AWARD NUMBER: W81XWH-21-1-0798

TITLE: Nanovesicle-Mediated Targeting of YAP in Cholangiocarcinoma to Enhance Chemotherapy Sensitivity

PRINCIPAL INVESTIGATOR: Rory Smoot, M.D.

CONTRACTING ORGANIZATION: Mayo Clinic

REPORT DATE: SEPTEMBER 2023

TYPE OF REPORT: Annual

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

Command

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
SEPTEMBER 2023	Annual	15AUG2022 - 14AUG2023

4. TITLE AND SUBTITLE

Nanovesicle-Mediated Targeting of YAP in Cholangiocarcinoma to Enhance Chemotherapy Sensitivity

5a. CONTRACT NUMBER
W81XWH-21-1-0798

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Rory Smoot, M.D.

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Mayo Clinic
200 First Street SW
Rochester, MN 55905-0002

8. PERFORMING ORGANIZATION REPORT NUMBER

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

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

10. SPONSOR/MONITOR'S ACRONYM(S)
USAMRAA

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

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Background

Cholangiocarcinoma, a primary liver cancer, is a highly lethal cancer with limited treatment options. While surgery offers the only chance for cure, the majority of patients present with disseminated disease and standard of care therapies offer approximately three months of additional survival. Insights into the molecular drivers of this disease suggest the transcriptional co-activator YAP (and its homologue TAZ) are active in cholangiocarcinoma and can drive resistance to standard chemotherapy. Direct targeting of these proteins has not been possible *in vivo* utilizing standard approaches. Small-interfering RNA based strategies offer promise but are limited by stability and delivery issues. Encapsulating small-interfering RNA in nanovesicles is a strategy that has been suggested to overcome the stability and delivery issues. Nanovesicle encapsulated small interfering RNA is a novel technology that has not previously been evaluated as a targeting/therapeutic method for YAP/TAZ. This proposal seeks to evaluate this novel technology in multiple preclinical models of cholangiocarcinoma, which falls under the FY20 PRCRP Topic Area of liver cancer.

Objective/Hypothesis

The overall research objective is to evaluate the therapeutic efficacy of nanovesicle based small-interfering RNA targeting YAP/TAZ as a single agent and in combination with a standard of care chemotherapy regimen: gemcitabine and cisplatin.

Specific Aims

The specific aims of this proposal are: 1) define the delivery efficiency and on-target effects of nanovesicle based small-interfering RNA targeting YAP/TAZ in cholangiocarcinoma cell lines, organoids, and *in vivo* models; 2) define the single-agent therapeutic effects of nanovesicle based small-interfering RNA targeting YAP/TAZ in cholangiocarcinoma cell lines, organoids, and *in vivo* models; and 3) define the ability of nanovesicle based small-interfering RNA targeting YAP/TAZ in cholangiocarcinoma cell lines, organoids, and *in vivo* models to sensitize these preclinical models to gemcitabine and cisplatin combinatorial therapy.

Study Design

This proposal will utilize multiple, validated, pre-clinical models of cholangiocarcinoma unique to our research group. This includes patient derived organoids, patient derived xenografts, and a syngeneic immunocompetent murine cholangiocarcinoma model. We will utilize six unique patient derived organoid models, and a minimum of three unique patient derived xenograft models. Milk-derived nanovesicles will be produced, loaded with validated small-interfering RNA, and then decorated with an RNA aptamer against the cholangiocarcinoma cell-surface molecule EPCAM. Fluorescent-based imaging will be utilized to define delivery efficiency. Immunoblot and RT-PCR will be utilized to define on-target effects. Therapeutic efficacy will be determined by cell death assay and caspase 3/7 assay *in vitro*. *In vivo* efficacy will be determined by tumor size, TUNEL staining, and plasma organ function markers.

Innovation

The innovation of this proposal is both conceptual and technical. Conceptually, targeting YAP and/or TAZ utilizing RNA based strategies has not been attempted before *in vivo*. Technically, utilizing a milk-derived nanovesicle decorated with a targeting aptamer is a novel approach that is untested in this disease model, with this target.

Military Relevance

One predisposing factor for development of cholangiocarcinoma is infection with hepatitis C. The veterans administration beneficiary population has an elevated incidence of hepatitis C as compared to the general population and as such is at higher risk for developing this devastating cancer. Furthermore, no highly effective therapies for this cancer have been discovered. Based on these factors the FY20 PRCRP Military Health Focus Area to be studied is mission readiness through addressing the lack of treatments available for this devastating cancer affecting service members, VA beneficiaries, family, and the general public.

15. SUBJECT TERMS

Cholangiocarcinoma, nanovesicle, siRNA, YAP, patient-derived xenograft

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	36	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. INTRODUCTION:

The goal of this project is to assess the ability to therapeutically target YAP and TAZ mediated cell-survival signaling in cholangiocarcinoma. We will utilize milk-derived nanovesicles loaded with siRNA and linked to a targeting aptamer for EPCAM. The purpose is to see if the gene targets can be successfully downregulated through this approach, whether cells and/or tumor models are less viable when treated with the nanovesicles, and whether this nanovesicle treatment also improves the response to standard chemotherapy treatments. The effects will be evaluated in cell lines models and in vivo mouse models.

2. KEYWORDS:

15. SUBJECT TERMS

Cholangiocarcinoma, nanovesicle, siRNA, YAP, patient-derived xenograft

3. ACCOMPLISHMENTS:

What are the major goals of the project?

- Specific Aim 1: Assess delivery and on-target effects of aptamer-targeted MDNV-siRNA
  - Major Task 1: Assess delivery and target engagement aptamer-targeted MDNV in CCA models
  - Major Task 2: Assess delivery and target effects of aptamer-targeted MDNV in vivo
- Specific Aim 2: Assess proliferation/cell death effects of aptamer-targeted MDNV-siRNA
  - Major Task 3: Define effects in vitro
  - Major Task 4: Define effects in vivo
- Specific Aim 3: Evaluate therapeutic efficacy of combining aptamer-targeted MDNV-siRNA with chemotherapy
  - Major Task 5: Test aptamer-targeted MDNV-siRNA with chemotherapy in vitro
  - Major Task 6: Test aptamer-targeted MDNV-siRNA with chemotherapy in vivo

What was accomplished under these goals?

Please see attached SOW with integrated data/outcomes. Major Tasks 1 and 2 have been completed. Substantial progress has been made with significant results on Major tasks 3-6 including in vivo studies A manuscript is being drafted as we work to complete all aspects of the SOW

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

Nothing to report

How were the results disseminated to communities of interest?

Poster presentations occurred at the 2023 Annual Cholangiocarcinoma Foundation Meeting and the 2023 Annual AACR meeting.

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

We will continue to assess the efficiency of nanovesicle delivery in our in vivo models and the on-target effects of nanovesicle delivery. In accordance with our statement of work and our current progress we anticipate completing these studies during the scheduled time period.

4. IMPACT:

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

We have now demonstrated that aptamer-targeted milk-derived nanovesicles are an effective delivery platform for siRNA-based approaches in CCA cell line models and we have demonstrated initial efficacy in our in vivo models

What was the impact on other disciplines?

Based on the success of this approach we are utilizing these approaches outside of the DOD IDEA project to attempt to target immunomodulatory molecules in CCA tumor models and inducers of ferroptosis.

What was the impact on technology transfer?

A provisional patent has been filed.

Docket #: 07039-2160P01
Type: Provisional
Entity: Small
Priority App #:
Application #: 63/406,527
Patent #:
Publication #:
US Bar: 00/00/00
Expiration: 9/14/2023
Assignee: , Mayo Foundation for Medical Education and Research (as Assignee)

Country: US
Status: Filed
PCT Filed: 00/00/00
Priority Date: 00/00/00
Filed: 9/14/2022
Issued: 00/00/00
Published: 00/00/00
PCT Bar: 00/00/00
Abandoned: 00/00/00

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Nothing to report

Changes in approach and research for changes

Nothing to report

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

Minor delays in obtaining aptamer due to supply chain issues. This did not impact our ability to complete the studies as previously scheduled and the supply chain issue has been resolved. No new issues anticipated.

Changes that had a significant impact on expenditures

Nothing to report

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

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:

- **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.

