim 1: To characterize the effects of chronic e-cigarette smoking on systemic oxidative stress. The working hypothesis for this aim is that the EC use is associated with an increase in systemic oxidative stress. To attain this Aim, we will measure the validated and sensitive markers of oxidative stress: plasma and urinary levels of F2-isoprostanes, in nonsmokers,

chronic EC users, TC smokers as positive controls. Aim 2: To determine the acute effects of e-cigarette smoking on endothelial cell integrity. The working hypothesis for this aim is that the use of e- cigarettes leads to endothelial injury resulting in an increase in the number of endothelial progenitor cells (EPC). We will measure the levels of EPC and their colony-forming units in EC users and TC smokers immediately before and after smoking a cigarette or EC use using nonsmokers as controls. Aim 3: To identify the effects of chronic e-cigarette usage on endothelial function.

Status of Support: Completed

Project Number: R03 HL132570-02

Name of PD/PI: Shingarev

Source of Support: NIH/NHLBI

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 09/01/16-08/31/21

*Total Award Amount (including Indirect Costs):

Grants Officer: POSTOW, LISA; lisa.postow@nih.gov

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2019	0.60 calendar
2. 2020	0.60 calendar
3. 2021	0.60 calendar

CURRENT

*Title: Nanotechnology as a therapeutic approach in arteriovenous fistula maturation

*Major Goals: Arteriovenous fistula (AVF) maturation failure is a significant clinical problem in the hemodialysis patient population. Targeted nanomedicine is a rapidly growing area of research that is a promising approach to treat a wide spectrum of diseases, including cardiovascular disease and cancer. This hypothesis will be tested in two Specific Aims, using a combination of genetic approach (Aim 1) and nanotechnology (Aim 2). Aim 1: To determine the causal role of ETS-1 and MMP-2/9 in pathological AVF development in rodents with CKD. Aim 2: To investigate the therapeutic potency of ETS-1 and MMP-2/9 inhibition by targeted nanomedicine in enhancing AVF development in rodents with CKD. This translational project is innovative and significant, as it investigates a novel molecular pathway of AVF maturation failure and uses a novel nanotechnology for treating/preventing this clinical problem. Successful completion of these aims will identify important targets for developing innovative nanomedicine to enhance AVF maturation.

*Status of Support: Active

Project Number: R01DK129299

Name of PD/PI: Jaimes, E

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 7/1/2021 - 5/31/2025

*Total Award Amount (including Indirect Costs):

Grants Officer: GOSSETT, DANIEL ROBERT; daniel.gossett@nih.gov

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	1.97 calendar
2. 2023	1.64 calendar
3. 2024	1.64 calendar
4. 2025	1.64 calendar

*Title: Mesoscale Nanotechnology: A Novel Therapeutic Strategy in Polycystic Kidney Disease

*Major Goals: The objective of this proposal is to test this hypothesis using the newly-developed mesoscale nanoparticles encapsulating an anti sense oligonucleotide against mTOR or an oligonucleotide against miR-17.

*Status of Support: Active

Project Number: W81XWH2110188

Name of PD/PI: Jaimes, E

Source of Support: Congressionally Directed Medical Research Programs

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 4/1/2021 - 3/31/2023

*Total Award Amount (including Indirect Costs):

Contracting Officer: Stephanie Davis; stephanie.p.david12.civ@mail.mil

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	0.60 calendar
2. 2023	0.60 calendar

*Title: Drug Disposition and Nephrotoxicity

*Major Goals: Influence of Drug Disposition on Kidney Injury. . This proposal will systematically investigate the ability of 5-HT3 antagonists to inhibit cisplatin transport and exacerbate toxicity. Structural and pharmacokinetic differences between the 5-HT3 antagonists are expected to impart different likelihoods for inhibiting cisplatin transport. We propose in vitro studies with transfected cells and primary human proximal tubule cells along with animal experiments and a prospective, randomized study of cancer patients receiving cisplatin. We will assess the ability of 5-HT3 antagonists to alter cisplatin excretion, pharmacokinetics, intra-renal exposures and toxicity, likely revealing a novel mechanism for kidney injury in cancer patients

*Status of Support: Active

Project Number: R01 GM123330

Name of PD/PI: Aleksunes, L/Jaimes, E

Source of Support: National Institute of General Medical Sciences

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 9/15/2018 - 7/31/2022

*Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
4. 2022	0.12 calendar

PENDING

*Title: Intensive blood Pressure Control during Cardio Toxic Breast Cancer Treatment (PROTECT) Trial

*Major Goals: There is a critical need to develop effective strategies to mitigate the cardiotoxic effects of breast cancer therapies and improve cardiovascular (CV) health in breast cancer survivors. We propose a randomized controlled trial (RCT) of intensive systolic blood pressure (SBP) control versus usual care among 120 breast cancer patients with hypertension and scheduled to receive cardiotoxic cancer treatment. Results will provide: 1) evidence on the benefit of SBP lowering for breast cancer patients receiving cardiotoxic treatment; 2) functional and mechanistic insight into effects of SBP lowering during cardiotoxic treatment; and 3) guidance on strategies to improve CV health in cancer patients.

*Status of Support: Pending

Project Number: 1 R01 CA273923-01

Name of PD/PI: Yu, A

Source of Support: National Cancer Institute

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 9/1/2022 - 8/31/2027

*Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
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1.	2023	0.24 calendar
2.	2024	0.24 calendar
3.	2025	0.24 calendar
4.	2026	0.24 calendar
5.	2027	0.24 calendar

*Title: Targeted approaches for hematopoietic stem cell transplantation-associated kidney injury

*Major Goals: Allogeneic hematopoietic stem cell transplantation is a highly effective cancer treatment, but it is associated with serious complications, including acute kidney injury that causes non-relapse mortality in these patients. This work will investigate this disease to understand its pathophysiology and to identify potential therapeutic targets. It will also investigate a novel nanoparticle technology for the potential to selectively deliver drugs to the kidneys in this disease, and the effects and safety of kidney-targeted delivery of experimental therapeutics against the newly-identified targets in this disease.

