NIH NATIONAL CANCER INSTITUTE

CENTER TO REDUCE CANCER HEALTH DISPARITIES

CURE
CONTINUING UMBRELLA OF RESEARCH EXPERIENCES
A program of the National Institutes of Health

Professional Development Workshop & Mentored Mock Review

July 19-22, 2021

Transitioning to Independence: Charting Your Course to a Cancer Research Career

Welcome Letter

Dear Attendees:

On behalf of the National Cancer Institute (NCI) Center to Reduce Cancer Health Disparities (CRCHD), I am delighted to welcome you to the 2021 Professional Development Workshop and Mentored Mock Review (PDW & MMR). We chose this year's theme, "Transitioning to Independence: Charting Your Course to a Cancer Research Career," to provide you with an opportunity to learn about current hot topics in cancer research, pathways to research independence, and tools to successful scientific writing.

Over the course of the next few days, you will learn skills, tips, and techniques that will prepare you to be successful in attaining an independent research position and also equip you with fundamental proficiencies that can support you throughout your career. You will receive information about NCI's current cancer research priorities, acquire tools to build resilience as a successful cancer researcher, learn tips for navigating an independent cancer research career and building meaningful mentor-mentee relationships, and gain actionable skills and techniques for writing an effective grant proposal and high-impact manuscript. In addition, the Mentored Mock Review will provide you with invaluable insight into the NIH peer review process, what it takes to review and critique a grant application, and what constitutes a successful R01 grant.

Despite the virtual format, the 2021 PDW & MMR strongly encourages and will offer various opportunities for you to meet and interact with other Continuing Umbrella of Research Experiences (CURE) grantee attendees and NCI program staff. A flash talk session, along with two poster sessions, will give you a snapshot of the breadth of research CRCHD supports, and small meetups throughout the event will allow you time to build critical connections with fellow attendees.

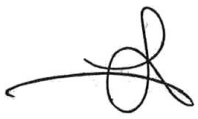
We trust that you will find the sessions to be informative and inspirational, and we hope that you leave the PDW & MMR with new knowledge and skills to chart your course to a successful cancer research career.

This year's workshop objectives are to:

- Promote awareness of NCI cancer research priorities
- Enhance skills for writing and publishing manuscripts in high-impact journals
- Increase understanding of the pathways for research independence within and outside of NCI
- Promote awareness of current NCI/NIH grants policies and guidelines
- Develop competencies for resilience in cancer research careers
- Provide opportunities for professional engagement among participants and NCI and NIH program staff
- Understand critical elements of mentor-mentee relationships for success.

We respect the skills and knowledge that each of you brings to this workshop and look forward to your active participation. We are confident that together we will make this a rewarding workshop that will further enhance a talented network of tomorrow's leaders in the cancer and cancer health disparities research workforce.

Sincerely,



Sanya A. Springfield, Ph.D.
Director, Center to Reduce Cancer Health Disparities

Agenda

Professional Development Workshop
Monday, July 19, 2021

All times listed in the agenda are eastern time.

1:00–1:15 PM **Welcome Remarks**
Dr. Alison Lin
NCI CRCHD

1:15–2:00 PM **Keynote Address**
Dr. John M. Carethers
University of Michigan

2:00–4:00 PM **Plenary Session: NCI Research Priorities and Hot Topics in Cancer**
Moderator: Dr. Tiffany Wallace
NCI CRCHD

2:00–3:00 PM **Presentations by**
Dr. Robert T. Croyle
NCI Division of Cancer Control and Population Sciences (DCCPS)

Dr. Ron Johnson
NCI Division of Cancer Biology (DCB)

Dr. Vikrant Sahasrabuddhe
NCI Division of Cancer Prevention (DCP)

Dr. Pushpa Tandon
NCI Division of Cancer Treatment and Diagnosis (DCTD)

3:00–3:15 PM **Discussion**

3:15–4:00 PM Breakout Sessions – Attendee's Choice

4:00–4:15 PM **Break and Evaluation**

4:15–5:15 PM **Flash Talks**
Moderators: Drs. Hana Odeh and Maria Jamela Revilleza
NCI CRCHD

5:15–5:30 PM **Evaluation and Adjournment of Day 1**

Agenda

Professional Development Workshop
Tuesday, July 20, 2021

All times listed in the agenda are eastern time.

12:00–12:45 PM **Poster Session I (Odd Numbers)**

12:45–1:00 PM **Break**

1:00–1:15 PM **Recap of Day 1 and Flash Talk Awards**
Dr. Mary Ann S. Van Duyn
NCI CRCHD

1:15–2:30 PM **Panel Discussion: The Nuts and Bolts of Publishing a Manuscript**
Moderator: Dr. Anil Wali
NCI CRCHD

1:15–2:00 PM **Presentations by**
Dr. Barnett S. Kramer
Senior Scientific Advisor, NCI DCCPS

Dr. Jamie Wilson
Chief Editor, Nature Immunology

Dr. Christopher Li
Senior Editor, Cancer Epidemiology, Biomarkers & Prevention

2:00–2:30 PM **Discussion**

2:30–3:30 PM **Panel Discussion: Navigating an Independent Research Career at NCI**
Moderator: Dr. Jessica Calzola
NCI CRCHD

2:30–3:00 PM **Presentations by**
Dr. Nirali N. Shah
Lasker Clinical Research Scholar, NCI Center for Cancer Research (CCR)

Dr. Natalie Porat-Shliom
Earl Stadtman Investigator, NCI CCR

Dr. Mitchell Machiela
Earl Stadtman Investigator, NCI Division of Cancer Epidemiology and Genetics (DCEG)

3:00–3:30 PM **Discussion**

Agenda

3:30–3:40 PM **Break and Evaluation**

3:40–4:40 PM **Panel Discussion: Navigating an Independent Research Career Outside NCI**
Moderator: Dr. Samson Gebreab
NCI CRCHD

3:40–4:20 PM **Presentations by**
Dr. Brian Gonzalez
H. Lee Moffitt Cancer Center

Dr. Sophia George
Leonard M. Miller School of Medicine, Sylvester Comprehensive Cancer Center, University of Miami

Dr. Cathrine Hoyo
North Carolina State University

4:20–4:40 PM **Discussion**

4:40–5:20 PM **Breakout Discussion: Building a Meaningful Mentoring Relationship**
Moderator: Dr. Eric Johnson Chavarria
NCI CRCHD

5:20–5:30 PM **Evaluation and Adjournment of Day 2**

Agenda

Professional Development Workshop
Wednesday, July 21, 2021

All times listed in the agenda are eastern time.

