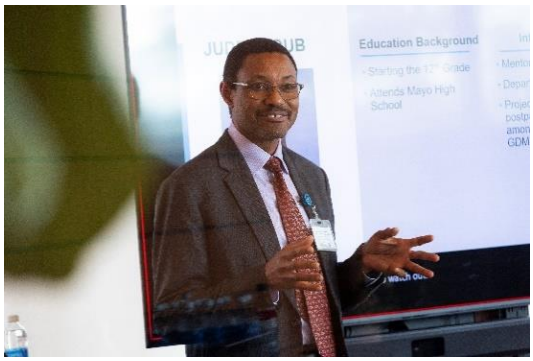
Hepatobiliary Cancer SPORE Quarterly Newsletter

Fall/Winter (2024-2025)

FEATURES

Dr. Lewis Roberts (SPORE MPI): 2024 Distinguished Mayo Clinic Investigator



For nearly 30 years, Lewis Roberts, M.B., Ch.B., Ph.D., has worked to understand the epidemiology and molecular pathogenesis of hepatobiliary cancers, including hepatocellular carcinoma, cholangiocarcinoma and gallbladder cancer.

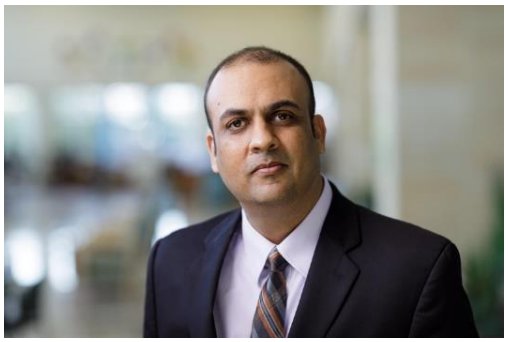
Dr. Roberts' laboratory has made major, unique and widely acknowledged contributions to the understanding and treatment of hepatocellular carcinoma and cholangiocarcinoma through basic and patient-oriented studies that span the development, progression and metastasis of liver and biliary cancers. He has had continuous independent NIH funding for over 25 years and has been a grant reviewer for the NIH since 2005, as well as for several national research agencies.

Dr. Roberts' immense body of work has led to over 500 manuscripts in high-impact journals, and he has mentored over 200 students, residents, fellows, postdoctoral candidates, junior faculty and visiting professors, many of whom have become independent, grant-funded investigators nationally and internationally in liver disease research.

His humanitarian work, mentoring of underrepresented minorities and health disparities research have been recognized worldwide. In 2015, Dr. Roberts was named the Peter and Frances Georgeson Professor in Gastroenterology Cancer Research at Mayo Clinic.

Dr. Roberts is a consultant in the Division of Gastroenterology and Hepatology, a clinician investigator and a professor of medicine. He is also the director of Research Longitudinal Experience at Mayo Clinic Alix School of Medicine and associate director of Predoctoral Programs M.D.-M.S. at Mayo Clinic Center for Clinical and Translational Science

Dr. Mitesh Borad (P2/P3 Co-Leader): Named Professorship and Arizona Investigator of the Year



Dr. Borad, Hematology/Oncology, is a professor of medicine and the Getz Family Research Professor. As a specialist in medical oncology, drug development and genomics, Dr. Borad has been extensively involved in developing new cancer therapeutic platforms that use genomic medicine, gene and virus therapies, with a focus on tumors of the liver, bile ducts and pancreas.
In a groundbreaking effort initiated in 2010, along with his colleagues at Mayo Clinic and the Translational Genomics Research Institute, Dr. Borad accomplished one of the first successful implementations of whole genome and transcriptome sequencing in a clinical workflow, providing the push for routine clinical genomic profiling in the clinic only a decade and a half later.
He has served as a principal investigator in 50 phase 1 clinical studies and as a co-investigator in hundreds of additional trials. In a nomination letter, Dr. Borad is described as "the most experienced and prolific expert within the Mayo enterprise for his work as an investigator of phase 1 clinical trials and is viewed as an international expert by his peers."