*Status of Support: Pending

Project Number: 1 R01 DK135031-01

Name of PD/PI: Heller, D

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 9/1/2022 - 8/31/2027

*Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	1.80 calendar
2. 2024	1.80 calendar
3. 2025	1.80 calendar
4. 2026	1.80 calendar
5. 2027	1.80 calendar

*Title: Nanoparticle targeted siRNA therapy of ischemic kidney injury

*Major Goals: The proposed work in this project is very promising for the development of novel therapeutics for ischemic renal disease. Together, our labs will evaluate multiple siRNA therapeutics loaded inside kidney-targeted nanoparticles in a mouse model of ischemia reperfusion-induced acute kidney injury. Our lab is committed to conducting the animal disease model experiments and evaluating the immune effects of inhibiting renal inflammatory cytokine release. In our prior studies, we demonstrated the feasibility of targeting polymeric nanoparticles specifically to the renal proximal tubules in a mouse model of ischemic AKI and its therapeutic potential. These preliminary studies with DNA antagonist oligonucleotide and peptide cargoes increase the likelihood of success of the proposed collaborative studies in treating kidney disease.

*Status of Support: Pending

Project Number: C01 R01-PA-20-185 (CCNY - Williams)

Name of PD/PI: Jaimes, E

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 7/1/2022 - 6/30/2027

*Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	1.20 calendar
2. 2024	1.20 calendar
3. 2025	1.20 calendar
4. 2026	1.20 calendar
5. 2027	1.20 calendar

*Title: Acute kidney injury post-nephrectomy: novel preventative strategies

*Major Goals: Reductions in kidney function are common after partial removal of a kidney for cancer. Unfortunately, no effective preventive interventions are available. In this study we will test the effect of a drug that reduces the amount of substances linked to this damage. If successful, it will be implemented in clinical practice for patients undergoing this type of surgeries and perhaps in other clinical situations.

*Status of Support: Pending

Project Number: 1 R01 DK128440-01A1

Name of PD/PI: Jaimes, E

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 7/1/2022 - 6/30/2025

*Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	1.50 calendar
2. 2024	1.50 calendar
3. 2025	1.50 calendar

*Title: E-Cigarettes and chronic kidney disease progression

*Major Goals: There are over 6 million electronic cigarette users in the U.S., and this number is rapidly growing. Although there is vast knowledge about adverse impact of tobacco smoking on human health, the effects of electronic cigarettes on health and disease remain largely unknown. In this study we will determine the effects of products present in the aerosol of e-cigarettes on the severity of renal disease induced by diabetes.

*Status of Support: Pending

Project Number: 1 R01 DA055924-01

Name of PD/PI: Jaimes, E

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 4/1/2022 - 3/31/2027

*Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	2.40 calendar
2. 2024	2.40 calendar
3. 2025	2.40 calendar
4. 2026	2.40 calendar
5. 2027	2.40 calendar

*Title: Renal-targeted gene therapy to treat fibrotic chronic kidney disease

*Major Goals: We will determine the efficacy of a nanotechnology based approach for the treatment of chronic kidney disease in a model of hypertension induced renal injury. We will targets involved in renal disease progression that could potentially be applicable to the clinic.

*Status of Support: Pending

Project Number: Jaimes_CUNY Consortium June 2021

Name of PD/PI: Jaimes, E

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 4/1/2022 - 3/31/2027

*Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
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1.	2023	1.00 calendar
2.	2024	1.00 calendar
3.	2025	1.00 calendar
4.	2026	1.00 calendar
5.	2027	1.00 calendar

*Title: COVID-19 and Kidney Injury: Urinary Cell Transcriptomics of Kidney Injury in a Novel Nonhuman Primate Model of SARS-CoV-2

*Major Goals: Studies in this proposal will characterize the histopathology of kidney injury in non-human primates infected with COVID-19. This study will also characterize the role of activation of the renin angiotensin system in the pathogenesis of renal injury in non-human primates infected with COVID. The scope of this subcontract is:

- 1) Work in concert with Drs. Prieto on study conduct, problem solving, data analysis, research publications, and grant writing.

*Status of Support: Pending

Project Number: Tulane Grant

Name of PD/PI: Jaimes, E

Source of Support: Tulane University

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 4/1/2022 - 3/31/2024

*Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.24 calendar
2. 2024	0.24 calendar

OVERLAP:

None.

PREVIOUS/CURRENT/PENDING SUPPORT

PREVIOUS

*Title: Nanotechnology

*Status of Support: Completed

Project Number: GC259587

Name of PD/PI: Heller

Source of Support: Louis and Rachel Rudin Foundation

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 4/10/2020 - 4/9/2021

*Total Award Amount (including Indirect Costs):

Foundation Director: Alice H. Eaton

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2021	0.00 calendar

*Title: Development of effective therapies for all tumors driven by BRAF mutants (Project 2)

*Major Goals: The PI3K/AKT/mTOR pathway is dysregulated by mutation in many human tumors. Inhibitors of components of this pathway, such as TORC1, have had only limited success in clinic, however. The purpose of this proposal is to address outstanding problems with TORC1-targeted therapies and to develop more effective therapeutic strategies.

Specific Aim 1-Determine the sensitivity of BRAF mutant tumor models to the selective RAF dimer disrupter PLX8394 Specific Aim 2-Determine the mechanism of the adaptive response to BRAF dimer disrupters and test combination therapies based on the data. Specific Aim 3-Selective targeting of nanoparticle encapsulated drugs.