2023 Cholangiocarcinoma Foundation Meeting -Poster
2023 AACR Meeting - Poster

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

Nothing to report

- **Technologies or techniques**

Nothing to report

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

Docket #: 07039-2160P01
Type: Provisional
Entity: Small
Priority App #:
Application #: 63/406,527
Patent #:
Publication #:
US Bar: 00/00/00
Expiration: 9/14/2023
Assignee: , Mayo Foundation for Medical Education and Research (as Assignee)

Country: US
Status: Filed
PCT Filed: 00/00/00
Priority Date: 00/00/00
Filed: 9/14/2022
Issued: 00/00/00
Published: 00/00/00
PCT Bar: 00/00/00
Abandoned: 00/00/00

- **Other products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Rory Smoot
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0001-8543-661X
Nearest person month worked:	0.36 calendar months
Contribution to Project:	Study design, data evaluation
Funding Support:	Current Award
Name:	Tushar Patel
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.00 calendar months
Contribution to Project:	Study design, data evaluation, nanovesicle production
Funding Support:	N/A
Name:	Shohei Takaichi
Project Role:	Post-doc fellow
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	4.00 calendar months
Contribution to Project:	Experimental design and completion
Funding Support:	Current Award
Name:	Mincheng Yu
Project Role:	Post-doctoral fellow
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	4 calendar months
Contribution to Project:	Experimental design and conduct
Funding Support:	China Scholarship Council
Name:	Jack Sample
Project Role:	Post-doctoral fellow
Research Identifier:	N/A
Nearest person month worked:	4 calendar months
Contribution to Project:	Experimental design and conduct
Funding Support:	Mayo Clinic

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

Please see attached other support document

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORT REQUIREMENTS

COLLABORATIVE AWARDS:

N/A

QUAD CHARTS:

N/A

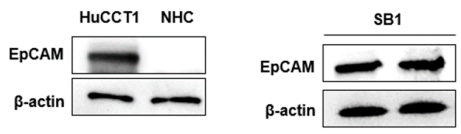
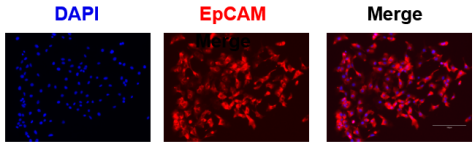
9. APPENDICES:

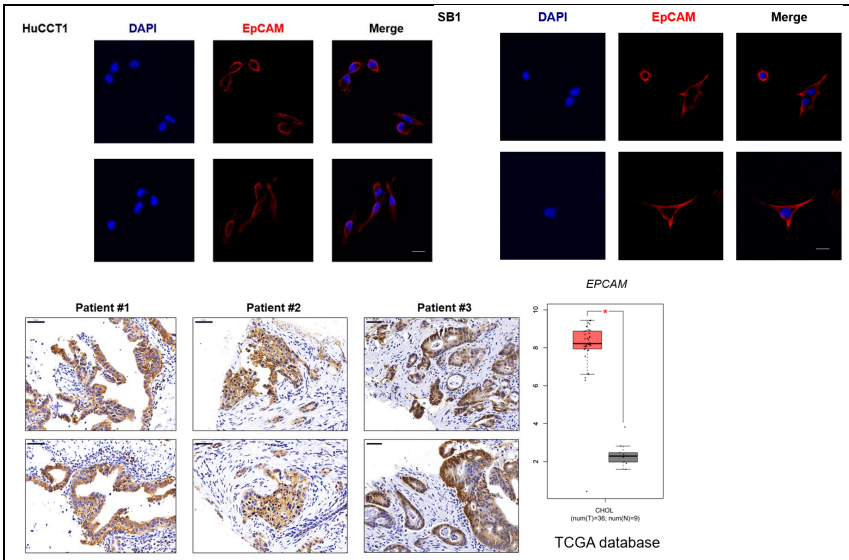
- Statement of Work
- Other Support Document

STATEMENT OF WORK – 09/01/2023
START DATE – 07/01/2021

Site 1: Mayo Clinic
200 1st St SW
Rochester, MN 55905
PI: Rory Smoot

Site 2: Mayo Clinic
4500 San Pablo Road
Jacksonville, FL 32224
Collaborator: Tushar Patel

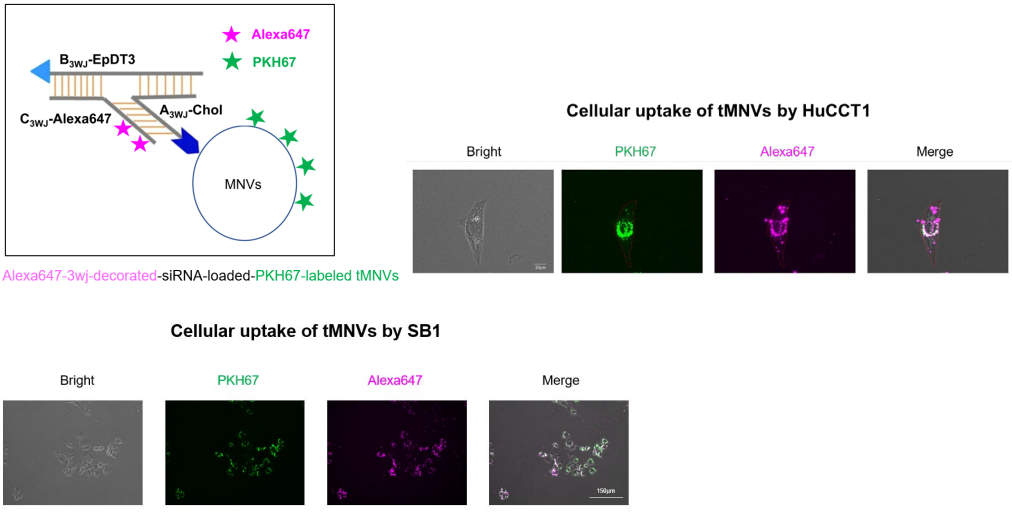
Specific Aim 1: Assess delivery and on-target effects of aptamer-targeted MDNV-siRNA	**Timeline**	**Site 1**	**Site 2**
Major Task 1: Assess delivery and target engagement aptamer-targeted MDNV in CCA models	Months		
Subtask 1: Production of nanovesicles	1-36		X
Completed/ongoing for ongoing studies			
Subtask 2: Submission of HRPO protocol for organoid/PDX use	1-4	X	
Completed			
Subtask 3: Submission of ACURO protocol for animal model usage	1-4	X	
Completed			
Subtask 4: Evaluate EPCAM expression on CCA models Cell lines used: HuCCT-1, KMCH,SB1, RBE, SNU-1079, patient-derived organoids (x6) Cell lines available and validated/fingerprinted in lab. Human: HuCCT1, KMCH, RBE, SNU-1079. Mouse: SB1. Assay: Immunoblot	1-6	X	
Results for Subtask 4   Cells derived from AKT/Fbxw7ΔF mice			



Completed: We have completed evaluation of EPCAM expression by immunoblot, immunofluorescence and IHC. We utilized the CCA cell line HuCCT1. The mouse CCA cell lines SB1 and FAC (FbxW7ΔF/AKT). We demonstrated strong and uniform staining of human tumor samples and demonstrated in the TCGA database that EPCAM is strongly overexpressed in CCA tumors compared to paired normal tissue.

Subtask 5: Evaluation of delivery aptamer-targeted MDNV to CCA cell lines and organoids Cell lines used: HuCCT-1, KMCH,SB1, RBE, SNU-1079, patient-derived organoids (x6) Assay: Fluorescent microscopy	1-6	X	

