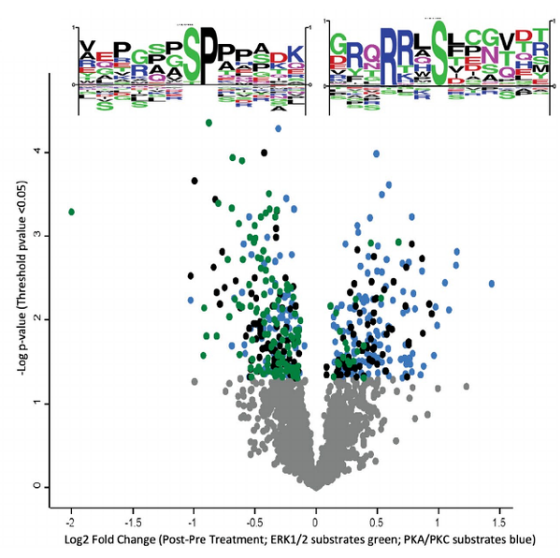
Volume 2, Issue 5 **December 1, 2021**



Post-translational modification enrichment analysis of changes in kinase signaling following treatment for HCV deduced from changes in kinase substrate motif phosphorylation. From *Ball et al., J Viral Hepat. 2021 Nov;28(11):1614-1623.*

On the Inside

A Note from the Directors

Don C. Rockey
DDRCC Director

Entering the thick of the holiday season, we are already submitting our annual renewals and looking ahead to Year 3 of the DDRCC and CDLD. It's very rewarding for us to see the progress we have made even as we plan for the further challenges ahead. COVID continues to be a complication, though one that perhaps is on the wane. On the horizon in the

Stephen Duncan
CDLD Director

next several months are exchange visits within the **Eastern DDRCC Alliance network** (this Spring) and the annual **DDRC Symposium and Retreat** on **April 8, 2022.** Please mark your calendars to block this day and stay tuned for details as they develop!

A final reminder that we are receiving Letters of Intent for our combined **Pilot & Feasibility Awards** program until **December 8, 2022**. Please see the award category descriptions and contact information in the note below.

Our **7 am Clinical / Translational** and **11 am Basic Science** virtual enrichment series still have some available slots in 2022 so, as always, please let us know if you'd like to hear from a particular guest speaker (**email Antonis** or **Don**).

All our best wishes for the holiday season, and hopes for an even better 2022.

Don and Steve

Research Focus

The Digestive Disease Research Core Center continues to welcome new members to our ranks. As part of our goal to build community and collaboration, we are profiling these investigators to increase awareness of the increasing richness of scientific effort and thought in digestive disease here at MUSC. A list of the current DDRCC Full Membership may be found on the **Member Directory** page of the **DDRCC Website**.