*Status of Support: Completed

Project Number: GC24205

Name of PD/PI: Rosen/ Heller

Source of Support: Center for Experimental Therapeutics

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 1/1/2019 - 3/31/2021

*Total Award Amount (including Indirect Costs):

Program Coordinator: Claudia Little, littlec@mskcc.org

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2020	1.20 calendar
2. 2021	1.20 calendar

*Title: Integration of Advanced Genomic and Bioengineering Approaches for Early Detection and Prevention of Ovarian Cancer

*Major Goals: Specific Aim 1: To determine whether genetic aberrations in fallopian tube precursors can be detected in Pap smear specimens.

Specific Aim 2: To develop an implantable carbon nanotube-based device to detect known ovarian cancer biomarkers in the vicinity of the fallopian tube.

Specific Aim 3: To investigate whether BET inhibitors prevent ovarian cancer by eradicating cancer initiating cells.

*Status of Support: Completed

Project Number: GC243299

Name of PD/PI: Heller

Source of Support: Honorable Tina Brozman Foundation, The

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 1/1/2018 - 12/31/2020

*Total Award Amount (including Indirect Costs):
Grants Management Officer: Beverly M Wolfer: bwolfer@tinaswish.org

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2019	0.80 calendar
2. 2020	0.80 calendar

*Title: In Vivo Reporter for Niemann-Pick Type C Drug Discovery

*Major Goals: We propose to develop a new technology to measure the Niemann-Pick Disease Type C phenotype in vivo in order to accelerate the pace of research and drug development for therapies.

Aim 1. Assess reporter pharmacokinetics, safety, and response in lysosomal storage disease.

Aim 2. Validate the reporter as a drug validation tool for Niemann-Pick type C disease therapies in vivo.

*Status of Support: Completed

Project Number: Ara Parseghian Medical Research Grant

Name of PD/PI: Heller

Source of Support: University of Notre Dame

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 7/1/2018 - 6/30/2019

*Total Award Amount (including Indirect Costs):

Contact: Sean Kassen; skassen@nd.edu

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2019	0.60 calendar

*Title: Renal tubule-specific nanotherapeutics for acute kidney injury

*Major Goals: We propose to develop a method to address the lack of therapies for the treatment of acute kidney injury (AKI) which accounts for approximately 2% of hospital admissions in the United States and is associated with increased morbidity and mortality. We developed a new drug delivery technology that targets therapeutic compounds to the renal tubules, which is the main tissue involved in the disease. This project will assess the mechanism of action and translational potential of this platform.

Specific Aim 1: Characterize the route of nanoparticle uptake in the renal interstitium and tubules. Specific

Aim 2: Assess the pharmacologic parameters of kidney-targeted ROS inhibitors.

Specific Aim 3: Assess the efficacy and therapeutic mechanism of tubule-specific ROS inhibitor therapy

*Status of Support: Completed

Project Number: 5 R01 DK114321-02

Name of PD/PI: Heller / Jaimes

Source of Support: NIDDK

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 8/1/2018 - 7/31/2021

*Total Award Amount (including Indirect Costs):

Contracting/Grants Officer: Carolyn Kofa; kofac@extra.niddk.nih.gov

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2019	1.00 calendar
2. 2020	1.00 calendar
3. 2021	1.00 calendar

CURRENT

*Title: Nanotechnology as a therapeutic approach in arteriovenous fistula maturation

*Major Goals: Specific Aim 1: To determine the causal role of ETS-1 and MMP-2/9 in pathological AVF development in rodents with CKD.

Specific Aim 2: To investigate the therapeutic potency of ETS-1 and MMP-2/9 inhibition by targeted nanomedicine in enhancing AVF development in rodents with CKD.

*Status of Support: Active

Project Number: R01 DK129299

Name of PD/PI: Shiu, Y-T, Jaimes, E

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 7/1/2021 - 5/31/2025

*Total Award Amount (including Indirect Costs):

Contracting Officer: Daniel Gossett; daniel.gossett@nih.gov

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	1.00 calendar
2. 2023	1.00 calendar
3. 2024	1.00 calendar
4. 2025	1.00 calendar

*Title: Mesoscale Nanotechnology: A Novel Therapeutic Strategy in Polycystic Kidney Disease

*Major Goals: The objective of this proposal is to test this hypothesis using the newly-developed mesoscale nanoparticles encapsulating an anti sense oligonucleotide against mTOR or an oligonucleotide against miR-17.

*Status of Support: Active

Project Number: W81XWH2110188

Name of PD/PI: Jaimes, E

Source of Support: Congressionally Directed Medical Research Programs

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 4/1/2021 - 3/31/2023

*Total Award Amount (including Indirect Costs):

Contracting Officer: Stephanie Davis; stephanie.p.david12.civ@mail.mil

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	0.60 calendar
2. 2023	0.60 calendar

*Title: A novel approach to enhance drug delivery for pediatric brain tumors

*Major Goals: Specific Aim 1: To assess the in vivo molecular profiles of radiation resistant perivascular niche cells in an autochthonous GEM brain tumor model.

Specific Aim 2: To assess efficacy of P-selectin-mediated targeting of combination SMO and PI3K inhibitors.

*Status of Support: Active

Project Number: AWD-GC-241932

Name of PD/PI: Heller, D

Source of Support: Emerson Collective

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 7/1/2020 - 6/30/2022

*Total Award Amount (including Indirect Costs):

Research and Venture Grants Manager: Katherine Szarama,

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
2. 2022	0.60 calendar

*Title: Tumor-Selective Delivery Approaches for Medulloblastoma

*Major Goals: This work proposes a new therapeutic strategy to deliver conventional or molecularly

targeted therapies across the blood-brain barrier specifically to primary brain tumors.

Specific Aim 1: To evaluate the P-selectin-mediated targeting, role of radiation, and mechanism of extravasation across the blood-brain barrier in medulloblastoma.