"Dr. Borad's numerous contributions as a researcher, leader and educator make him most deserving of this recognition," says William Faubion Jr., M.D., Dean of Research at Mayo Clinic Arizona and the Michael S. and Mary Sue Shannon Family Director, Center for Regenerative Biotherapeutics. "He has done an exceptional job of moving genomic medicine and early phase clinical trials research into clinical practice, which over the years have rapidly moved from being safety studies to proof-of-concept efficacy studies."

His research has been instrumental in Food and Drug Administration (FDA) approval of the drugs infigratinib and pemigatinib and the advancement of many other anti-neoplastic agents, including ivosidenib, nab-paclitaxel and vismodegib.

Dr. Borad's lab has been funded by the FDA, the National Cancer Institute (NCI), the National Institutes of Health (NIH) and the Department of Defense since 2011. As a mentor, he has trained more than 40 individuals across the spectrum of academic medicine and research.

He has published more than 200 papers in high-impact journals including the New England Journal of Medicine, Nature, Nature Medicine and Science Advances. He is the recipient of numerous national and international awards, including the NIH New Innovator Award; the NCI Paul Calabresi Career Development Award; and the Mark Clements Award for Vision, Innovation and Collaboration from the Cholangiocarcinoma Foundation for his efforts toward establishing the International Cholangiocarcinoma Research Network and serving as its chair from 2020 to 2023.

Dr. Borad is the co-leader of the Novel Therapeutics and Therapeutic Modalities Program (NTTM) within the Mayo Clinic Comprehensive Cancer Center and has served as the director of the Precision Cancer Therapeutics Program within the Center for Individualized Medicine and as the co-leader of the Gene and Virus Therapy Program.

He received his medical degree from the University of Medicine and Dentistry of New Jersey and served a fellowship in medical oncology at Tulane University School of Medicine. He completed his residency in internal medicine at Cedars-Sinai Medical Center. He was a drug development and genomics medicine scholar at the Translational Genomics Research Institute before joining Mayo Clinic in 2008.

Dr. Mark McNiven (SPORE PI)**: Named as 2024 ASCB Fellow**

The American Society for Cell Biology (ASCB) is pleased to present its cohort of 17 new Fellows for 2024.

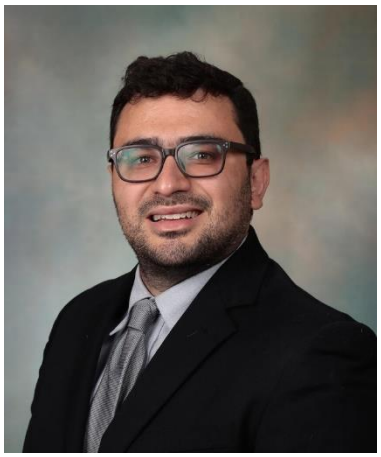
Election as a Fellow of ASCB is an honor bestowed upon ASCB members by their peers. The list of Fellow nominees is reviewed and approved by the ASCB Council. The new cohort of ASCB Fellows will be formally recognized at Cell Bio 2024, the joint meeting of the ASCB and the European Molecular Biology Organization (EMBO) in San Diego, CA.

CEP/DRP AWARDEES

DRP Awardee: Henrique Borges da Silva, Ph.D.

Department of Immunology, Mayo Clinic Arizona

"P2RX7-mediated extracellular ATP sensing for CD8+ T cell immune responses against HCC"



Lay Abstract: Therapies that re-activate the immune system (immunotherapies) are a non-invasive alternative for cancer eradication, and have saved the lives of many cancer patients, but unfortunately most patients do not respond effectively to these therapies. This is especially true in the case of liver cancers, which are particularly successful in inhibiting immune responses. Patients that respond well to immunotherapies usually have a high count of tumor-killing cells, called CD8+ T cells, but we do not know how we can increase their numbers in combination with immunotherapy. These cells can respond to molecules freely present in the tumor tissue – the so-called "tumor microenvironment". To circumvent the tumor defenses against our immune system, the application of new strategies to re-purpose these tumor microenvironment molecules to activate immune responses should be done. Yet, without in-depth understanding of how this can be done, it is difficult to predict which patients will respond, or which therapies should be prescribed. The purpose of this project is to use research models and patient samples to determine how cancer cells and tumor microenvironment molecules interact with immune cells within liver tumors. Our research program has a long-standing interest in the investigation of the tumor microenvironment and uses a myriad of cutting-edge quantification and imaging techniques, such as high-throughput spectral flow cytometry, which enables the quantification and description of dozens of immune cell types at once. Our preliminary data have revealed that the effect of one microenvironment molecule, extracellular ATP, may positively impact the accumulation of tumor-killing cells within solid tumors. Our main goal is to understand how this molecule can impact the antitumor responses to liver cancers. Understanding these fundamental mechanisms governing the immune response is critical for the design of effective therapeutic regimens against advanced liver cancers.