Welcome to our New CDLD Junior Investigator

Defining the KRAS mutation-specific interactome in pancreatic cancer

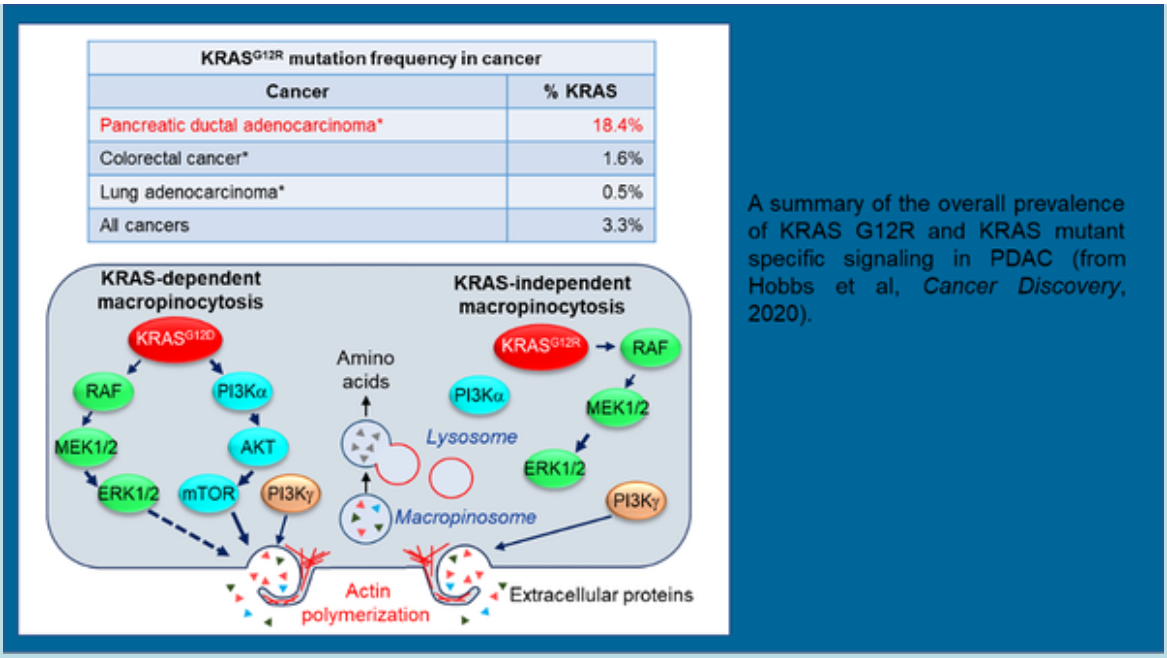
Contact Dr. Hobbs

Aaron Hobbs, PhD

Department of Cell and Molecular Pharmacology & Experimental Therapeutics

Aaron Hobbs, PhD currently serves as an Assistant Professor in the Department of Cell and Molecular Pharmacology and Experimental Therapeutics at MUSC. He received his PhD in Biochemistry and Biophysics from the University of North Carolina at Chapel Hill. He continued his studies at UNC-Chapel Hill by completing a postdoctoral fellowship in KRAS-mutant cancer signaling under the mentorship of Dr. Channing Der at the Lineberger Comprehensive Cancer Center.

Dr. Hobbs joined the MUSC faculty in August of 2020. His postdoctoral research centered on the question of whether all KRAS mutant proteins were created equal, thereby challenging the long-standing dogma in the RAS and cancer research fields. Despite the more than 200 different RAS missense mutations found in human cancers, it was widely assumed that all RAS mutant proteins shared identical defects in function and acted similarly as cancer drivers. One KRAS mutant protein, KRAS G12R, displays an uneven prevalence among cancers that harbor the highest occurrence of KRAS mutations, suggesting context-specific properties. Dr. Hobbs showed that KRAS G12R was defective in regulating macropinocytosis, a metabolic process essential for PDAC tumorigenic growth. Applying biochemical, structural and cellular analyses, he determined that KRAS G12R is defective in its interaction with the lipid kinase PI3K gamma, a RAS effector essential for RAS-driven tumorigenesis. His studies showed that the related PI3K gamma isoform is upregulated in PDAC, independent of KRAS, enabling restoration of macropinocytosis. Finally, he established that KRAS G12R-mutant PDAC exhibits distinct therapeutic vulnerabilities.



A summary of the overall prevalence of KRAS G12R and KRAS mutant specific signaling in PDAC (from Hobbs et al, *Cancer Discovery*, 2020).

With the support of the DDRCC/CDLD Proteomics core and Cell Models Core, the Hobbs lab will determine what makes each RAS mutant protein uniquely able to drive tumorigenesis. By utilizing a proximity ligation assay, they will determine the direct protein interactions of numerous RAS mutant proteins in both 2D and 3D cell culture, with an emphasis in determining molecular targets that can be easily transitioned to the clinic. Their longstanding goal is to develop KRAS mutation selective targeted therapies to fulfill the promise of personalized medicine while also raising the overall survival of one of the most deadly human cancers.

For additional details about the Hobbs lab and opportunities for collaboration, please contact Dr. Hobbs.