Results for Subtask 5

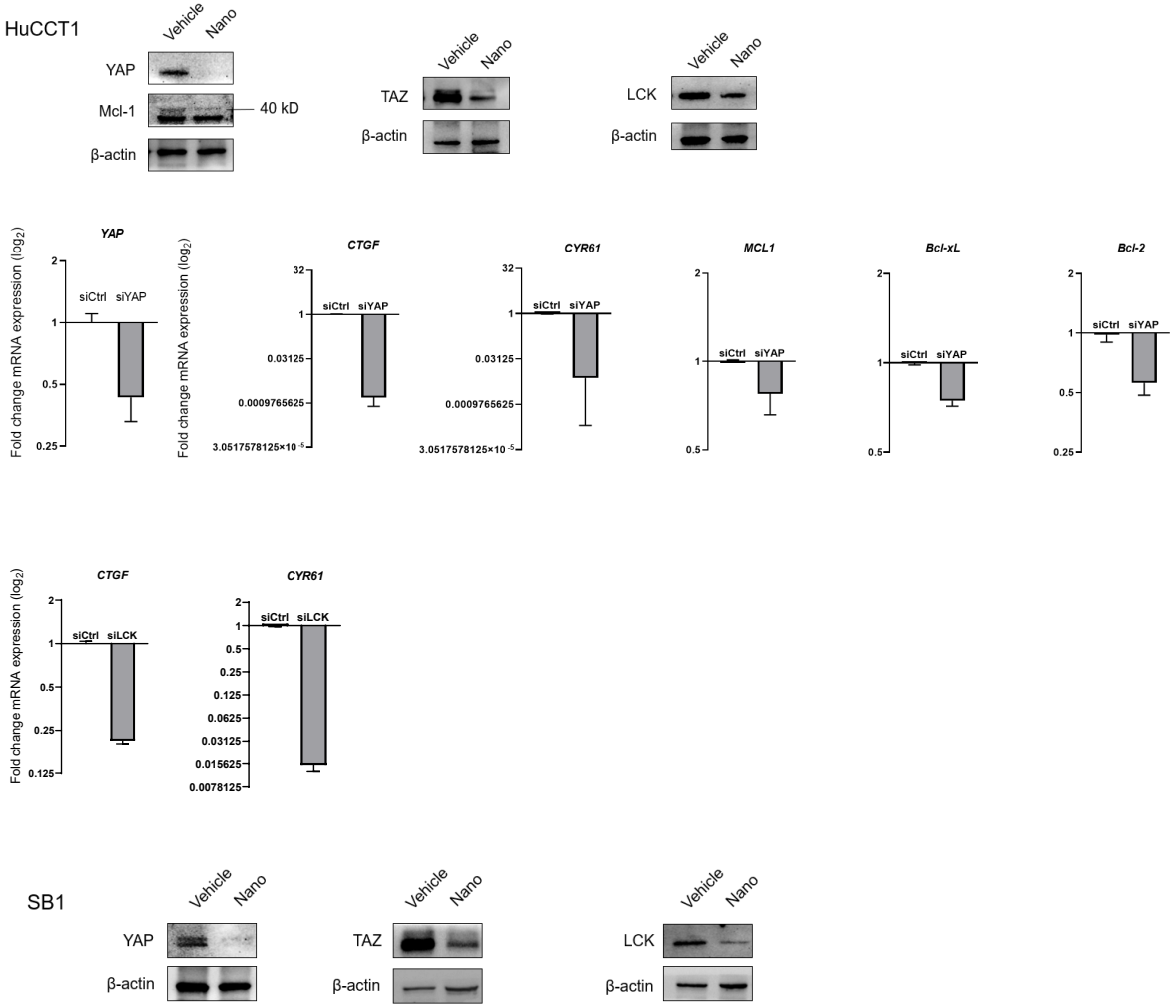


Completed: We have successfully demonstrated delivery of aptamer targeted nanovesicles to CCA cell lines HuCCT1 and SB1. The approach included imaging of the aptamer itself which includes and fluorophore (Alexa647) as we as loading the empty nanovesicles themselves with

a fluorescent dye (PKH67). By combining imaging of both the aptamer and the dye loaded nanovesicles we were able to ensure that naked/unlinked aptamer was not being taken up alone in the cell lines.

Subtask 6: Evaluation of Target protein effects Cell lines used: HuCCT-1, KMCH,SB1, RBE, SNU-1079, patient-derived organoids (x6) Assays: Immunoblot, RT-PCR, IF, Luciferase reporter assay	6-12	X	

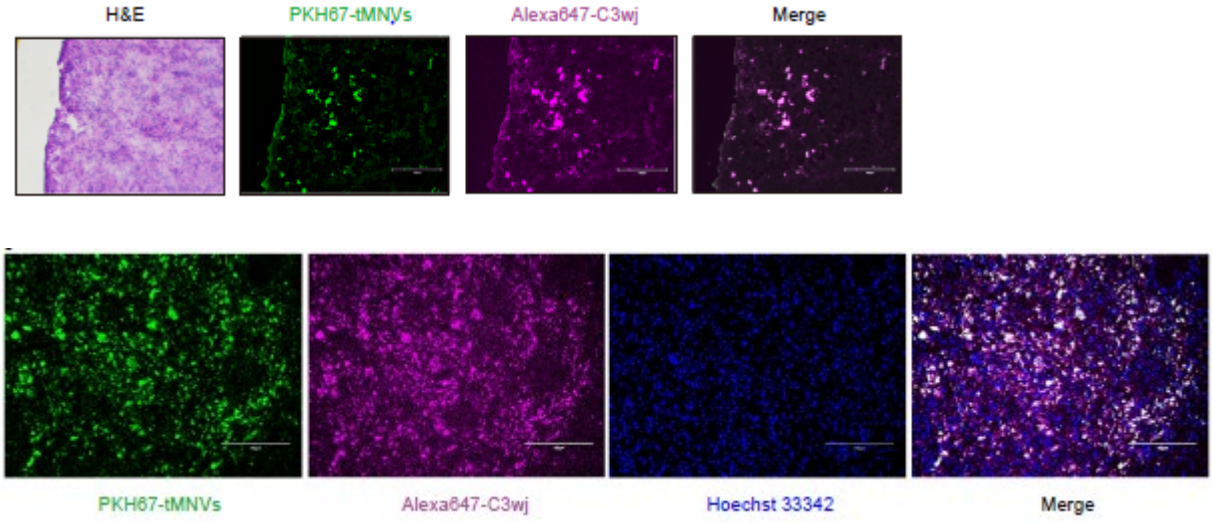
Results for Subtask 6



Completed: We have demonstrated successfully knockdown of YAP, TAZ, and LCK in the CCA cell lines HuCCT1 and SB1 utilizing the aptamer-targeted siRNA containing nanovesicles. Compared to non-targeting siRNA control (vehicle) protein targets are downregulated. RT-PCR for YAP and the YAP target genes CTGF, CYR61, MCL1, BCLxL and BCL2 demonstrated both target downregulation as well as downstream targets. Similarly downregulation of LCK (a known YAP activator) is associated with decreases in YAP target genes in HuCCT1 cell lines.

Milestone(s) Achieved: Delivery efficiency and on-target effects of aptamer-targeted MDNV-siRNA defined in vitro	12		
Major Task 2: Assess delivery and targeted effects of aptamer-targeted MDNV in vivo			
Subtask 1: Evaluation of delivery aptamer-targeted MDNV to CCA in vivo models Models: SB1, PDX (See table at end) Assay: Fluorescent microscopy	12-24	X	