Specific Aim 2: To assess the efficacy and toxicity of P-selectin-targeted chemotherapy/SHH pathway inhibition in Sonic hedgehog-driven medulloblastoma.

Specific Aim 3: To assess the effect of focal radiation of primary MB tumor on P-selectin targeted and nanoparticle drug delivery to brain tumor leptomeningeal metastases in vivo.

*Status of Support: Active

Project Number: 5 R01 NS116353-03

Name of PD/PI: Heller, D

Source of Support: National Institute of Neurological Disorders and Stroke

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 3/15/2020 - 12/31/2024

*Total Award Amount (including Indirect Costs):

Contracting/Grants Officer: Aaron Kinchen: ak284o@nih.gov

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
3. 2022	1.20 calendar
4. 2023	1.20 calendar
5. 2024	1.20 calendar

*Title: Tumor-specific PI3K inhibition in breast cancer

*Major Goals: Specific Aim 1: Assess P-selectin-mediated targeting to the breast tumor microenvironment

Specific Aim 2: Enhance nanoparticle localization via radiation-induced endothelial activation

Specific Aim 3: Assess efficacy of P-selectin-mediated targeting of PI3K inhibitors/drug combinations

The goal of this project is to investigate a new strategy for the treatment of breast

cancers—targeting precision medicines specifically to cancer tissues to a novel molecular target on tumor blood vessels.

*Status of Support: Active

Project Number: RSG-18-014-01-CDD

Name of PD/PI: Heller, D

Source of Support: American Cancer Society

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 7/1/2018 - 6/30/2022

*Total Award Amount (including Indirect Costs):

Contracting/Grants Officer: Lynne Elmore, PhD; lynne.elmore@cancer.org

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
4. 2022	1.20 calendar

*Title: CAREER: A Quantitative Nanosensor to Measure Redox Potential in Living Systems

*Major Goals: Specific Aim 1: Engineer the optoelectronic doping of carbon nanotubes.

Specific Aim 2: Assess targeting and response in cellular environments.

Specific Aim 3: Measure redox landscapes in disease states.

To develop a nanoscale sensor for measure redox potential in live cancer cells and tissues.

*Status of Support: Active

Project Number: 1752506

Name of PD/PI: Heller, D

Source of Support: National Science Foundation

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 2/1/2018 - 1/31/2023

*Total Award Amount (including Indirect Costs):

Contracting/Grants Officer: W. Powell; wpowell@nsf.gov

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
5. 2023	0.20 calendar

*Title: P-selectin-Mediated Targeting of PI3K Nanomedicines to the Tumor Microenvironment

*Major Goals: Aim 1: Assess P-selectin-mediated targeting to the tumor microenvironment.

Aim 2: Enhance nanoparticle localization via radiation-induced endothelial activation

Aim 3: Assess efficacy of P-selectin-mediated targeting of PI3K inhibitors. This work proposes a new therapeutic strategy to address solid tumors in general and head and neck squamous cell carcinoma (HNSCC) in particular. HNSCC is the 6th most common cancer worldwide. The researchers propose to investigate the targeting of personalized therapy directly to the tumor environment and to gain an understanding of how this targeting changes the efficacy and toxicities of this therapy in HNSCC.

*Status of Support: Active

Project Number: 5R01CA215719-04

Name of PD/PI: Heller, D

Source of Support: National Cancer Institute

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 12/15/2017 - 11/30/2022

*Total Award Amount (including Indirect Costs):

Contracting/Grants Officer: Rogers Gross; rogers.gross@nih.gov

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
5. 2022	2.40 calendar

*Title: Targeted Nanoformulation and Delivery Strategy to Improve the Utility of PROTACS

*Major Goals: Our lab has developed a nascent nanotherapeutic drug delivery platform to encapsulate and deliver nearly any PROTAC to modulate its pharmacologic properties and enrich its concentration in tumor tissues. This project will investigate the potential for nanoformulation-based drug delivery systems to modulate the pharmacokinetic and absorption, distribution, metabolism and excretion properties of PROTACS, without sacrificing binding affinity, in order to improve therapeutic index.

*Status of Support: Current

Project Number: ETC Independent Investigator Application

Name of PD/PI: Heller, D

Source of Support: Center for Experimental Therapeutics

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 4/1/2022 - 3/31/2023

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.60 calendar

*Title: Monitoring Intrauterine Biomarkers to Detect Pre-Invasive Disease

*Major Goals: Aim 1. Design a high-affinity p53 auto-antibody nanosensor. Aim 2. Assess sensor response in uteri of hysterectomy patients. Aim 3. Conduct first-in-woman clinical trial

*Status of Support: Current

Project Number:

Name of PD/PI: Heller, D

Source of Support: Honorable Tina Brozman Foundation, The

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 1/2022 – 12/2023

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
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1.	2021	0.60 calendar
1,	2022	060 calendar

PENDING

*Title: Implantable Nanosensor for Early-Stage Ovarian Cancer Detection

*Major Goals: This project aims to develop a technology to detect biomarkers quantitatively in humans to enable diagnoses at early stages, when ovarian cancer is most curable.

*Status of Support: Pending

Project Number: OC210292

Name of PD/PI: Heller, D

Source of Support: Congressionally Directed Medical Research Programs

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 9/30/2022 - 9/29/2025

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.60 calendar
2. 2024	0.60 calendar
3. 2025	0.60 calendar

*Title: Hijacking epigenetic regulation of neuronal maturation by EZH2 inhibition for treatment of medulloblastoma

*Major Goals: Dr. Heller is the Head of the Cancer Nanomedicine Laboratory and Assistant Member in the Molecular Pharmacology Program at Memorial Sloan Kettering Cancer Center. Dr. Heller will be responsible for the overall administration and direction of the project at the Memorial Sloan Kettering Site. Dr. Heller will supervise the researchers in his lab in the assembly, characterization, and optimization of all drug-loaded nanoparticles in Aim 3 of the project. Dr. Heller's laboratory will also conduct pharmacokinetics and biodistribution studies of each drug-loaded nanoparticle formulation in vivo, before transferring material to the Raju lab for assessments in medulloblastoma models. Dr. Heller will communicate with all parties to plan studies using the nanoparticles and to assess experimental results.