12:00–12:45 PM **Poster Session II (Even Numbers)**

12:45–1:00 PM **Break and Evaluation**

1:00–1:15 PM **Recap of Day 2 and Action Items on Mentoring**
Dr. LeeAnn Bailey
NCI CRCHD

1:15–2:15 PM **Plenary Interactive Session: Building Resilience and Wellness in Cancer Research Careers**
Ms. Jennifer Wiggins
NIH Office of Intramural Training and Education (OITE)

Moderator: Ms. Sandra L. San Miguel
NCI CRCHD

2:15–3:00 PM **Plenary Session: NCI Grants Policy Updates**
Moderator: Dr. Anthony DiBello
NCI CRCHD

2:15–2:30 PM **Presentations by**
Dr. Anandarup Gupta
NCI Division of Extramural Activities

Mr. Shane Woodward
NCI Office of Grants Administration

2:30–3:00 PM **Discussion**

3:00–3:15 PM **Break and Evaluation**

3:15–5:15 PM **Plenary Interactive Session: Dramatic Grant Writing: Not Your Mother's Boring Grant Session**
Dr. Victoria L. Seewaldt
City of Hope Comprehensive Cancer Center

Dr. Robert Winn
Massey Cancer Center, Virginia Commonwealth University

Agenda

Grant Writing Team
Dr. Sophia George
Leonard M. Miller School of Medicine, Sylvester Comprehensive Cancer Center, University of Miami

Dr. Venkat Krishnan
Genentech

Dr. Amy Leung
Beckman Research Institute, City of Hope Comprehensive Cancer Center

Dr. Deborah Gail Lefkowitz
University of California, Riverside

Moderators: Drs. Jessica Calzola and Alison Lin
NCI CRCHD

5:15–5:30 PM **Closing Remarks, Evaluation, and Adjournment**
Drs. Sanya A. Springfield and H. Nelson Aguila
NCI CRCHD

Agenda

PDW Mentored Mock Review
Thursday, July 22, 2021

All times listed in the agenda are eastern time.

1:00–1:10 PM **Introductions**
Dr. Mulualem Tilahun
NCI CRCHD

1:10–1:30 PM **Reviewer Orientation**
Dr. Svetlana Kotliarova
NIH Center for Scientific Review (CSR)

1:30–3:10 PM **Mock Review Exercise**
Dr. Svetlana Kotliarova
NIH CSR

Moderators: Drs. Mulualem Tilahun and Anthony DiBello
NCI CRCHD

1:30–2:00 PM Review of Application #1 by Group 1

2:05–2:35 PM Review of Application #2 by Group 2

2:40–3:10 PM Review of Application #3 by Group 3

3:10–3:20 PM **Break and Evaluation**

3:20–4:10 PM **Introduction to the Early Career Reviewer Program**
Moderator: Dr. Mulualem Tilahun
NCI CRCHD

3:20–3:50 PM **Presentation by**
Dr. Svetlana Kotliarova
NIH CSR

3:50–4:10 PM **Discussion**

Agenda

4:10–5:00 PM **Panel Discussion**
Moderator: Dr. Anthony DiBello
NCI CRCHD

Dr. Svetlana Kotliarova
NIH CSR

Dr. Susan A. McCarthy
NCI DCB

Dr. Vikrant Sahasrabuddhe
NCI DCP

Dr. Mulualem E. Tilahun
NCI CRCHD

Dr. Anil Wali
NCI CRCHD

Dr. Tiffany Wallace
NCI CRCHD

5:00–5:15 PM **Evaluation and Adjournment of Mock Review Session**

Speaker Bios

PDW Main Workshop Presenter Bios

Sanya A. Springfield, Ph.D.—Director, CRCHD, NCI

Dr. Springfield is Director of NCI's Center to Reduce Cancer Health Disparities, where she supports programs, initiatives, and activities to spawn cancer health disparities research, increase workforce diversity, and create networks for community outreach, education, and engagement. Within NCI, she is a member of the Scientific Program Leadership (SPL), where she champions the need for continued investment for diversity training and education programs and to reduce cancer health disparities. She previously served as Chief of the NCI Diversity Training Branch, where she conceived, implemented, and oversaw the Continuing Umbrella of Research Experiences (CURE) program. Utilizing a unique, holistic, training pipeline approach, CURE seeks to increase the number of competitive cancer researchers from racial and ethnically diverse and other underserved populations. Dr. Springfield expanded the CURE program by launching a middle school program as part of a CURE early intervention strategy and an Intramural CURE (iCURE) program aimed at enhancing the diversity of the NCI intramural research workforce. Prior to this, Dr. Springfield had expanded the diversity training landscape through creation and implementation of the Partnerships to Advance Cancer Health Equity (PACHE). PACHE aims to improve the cancer research infrastructure at institutions serving underserved health disparity populations and underrepresented students (ISUPS) and enhance the ability of NCI-Designated Cancer Centers to address cancer health disparities in their communities.

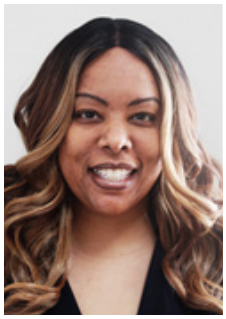
Dr. Springfield serves on a variety of trans-NIH/NCI scientific and programmatic committees focused on increasing workforce diversity. For her vision and leadership in promoting diversity in biomedical research, she was honored with the NIH Director's Award and the NCI Director's Award. Dr. Springfield also serves as a member of the American Association for Cancer Research (AACR) Minorities in Cancer Research (MICR) and the Science Education and Career Development Committee, and played a vital role in establishing the annual AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved.

Dr. Springfield received her Ph.D. in physiology and biophysics from Howard University and was the third African-American neuroscientist in the world. After completing her postdoctoral studies at the Robert Wood Johnson School of Medicine, she joined the faculty at City College of New York. Dr. Springfield left the academic ranks to serve as a Program Director at the National Science Foundation, and then entered NIH as a Grants Associate, after which she joined NCI.

H. Nelson Aguila, D.V.M.—Deputy Director, CRCHD, NCI

Dr. Aguila is Deputy Director of the National Cancer Institute's CRCHD. In this capacity, he plays a central role in coordination of the day-to-day functions of the Center and development of strategic planning, priority-setting, and management of CRCHD's disparities research, diversity training, and community education/outreach efforts. Previously, Dr. Aguila served as Chief of CRCHD's Diversity Training Branch. Prior to coming to NIH, Dr. Aguila worked at the Food and Drug Administration as a Reviewer Toxicologist at the Center for Veterinary Medicine. Earlier in his career, he held senior research scientist positions in neuropathology at the University of Miami and later in cancer gene therapy at Aventis-Gencell. Dr. Aguila earned his Doctor of Veterinary Medicine degree at Austral University in Chile and trained as a neurobiologist at The University of Texas Southwestern Medical Center, Dallas.