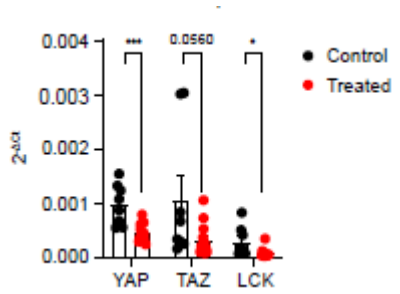
Results for Subtask 1

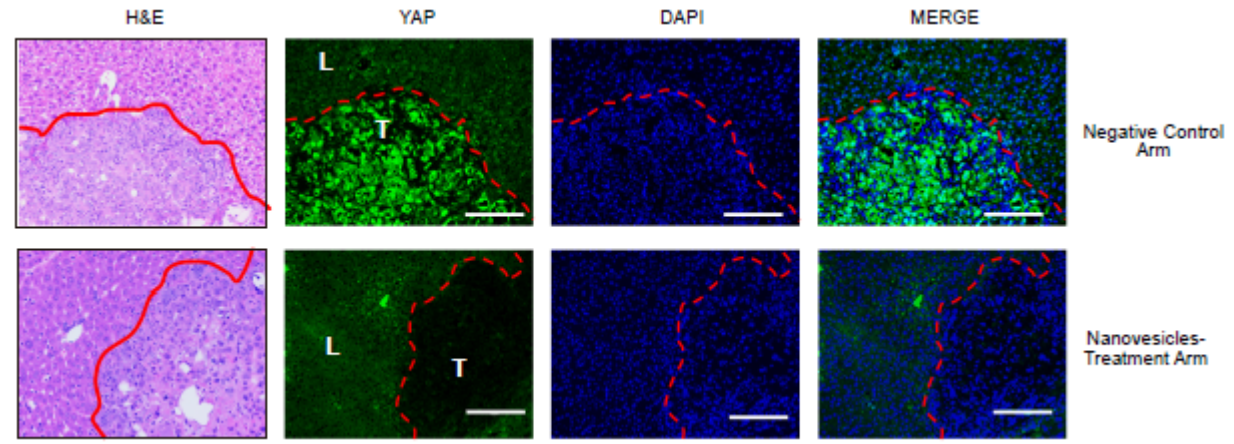


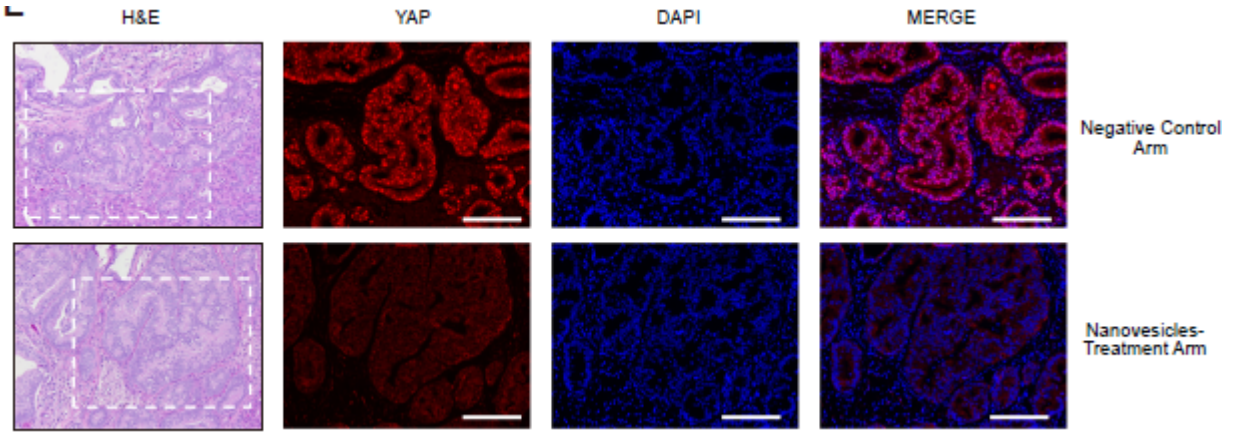
Completed: Vesicles are loaded with PKH67dye and the Alxea647 fluorophore on the three-way junction is separately imaged by fluorescent microscopy after delivery of 2x10e11 vesicles to tumor bearing animals via tail vein injection. Upper panel SB1 syngeneic model. Lower panel patient derived xenograft model.

Subtask 2: Evaluate on target effects in vivo Models: SB1, PDX (See table at end) Assays: IHC, RT-PCR, Immunoblot	12-24	X	

Results for Subtask 2

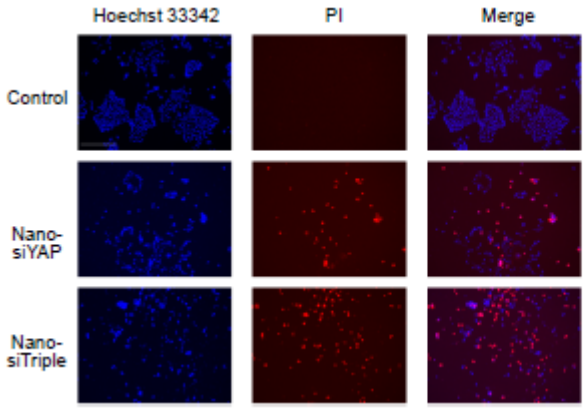
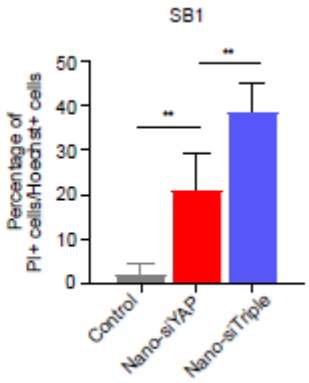


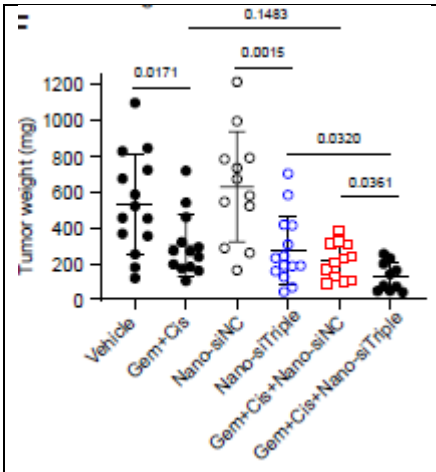


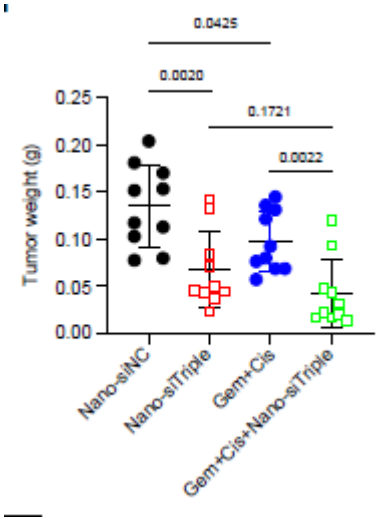


Completed: Following in vivo administration of nanovesicles every 3 days x 5 dose the mRNA levels of YAP, TAZ, and LCK are assessed by RT-PCR (upper panel). Immunofluorescence for YAP was undertaken in the syngeneic SB1 model (middle panel) and a patient derived xenograft model (lower panel).

Milestone(s) Achieved: Delivery efficiency and on-target effects of aptamer-targeted MDNV-siRNA defined in vivo	24		
Specific Aim 2: Assess proliferation/cell death effects of aptamer-targeted MDNV-siRNA			
Major Task 3: Define effects in vitro			
Subtask 1: Assess proliferation, cell death, and apoptosis in vitro	12-18	X	

Cell lines used: HuCCT-1, KMCH,SB1, RBE, SNU-1079, patient-derived organoids (x6) Cell lines available and validated/fingerprinted in lab. Human: HuCCT1, KMCH, RBE, SNU-1079. Mouse: SB1. Assays: Caspase 3/7, MTS, Cell titer glo			
Results for subtask 1   **In progress:** Staining with propidium iodide (PI) was completed following exposure of cells to nanovesicles containing either YAP siRNA alone or YAP, TAZ, and LCK siRNAs. Cell death was determined by quantifying the percentage of PI positive cells. Hoechst 33342 was utilized as a counterstain to mark cells. Additional cell lines and caspase 3/7 assays are ongoing.			
Milestone(s) Achieved: Cell death/proliferation effects defined in vitro	18		
Major Task 4: Define effects in vivo			
Subtask 1: Assess tumor growth, cell death and apoptosis in vivo Models: SB1, PDX (See table at end) Assay: Immunoblot, TUNEL staining, morphology	12-24	X	
Results for subtask 1			



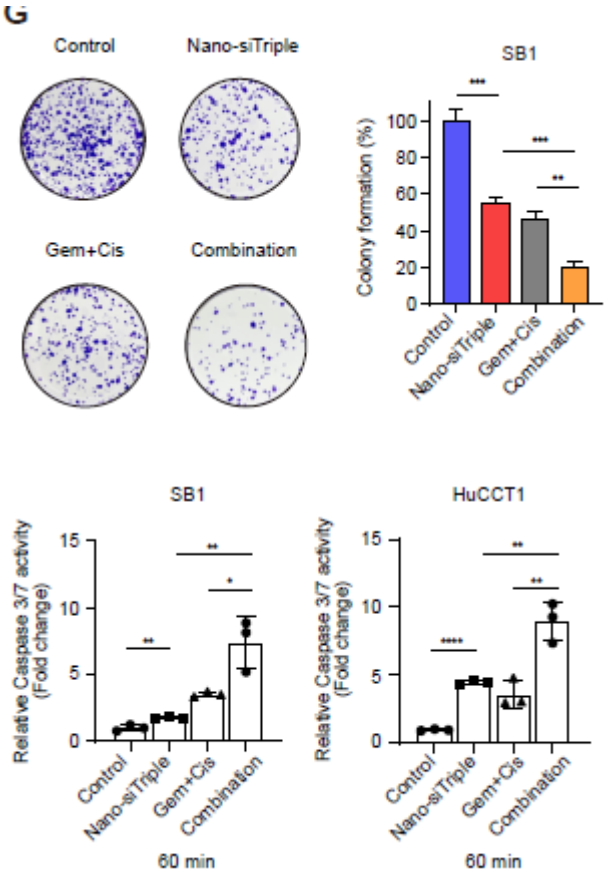


In progress: We have completed the initial testing of combined targeting nanovesicle treatments in both the syngeneic model and a single patient derived xenograft model. This has been completed both in isolation and in combination with gemcitabine and cisplatin chemotherapy. The evaluation of individual siRNA (YAP, TAZ) is ongoing. Upper panel indicates final tumor weight in the syngeneic model following in vivo treatment. Lower panel indicates the final tumor weight in the patient derived xenograft model following in vivo treatment.