CEP Awardee: Caitlin Conboy, M.D., Ph.D.

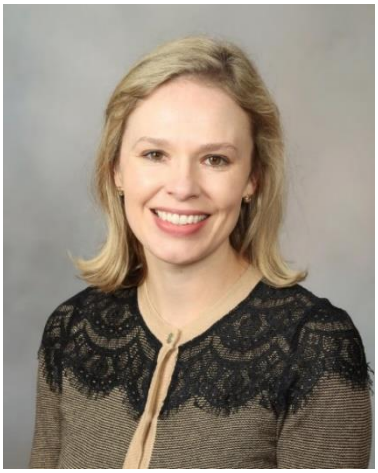
Department of Oncology, Mayo Clinic Rochester

"Targeting aberrant glycoproteins in ARID1A and PBRM1-deficient cholangiocarcinoma"

Lay Abstract: Although we commonly think of cancer as resulting from mutations in a cell's DNA, epigenetic packaging of DNA into chromatin has profound effects on gene expression, cell signaling, and cell behavior. ARID1A and PBRM1, two proteins that participate in chromatin remodelling, are frequently mutated in cholangiocarcinoma (CCA). Yet how these mutations cause cancer is not understood and is necessary for developing therapies. In our preliminary work, we developed mouse models of CCA caused by loss of ARID1A and PBRM1. We identified downstream gene expression changes that may modify the tumor microenvironment. We now propose to further investigate the how ARID1A and PBRM1 mutations impact the tumor microenvironment and investigate two genes of interest, periostin and UXS1, as potential therapeutic targets in CCA.

CEP Awardee: Moira Hilscher, M.D.
Department of Gastroenterology, Mayo Clinic Rochester

"Study of HCC in FALD"



Lay Abstract: Fontan associated liver disease (FALD) occurs in all patients who have undergone Fontan repair for single ventricle congenital heart defects. The most feared complication of FALD is hepatocellular carcinoma (HCC) which is associated with a poor prognosis in this patient population. The cause of HCC in patients with FALD is unclear as it commonly occurs in the absence of cirrhosis or significant inflammation. Our prior studies show that FALD is associated with a decrease in the amount of T cells in the liver. We propose that this creates a permissive environment which facilitates the development of HCC. In this application, we plan spatial transcriptomic studies in order to obtain a more in-depth understanding of the immune environment in the liver in FALD and its impact on the development of HCC. We plan to test our findings in a murine model of HCC in the setting of hepatic congestion. Overall, we expect that this proposal will help identify novel therapeutic approaches to HCC in FALD which address the underlying immune defects.

AWARD APPLICATION

The annual Blue Faery Award for Excellence in Liver Cancer Research honors one researcher who has made significant contributions to the advancement of scientific knowledge in the diagnosis, treatment, prevention, or understanding of liver cancer.

We encourage anyone doing innovative HCC-specific research to apply by January 31, 2025. Learn more here: https://www.bluefaery.org/blue-faery-award

Dr. Lewis Roberts (SPORE MPI) was the 2022 winner.

EVENTS

The Florida Healthy Liver Program Liver Cancer Prevention in Primary Care
Friday, January 24, 2025 / 4-5 pm EST
Tallahassee, FL / Durell Peaden Auditorium

Dear Alumni, Faculty, Staff, and Students,
You are cordially invited to attend a Special Grand Rounds preceding the Research Fair on Friday, January 24th, at 4:00 PM in the Durell Peaden Auditorium.

This session will feature presentations by the Mayo Clinic and FSU PrimaryHealth™ Faculty.