*Status of Support: Pending

Project Number: C01_PA-20-185_NYU

Name of PD/PI: Heller, D

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 9/1/2022 - 8/31/2027

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.60 calendar
2. 2024	0.60 calendar
3. 2025	0.60 calendar
4. 2026	0.60 calendar
5. 2027	0.60 calendar

*Title: Targeting Proliferative and Drug Resistance Pathways in Triple Negative Breast Cancer Stem Cells

*Major Goals: N/A

*Status of Support: Pending

Project Number: C01 MSSM

Name of PD/PI: Heller, D

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 9/1/2022 - 8/31/2027

*Total Award Amount (including Indirect Costs): Contracting Officer:

N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	1.20 calendar
2. 2024	1.20 calendar
3. 2025	1.20 calendar
4. 2026	1.20 calendar
5. 2027	1.20 calendar

*Title: Targeted approaches for hematopoietic stem cell transplantation-associated kidney injury

*Major Goals: Allogeneic hematopoietic stem cell transplantation is a highly effective cancer treatment, but it is associated with serious complications, including acute kidney injury that causes non-relapse mortality in these patients. This work will investigate this disease to understand its pathophysiology and to identify potential therapeutic targets. It will also investigate a novel nanoparticle technology for the potential to selectively deliver drugs to the kidneys in this disease, and the effects and safety of kidney-targeted delivery of experimental therapeutics against the newly-identified targets in this disease.

*Status of Support: Pending

Project Number: 1 R01 DK135031-01

Name of PD/PI: Heller, D

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 9/1/2022 - 8/31/2027

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	2.40 calendar
2. 2024	2.40 calendar
3. 2025	2.40 calendar
4. 2026	2.40 calendar
5. 2027	2.40 calendar

*Title: Clinical Development of Implantable Nanosensor for Early-Stage Ovarian Cancer Detection

*Major Goals: This project aims to develop a technology to detect biomarkers at early stages of disease, when they are most curable. This clinical trial will provide technological improvements and critical data to enable further development of this implantable sensor technology for the detection of cancer and other diseases.

*Status of Support: Pending

Project Number: 1 R01 EB033174-01A1

Name of PD/PI: Heller, D

Source of Support: National Institute of Biomedical Imaging and Bioengineering

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 7/1/2022 - 6/30/2026

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	1.20 calendar
2. 2024	1.20 calendar
3. 2025	1.20 calendar
4. 2026	1.20 calendar

*Title: Derivation of pancreatic islet-like organoids from human gastric stem cells

*Major Goals: The Heller Lab has extensive experience in the development of nanomedicines and their preclinical applications in animal models of cancer. Dr. Heller will communicate with Dr. Zhou and the members of his laboratory to ensure the completion of all aims of the project. Dr. Heller will supervise all work in his lab at Memorial Sloan Kettering Cancer Center. Dr. Heller will advise on and provide nanoparticle drug carriers for the delivery of RNA. The Heller Lab will also facilitate cellular and in vivo studies in coordination with Dr. Zhou's lab.

*Status of Support: Pending

Project Number: C01 WCMC NIH R01

Name of PD/PI: Heller, D

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 7/1/2022 - 6/30/2027

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.60 calendar
2. 2024	0.60 calendar
3. 2025	0.60 calendar
4. 2026	0.60 calendar
5. 2027	0.60 calendar

*Title: Nanosensor Array Platform to Capture Whole Disease Fingerprints

*Major Goals: Serum biomarker measurements have been widely used as diagnostic indicators, but many markers are not sufficiently sensitive or specific assessments of disease state. This work builds a platform technology to detect whole disease fingerprints from patient biofluids to improve diagnoses and biomarker discovery processes. We will initially focus this effort on the outstanding need for improved detection of high-grade serous ovarian cancer.

*Status of Support: Pending

Project Number: 1 R01 EB033651-01

Name of PD/PI: Heller, D

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 7/1/2022 - 6/30/2027

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	1.20 calendar
2. 2024	1.20 calendar
3. 2025	1.20 calendar
4. 2026	1.20 calendar
5. 2027	1.20 calendar

*Title: Novel PTK6 PROTAC degraders to target triple negative breast cancer

*Major Goals: Dr. Daniel Heller's Laboratory at Memorial Sloan Kettering Cancer Center will synthesize novel nanoparticles for the targeted delivery of PTK6 inhibitors. The Heller Lab will conduct a full characterization of the nanoparticles, including drug loading, size, and zeta potential measurements. The lab will conduct in vitro and in vivo assessments, including pharmacokinetics/biodistribution via fluorescence imaging and mass spectrometry, and pharmacodynamics experiments and target inhibition via biochemical assays. In vivo efficacy and safety studies on both the nanoparticle and unencapsulated drug will be conducted using xenograft models in the Heller Lab. Nanoparticles will also be provided to the Irie lab for additional in vivo efficacy experiments. Dr. Heller will communicate regularly with Dr. Irie, including biweekly Zoom meetings, to ensure coordination of procedures and experiments.