Milestone(s) Achieved: Cell death/proliferation effects defined in vivo	24		
Specific Aim 3: Evaluate therapeutic efficacy of combining aptamer-targeted MDNV-siRNA with chemotherapy			
Major Task 5: Test aptamer-targeted MDNV-siRNA with chemotherapy in vitro			
Subtask 1: Define IC20 for gemcitabine/cisplatin for cell lines/organoids Cell lines used: HuCCT-1, KMCH,SB1, RBE, SNU-1079, patient-derived organoids (x6)	18-24	X	

Cell lines available and validated/fingerprinted in lab. Human: HuCCT1, KMCH, RBE, SNU-1079. Mouse: SB1. Assay: Cell titer glo			
Subtask 2: Define therapeutic effects of combinatorial therapy in vitro. Cell lines used: HuCCT-1, KMCH,SB1, RBE, SNU-1079, patient-derived organoids (x6) Assay: Cell titer glo, caspase 3/7 assay	24-30	X	

Results for subtask 2

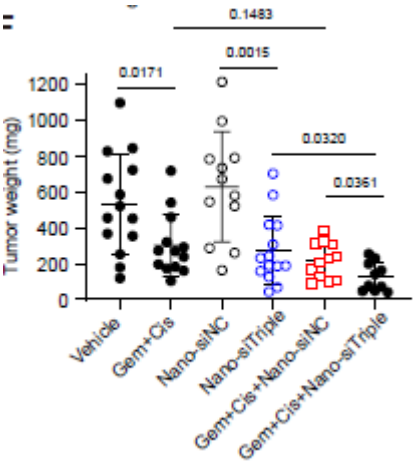


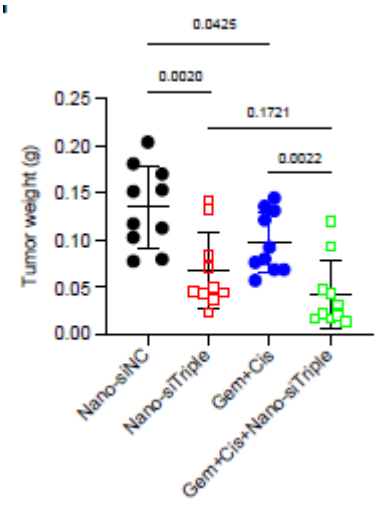
In progress: We have completed colony formation assay (upper panel) and caspase 3/7 assay (lower panel) to assess the effects of combining nanovesicle treatment with gemcitaine and cisplatin in vitro in both the SB1 cell line and the HuCCT1 cell lines. Further cell line studies are ongoing.

Milestone(s) Achieved: Preclinical data demonstrating efficacy of combinatorial therapy in vitro	30		
Major Task 6: Test aptamer-targeted MDNV-siRNA with chemotherapy in vivo			
Subtask 1: Define therapeutic effects of combinatorial therapy in vivo	24-36	X	

Models: SB1, PDX (See table at end) Assay: Immunoblot, TUNEL staining, morphology, RT-PCR			

Results for subtask 1





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Milestone(s) Achieved: Preclinical data demonstrating efficacy of combinatorial therapy in vivo	36		

Abbreviations: MDNV-milk-derived nanovesicles, siRNA-small interfering RNA, PDX-patient derived xenograft, IF-immunofluorescence, IHC-immunohistochemistry, GC-Gemcitabine and Cisplatin, Scr-Scramble

Animal study information:

Strains: C57Bl/6 -obtained from Jackson Labs; NOD/SCID – obtained from Jackson Labs

Task/Sub	Strain	Model	Treatment (N)	Control (N)	Total
MT2/ST1	C57Bl/6	SB1	5	0	5
MT2/ST1	NOD/SCID	PDX	5	0	5
MT2/ST2	C57Bl/6	SB1	30 (YAP,TAZ, YAP/TAZ)	10 (Scr)	40
MT4/ST1	NOD/SCID	PDX (3 unique)	90 (YAP, TAZ, YAP/TAZ x3)	30 (Scr)	120
MT6/ST1	C57Bl/6	SB1	40 (GC, YAP+GC, TAZ +GC, YAP/TAZ+GC)	40 (Veh/Scr)	80
	NOD/SCID	PDX (3 unique)	120 (GC, YAP+GC, TAZ +GC, YAP/TAZ+GC)	120 (Veh/Scr)	240

PREVIOUS-CURRENT-PENDING SUPPORT FOR DOD

SMOOT, RORY

PREVIOUS/COMPLETED (COMPLETED WITHIN THE LAST 5 YEARS)

Grant title/Name of PD/PI/Project number	Mechanisms of Oncogenesis in the primary liver cell cancer cholangiocarcinoma Smoot, Rory (PI) W81XWH-18-1-0297
Person months Year (YYYY) | Person Months (##.##) 3. 2021 | 4.20	
Source of Support	Department of Defense
Grants Officer Name & Address of Funding Agency	Congressionally Directed Medical Research Program Office Email: usarmy.detrick.medcom-cdmrp.mbx.cdmrp-reporting@mail.mil
Project/Proposal start and end date (MM/YYYY)	08/2018 – 07/2021
Total Award Amount (including indirect costs)	
Project Goals	The Overall Objectives remain to understand and define the cellular mechanisms contributing to the development and progression of biliary tract cancer, termed cholangiocarcinoma (CCA)
Specific Aims	(1) YAP TYROSINE PHOSPHORYLATION a. Is due to activation of a specific SFK member b. Regulates YAP nuclear localization and transcriptional co-activation in CCA independent of canonical Hippo pathway regulation (2) YAP TYROSINE PHOSPHORYLATION ALTERS THE TRANSCRIPTIONAL PROGRAM OF YAP a. By altering the specificity of enhancer and transcription factor binding b. Leading to upregulation of pro-survival signaling cascades (3) INHIBITION OF YAP TYROSINE PHOSPHORYLATION IS THERAPEUTIC IN CCA a. By genetic silencing of SFK-driven tyrosine phosphorylation in a YAP-driven murine model of CCA b. By SFK pharmacologic inhibition in patient derived xenografts (PDX)
Overlap	N/A

Grant title/Name of PD/PI/Project number	Augmenting YAP activation to accelerate liver regeneration Smoot, Rory (PI) Project number – N/A
Person months Year (YYYY) / Person Months (##.##) 1. 2019 / 0.00	
Source of Support	Center for Biomedical Discovery Pilot Grant Program
Grants Officer Name & Address of Funding Agency	Mark McNiven, Ph.D. Center for Biomedical Discovery Mayo Clinic 200 First Street SE Rochester, MN 55905
Project/Proposal start and end date (MM/YYYY)	10/2019 – 12/2019
Total Award Amount (including indirect costs)	
Project Goals	The overall goal of this study is to evaluate novel therapeutics targeting YAP/Hippo as treatment for liver regeneration
Specific Aims	SPECIFIC AIM #1. Evaluate SHP2 inhibitor as a driver of liver regeneration in a mouse partial hepatectomy model.
Overlap	N/A

Grant title/Name of PD/PI/Project number	Activating the Hippo pathway effector YAP to augment liver regeneration Smoot, Rory (PI) P008220008
Person months Year (YYYY) / Person Months (##.##) 2. 2021 / 0.24	
Source of Support	Regenerative Medicine Minnesota
Grants Officer Name & Address of Funding Agency	Gregory Gores, M.D. Center for Regenerative Medicine Mayo Clinic 200 First Street SE Rochester, MN 55905
Project/Proposal start and end date (MM/YYYY)	03/2020 – 02/2022
Total Award Amount (including indirect costs)	
Project Goals	The overall goal of this study is to evaluate novel therapeutics targeting YAP/Hippo as treatment for liver regeneration
Specific Aims	SPECIFIC AIM #1. Determine the effects of the SHP2 inhibitor on liver regeneration. SPECIFIC AIM #2. Determine the effects of novel MST1 inhibitors on liver regeneration
Overlap	N/A

Grant title/Name of PD/PI/Project number	Satter Family Foundation Cancer Research Fellowship Smoot, Rory (PI) Program number – N/A
Person months	
Year (YYYY) / Person Months (##.##)	
3. 2021 / 0.00	
Source of Support	Development – Gifts from benefactors
Grants Officer Name & Address of Funding Agency	Bill Faubion Mayo Clinic 200 First Street SW Rochester, MN 55905 Faubion.William@mayo.edu
Project/Proposal start and end date (MM/YYYY)	10/2019 – 09/2022
Total Award Amount (including indirect costs)	
Project Goals	Multiomics characterization of cholangiocarcinoma
Specific Aims	1. Perform deep proteomic evaluation of CCA tumor models and human tumors 2. Incorporate transcriptomic and genomic characteristics 3. Identify new therapeutic targets
Overlap	None