Notes from the DDRCC

SAVE THE DATE

3rd Annual MUSC Digestive Disease Research Center

RETREAT AND SYMPOSIUM

Friday, April 8, 2022

Agenda and further details will be pending

FINAL REMINDER

RFA: Pilot & Feasibility Awards

LETTER OF INTENT DUE DECEMBER 8, 2021

The MUSC COBRE in Digestive & Liver Diseases (MUSC CDLD) and the MUSC Digestive Diseases Research Core Center (MUSC DDRCC) invite investigators to apply to the Pilot and Feasibility (P/F) Funding Program. The primary objective of the P/F Program is to support junior and new MUSC investigators who are interested in pursuing basic, clinical or translational research of diseases that affect the liver and/or gastrointestinal system. Applications that develop or strengthen collaborative interactions amongst the MUSC digestive disease research community are highly encouraged. Proposed projects must have a high likelihood for progression to extramural funding and directly utilize one or more of the CDLD and/or DDRCC Core Resource Centers. **It is anticipated that the P/F Program will fund up to four grants. Projects can request up to $50,000 in direct costs for up to a 12-month period.** P/F awardees may be invited to apply for a second year of funding through a competitive renewal.

The P/F Program will support four general grant categories, with **promising new investigators given the highest priority**. Proposed projects must involve digestive and/or liver disease research.

Grant Category	Brief Description

Early Career	MUSC faculty at the Assistant or Associate Professor level who have not had previous extramural independent support as Principal Investigator (e.g., NIH R01, P01 subproject or equivalent) are eligible. Those with current extramural independent support as Principal Investigator are ineligible. Investigators supported by Career Development or Fellowship awards (K01, K08 or similar) are considered eligible. Applicant's funded through the CDLD are expected to identify a mentor who is an established investigator in the digestive disease field.
New Direction	MUSC faculty who have previously or are currently funded through the NIH or similar mechanism and are interested in applying their expertise to digestive and/or liver disease research. Faculty can be of any rank but should have a record of accomplishment in their chosen field. The proposed project cannot overlap with any ongoing funded project.
High Impact	MUSC faculty who wish to explore innovative new ideas that represent a significant departure from their ongoing funded projects. Justification of the new direction is essential. Faculty can be of any rank but should have a record of accomplishment in the digestive or liver disease field. The proposed project cannot overlap with any ongoing funded project.
Fast Forward	MUSC faculty who need to add preliminary or supportive data for the direct development of a grant submission. Awards are limited to MUSC faculty who have submitted an extramural grant application, received a summary statement, and need additional critical data for a successful resubmission. Faculty can be of any rank.

Applicants should submit a letter of intent (LOI) via email to Caroline Westwater. LOIs should be submitted as a single PDF. Questions regarding this RFA can be directed to Caroline Westwater, Stephen Duncan , or Don Rockey.

Awards and Other News

Eric Meissner

Lauren Ball

Don Rockey

EUREKAlert!

COBRE JI Eric Meissner, MD, Proteomics Core co director Lauren Ball, PhD and DDRCC Director Don Rockey, MD, PhD were recently featured in an **MUSC Catalyst** article and a **EUREKA alert** press release about their

collaborative publication in the Journal of Viral Hepatitis (Dr. Meissner, corresponding author). In work supported by the DDRCC, they reported on the beneficial effect of early treatment for Hepatitis C virus (HCV) in decreasing the levels of proteins indicative of liver scarring and cirrhosis. This work has important implications for the early diagnosis of HCV, as well as for the development of new treatments for HCV driven cirrhosis. **Congratulations to the team!**

We like to hear about your progress and achievements!

Please sent your news and announcements to the DDRC Digest via email to the Center Manager.

Updates from Our Cores

Clinical Component and Biostatistics

Leadership

Paul J. Nietert, PhD
Director
DDRCC

Ramesh Ramakrishnan, PhD
Director, CDLD

Mat Gregoski, PhD
Biostatistician
DDRCC/CDLD

Biostatistics Collaborations

Successful research efforts in clinical sciences invariably involve collaboration or consultation with biostatisticians. Our DDRCC and CDLD members have access to high-quality, state-of-the-art biostatistics services led by **Dr Paul J. Nietert** (DDRCC) and Dr. **V. "Ramesh" Ramakrishnan (CDLD)**, with the assistance of Mat Gregoski, PhD.