*Status of Support: Pending
Project Number: C01 R01 MSSM
Name of PD/PI: Heller, D
Source of Support: National Institutes of Health
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 7/1/2022 - 6/30/2027
*Total Award Amount (including Indirect Costs):
Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.60 calendar
2. 2024	0.60 calendar
3. 2025	0.60 calendar
4. 2026	0.60 calendar
5. 2027	0.60 calendar

*Title: A clinically translatable nanotherapeutic approach to enhance BBB drug delivery in DIPG
*Major Goals: n/a
*Status of Support: Pending
Project Number: C01 CHAD-MSSM
Name of PD/PI: Heller, D
Source of Support: Mount Sinai School of Medicine
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 7/1/2022 - 6/30/2025
*Total Award Amount (including Indirect Costs):
Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.60 calendar
2. 2024	0.60 calendar
3. 2025	0.60 calendar

*Title: Reinforcement mechanisms of opioid-context associations in females
*Major Goals: N/A
*Status of Support: Pending
Project Number: C01-WCMC-Heller-6/5/2021
Name of PD/PI: Heller, D
Source of Support: National Institutes of Health
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 4/1/2022 - 3/31/2024
*Total Award Amount (including Indirect Costs):
Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.60 calendar
2. 2024	0.60 calendar

*Title: Novel PTK6 PROTAC degraders for the treatment of TNBC
*Major Goals: Subtask 1: Establish biodistribution and PK/PD relationships for P-selectin nanoparticle encapsulated MS105 (NP-MS105) and compare to “free”MS105. 5 female NSG mice/treatment group for three time points.
Subtask 2: Test anti-tumor efficacy of NP-MS105 against (MDA-MB231) TNBC xenografts (primary and metastatic models). n=12/treatment group for triplicate experiments in female NSG mice. Metastasis to be

followed by serial IVIS imaging

Subtask 3: Encapsulate and evaluate new PTK6 degraders synthesized and prioritized based on studies in Aims 1 and 2. Two new “nano-degraders” to be tested for anti-tumor efficacy against MDA-MB231 TNBC xenografts. 12 NSG mice/treatment group will be used

*Status of Support: Pending

Project Number: C01 DoD MSSM

Name of PD/PI: Heller, D

Source of Support: Congressionally Directed Medical Research Programs

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 4/1/2022 - 3/31/2025

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.60 calendar
2. 2024	0.60 calendar
3. 2025	0.60 calendar

*Title: Inducing neural maturation in medulloblastoma by targeting EZH2

*Major Goals: Dr. Heller will supervise the researchers in his lab in the assembly, characterization, and optimization of all drug-loaded nanoparticles in Aim 3 of the project.

*Status of Support: Pending

Project Number: C01 1 R56NS122987 - 01

Name of PD/PI: Heller, D

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 4/1/2022 - 3/31/2027

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.60 calendar
2. 2024	0.60 calendar
3. 2025	0.60 calendar
4. 2026	0.60 calendar
5. 2027	0.60 calendar

*Title: Machine-Learning Assisted Array Screening Platform for High-Risk HPV Infection

*Major Goals: High-risk human papillomavirus (HPV) infections are associated with 45,000 new cancer cases every year in the US. HPV includes a family of DNA viruses that infect basal epithelial cells and are divided into low- and high-risk types. High-risk, oncogenic HPV types are highly associated with cancer of the cervix, oropharynx, anus, vagina, vulva, and penis. Over 95% of cervical cancer cases are associated with high risk HPV, while over 90% of anal cancer, 70% of vaginal and vulvar cancer, 60% of oropharyngeal cancer, and 60% of penile cancer cases are associated with high-risk HPV. Over 80 million Americans were estimated to be infected with an HPV type in 2018, with over 14 million new infections that year.

*Status of Support: Pending

Project Number: CCNY Pilot Project Grant

Name of PD/PI: Heller, D

Source of Support: City College of New York

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 3/1/2022 - 2/28/2023

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.60 calendar

*Title: Early Warning System for Cytokine Storm

*Major Goals: Cytokine release syndrome (CRS) is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction. CRS is common in patients with infectious diseases, including COVID-19 (approx. 9% of hospitalized patients), and in immunotherapies, wherein elevated levels of cytokines lead to adverse clinical outcomes.

*Status of Support: Pending

Project Number: NYS Biodefense 21879435

Name of PD/PI: Heller, D

Source of Support: New York State Biodefense Commercialization Fund

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 2/1/2022 - 1/31/2023

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	0.60 calendar
2. 2023	0.60 calendar

*Title: Chemical Gating of a Tube-in-Tube Semiconductor

*Major Goals: Dr. Heller is the Head of the Cancer Nanomedicine Laboratory and Associate Member in the Molecular Pharmacology Program at Memorial Sloan Kettering Cancer Center. Dr. Heller will be responsible for the overall administration and direction of the project at the Memorial Sloan Kettering Site. Dr. Heller's Lab will work with Dr. Ramanathan from the Department of Laboratory Medicine to identify, collect, handle, and store patient biofluids from ovarian cancer and COVID-19 patients, as well as healthy individuals. Heller's lab will conduct biomarker measurements using biochemical assays. Heller will also provide clinical/biological direction to the project and will seek additional advice from other clinicians and researchers at MSK if needed.

*Status of Support: Pending

Project Number: C01-UMD-3-5-2021

Name of PD/PI: Heller, D

Source of Support: National Institutes of Health

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 1/3/2022 - 1/2/2027

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.60 calendar
2. 2024	0.60 calendar
3. 2025	0.60 calendar
4. 2026	0.60 calendar
5. 2027	0.60 calendar

*Title: P-selectin-targeted PTK6 degradation to suppress metastases of triple negative breast cancer

*Major Goals: PTK6 is a critical molecular driver of growth and metastases of triple negative breast cancer (TNBC), a high-risk breast cancer subtype associated with significant mortality, and which is disproportionately diagnosed in younger women and African Americans. Previously, we showed that inhibiting PTK6 in TNBC tumors blocks their growth and metastases. We have developed a novel strategy involving both a new type of drug against PTK6 and a method to target it to TNBC tumors. The immediate goal of our study is to evaluate the delivery efficiency and efficacy of this therapeutic against TNBC

primary and metastatic cancers in mouse models. The successful completion of our proposed studies will lead to clinical translation of a novel targeted therapy for TNBC that will improve patient outcomes. In addition, this therapeutic modality can be applied for the treatment of many other cancer types.