Grant title/Name of PD/PI/Project number	AHPBA Research Development Grant Smoot, Rory (PI) Project number – N/A
Person months	
Year (YYYY) / Person Months (##.##)	
2. 2021 / 0.00	
Source of Support	Americas Hepato-Pancreato-Biliary Association
Grants Officer Name & Address of Funding Agency	Jill Willhite AHPBA Headquarters 2508 W 71st Street Prairie Village, KS jill@lp-etc.com 970.691.1258
Project/Proposal start and end date (MM/YYYY)	07/2020 – 06/2022
Total Award Amount (including indirect costs)	
Project Goals	The overall goal is to evaluate nano-vesicle mediated delivery of RNA based molecules to cholangiocarcinoma.
Specific Aims	SPECIFIC AIM #1. Evaluate if YAP levels and tyrosine phosphorylation can be reduced in CCA by aptamer-targeted nanovesicle delivery of siRNA targeting YAP and/or LCK SPECIFIC AIM #2. Determine if downregulation of YAP levels and

	tyrosine phosphorylation increases the sensitivity of CCA to gemcitabine and cisplatin combinatorial therapy in organoid cultures and animal models of CCA.
Overlap	None

Grant title/Name of PD/PI/Project number			Identification and targeting oncogenic LCK signaling in cholangiocarcinoma Watkins, Ryan (PI); Smoot, Rory (Co-Investigator) Program number – N/A
Person months			
	Year (YYYY)	Person Months (##.##)	
	2. 2022	0.00	
Source of Support			Eagles Funds for Cancer Research
Grants Officer Name & Address of Funding Agency			Sandra Bisbee Mayo Clinic Cancer Center Mayo Clinic Rochester, MN 55905 Bisbee.sandra@mayo.edu
Project/Proposal start and end date (MM/YYYY)			06/2021 – 05/2023
Total Award Amount (including indirect costs)			
Project Goals			The major goal of this award is to develop a proteomics-based signature predicting therapeutic sensitivity in CCA.
Specific Aims			SA1: Validate proteomics signature in CCA PDX using a novel LCK inhibitor SA2: Predict novel therapeutic targets based on proteomic and phosphoproteomic signatures.
Overlap			None

Grant title/Name of PD/PI/Project number			Evaluation of YAP in cholangiocarcinoma Smoot, Rory (PI) Project number – N/A
Person months			
	Year (YYYY)	Person Months (##.##)	
	1. 2022	0.12	
Source of Support			Cedilla Therapeutics
Grants Officer Name & Address of Funding Agency			Brandon Nicolay Cedilla Therapeutics 245 First Street, 3rd Floor Cambridge, MA 02142 Bnicolay@CedillaTX.com
Project/Proposal start and end date (MM/YYYY)			04/2022 – 11/2022
Total Award Amount (including indirect costs)			

Project Goals	The major goal of this award is to Assess the therapeutic efficacy of a novel YAP-TEAD inhibitor in CCA preclinical tumor models.
Specific Aims	SA1: Characterize the single cell transcriptomic changes in human liver regeneration SA2: Characterize the single cell transcriptomic changes in mouse liver regeneration models with and without YAP targeted therapy.
Overlap	None

CURRENT/ACTIVE

Grant title/Name of PD/PI/Project number	Mayo Clinic Hepatobiliary SPORE McNiven, Mark (PI); Smoot, Rory (Co-Investigator/Co-Project Leader) P50CA 210964-4
Person months	

Year (YYYY)	Person Months (##.##)
1. 2018	2.40
1. 2019	2.40
2. 2020	2.40
3. 2021	2.23
4. 2022	2.40

Source of Support	National Cancer Institute
Grants Officer Name & Address of Funding Agency	Steven Nothwehr nothwehrs@mail.nih.gov
Project/Proposal start and end date (MM/YYYY)	09/2018 – 08/2023
Total Award Amount (including indirect costs)	
Project Goals	The Mayo Clinic SPORE in Hepatobiliary Cancers (HBCs) will achieve its goals by applying expert skill, closely coordinative leadership, innovative technologies, and a vast retinue of resources, all designed to build a strong continuum of basic, clinical, and translational research. Mayo is well positioned to support SPORE programming given its historic interdisciplinary infrastructure (including 6 current NCI-sponsored SPORES) that closely links basic and clinical research. This team-based approach is a Mayo hallmark and a cornerstone to the SPORE's organizational structure. Likewise, the SPORE leadership, both overall and for each project, relies on a team approach consisting of at least one Principal Investigator from basic and one from clinical/applied science. The HBCs SPORE will springboard from an already solid research base combined with promising translational proposals, both grounded on talented Mayo investigators with years of cancer research experience.
Specific Aims	1) Provide leadership and organization that drives outstanding translational liver and biliary cancer research. The overall

	SPORE leadership is well equipped to guide the HBCs program forward, combining a patient-centered approach to clinical care, a rigorous research perspective, and an experienced hand in education and mentorship. 2) Build an organizational matrix that facilitates collaboration and communication—both within projects and across the HBCs SPORE and promote interactions across the larger cancer SPORE research community. Mayo Clinic thrives on an extensive systems-driven administrative backbone. That structure will benefit the SPORE program, supporting horizontal and vertical intra- and inter-SPORE collaborations with other NIH programs and industry, swift resource sharing, and precise fiduciary responsibility. 3) Provide resources to develop innovative research projects in translational liver and biliary cancer research. Developmental research opportunities are a strategic priority to Mayo's senior leaders and Cancer Center directors. The HBCs SPORE will stimulate innovative research concepts through a competitive developmental award process and sustained facilitation. 4) Foster career development in translational liver and biliary cancer research. The HBCs SPORE, backed by Mayo Clinic and the Mayo Clinic Cancer Center, will provide extensive resources and mentorship to new and junior investigators via its Career Enhancement Program. Mayo's already extensive SPORE programming combined with its Center for Clinical and Translational Science (CCaTS) provides consistent, ongoing career track support for investigators seeking a career in translational cancer research. 5) Assure ongoing program excellence through rigorous internal and external review. The HBCs SPORE is grounded on a solid core of internal research leaders and a diverse pool of outstanding external liver and biliary scientists, clinicians, and, especially, patient advocates. Advisement will include not only scientific review, but also administrative and financial accountability.
Overlap	None

Grant title/Name of PD/PI/Project number	Nanovesicle-mediated targeting of YAP in cholangiocarcinoma to enhance chemotherapy sensitivity Smoot, Rory (PI) W81XWH-21-1-0798

Person months			
	Year (YYYY)	Person Months (##.##)	
	1. 2021	0.36	
	1. 2022	0.36	
	2. 2023	0.36	
Source of Support			Department of Defense
Grants Officer Name & Address of Funding Agency			Congressionally Directed Medical Research Program Office Phone: 301-619-7071 Email: usarmy.detrick.medcom-cdmrp.mbx.cdmrp-reporting@mail.mil
Project/Proposal start and end date (MM/YYYY)			08/2021 – 08/2024
Total Award Amount (including indirect costs)			
Project Goals			To assess the therapeutic efficacy of siRNA delivered by aptamer-targeted nanovesicles in preclinical models of cholangiocarcinoma.
Specific Aims			1. Assess ability to downregulate YAP and TAZ via nanovesicles in vitro and in vivo. 2. Assess the effects of YAP/TAZ downregulation on cancer viability in vitro and in vivo 3. Assess the sensitization of cholangiocarcinoma models to gemcitabine and cisplatin in combination with YAP/TAZ targeting nanovesicles
Overlap			None

Grant title/Name of PD/PI/Project number			Understanding cholangiocyte derived signals to drive hepatocyte regeneration Smoot, Rory (PI) P009627504
Person months			
	Year (YYYY)	Person Months (##.##)	
	1. 2022	0.12	
	2. 2023	0.12	
Source of Support			Regenerative Medicine Minnesota
Grants Officer Name & Address of Funding Agency			Gregory Gores, M.D. Center for Regenerative Medicine Mayo Clinic 200 First Street SE Rochester, MN 55905 Gores.gregory@mayo.edu 507-284-0686
Project/Proposal start and end date (MM/YYYY)			03/2022 – 02/2024
Total Award Amount (including indirect costs)			
Project Goals			The goal is to identify new optimization strategies for using these medications, and to identify new therapeutic targets to further augment liver regeneration by examining mechanisms

	by which targeting the molecule YAP with medications can facilitate liver regeneration.
Specific Aims	SA1: Characterize the single cell transcriptomic changes in human liver regeneration SA2: Characterize the single cell transcriptomic changes in mouse liver regeneration models with and without YAP targeted therapy.
Overlap	None