Virtual Workshop: **Spatial Biology: Technologies, Analytics, & Applications**
Friday, January 31, 2025 / 10 an – 5:15 pm CST
Use this link to register by 5:00 PM on Tuesday, January 28 https://surveys.mayoclinic.org/jfe/form/SV_a3n0S7ZF5CVC9Rs
Once you register, you will be emailed the ZOOM link to participate.

SAVE THE DATE
SPORE Mini Retreat
Wednesday, February 12, 2025
1-5 pm CST
RST Location: Guggenheim 15-98
Virtual Option: TEAMS Link: Join the meeting now

PAST EVENTS

- 2025 SPORE GI Investigators Meeting
  Hosted by UNC at Chapel Hill
  January 9-10, 2025

COMMUNITY ENGAGEMENT AND DIVERSITY COUNCIL

Our SPORE continues to engage our patient communities in the catchment areas around Mayo Clinic-Rochester (Midwest), Mayo Clinic-FL, and Mayo Clinic-AZ via multiple initiatives.

Please contact Dr. Lewis Roberts at roberts.lewis@mayo.edu to get involved!

We value the participation of SPORE investigators, administrators, and especially our Patient Advocates.

RECENT PUBLICATIONS

Articles were identified through a PubMed search of Mayo investigators.

CMTM6 mediates the Warburg effect and promotes the liver metastasis of colorectal cancer. Shaha A, Wang Y, Wang X, Wang D, Guinovart D, Liu B, Kang N. Exp Mol Med. 2024 Sep;56(9):2002-2015. doi: 10.1038/s12276-024-01303-1. Epub 2024 Sep 2. PMID: 39218981; PMCID: PMC11447025.

Liver cancer multiomics reveals diverse protein kinase A disruptions convergently produce fibrolamellar hepatocellular carcinoma. Requena D, Medico JA, Soto-Ugaldi LF, Shirani M, Saltsman JA 3rd, **Torbenson MS**, Coffino P, **Simon SM**. Nat Commun. 2024 Dec 30;15(1):10887. doi: 10.1038/s41467-024-55238-2. PMID: 39738196; PMCID: PMC11685927.

Transposon-based oncogene integration in Abcb4(Mdr2)$^{-/-}$ mice recapitulates high susceptibility to cholangiocarcinoma in primary sclerosing cholangitis. Huang P, Wei G, Kirkpatrick JD, Lin Y, Tan L, Matta H, Nasser I, Huang M, Chen L, Petitjean M, Skelton-Badlani D, Gao W, Vaid K, Zhao S, Lugovskoy A, Alenzi M, Chen X, **Gores GJ**, Popov YV. J Hepatol. 2025 Jan;82(1):84-96. doi: 10.1016/j.jhep.2024.07.016. Epub 2024 Jul 30. PMID: 39089631; PMCID: PMC11655257.

Alcohol-associated liver disease: The time to act is now. Malhi H, **Gores GJ**. Hepatology. 2024 Dec 1;80(6):1305-1306. doi: 10.1097/HEP.0000000000001022. Epub 2024 Jul 17. PMID: 39018554.

Central role for cholangiocyte pathobiology in cholestatic liver diseases. Jalan-Sakrikar N, Guicciardi ME, O'Hara SP, Azad A, LaRusso NF, **Gores GJ**, Huebert RC. Hepatology. 2024 Sep 9. doi: 10.1097/HEP.0000000000001093. Epub ahead of print. PMID: 39250501.

Immunohistochemical basis for FAP as a candidate theranostic target across a broad range of cholangiocarcinoma subtypes. Jorgenson LC, **Torbenson MS,** Halfdanarson TR, **Kankeu Fonkoua LA**,

Tran NH, **Roberts LR, Smoot RL**, Goenka AH, Thompson SM. Front Nucl Med. 2024 Nov 27;4:1480471. doi: 10.3389/fnume.2024.1480471. PMID: 39664608; PMCID: PMC11631625.

Surgical and oncologic outcomes for liver resections of cystic neuroendocrine tumor liver metastasis. Ammann M, Adjei Antwi SK, Gudmundsdottir H, Hackl H, Santol J, Guillot BE, Pappalettera G, Thiels CA, **Warner SG**, Truty MJ, Kendrick ML, **Smoot RL**, Nagorney DM, Cleary SP, Halfdanarson TR, Starlinger PP. Eur J Surg Oncol. 2025 Jan;51(1):109464. doi: 10.1016/j.ejso.2024.109464. Epub 2024 Nov 15. PMID: 39580261.