Services available include, but are not limited to:

- **Simple data analysis for an abstract**
- **Study sample size recommendations for NIH grant proposals**
- **Complex experimental design**
- **Analysis of longitudinal clustered data**
- **Analysis of high-throughput data**

Whatever the need, Drs. Nietert and Ramakirshnan and their team will enthusiastically respond your request for support. They share your goal of promoting research studies that seek to improve clinical outcomes for patients with digestive diseases.

The biostatistics team recommends consultation for all of your research projects. Feel free to approach the team as early as when you are formulating the specific aims. Ultimately, the yardstick they will use for measuring their success is the number of funded grants (from sources such as the NIH and VA) and of quality publications from DDRCC and CDLD members that result from collaborations with the biostatistics team.

The procedure for seeking such consultation is just a few clicks away and is **free** for **CDLD and DDRCC Full Members**. As soon as a research idea emerges, place a SCTR SPARC request (see below), with Mat Gregoski as the point of contact. A team member will soon contact you to begin the collaboration.

To initiate a collaboration with the Biostatistics Core:

Go to sparc.musc.edu

1. Click on the green South Carolina Clinical and Translational Research Institute (**SCTR)** button on the left (middle of the page)
2. Select: "Biostatistics, Design & Epidemiology" from the drop-down menu
3. Input any relevant study information
4. Make sure to hit "**SUBMIT**."

DDRCC and CDLD Enrichment Seminar Series

We were privileged to host an outstanding series of virtual seminars this year, featuring speakers of national and international renown. All of the GI & Hepatology 7am series were recorded, and are available through Box. A few notable highlights are mentioned below. The complete collection of recorded talks are available to DDRCC and CDLD members **here**.

DDRCC / CDLD / GI and Hepatology Grand Rounds: Wednesday, 7am EST (Zoom)

December 1

Stacey Maurer, PhD, and Brian Haver, Psy, MPH MUSC

CBT-GI: Cognitive Behavioral Therapy for Gastrointestinal Conditions

December 8

Ryan Stidham, MD, MSc University of Michigan

Applications for Artificial Intelligence in IBD

December 15

Theo Heller, MD NIDDK

Non-cirrhotic portal hypertension; it is all about the pressure!

December 22, 29

No Seminar

Holiday break

January 5

GI & Hepatology Fellows MUSC

Clinical case presentations

January 12

William Bulsiewicz, MD, MSCI Lowcountry Gastroenterology

Personalized Nutrition: Where we are today and where this is going soon

January 19

Jennifer F. Walijee, MD, MPH, MS University of Michigan

Integrated care models of IBS – what, why and how

January 26

TBD TBD

TBD

DDRCC/CDLD/ RMCB Virtual Seminar Series:
Wednesday, 11 am EST (Zoom)

December 1

George Daley, MD, PhD Harvard Medical School

Blood from a petri dish

To receive notifications for our Enrichment series seminars, please contact the DDRCC Center Manager.

Selected GI Publications by our Members

Each newsletter, we highlight a subset of the many outstanding papers published and presented by our DDRC members. We strive to mention particularly significant primary research papers where our members were lead authors or key contributors, and to represent the broad scope of clinical, basic science and clinical-translational research interests across our membership. To assist us in these efforts, we continue to encourage you to **email Kyu**, our center manager, about your particularly significant papers and presentations.

While space does not allow us to list a comprehensive month-to-month list of our member publications, such a list can be found on our DDRCC website **here**.

A complete listing of our DDRCC member publications since its inception can also be found through NCBI **here**.

October, 2021 - November, 2021

Cotton PB. Collecting delayed adverse events after ERCP. Gastrointest Endosc. 2021 Oct;94(4):877. PubMed PMID: 34530980**.**

Cen B, Wei J, Wang D, Xiong Y, Shay JW, **DuBois RN**. Mutant APC promotes tumor immune evasion via PD-L1 in colorectal cancer. Oncogene. 2021 Oct;40(41):5984-5992. PubMed PMID: 34385594; PubMed Central PMCID: PMC8526383.

Sandler RS, Davidson NO, Monga SP, **Rockey DC**. Silvio O. Conte Digestive Disease Research Core Centers-Connecting People, Creating Opportunities, Developing Careers. Gastroenterology. 2021 Oct;161(4):1085-1089. PubMed PMID: 34175277; PubMed Central PMCID: PMC8463423.