Grant title/Name of PD/PI/Project number			Mechanisms of carcinogenesis and therapeutic resistance in cholangiocarcinoma (NIH Relief) Smoot, Rory (PI) Program number – N/A
Person months			
	Year (YYYY)	Person Months (##.##)	
	1. 2022	0.12	
Source of Support			NIH Relief Program
Grants Officer Name & Address of Funding Agency			Mayo Clinic 200 First Street SE Rochester, MN 55905
Project/Proposal start and end date (MM/YYYY)			07/2022 – 06/2023
Total Award Amount (including indirect costs)			
Project Goals			The major goal of this project is to expand our understanding of drivers of carcinogenic signaling in CCA, specifically the role of LCK and its downstream targets, while also likely identifying additional novel therapeutic targets.
Specific Aims			1. LCK PROMOTES CARCINOGENIC SIGNALING IN CCA CELLS a. Via ligand-independent activation of the receptor tyrosine kinase AXL b. Sensitizing the cancer cells to LCK and/or AXL inhibition 2. ADVANCED PROTEOMIC PROFILING CAN IDENTIFY ACTIVATION SIGNATURES IN CCA a. Distinguishing preclinical models dependent on LCK signaling for survival b. Revealing pathways providing therapeutic escape from LCK inhibition 3. PROTEOMIC EVALUATION OF HUMAN CCA TUMORS IDENTIFIES DISTINCT SUBSETS a. Such that elevated LCK activity classifies a specific molecular subset of CCA b. Characterizing LCK activation as a prognostic marker
Overlap			None

Grant title/Name of PD/PI/Project number			Sensitizing cholangiocarcinoma to immune checkpoint blockade through the modulation of TAP-TEAD signaling Tomlinson, Jennifer (PI); Smoot, Rory (Mentor)
Person months			
	Year (YYYY)	Person Months (##.##)	
	1. 2023	0.00	
Source of Support			Cholangiocarcinoma Foundation
Grants Officer Name & Address of Funding Agency			Kristine Hamilton Assistant Operations Officer Cholangiocarcinoma Foundation 888-936-6731 x26
Project/Proposal start and end date (MM/YYYY)			05/2023 – 05/2024
Total Award Amount (including indirect costs)			
Project Goals			This proposal seeks to: 1) further understand how YAP signaling contributes to therapeutic resistance in CCA, with a particular focus on the role of YAP modulation of the tumor immune microenvironment and 2) to explore novel therapeutic targeting of the YAP signaling axis.
Specific Aims			The specific aims of the proposal would seek to answer the following questions: 1) Does YAP signaling promote an immunosuppressive microenvironment in CCA? 2) Does YAP-TEAD inhibition lead to increased sensitivity of CCA to immunotherapy?
Overlap			None

PENDING

Grant title/Name of PD/PI/Project number			Mechanisms of carcinogenesis and therapeutic resistance in cholangiocarcinoma Smoot, Rory (PI) R01CA 272512-1
Person months			
	Year (YYYY)	Person Months (##.##)	
	1. 2022	3.60	
	2. 2023	3.60	
	3. 2024	3.60	
	4. 2025	3.60	
	5. 2026	3.60	
Source of Support			National Cancer Institute
Grants Officer Name & Address of Funding Agency			TBD
Project/Proposal start and end date (MM/YYYY)			07/2022 – 06/2027
Total Award Amount (including indirect costs)			

Project Goals	The major goal of this project is to expand our understanding of drivers of carcinogenic signaling in CCA, specifically the role of LCK and its downstream targets, while also likely identifying additional novel therapeutic targets.
Specific Aims	1. LCK PROMOTES CARCINOGENIC SIGNALING IN CCA CELLS a. Via ligand-independent activation of the receptor tyrosine kinase AXL b. Sensitizing the cancer cells to LCK and/or AXL inhibition 2. ADVANCED PROTEOMIC PROFILING CAN IDENTIFY ACTIVATION SIGNATURES IN CCA a. Distinguishing preclinical models dependent on LCK signaling for survival b. Revealing pathways providing therapeutic escape from LCK inhibition 3. PROTEOMIC EVALUATION OF HUMAN CCA TUMORS IDENTIFIES DISTINCT SUBSETS a. Such that elevated LCK activity classifies a specific molecular subset of CCA b. Characterizing LCK activation as a prognostic marker
Overlap	None

Grant title/Name of PD/PI/Project number			Single cell proteomics for diagnosis of cholangiocarcinoma Mun, Dong(PI); Smoot, Rory (Co-Mentor) K99/R00CA 286731-1
Person months			
	Year (YYYY)	Person Months (##.##)	
	1. 2023	0.00	
	2. 2024	0.00	
	3. 2025	0.00	
	4. 2026	0.00	
	5. 2027	0.00	
Source of Support			National Cancer Institute
Grants Officer Name & Address of Funding Agency			TBD
Project/Proposal start and end date (MM/YYYY)			09/2023 – 08/2028
Total Award Amount (including indirect costs)			
Project Goals			Development of single cell proteomics strategy for diagnosis of cholangiocarcinoma
Specific Aims			SPECIFIC AIM 1. To improve the depth of single cell proteome coverage for highly sensitive and accurate identification of malignant cells from bile duct bushings

	SPECIFIC AIM 2. To use SCP analysis for detection of malignant cells obtained from bile duct brushings in suspected cases of cholangiocarcinoma SPECIFIC AIM 3. To develop and validate a machine learning-based strategy for accurate diagnosis of cholangiocarcinoma
Overlap	None

IN-KIND

None

FOREIGN CONTRACTS/GRANTS OR OTHER AGREEMENTS

None

Patel, Tushar

PREVIOUS/COMPLETED (COMPLETED WITHIN THE LAST 5 YEARS)

Grant title/Name of PD/PI/Project number			Extracellular non-coding RNA biomarkers of hepatocellular cancer/Patel/ UH3TR000884-5
Person months			
	Year (YYYY)	Person Months (##.##)	
	5. 2019	3.60 CM	
Source of Support			National Center for Advancing Translational Sciences
Grants Officer Name & Address of Funding Agency			Danilo Tagle 6701 Democracy Boulevard Bethesda MD 20892-4874 Phone: 1-301-594-8966
Project/Proposal start and end date (MM/YYYY)			08/2013-07/2020 NCE
Total Award Amount (including indirect costs)			
Project Goals			The overall goal of this application is to identify and qualify exosomal non-coding RNA based biomarkers in the circulation to detect early-stage disease in patients at risk, to predict recurrence after surgery and to monitor response to therapy in patients with hepatocellular cancer (HCC).
Specific Aims			1. Develop novel analytical assays for circulating exRNA; and 2. Identify a clinically relevant biomarker that will be useful as a diagnostic, prognostic, or treatment response marker for patients with HCC.
Overlap			None

Grant title/Name of PD/PI/Project number			MAY2013-02-02 CPN Study - Pilot Study of EGFR Inhibition with Eriotinib in Cirrhosis to Inhibit Fibrogenesis and Prevent Hepatocellular Carcinoma (Mayo Performance Site with Dr P Limburg's NCI HHSN261201200042I award at MCR)/Patel/HHSN261201200042I, HHSN26100006
Person months			
	Year (YYYY)	Person Months (##.##)	
	3. 2020	0.12 CM	
Source of Support			National Cancer Institute
Grants Officer Name & Address of Funding Agency			National Cancer Institute 31 Center Drive, Building 31 Bethesda, Maryland, 20814 Phone: 1-800-422-6237
Project/Proposal start and end date (MM/YYYY)			09/2014-06/2021
Total Award Amount (including indirect costs)			
Project Goals			To evaluate the utility of the use of EGFR inhibitor for prevention of cancer
Specific Aims			Pilot clinical study to evaluate the use of Erlotinib in persons with fibrosis

Overlap	None

Grant title/Name of PD/PI/Project number		Administrative Supplement to Build an Infrastructure for Liver Cancer Research (Sub on McNiven's NCI Grant at MCR)/Patel/CA015083
Person months		
Year (YYYY)	Person Months (##.##)	
1. 2018	0.60 CM	
Source of Support		National Cancer Institute
Grants Officer Name & Address of Funding Agency		National Cancer Institute 31 Center Drive, Building 31 Bethesda, Maryland, 20814 Phone: 1-800-422-6237
Project/Proposal start and end date (MM/YYYY)		03/2017-02/2019
Total Award Amount (including indirect costs)		
Project Goals		To support an infrastructure for discovery and translational studies in liver cancers
Specific Aims		To establish laboratory-based studies in liver cancers
Overlap		None