Factor Antigen Improves Risk Stratification for Patients with a Diagnosis of Resectable Hepatocellular Carcinoma. Pereyra D, Mandorfer M, Santol J, Gregory L, Koeditz C, Ortmayr G, Schuetz C, Rumpf B, Ammon D, Laengle J, Schwarz C, Jonas JP, Pinter M, Lindenlaub F, Tamandl D, Thiels C, Warner S, **Smoot R**, Truty M, Kendrick M, Nagorney D, Cleary S, Gruenberger T, Reiberger T, Starlinger P. Von Willebrand Ann Surg Oncol. 2024 Oct;31(10):6526-6536. doi: 10.1245/s10434-024-15618-w. Epub 2024 Jun 19. PMID: 38896229.

Enhancing immune response and survival in hepatocellular carcinoma with novel oncolytic Jurona virus and immune checkpoint blockade. Tesfay MZ, Zhang Y, Ferdous KU, Taylor MA, Cios A, Shelton RS, Simoes CC, Watters CR, Barro O, Elliott NM, Mustafa B, Chamcheu JC, Graham AL, Washam CL, Alkam D, Gies A, Byrum SD, Giorgakis E, Post SR, Kelly T, Ying J, Moaven O, Chabu CY, Fernandez-Zapico ME, Duda DG, **Roberts LR**, Govindarajan R, Borad MJ, Cannon MJ, Basnakian AG, Nagalo BM. Mol Ther Oncol. 2024 Nov 26;32(4):200913. doi: 10.1016/j.omton.2024.200913. PMID: 39758249; PMCID: PMC11697550.

Cell-free DNA methylation-based inflammation score as a marker for hepatocellular carcinoma among people living with HIV. Kim K, Zheng Y, Joyce BT, Nannini DR, Wang J, Qu Y, Hawkins CA, Okeke E, Lesi OA, **Roberts LR**, Gursel DB, Abdulkareem FB, Akanmu AS, Duguru MJ, Davwar P, Nyam DP, Adisa RA, Imade G, Wei JJ, Kocherginsky M, Kim KY, Adeyemo WL, Odeghe E, Wehbe FH, Achenbach C, Sagay A, Ogunsola F, Murphy RL, Hou L. Hepatol Int. 2024 Dec 20. doi: 10.1007/s12072-024-10768-1. Epub ahead of print. PMID: 39704909.

Surveillance for Hepatocellular Carcinoma. **Roberts LR**. Clin Liver Dis. 2025 Feb;29(1):17-31. doi: 10.1016/j.cld.2024.09.001. Epub 2024 Oct 28. PMID: 39608955.

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Opposing regulation of the STING pathway in hepatic stellate cells by NBR1 and p62 determines the progression of hepatocellular carcinoma. Nishimura S, Linares JF, L'Hermitte A, Duran A, Cid-Diaz T, Martinez-Ordoñez A, Ruiz-Martinez M, Kudo Y, Marzio A, Heikenwalder M, **Roberts LR**, Diaz-Meco MT, Moscat J. Mol Cell. 2024 Dec 5;84(23):4660-4676.e10. doi: 10.1016/j.molcel.2024.09.026. Epub 2024 Oct 17. PMID: 39423823.

Severe acute liver disease in adults: Contemporary role of histopathology. Clouston AD, Gouw ASH, Tiniakos D, Bedossa P, Brunt EM, Callea F, Dienes HP, Goodman ZD, Hubscher SG, Kakar S, Kleiner DE, Lackner C, Park YN, Roberts EA, Schirmacher P, Terracciano L, **Torbenson M**, Wanless IR, Zen Y, Burt AD. Histopathology. 2024 Oct;85(4):549-561. doi: 10.1111/his.15212. Epub 2024 May 21. PMID: 38773813.

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REMINDERS

Acknowledge the HBC SPORE **P50 CA210964** in your abstracts, presentations, and publications.

LIVER SPORE CONTACTS

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