Speaker Bios



LeeAnn Bailey, M.B.B.S., M.S., Ph.D.—Chief, Integrated Networks Branch, CRCHD, NCI

Dr. Bailey has been Chief of the Integrated Networks Branch of NCI's CRCHD since 2016. In this role, she manages, develops, and assesses strategies for enhancing the integration and dissemination of diversity training, women's health, and sexual and gender minority efforts within and across NCI, as well as within the scientific community and underserved communities through NCI-supported networks. She also identifies and leverages opportunities to address unmet needs in cancer health disparities research. Prior to joining NCI, she was a healthcare consultant at Deloitte Consulting LLP. She also has been a Principal Investigator researching tissue engineered products and cellular inflammatory responses at the National Institute of Standards and Technology as well as an adjunct professor at Morgan State University. Dr. Bailey received her M.B.B.S (M.D. equivalent) from the University of Adelaide Medical School with an emphasis on aboriginal health and pediatric oncology. She also has a Ph.D. in biochemistry and molecular genetics and an M.S. in biological and physical sciences from the University of Virginia School of Medicine.

John M. Carethers, M.D., M.A.C.P.—John G. Searle Professor and Chair, Department of Internal Medicine, University of Michigan

Dr. Carethers is the John G. Searle Professor and Chair of the Department of Internal Medicine at the University of Michigan. He received his B.S. in biological sciences with a minor in chemistry from Wayne State University and his M.D. with high distinction from the same institution. Dr. Carethers completed internship and residency in internal medicine at Massachusetts General Hospital, followed by a fellowship in gastroenterology at the University of Michigan. He was then recruited to the University of California, San Diego (UCSD), where he grew his laboratory-based research in the area of DNA mismatch repair and colorectal cancer pathogenesis and cared for general medicine and gastroenterology patients. His leadership roles included gastroenterology fellowship director, gastroenterology Section Chief for the San Diego VA Hospital, then Division Chief for the University of California, San Diego, before being recruited to Michigan. Dr. Carethers' research interests are focused on the genetics and pathogenesis of colorectal cancers. He also has interest in colorectal cancer disparities as they relate to genetics and outcomes. He has published over 250 manuscripts and book chapters. He is the former Principal Investigator of the San Diego State University/UCSD Cancer Center Comprehensive Partnership U54 grant, which addresses cancer disparities, and was the founding Director of the NIH-funded UCSD Gastroenterology Center grant. He was Senior Associate Editor for *Gastroenterology*, was President of the American Association of Physicians, and will be President of the American Gastroenterological Association in 2022. He is an elected member of the National Academy of Medicine and the American Academy of Arts & Sciences.

Speaker Bios

Jessica Calzola, P.M.P., Ph.D.—Program Director, CRCHD, NCI

Dr. Calzola has been a Program Director in the Office of the Director of NCI's CRCHD since 2019. In this role, her primary responsibility is program management for the Intramural Continuing Umbrella of Research Experiences program. Prior to joining NCI, Dr. Calzola was a Program Manager with Leidos, supporting the Army's Medical Research Program in Systems Biology at Fort Detrick in Frederick, MD. She also had a previous role providing project and program management support to the Congressionally Directed Research Program (CDMRP)—specifically, the Parkinson's Research Program—as well as the Joint Program Committee-6/Combat Casualty Care Research Program (JPC-6/CCCRP). In these roles she helped recruit, coordinate, and execute programmatic review meetings and other program requirements. Dr. Calzola earned her B.S. in biochemistry from Juniata College in Pennsylvania. As an undergraduate, she was selected for the National Institutes of Health Undergraduate Scholarship Program, in which she conducted basic research for a summer with Dr. Susan Gottesman at NCI. Dr. Calzola then went on to get her Ph.D. in microbiology and molecular genetics from Rutgers University. Her postdoctoral training was done in the Proteomic section of the Laboratory of Systems Biology at the National Institute of Allergy and Infectious Diseases, where she worked on modeling toll-like receptor 4 signaling.

Robert T. Croyle, Ph.D.—Director, Division of Cancer Control and Population Sciences, NCI

Dr. Croyle was appointed Director of the Division of Cancer Control and Population Sciences (DCCPS), NCI, in July 2003. In this role, he is responsible for overseeing a research portfolio and operating budget of more than a half billion dollars and serves on NCI's Scientific Program Leaders Committee. As a Division, DCCPS covers a wide range of scientific domains and disciplines, including epidemiology, behavioral science, surveillance and statistics, cancer survivorship, and health services and outcomes research. He previously served as the Division's Associate Director for the Behavioral Research Program, leading its development and expansion. Before coming to NCI in 1998, Dr. Croyle was Professor of Psychology and a member of the Huntsman Cancer Institute at the University of Utah in Salt Lake City. Prior to that, he was a visiting investigator at the Fred Hutchinson Cancer Research Center in Seattle, visiting Assistant Professor of Psychology at the University of Washington, and Assistant Professor of Psychology at Williams College in Massachusetts.

Dr. Croyle received his Ph.D. in social psychology from Princeton University in 1985, and graduated Phi Beta Kappa with a B.A. in psychology from the University of Washington in 1978. His research has examined how individuals process, evaluate, and respond to cancer risk information, including tests for inherited mutations in *BRCA1* and *BRCA2*. His research has been published widely in professional journals in behavioral science, public health, and cancer, and he has edited two volumes: *Mental Representation in Health and Illness* (1991) and *Psychosocial Effects of Screening for Disease Prevention and Detection* (1995). He is co-editor of the *Handbook of Cancer Control and Behavioral Science* (2009) and co-author of *Making Data Talk: Communicating Data to The Public, Policy Makers and The Press* (2009). He is also co-editor of *Strategies for Team Science Success* (2019). Dr. Croyle is a member of the Academy of Behavioral Medicine Research, a Fellow of the Society of Behavioral Medicine, a Fellow of the American Psychological Association (APA), a Fellow of the American Psychological Society, and a recipient of several awards for his research and professional service. His efforts on journal editorial boards include being associate editor for *Cancer Epidemiology*, *Biomarkers and Prevention*, and consulting editor for *Health Psychology* and the *British Journal of Health Psychology*. Dr. Croyle received the APA Nathan Perry Career Service to Health Psychology Award in 2009 and an APA Presidential Citation for science and leadership in 2012. He received the NIH Merit Award in 1999, 2002, and 2008; the NIH Director's Award in 2000 and 2015; and the NIH Office of the Director Honor Award in 2013. In 2014, he received the Distinguished Achievement Award and, in 2021, the Distinguished Service Award from the American Society of Preventive Oncology.