Grant title/Name of PD/PI/Project number		Blood Sample Collection to Evaluate Biomarkers for Hepatocellular Carcinoma/Patel/2017-01 (Control Group)
Person months		
Year (YYYY)	Person Months (##.##)	
2. 2019	0.07 CM	
Source of Support		Exact Sciences
Grants Officer Name & Address of Funding Agency		Exact Sciences 5505 Endeavor Lane Madison, WI 53719 Phone: 1-844-870-8870
Project/Proposal start and end date (MM/YYYY)		09/2018-09/2020
Total Award Amount (including indirect costs)		
Project Goals		To evaluate biomarkers of liver cancer
Specific Aims		To collect samples for evaluation of biomarker potential for detection of hepatocellular cancer
Overlap		None

Grant title/Name of PD/PI/Project number		Blood Sample Collection to Evaluate Biomarkers for Hepatocellular Carcinoma/Patel/2017-01 (HCC Group)
Person months		
Year (YYYY)	Person Months (##.##)	
2. 2019	0.09 CM	
Source of Support		Exact Sciences

Grants Officer Name & Address of Funding Agency	Exact Sciences 5505 Endeavor Lane Madison, WI 53719 Phone: 1-844-870-8870
Project/Proposal start and end date (MM/YYYY)	09/2018-09/2020
Total Award Amount (including indirect costs)	
Project Goals	To evaluate biomarkers of liver cancer
Specific Aims	To collect samples for evaluation of biomarker potential for detection of hepatocellular cancer
Overlap	None

Grant title/Name of PD/PI/Project number			International Cholangiocarcinoma Research Network (ICRN) (PS with Dr. Roberts at MCR)/Patel/N/A
Person months			
	Year (YYYY)	Person Months (##.##)	
	1. (2021)	0.00 CM	
Source of Support			Cholangiocarcinoma Foundation
Grants Officer Name & Address of Funding Agency			Stacie Lindsay Cholangiocarcinoma Foundation 5526 West 13400 South, #510 Herriman, Utah 84096 U.S.A. Phone: 1-888-936-6731
Project/Proposal start and end date (MM/YYYY)			01/2021-12/2021
Total Award Amount (including indirect costs)			
Project Goals			Biosample collection from patients with cholangiocarcinoma
Specific Aims			To collect samples for evaluation of biomarker potential for detection of cholangiocarcinoma
Overlap			None

CURRENT/ACTIVE

Grant title/Name of PD/PI/Project number			Project 3: Inhibition of SCD1 as a therapeutic strategy for HCC (Hepatobiliary SPORE - PS on Dr. McNiven & Roberts P50 at MCR)/Patel/P50CA210964-4
Person months			
	Year (YYYY)	Person Months (##.##)	
	1. 2018	1.80 CM	
	2. 2019	1.80 CM	
	3. 2020	1.80 CM	
	4. 2021	1.80 CM	
	5. 2022	1.80 CM	
Source of Support			National Cancer Institute
Grants Officer Name & Address of Funding Agency			National Cancer Institute 31 Center Drive, Building 31 Bethesda, Maryland, 20814

	Phone: 1-800-422-6237
Project/Proposal start and end date (MM/YYYY)	09/2018-08/2023
Total Award Amount (including indirect costs)	
Project Goals	To evaluate the use of novel inhibitors of SCD1 for the treatment of hepatocellular cancer
Specific Aims	To evaluate the mechanisms of action and therapeutic utility of SCD1 inhibitors for the therapy of hepatocellular cancer
Overlap	None

Grant title/Name of PD/PI/Project number			Core C: Biospecimens for the Hepatobiliary SPORE (PS on Hepatobiliary SPORE Resubmission)/Patel/P50CA210964-4
Person months			
	Year (YYYY)	Person Months (##.##)	
	1. 2019	0.12 CM	
	2. 2020	0.12 CM	
	3. 2021	0.12 CM	
	4. 2022	0.12 CM	
Source of Support			National Cancer Institute
Grants Officer Name & Address of Funding Agency			National Cancer Institute 31 Center Drive, Building 31 Bethesda, Maryland, 20814 Phone: 1-800-422-6237
Project/Proposal start and end date (MM/YYYY)			09/2019-08/2023
Total Award Amount (including indirect costs)			
Project Goals			To support biospecimen collection for the Hepatobiliary Spore
Specific Aims			Biospecimen collection and storage at Mayo Clinic in Florida
Overlap			None

Grant title/Name of PD/PI/Project number			Extracellular vesicle RNA signaling in liver tumor microenvironment (Resubmission of CA217833)/Patel/R01CA217833-5
Person months			
	Year (YYYY)	Person Months (##.##)	
	1. 2018	3.00 CM	
	2. 2019	2.28 CM	
	3. 2020	2.28 CM	
	4. 2021	3.00 CM	
	5. 2022	2.28 CM	
Source of Support			National Cancer Institute
Grants Officer Name & Address of Funding Agency			Elizabeth Woodhouse National Cancer Institute 31 Center Drive, Building 31 Bethesda, Maryland, 20814

	Phone: 1-800-422-6237
Project/Proposal start and end date (MM/YYYY)	02/2018-01/2023
Total Award Amount (including indirect costs)	
Project Goals	To identify extracellular vesicle RNA based signaling within the liver tumor microenvironment. The overall objective of this proposal is to understand the molecular mechanisms by which ncRNA are released within extracellular vesicles and their involvement in tumor cell-stromal cell interactions.
Specific Aims	1. To identify extracellular vesicle ncRNA markers or mediators of tumor-stromal interactions, properties of the released vesicles that act as carriers of the ncRNA, effect of environmental stress-activated signaling pathways on vesicle release and ncRNA content and mechanisms by which ncRNA can get sorted for release within vesicles during tumor stromal interactions. 2. Define the mechanistic relationship between regulated release of extracellular vesicles, functional non-coding RNA and tumor cell- stromal cell interactions.
Overlap	None

Grant title/Name of PD/PI/Project number			Nanovesicle -mediated targeting of YAP in cholangiocarcinoma to enhance chemotherapy sensitivity (PS with Dr Smoot at MCR)/Patel/W81XWH-21-1-0798
Person months			
	Year (YYYY)	Person Months (##.##)	
	1. 2021	0.11 CM	
	2. 2022	0.11 CM	
	3. 2023	0.11 CM	
Source of Support			Department of Defense
Grants Officer Name & Address of Funding Agency			Department of Defense Congressionally Directed Medical Research Program Office
Project/Proposal start and end date (MM/YYYY)			08/2021-08/2024
Total Award Amount (including indirect costs)			
Project Goals			To assess the therapeutic efficacy of siRNA delivered by aptamer-targeted nanovesicles in preclinical models of cholangiocarcinoma.
Specific Aims			1. Assess ability to downregulate YAP and TAZ via nanovesicles in vitro and in vivo. 2. Assess the effects of YAP/TAZ downregulation on cancer viability in vitro and in vivo 3. Assess the sensitization of cholangiocarcinoma models to gemcitabine and cisplatin in combination with YAP/TAZ targeting nanovesicles
Overlap			None

PENDING

Grant title/Name of PD/PI/Project number		Establishing a novel mass spectrometry technology for analysis of cancer-derived extracellular vesicles Patel, Tushar (PI) N/A
Person months		
Year (YYYY)	Person Months (##.##)	
1. 2023	0.60 CM	
2. 2024	0.60 CM	
3. 2025	0.60 CM	
4. 2026	0.60 CM	
5. 2027	0.60 CM	
Source of Support		National Institutes of Health
Grants Officer Name & Address of Funding Agency		TBD
Project/Proposal start and end date (MM/YYYY)		12/2023 – 11/2028
Total Award Amount (including indirect costs)		
Project Goals		The goals of this project are to validate a novel mass spectrometry technology for the detection of cancer-derived vesicles and to explore EV based biomarkers of hepatocellular cancer
Specific Aims		1. Refine NP-SIMS to enable rapid and multiplexed detection of EV surface and cargo molecules with individual particle resolution. 2: Employ normal and HCC liver cultures to harvest EVs for mass spectrometry analysis 3: Apply NP-SIMS for analysis of plasma samples from HCC patients.
Overlap		None

IN-KIND

None

FOREIGN CONTRACTS/GRANTS OR OTHER AGREEMENTS

None