*Status of Support: Pending

Project Number: ACS Pilot Grant

Name of PD/PI: Heller, D

Source of Support: American Cancer Society

Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 1/1/2022 - 12/31/2022

*Total Award Amount (including Indirect Costs):

Contracting Officer: N/A

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	0.60 calendar

POSITIONS AND SCIENTIFIC APPOINTMENTS

<i>Graduate Field Faculty</i> , Meinig School of Biomedical Engineering, Cornell University	(2/2021-present)
<i>Bristol-Myers Squibb/James D. Robinson III Junior Faculty Chair</i> , Memorial Sloan-Kettering Cancer Center, New York, New York	(9/2018-present)
<i>Associate Member</i> , Molecular Pharmacology Program, Memorial Sloan Kettering Cancer Center, New York, New York	(7/2018-present)
<i>Associate Professor</i> , Physiology, Biophysics & Systems Biology Graduate Program, Weill Cornell Medicine, Cornell University, New York, New York	(7/2018-present)
<i>Associate Professor</i> , Department of Pharmacology, Weill Cornell Medicine, Cornell University, New York, New York	(7/2018-present)
<i>Assistant Professor</i> , Physiology, Biophysics, & Systems Biology Graduate Program, Weill Cornell Medicine, Cornell University, New York, New York	(8/2012-7/2018)
<i>Assistant Professor</i> , Department of Pharmacology, Weill Cornell Medicine, Cornell University, New York, New York	(8/2012-7/2018)
<i>Faculty Member</i> , Center for Molecular Imaging & Nanotechnology, Memorial Sloan Kettering Cancer Center, New York, New York	(6/2012-present)
<i>Assistant Member</i> , Molecular Pharmacology Program, Memorial Sloan Kettering Cancer Center, New York, New York	(6/2012-7/2018)
<i>Damon Runyon Fellow</i> , Koch Institute for Integrative Cancer Research, Robert Langer Group, Massachusetts Institute of Technology, Boston, Massachusetts	(7/2010-5/2012)
<i>Postdoctoral Research Associate</i> , Koch Institute for Integrative Cancer Research, Robert Langer Group, Massachusetts Institute of Technology, Boston, Massachusetts	(2/2010-6/2010)
<i>Researcher</i> , Visigen Biotechnologies, Houston, Texas	(9/2002-6/2003)
<i>Visiting Scientist</i> , Rice Quantum Institute, Robert Curl Group, Rice University, Houston, Texas	(5/2002-6/2003)

Visiting Scientist, Department of Chemistry, T. Randall Lee Group,
University of Houston, Houston, Texas

(4/2002-6/2003)

Science Teacher, 7th and 8th grades, The Kinkaid School, Houston, Texas

(8/2000-5/2002)

RESOURCES AND OTHER SUPPORT (NOT LISTED ABOVE)

OVERLAP:

NO OVERLAP

**For New and Renewal Applications – DO NOT SUBMIT UNLESS REQUESTED
PHS 398 OTHER SUPPORT**

*Name of Individual: **Mrug, M.**
Commons ID: MMRUG01

Other Support – Project/Proposal

ACTIVE

*Title: **Intra-renal T-cell Heterogeneity in ADPKD Patients**

Major Goals: This project is focused on effects of microbiota on Th17 activity and renal cystogenesis.

*Status of Support: Active

Project Number: 1I01BX004232-01A2

Name of PD/PI: Mrug, M.

*Source of Support: Veteran's Administration

*Primary Place of Performance: University of Alabama at Birmingham

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/2019 – 03/2023

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months
4. 2022	1.8 calendar
5. 2023	1.8 calendar

*Title: **Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) IV: Prognosis for End- Stage Renal Disease and Biomarker Validation**

Major Goals: This is a prospective multi-center cohort study to characterize ADPKD progression.

*Status of Support: Active

Project Number: R01 DK113111

Name of PD/PI: Yu, A.

*Source of Support: NIH/NIDDK

*Primary Place of Performance: University of Alabama at Birmingham

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/2017 – 03/2023

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Name of Individual: Mrug, Michal
Commons ID: MRUG01

Year (YYYY)	Person Months
5. 2022	0.6 calendar
6. 2022	0.6 calendar

***Title: Mononuclear Phagocytes in the Pathogenesis of Acute Kidney Injury**

Major Goals: The major goal is to determine the origin and function of renal mononuclear phagocytes in the kidney and the roles that they play in the initial injury and the repair processes after AKI.

*Status of Support: Active

Project Number: R01 DK118932

Name of PD/PI: George, J.

*Source of Support: NIH/NIDDK

*Primary Place of Performance: University of Alabama at Birmingham

Project/Proposal Start and End Date: (MM/YYYY) (if available): 03/2019 – 12/2023

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months
3. 2022	0.6 calendar
4. 2023	0.6 calendar

***Title: Injury Response Mediated Pathogenesis in Renal Ciliopathies**

Major Goals: The main objective is to test the hypothesis that cilia dysfunction results in an aberrant response to renal injury, causing altered signaling between the tubule epithelium and macrophages, increased cell proliferation, cyst expansion, and fibrosis.

*Status of Support: Active

Project Number: R01 DK115752

Name of PD/PI: Yoder, B.

*Source of Support: NIH/NIDDK

*Primary Place of Performance: University of Alabama at Birmingham

Project/Proposal Start and End Date: (MM/YYYY) (if available): 01/2018 – 12/2022

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months
4. 2022	0.6 calendar

Name of Individual: Mrug, Michal
Commons ID: MRUG01

***Title: Multicenter, Randomized, Double-Blind, Placebo-Controlled Two Stage Study to Characterize the Efficacy, Safety, Tolerability and Pharmacokinetics of GZ/SAR402671 in Patients at Risk of Rapidly Progressive Autosomal Dominant Polycystic Kidney Disease (ADPKD)**

Major Goals: The main objective is to test the efficacy, safety, tolerability and pharmacokinetics of GZ/SAR402671 in Patients at Risk of Rapidly Progressive ADPKD.