Speaker Bios

Anthony DiBello, Ph.D.—Program Director, CRCHD, NCI

Dr. DiBello has been a Program Director in the Diversity Training Branch of NCI's CRCHD since October 2020. He is primarily responsible for managing the Kirschstein NRSA Predoctoral Fellowship to Promote Diversity in Health-Related Research (F31 - Diversity) program for NCI. In this role, he also supports portfolio analysis and program evaluation efforts. Prior to joining NCI, Dr. DiBello served as a Data Management and Research Officer at the International Monetary Fund (IMF) and the World Bank. While at IMF/World Bank, Dr. DiBello conducted interdisciplinary research focused on relationships between environmental health, climate, economic inequality, and economic/social welfare. Before joining the IMF, Dr. DiBello spent years, first at the Johns Hopkins University School of Medicine and later at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), conducting biomedical research investigating the mechanisms that govern ubiquitin signaling and its role in responding to cell stress and DNA damage. Dr. DiBello earned a dual B.S. in physics and mathematics, as well as a B.A. in philosophy, from Northern Kentucky University. He received his Ph.D. in biophysics and biophysical chemistry from the Johns Hopkins University School of Medicine, where he completed his thesis on the regulation of ubiquitin conjugation and removal. His postdoctoral training, completed at NIDDK, focused on an investigation into the regulation of the cellular response to misfolded protein stress by ubiquitin signaling.

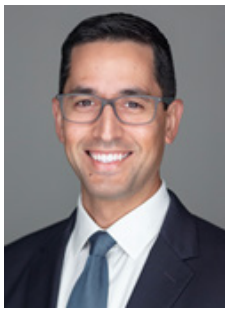
Samson Gebreab, M.Sc., Ph.D.—Program Director, CRCHD, NCI

Dr. Gebreab has been a Program Director in the Diversity Training Branch of NCI's CRCHD since 2020. In this role, he contributes to the grant management of Feasibility Studies to Build Collaborative Partnerships in Cancer Research (P20), NCI Research Supplements to Promote Diversity in Health-Related Research, and NCI Supplements to Promote Reentry into Biomedical and Behavioral Research Careers, and conducts analyses on research activities and funding addressing cancer health disparities and minority health. Prior to joining CRCHD, Dr. Gebreab worked as a Mathematical Statistician at the Center for Tobacco Products, U.S. Food and Drug Administration (FDA). In this role, he served on FDA's lead working groups on sampling design and data analyses and data delivery for the PATH Study and scientific reviewer for tobacco-related regulatory research projects. Prior to joining FDA, Dr. Gebreab was a Staff Scientist at the National Human Genome Research Institute (NHGRI) and served as an Associate Investigator in Genomics, Environmental and Social Determinants of Cardiovascular Disease in African Americans. While at NHGRI, his research focused on health disparities, especially in African Americans, examining the impact of socioeconomic position across lifespan, psychosocial factors, behavior, and neighborhood social and physical environments on health disparities and understanding the biological mechanisms contributing to racial/ethnic disparities in health outcomes. He was also actively involved in managing protocols and databases and mentoring summer students and postdoctoral fellows. Earlier in his career, Dr. Gebreab served as a Biostatistician/Epidemiologist on the Jackson Heart Study. He received his M.Sc. in geographic information science from Wageningen University, the Netherlands, and joint M.Sc. and Ph.D. degrees in statistics and spatial epidemiology from Utah State University. Dr. Gebreab completed a postdoctoral research fellowship at the University of Michigan School of Public Health, where he studied the influence of social determinants, such as socioeconomic status, neighborhood characteristics, and psychosocial factors, on cardiovascular outcomes.

Speaker Bios

Sophia George, Ph.D.—Associate Professor, Division of Gynecological Oncology, Department of Obstetrics and Gynecology, Leonard M. Miller School of Medicine, Sylvester Comprehensive Cancer Center, University of Miami

Dr. George is a molecular geneticist graduate from the University of Toronto, Ontario, Canada. She did postdoctoral training in molecular pathology in Gynecological Pathology at Princess Margaret Cancer Center within the Ontario Cancer Institute and a second postdoc at Duke University in the Department of Medical Oncology in hereditary breast cancer syndrome. She began her faculty position at the University of Miami, Miller School of Medicine in 2015. She is a Department of Defense Ovarian Cancer Academy Awardee. Her research interests lie in studying the pathogenesis of sporadic and hereditary breast and ovarian cancers. Dr. George has built a program of research in hereditary breast and ovarian cancers focused on women from the African Diaspora. Her innovative integrative approach to diseases affecting women of color uses molecular epidemiology and translational and basic sciences. The population of women she studies will swing the pendulum from having worse outcomes to increasing prevention, increasing inclusiveness in biomedical studies, and improving overall survival through the study of their genomes, cells, and communities. Dr. George is a native of the Caribbean and is part of a multidisciplinary team who studies the incidence of hereditary breast and ovarian cancer syndrome genetic mutations in Afro-Caribbean nationals. She is a co-leader of the Women's Cancer Working Group in the African Caribbean Cancer Consortium and co-Principal Investigator of the Transatlantic Gynecologic Cancer Research Consortium.



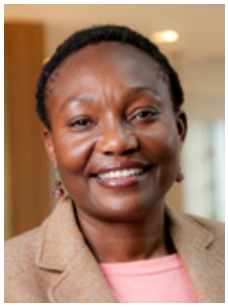
Brian Gonzalez, Ph.D.—Associate Member, H. Lee Moffitt Cancer Center

Dr. Gonzalez is an Associate Member at Moffitt Cancer Center. He aims to improve quality of life in cancer survivors and focuses on reducing disparities in quality of life. He develops risk prediction models to identify which cancer survivors are most likely to experience deterioration in quality of life and also creates interventions to improve quality of life using digital technologies.

Anandarup Gupta, Ph.D.—Program Coordinator, Scientific Review and Referral Officer, Division of Extramural Activities, NCI

Dr. Gupta is a Program Coordinator, Scientific Review and Referral Officer in the Division of Extramural Activities at the National Cancer Institute. He joined NCI in 2007. Prior to his current position at NCI, he was an Assistant Professor at the University of Maryland, Baltimore. He obtained his Ph.D. from the University of Connecticut in physiology, followed by postdoctoral fellowships at Yale University and Washington University in St. Louis. As a Program Coordinator, his primary responsibilities include coordination of the development, clearance, and publication of program initiatives as Funding Opportunity Announcements, including associated concepts and *NIH Guide* notices. As a Scientific Review Officer, Dr. Gupta's major responsibilities include conducting the Loan Repayment Program (LRP) reviews for NCI. LRPs are a set of programs established by Congress and designed to recruit and retain highly qualified health professionals into biomedical or biobehavioral research careers. As a Referral Officer, Dr. Gupta assists in the referral of NCI-assigned applications to the appropriate cancer activity areas across NCI's extramural Divisions, Offices, and Centers.