DelaCourt A, Black A, Angel P, Drake R, Hoshida Y, Singal A, Lewin D, Taouli B, Lewis S, Schwarz M, Fiel MI, **Mehta AS**. N-Glycosylation Patterns Correlate with Hepatocellular Carcinoma Genetic Subtypes. Mol Cancer Res. 2021 Nov;19(11):1868-1877. PubMed PMID: 34380744.

Swanson BA, Carson MD, Hathaway-Schrader JD, Warner AJ, Kirkpatrick JE, Corker A, **Alekseyenko AV**, **Westwater C**, Aguirre JI, **Novince CM**. Antimicrobial-induced oral dysbiosis exacerbates naturally occurring alveolar bone loss. FASEB J. 2021 Nov;35(11):e22015. PubMed PMID: 34699641.

G, D'Santos C, Tooze RM, Lorger M, **Syn WK**, Papakyriakou A, Giamas G, Bubici C, Papa

Accessing DDRC Cores

Quick Links for DDRCC and CDLD Core Use

A reminder that Full Members receive subsidized usage of our cores. Below are some summary details for accessing the cores and intiating projects.

Analytical Cell Models Core:

- The DDRCC and CDLD both **fully subsidize** the use of the ACC by its members.
- For iPSC projects, please contact the Core Director, **Dr. Steve Duncan**.
- For primary cell isolation, please contact **Dr. Don Rockey**.

Advanced Imaging Core:

- The DDRCC and CDLD both provide **full members** with a **25% discount** on facility fees.
- For imaging projects, please contact the Core Director, **Dr. John Lemasters** and Core Manager **Li Li**.

CDLD Animal Models Core:

- The CDLD **fully subsidizes** the use of the Animal Models Core for its **Junior Investigators**.
- Other **discounts** may currently apply for DDRCC members.
- For animal projects please contact the Core Director, **Dr. Suzanne Craig**.
- For gnotobiotic mouse models, please contact **Dr. Caroline Westwater**.
- For transgenic and CRISPR/Cas9 projects, please contact the TGE Director, **Dr. Alexander Awgulewitsch**.

DDRCC Proteomics Core (updated):

- **DDRCC full members** will now receive a **50% discount** from facility fees.
- For MS projects, please contact the Core Co-Director, **Dr. Lauren Ball**.

Clinical Component Core:

- The DDRCC and CDLD **fully subsidize** biostatistical consultations with the Clinical Component Core by all of its members, including biostatistical support and mentoring for its Junior Investigators and Pilot & Feasibility applicants and awardees.
- To start a project, visit the SPARC website and submit a Biostatistics, Design & Epidemiology request, and contact:
  - DDRCC Core Director, **Dr. Paul Nietert**
  - CDLD Director **Dr. Ramesh Ramakrishnan**.

CITE OUR GRANTS

FOR THE DDRCC:

This project was supported in part by NIH P30 DK123704 (*core facility*) at the MUSC Digestive Disease Research Core Center.

FOR THE COBRE CDLD:

P20 GM120457

This project was supported in part by NIH P20 GM120475 (core facility) at the MUSC Digestive Disease Research Core Center.

For queries regarding DDRCC news, membership and cores, please contact the Center Manager:

Kyu-Ho Lee, MD-PhD
Gastroenterology and Hepatology
Department of Medicine
CSB HE903B
96 Jonathan Lucas St
Charleston, SC 29425
(843) 792-1689
Email Dr. Lee

For queries regarding the COBRE in Digestive and Liver Disease, please contact the COBRE PI:

Stephen Duncan, DPhil
Department Chair
Regenerative Medicine and Cell Biology
BSB 657A MSC508
173 Ashley Ave
Charleston, SC 29425
(843) 792-9104
Email Dr. Duncan

Visit the DDRCC Website:
https://medicine.musc.edu/departments/dom/divisions/gastroenterology/research/labs-and-centers/ddrcc

Visit the CDLD Website:
https://medicine.musc.edu/departments/regenerative-medicine/cobre-digestive-liver-disease