*Status of Support: Active

Project Number: EFC15392

Name of PD/PI: Mrug, M.

*Source of Support: Sanofi US Services Inc.

*Primary Place of Performance: University of Alabama at Birmingham

Project/Proposal Start and End Date: (MM/YYYY) (if available): 02/2019 – 02/2024

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months
3. 2022	0.12 calendar
4. 2023	0.12 calendar
5. 2024	0.12 calendar

***Title: Childhood Cystic Kidney Disease Core Center**

Major Goals: The main objective is to develop and provide services that will help to advance understanding of pathogenesis, diagnostic specificity, and therapeutic approaches in patients with childhood cystic diseases.

*Status of Support: Active

Project Number: U54 DK126087

Name of PD/PI: Yoder, B; Mrug: PI-Core D

*Source of Support: NIH/NIDDK

*Primary Place of Performance: University of Alabama at Birmingham

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/2020 – 06/2025

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months
2. 2022	1.2 calendar
3. 2023	1.2 calendar

Name of Individual: Mrug, Michal
Commons ID: MRUG01

Year (YYYY)	Person Months
4. 2024	1.2 calendar
5. 2025	1.2 calendar

***Title: An Open-label Study of Lixivaptan in Subjects with Autosomal Dominant Polycystic Kidney Disease Who Previously Experienced Abnormal Liver Chemistry Test Results While Receiving Tolvaptan**

Major Goals: The proposed study will assess the sa

*Status of Support: Active

Project Number: PA-ADPKD-303

Name of PD/PI: Mrug, M.

*Source of Support: Palladio Biosciences, Inc.

*Primary Place of Performance: University of Alabama at Birmingham

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/2021 – 03/2025

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months
2. 2022	0.12 calendar
3. 2023	0.12 calendar
4. 2024	0.12 calendar
5. 2025	0.12 calendar

***Title: Phase 3 Study of the Efficacy and Safety of Lixivaptan in Participants with Autosomal Dominant Polycystic Kidney: The ACTION Study**

Major Goals: This Phase 3 trial will assess the efficacy and safety of lixivaptan in a broad population of adult participants with ADPKD.

*Status of Support: Active

Project Number: PA-ADPKD-301

Name of PD/PI: Mrug, M.

*Source of Support: Palladio Biosciences, Inc.

*Primary Place of Performance: University of Alabama at Birmingham

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/2022 – 03/2025

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Name of Individual: Mrug, Michal
Commons ID: MRUG01

Year (YYYY)	Person Months
3. 2023	0.12 calendar
4. 2024	0.12 calendar
5. 2025	0.12 calendar

***Title: Analytical Validation: Evaluation of Precision for the Autosomal Dominant Polycystic Kidney Disease (ADPKD) Progression Management System [APM System]; APM System Precision Study**

Major Goals: The proposed study will determine the precision of the APM System's automated quantitative TKV measurement by assessing the measurement precision under the same set of conditions over a short period of time (repeatability), and the measurement precision under a different set of conditions (reproducibility).

*Status of Support: Active

Project Number: Otsuka Study# 491-201-00001

Name of PD/PI: Mrug, M.

*Source of Support: Otsuka America, Inc.

*Primary Place of Performance: University of Alabama at Birmingham

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/2021 – 03/2022

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months
2. 2022	0.12 calendar

***Title: Mesoscale Nanotechnology: A Novel Therapeutic Strategy for Polycystic Kidney Disease**

Major Goals: The proposed study will test whether NP encapsulated with PKD drugs such as mTOR inhibitor would slow cystogenesis in Pkd mice.

*Status of Support: Active

Project Number: DoD PR202312

Name of PD/PI: Mrug/Jaimes

*Source of Support: U.S. Dept. of Defense

*Primary Place of Performance: University of Alabama at Birmingham

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/2021 – 03/2023

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Name of Individual: Mrug, Michal
Commons ID: MRUG01

Year (YYYY)	Person Months
2. 2022	0.6 calendar
3. 2023	0.6 calendar

*Title: **PKD1 and PKD2 Functional Variants Characterization Center (PVCC)**

Major Goals: The proposed PKD1 and PKD2 Functional Variants Characterization Center (PVCC) addresses the overarching challenge, the lack of safe, highly efficient therapeutics for ADPKD, and only partially validated supportive care/lifestyle recommendations.

*Status of Support: Active

Project Number: UAB SOM AMC21 Pilot Grant

Name of PD/PI: Mrug

*Source of Support: U.S. Dept. of Defense

*Primary Place of Performance: University of Alabama at Birmingham

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/2021 – 03/2023

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months
2. 2022	0.01 calendar
3. 2023	0.01 calendar

PENDING

*Title: **Cell-specific mitochondrial state & transcriptional divergence differentiating slow from rapidly progressive ADPKD**

Major Goals: The proposed research is relevant to public health because it focuses on identifying cell-specific mitochondrial differences between and across cell types during autosomal dominant polycystic kidney disease (ADPKD) progression.

*Status of Support: Pending

Project Number: R01 DK134310

Name of PD/PI: Lasseigne, B.

*Source of Support: NIH/NIDDK

*Primary Place of Performance: University of Alabama at Birmingham

Project/Proposal Start and End Date: (MM/YYYY) (if available): 10/2021 – 09/2023

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Name of Individual: Mrug, Michal
Commons ID: MRUG01

Year (YYYY)	Person Months
1. 2022	2.4 calendar
2. 2023	2.4 calendar

***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, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

***Signature:**

Date: April 29, 2022