Speaker Bios



Cathrine Hoyo, M.P.H., Ph.D.—Professor of Epidemiology; Co-Director, Integrated Health Sciences Facility Core; Director, Epidemiology and Environmental Epigenomics Laboratory, North Carolina State University

Dr. Hoyo is a Professor of Epidemiology in the Department of Biological Sciences, Co-Director of the Integrated Health Sciences Facility Core in the Center for Human Health and the Environment, and Director of the Epidemiology and Environmental Epigenomics Laboratory at North Carolina State University. A former CURE K01 recipient, Dr. Hoyo's influential research improves our understanding of how early development influences the risk of common chronic diseases, particularly those that exhibit racial/ethnic differences in incidence and/or mortality, including in certain cancers. Dr. Hoyo's group takes a two-pronged approach to this work—both following a cohort of newborns from the first trimester in order to pinpoint epigenetic targets, as well as conducting population-based, case-control studies of cancer in adults to assess to what extent the epigenetic targets contribute to these cancers in adulthood.

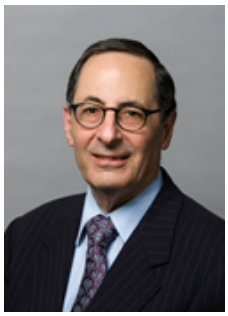
Ron Johnson, Ph.D.—Program Director, DNA and Chromosome Aberrations Branch, Division of Cancer Biology, NCI

Dr. Johnson is a Program Director in the DNA and Chromosome Aberrations Branch in the Division of Cancer Biology, National Cancer Institute. He oversees a portfolio of cancer biology research awards related to chemical and physical carcinogens, DNA damage, and gene expression with a focus on lung and liver cancers. Before joining NCI in 2011, Dr. Johnson was a Project Team Leader at the NIH Chemical Genomics Center, where his group profiled and screened small-molecule libraries using cell- and protein-based assays. Prior to his work at the National Institutes of Health, Dr. Johnson led research groups studying cell signaling in cancer and developmental biology in biotechnology and academic settings. He received a Ph.D. in biochemistry from the Johns Hopkins School of Medicine and completed postdoctoral studies in developmental biology at the Stanford School of Medicine.

Eric Johnson Chavarria, Ph.D.—Program Director, CRCHD, NCI

Dr. Johnson Chavarria has been a Program Director for the Intramural Continuing Umbrella of Research Experiences (iCURE) program within NCI's CRCHD since August 2019. In this role, he contributes to the iCURE program as lead training navigator and mentoring network coordinator for postbaccalaureate, graduate, and postdoctoral iCURE scholars. Prior to joining CRCHD, Dr. Johnson Chavarria served as an American Association for the Advancement of Science (AAAS) Science & Technology Policy Fellow in the Division of Cancer Biology (DCB) at NCI. While in DCB, he leveraged open innovation approaches to bridge emerging technology to address health challenges. These approaches included innovation labs and challenge prize competitions. Innovation labs are 5-day residential workshops that bring together investigators from disparate fields for collaboration to address intractable data and health problems. Challenge prize competitions, specifically data related, allow researchers across different fields to address health-related challenges by developing algorithms or tools to overcome barriers in data and metadata management, curation, and aggregation. Dr. Johnson Chavarria received his B.S. in physics from The University of Texas, San Antonio and his Ph.D. in biophysics from the University of Illinois, Urbana-Champaign for work developing an automated microfluidic platform for confinement of single cells in free solution using planar extensional flow. He then went on to complete postdoctoral research at Yale University in the Molecular Biophysics and Biochemistry Department, focusing on actin cytoskeleton force modulation and regulatory protein interactions under microfluidic flow induced tension.

Speaker Bios



Barnett S. Kramer, M.D., M.P.H.—Senior Scientific Advisor, Division of Cancer Control and Population Sciences, NCI

Dr. Kramer is the former Director of the Division of Cancer Prevention at the National Cancer Institute. He was Editor-in-Chief of the *Journal of the National Cancer Institute* (JNCI) from 1994–2012. He also served as Editor-in-Chief of NCI's Physician Data Query (PDQ) Editorial Board on Screening and Prevention and is a current member of that Board, as well as the PDQ Adult Treatment Editorial Board. He has extensive experience in primary cancer prevention studies as well as clinical screening trials of lung, ovarian, breast, and prostate cancers. He served as an investigator and was on the steering committee for two large practice-changing cancer screening trials sponsored by NCI: the Prostate, Lung, Colorectal, Ovarian (PLCO) Trial and the National Lung Screening Trial (NLST). His research interests also include the investigation of screening-detected cancers that are so indolent that they have little or no lethal potential for the person in whom they are detected (a phenomenon known as "cancer overdiagnosis"). He has a strong interest in weighing and reporting the strength of medical evidence and created a Medicine in the Media Workshop to help working journalists develop methods of reporting medical evidence, which ran for over a decade. Dr. Kramer often serves as a media contact for stories on cancer prevention, screening, cancer overdiagnosis, and critical evaluation of the literature.

Venkat Krishnan, Ph.D.—Senior Scientist, Genentech

Dr. Krishnan is currently a Senior Scientist in Cancer Immunotherapy at Genentech. His research interests are focused on identifying and implementing biomarkers in clinical trials of breast and gynecologic cancers. Dr. Krishnan graduated with a Ph.D. from Penn State University and received further training at the University of Chicago and Stanford, where he carried out preclinical validation studies and identified signals that could be used as biomarkers for ovarian cancer immunotherapy.

Deborah Gail Lefkowitz, Ph.D.—Assistant Professional Researcher, University of California, Riverside

Dr. Lefkowitz is an Assistant Professional Researcher at the University of California, Riverside in the Center for Health Disparities Research and Department of Anthropology. She received her B.A. summa cum laude in visual and environmental studies from Harvard University and her Ph.D. in social ecology from the University of California, Irvine. Her community-engaged research focuses on cancer survivorship, qualitative methods, and access to health, information, and legal services for medically underserved populations. She received a Ruth L. Kirschstein National Research Service Award from the National Cancer Institute (2016-2018) and a fellowship from the University of California Humanities Research Institute (2015) for her dissertation research. This interdisciplinary research examined breast cancer service delivery challenges and post-treatment needs in inland Southern California. In 2019, she received the Dean's Inclusive Excellence Research Award in recognition of her extensive community outreach to include patients/survivors consistently underrepresented in cancer research. Currently, Dr. Lefkowitz is Lead Researcher on a National Institute on Minority Health and Health Disparities Administrative Supplement; she employs a social ecological framework to investigate how low-income Southern Californians are seeking and obtaining health information during the COVID-19 pandemic. She is certified as an Oncology Patient Navigator–Certified Generalist through the Academy of Oncology Nurse & Patient Navigators and serves on the national Advisory Committee for the Cancer Legal Resource Center. The National Institute on Minority Health and Health Disparities selected her as a 2021 Health Disparities Research Scholar.

Speaker Bios

Amy Leung, Ph.D., Assistant Professor, Beckman Research Institute, City of Hope Comprehensive Cancer Center

Dr. Leung is an Assistant Professor at Beckman Research Institute at City of Hope. Utilizing both wetlab and computational approaches, her research focuses on understanding how retrotransposons are regulated in normal cells and how dysregulation of retrotransposons arise and contribute to development of cancer and metabolic diseases. She has published studies finding retrotransposons as important mediators of disease-related transcriptional networks. Prior to her current position, she received her doctorate from Cold Spring Harbor Laboratory School of Biological Sciences where she focused on the role of chromatin modifications in regulating transcription and chromosome organization and completed her postdoctoral work examining the role of long noncoding RNAs in obesity and diabetic complications.

Christopher Li, M.D., Ph.D.—Senior Editor, *Cancer Epidemiology, Biomarkers & Prevention*

Dr. Li completed his M.D. at the University of California, San Francisco and his Ph.D. in epidemiology at the University of Washington. He is a Full Professor at the Fred Hutchinson Cancer Research Center and is a Research Full Professor in the Department of Epidemiology at the University of Washington. His research spans breast and colorectal cancer early detection, screening, etiology, and survivorship. His work has identified novel risk factors related to the development of cancer and has evaluated the molecular features of cancer that are associated with poor outcomes. He also investigates the causes of disparities in cancer incidence, treatment, and mortality. Additionally, Dr. Li co-leads the Seattle-Puget Sound National Cancer Institute-funded Surveillance, Epidemiology, and End Results (SEER) cancer registry; the Coordinating Center for NCI's Population-based Research to Optimize the Screening Process (PROSPR) consortium focused on improving screening for cervical, colorectal, and lung cancers; and a Clinical Validation Center in NCI's Early Detection Research Network. In June 2019 Dr. Li was named the Hutch's inaugural Faculty Director of the Office of Diversity, Equity & Inclusion. He provides ongoing direct mentorship to minority researchers and also leads a supplement to the Cancer Center Support Grant focused on supporting the career development of underrepresented minority trainees and junior faculty in academic institutions all along the west coast through NCI's Geographic Management of Cancer Health Disparities Program. Nationally, he has served as both a member and Chair of the American Association for Cancer Research's (AACR) Minorities in Cancer Research Council. He also Co-Chaired AACR's annual conference on the Science of Cancer Health Disparities.

Alison Lin, Ph.D.—Acting Chief, Diversity Training Branch, CRCHD, NCI

Dr. Lin is Acting Chief of the Diversity Training Branch (DTB) of NCI's CRCHD. In this capacity, she plays a central role in the strategic planning of the Branch and program implementation to enhance workforce diversity in cancer research. Dr. Lin oversees management of NCI's diversity-focused training programs, including both the extramural Continuing Umbrella of Research Experiences (CURE) program and the Intramural CURE (iCURE) program. Previously, she served as Program Director in DTB since 2012 and led the development, implementation and management of the Youth Enjoy Science (YES) Research Education Program (R25) and the iCURE program. She also led management of the NCI Research Supplements to Promote Diversity in Health-Related Research and the NCI Supplements to Promote Reentry into Biomedical and Behavioral Research Careers. Prior to joining NCI, Dr. Lin served as an Instructor in Medicine at Harvard Medical School in Boston, where she conducted interdisciplinary research focused on understanding the molecular interactions of membrane proteins and their signaling mechanisms, particularly those that

modulate the cytoskeleton. Dr. Lin received her Ph.D. in physics/biophysics from the University of California, Santa Barbara for work on the optimization of non-viral cationic lipid DNA carriers in gene delivery. She received her B.S. in physics, summa cum laude, from the University of Minnesota, Twin Cities.

Mitchell Machiela, Sc.D., M.P.H.—Earl Stadtman Investigator, Division of Cancer Epidemiology and Genetics, NCI

Dr. Machiela received his M.P.H. in epidemiology from the University of Michigan and his Sc.D. in epidemiology from the Harvard T.H. Chan School of Public Health. He was appointed to the position of Earl Stadtman Tenure-Track Investigator in 2017.
Dr. Machiela's research is focused on understanding the role of inherited variation and acquired mutations in cancer risk. He is leading studies of large-scale genetic mosaicism to investigate the causes of acquired mosaic chromosomal alterations and their impact on cancer risk. Acquired mosaic chromosomal alterations have abundant potential to inform cancer etiology and drive oncogenic change. Dr. Machiela has found evidence suggesting mosaicism increases cancer risk for hematologic malignancies and select solid tumor subtypes. His research program continues to examine the influence of mosaicism on cancer risk in special exposure populations and various tissue types. He also conducts and analyzes genetic association studies to investigate the underlying genetic architecture of cancer (e.g., pediatric and adult cancers). Dr. Machiela is leading a genome-wide association study (GWAS) on Ewing sarcoma to identify susceptibility regions and elucidate the underlying genetic architecture and is also performing pan-cancer GWAS on adult malignancies in the Prostate, Lung, Colorectal, Ovarian (PLCO) study. Dr. Machiela is the creator of a web-based tool, LDlink, which interactively examines linkage disequilibrium in diverse population groups.

Hana Odeh, Ph.D.—Training Navigator and Program Director, CRCHD, NCI

Dr. Odeh is a Training Navigator and Program Director for NCI's Center to Reduce Cancer Health Disparities. In her role as a Training Navigator, she works closely with trainees and investigators to assess individual training needs and provide guidance in identifying Continuing Umbrella of Research Experiences (CURE) funding opportunities tailored to the investigator's career stage, as well as other NCI funding and career development opportunities. In her role as a Program Director, she provides programmatic expertise for the Feasibility Studies to Build Collaborative Partnerships in Cancer Research (P20) and the Comprehensive Partnerships to Advance Cancer Health Equity (CPACHE U54) programs. Additionally, Dr. Odeh works closely with the CURE Program Directors in CRCHD, across NCI/NIH, and with the Geographical Management of Cancer Health Disparities program regional coordinators to develop career development opportunities, grantsmanship/career development workshops, and other programmatic initiatives to advance workforce diversity. Prior to joining CRCHD, she provided experimental design and project management support for NCI's Biorepositories and Biospecimen Research Branch.
Dr. Odeh also served at the National Heart, Lung, and Blood Institute's (NHLBI's) Office of the Scientific Director (OSD) within the Intramural Program. At the NHLBI OSD, she worked closely with the Promotion and Tenure Committee and the Board of Scientific Counselors. Dr. Odeh received her Ph.D. in cell and developmental biology, followed by postdoctoral fellowships in breast and prostate cancer at the University of Michigan in Ann Arbor.

Speaker Bios

Natalie Porat-Shliom, M.Sc., Ph.D.—Earl Stadtman Investigator, Center for Cancer Research, NCI

Dr. Porat-Shliom is an Earl Stadtman Investigator in the Center for Cancer Research at the National Cancer Institute. She received her B.Sc. in biology, M.Sc. in neurobiology, and Ph.D. in cell biology from Tel-Aviv University, Israel. Her Ph.D. research was performed at the National Heart, Lung, and Blood Institute, through the Graduate Partnerships Program. She studied endocytosis and the role of endosomes in Ras signaling using live cell imaging. Her postdoctoral training was performed at the National Institute of Dental and Craniofacial Research, where she specialized in intravital microscopy, the study of cellular processes in live anesthetized mice. She applied this cutting-edge technology to study mitochondrial dynamics and function in the salivary gland, for which she received the NIH Pathway to Independence Award (K99/R00). In 2018, Dr. Porat-Shliom joined the National Cancer Institute as an Earl Stadtman Investigator. Her laboratory is studying the regulation of mitochondrial biology in the liver in response to metabolic stress using different light microscopy techniques.

Maria Jamela (Jay) R. Revilleza, Ph.D.—Program Director, CRCHD, NCI

Dr. Revilleza joined the Integrated Networks Branch of NCI's CRCHD as Program Director in February 2021. She is involved in projects related to cancer research and cancer disparities for integrated research, training, and outreach network programs. Prior to joining NCI, Dr. Revilleza was a Health Science Policy Analyst at the Tribal Health Research Office, Division of Program Coordination, Planning, and Strategic Initiatives, Office of the Director and, earlier, a Scientific Program Analyst in the Division for Research Capacity Building, National Institute of General Medical Sciences. She initially joined NIH as a postdoc in the Molecular Biology Section of the Laboratory of Immunology, National Institute of Allergy and Infectious Diseases. A former academician, she was an Associate Professor of Biochemistry and Molecular Biology at the University of the Philippines (UP) and professorial lecturer at American University. She received her Ph.D. in agricultural chemistry from UP, with a Fulbright dissertation and Molecular and Cell Biology Network-United Nations Educational, Scientific, and Cultural Organization grants at the University of California, Berkeley. She received her master's degree in food science (biochemistry minor) and an undergraduate degree in chemistry from UP, Los Baños.

Vikrant Sahasrabuddhe, M.B.B.S., M.P.H., Ph.D.—Program Director, Division of Cancer Prevention, NCI

Dr. Sahasrabuddhe is a Program Director in the NCI Division of Cancer Prevention where he oversees a scientific and programmatic portfolio of grants, cooperative agreements, and contract-funded studies on optimization and innovations in vaccination, screening, and precancer treatment strategies for cervical cancer and other human papillomavirus (HPV)-related cancers. Dr. Sahasrabuddhe directs two major NCI programs: the NCI Cervical Cancer "Last Mile" Initiative focused on expanding cervical cancer screening access to underscreened populations via evaluation of self-collection for HPV testing, and the U.S.-Latin American-Caribbean HIV/HPV-Cancer Prevention Clinical Trials Network program focused on prevention of HPV-related cancers in people living with HIV. In addition, Dr. Sahasrabuddhe serves as NCI project scientist on the Cancer Prevention Clinical Trials Network and on the Cancer Moonshot-funded Accelerated Cervical Cancer Control Initiative, and he advises the World Health Organization and the U.S. President's Emergency Plan for AIDS Relief for guideline development and evaluation efforts of cervical cancer prevention programs. Dr. Sahasrabuddhe received his medical degree from the University of Pune in India, his master's and doctorate degrees in public health from the University of Alabama at Birmingham and completed his fellowship training in epidemiology at the Johns Hopkins University and in

Speaker Bios

NCI's Intramural Research Program. Prior to joining NCI, Dr. Sahasrabuddhe served in academia as Research Associate Professor of Medicine at Vanderbilt University. He has published widely across a broad spectrum of clinical, epidemiologic, and implementation research areas on infection-associated cancers with high or rising incidence and mortality burden.

Sandra L. San Miguel, M.S.—Program Director, CRCHD, NCI

Ms. San Miguel has been a Program Director in the Integrated Networks Branch of NCI's CRCHD since 2016. In this role, she contributes to the grants management of the National Outreach Network program. Prior to joining NCI, Ms. San Miguel served in academia, holding faculty positions in the Department of Medicine - Epidemiology & Biostatistics at The University of Texas Health Science Center and in the Department of Biology and International Studies at Trinity University in San Antonio, Texas. Her expertise is in developing, implementing, and evaluating evidence-based, culturally sensitive behavioral interventions among racially/ethnically diverse populations within the U.S. and Latin America, with an emphasis on Latino cancer health disparities, patient navigation, recruitment into clinical trials/biorepositories, breast cancer genetic testing, and survivorship. Ms. San Miguel received her M.S. in counseling psychology from Our Lady of the Lake University and her B.A. in psychology from the University of the Incarnate Word, both in San Antonio, Texas.

Victoria L. Seewaldt, M.D.—Ruth Ziegler Professor and Chair of Population Sciences and Associate Director, Board of Scientific Advisors, City of Hope Comprehensive Cancer Center, NIH/NCI Board of Scientific Advisors

Dr. Seewaldt is the Ruth Ziegler Professor and Chair of Population Sciences and Associate Director of the City of Hope Comprehensive Cancer Center and also serves on the NIH/NCI Board of Scientific Advisors. Dr. Seewaldt is proud to be the daughter of a poor Slovak immigrant family that made good, as well as to be a wife and mother. Early in her career, she witnessed the devasting toll of triple-negative breast cancer in young African-American women. To this end, her career has focused on early detection and prevention of aggressive breast cancers. Dr. Seewaldt's work includes identifying the molecular signaling pathways that promote the initiation and early progression of both triple-negative and poor-prognosis luminal B breast cancers. The unique feature of her program is that scientific discovery can be translated immediately to improve early detection and prevention. Dr. Seewaldt believes in mentoring the next generation of physicians and scholars, and ensuring that our next generation of leadership reflects the diversity of the United States. She is a mentor to many young men and women from diverse backgrounds and is very proud that her mentees have gone on to become professors, researchers, and leading physicians.

Speaker Bios

Nirali N. Shah, M.D., M.H.Sc.—Lasker Clinical Research Scholar, Center for Cancer Research, NCI

Dr. Shah is a Lasker Clinical Research Scholar in the Center for Cancer Research at the National Cancer Institute. She is dually board certified in internal medicine and pediatrics and trained through the Harvard Combined Residency program. She then joined the Pediatric Hematology and Oncology Fellowship joint training program between the NCI Pediatric Oncology Branch (POB) and Johns Hopkins University and stayed on as an Associate Research Physician in the POB. In 2019, she was appointed as an NIH Lasker Clinical Research Scholar. She currently leads the Hematologic Malignancies Section (HMS), the goal of which is to implement early-phase immunotherapeutic approaches for high-risk hematologic malignancies. She currently leads efforts in CAR T-cell therapy in acute leukemia. Dr. Shah's research focuses on translation of immunotherapeutic approaches to treat high-risk hematologic malignancies in children, adolescents, and young adults. Her clinical work has included implementation of several phase I trials for the treatment of relapsed/refractory pediatric acute lymphoblastic leukemia (ALL). Prior trials have included a pediatric phase I trial of vincristine sulfate liposomal injections (Marqibo®), a pediatric phase I trial of moxetumomab pasudotox (an anti-CD22 targeted immunotoxin-based therapy), and a pilot trial using WT1 dendritic cell vaccines for the treatment of post-transplant relapsed leukemia. Results from the trials have included establishment of a safety profile, identification of a dose, and an understanding of pharmacokinetics leading to development of phase 2 multicenter studies that she will be leading. More recently, she has led the effort in CAR T-cell therapy targeting CD22 for the treatment of relapsed/refractory ALL and is leading a trial using a combinatorial CD19/CD22 targeted CAR T-cell approach.

Pushpa Tandon, Ph.D.—Program Director, Molecular Imaging Branch, Division of Cancer Treatment and Diagnosis, NCI

Dr. Tandon is a Program Director in the Molecular Imaging Branch within the Cancer Imaging Program, Division of Cancer Treatment and Diagnosis, NCI. She manages applications in the area of image-guided intervention, nanotechnology, molecular imaging, and global health. She also serves as Deputy Director for the Quantitative Imaging Network (QIN), managing outreach and associate membership of QIN. Dr. Tandon was awarded the State Department Embassy Fellowship to work in India to develop a joint program in alternative medicine. Before joining NCI, Dr. Tandon served as the Scientific Review Officer at the Center for Scientific Review, NIH. She has a Ph.D. in chemistry from Lucknow University, India, and came to the United States as a Fogarty Fellow to study alterations in G-protein-linked second messengers in the developing brain in response to neurotoxicants at the National Institute of Environmental Health Sciences. Her work was instrumental in the establishment of federal guidelines for regulation of pesticide exposure in humans. Dr. Tandon then moved to Harvard Medical School to study genetic and neurological aspects of epilepsy and other neurodegenerative disorders. She was developing therapeutics for neurological disorders at "WellStat Therapeutics" before joining NIH. She has numerous publications in peer-reviewed journals and has been nominated as Chair of a long-standing roundtable at the National Academies of Sciences.

Speaker Bios

Mary Ann S. Van Duyn, M.P.H., Ph.D.—Associate Deputy Director for Integration, CRCHD, NCI

Dr. Van Duyn is Associate Deputy Director for Integration within the Center to Reduce Cancer Health Disparities at NCI. In this capacity, she oversees the integration of CRCHD-supported disparities research, diversity training, and network-based efforts, and manages efforts to support the navigation of next-generation underrepresented cancer researchers. She also leads CRCHD's efforts in knowledge transfer and exchange through active dissemination of information, products, and evidence-based programs for cancer health disparities reduction within the public and scientific community. She previously served as Chief of the Health Promotions Branch, NCI Office of Communications. Her work before joining NIH focused on the development, implementation, and assessment of cancer prevention programs for diverse and underserved populations, and on the development of information delivery systems at community, national, and international levels. Dr. Van Duyn received a B.S. from Cornell University, an M.P.H. from the Johns Hopkins University Bloomberg School of Public Health, and a Ph.D. in population and behavioral sciences from the University of Maryland, College Park. Her training also includes a clinical care delivery-focused fellowship from the Harvard-affiliated Brigham and Women's Hospital.

Anil Wali, M.S., Ph.D.—Program Director, CRCHD, NCI

Dr. Wali has been a Program Director in the Integrated Networks Branch of NCI's CRCHD since 2009. In this role, he contributes to the grants management of CRCHD's Geographic Management of Cancer Health Disparities Program. He also provides technical and scientific expertise to the Comprehensive Partnerships to Advance Cancer Health Equity (CPACHE U54) program. Prior to joining NCI, Dr. Wali served as Associate Professor in the Departments of Surgery and Pathology at the NCI-designated Comprehensive Cancer Center Barbara Ann Karmanos Cancer Institute, Wayne State University. While at Wayne State University, Dr. Wali served as Principal Investigator on a Veterans Administration Merit Review award-funded project on the Role of Ubiquitin-Proteasome Pathway in Mesothelioma Carcinogenesis. He conducted an NCI clinical trial on asbestos-exposed patient populations to determine their risk for developing lung cancer and mesothelioma using high-throughput genomics and proteomics technologies. Dr. Wali received his B.S. and M.S. degrees from the University of Kashmir in Srinagar, India. He earned his Ph.D. at the Postgraduate Institute in Chandigarh, India. He completed postdoctoral fellowships at the Institute for Environmental Medicine at the University of Pennsylvania; at the FELS Institute for Cancer Research at Temple University; and in the Department of Pathology at Thomas Jefferson University.

Tiffany Wallace, Ph.D.—Program Director, CRCHD, NCI

Dr. Wallace has been a Program Director in the Office of the Director of NCI's Center to Reduce Cancer Health Disparities since 2014. In this role, she contributes to CRCHD's programmatic efforts to strengthen NCI's cancer health disparity research portfolio encompassing basic, clinical, translational, and population- based research. Additional roles include contributing to the grant management of basic cancer research in cancer health disparities and representing CRCHD in NCI's Provocative Questions Initiative. Prior to joining NCI, Dr. Wallace was an Oncology Scientist at Human Genome Sciences (HGS), a biopharmaceutical corporation acquired by GlaxoSmithKline in 2011. While at HGS, she managed oncology research programs and conducted preclinical development of promising cancer therapeutic drugs and biologics. She received her Ph.D. in biomedical sciences from the University of Florida in Gainesville and completed her postdoctoral training in the Laboratory of Human Carcinogenesis at NCI, where she conducted basic and translational research that provided novel insights on the role of biological

Speaker Bios

factors as they contribute to cancer health disparities. Her research included identification of biomarkers of aggressive disease in prostate and breast cancers, with a focus on variations between different racial/ethnic groups.

Jennifer Wiggins, M.A.—Wellness Advisor, Office of Intramural Training and Education, NIH

Ms. Wiggins is a licensed professional counselor who is passionate about transformational learning, strategic planning, and holistic care. She currently serves as a Wellness Advisor in the NIH Office of Intramural Training and Education (OITE). She specializes in fostering diversity and inclusion as it relates to organizational outcomes. Ms. Wiggins has ten years of experience providing individual and group psychotherapy, facilitating, teaching, and public speaking. Additionally, she has worked in both the private and public sectors.

Jamie Wilson, Ph.D.—Chief Editor, *Nature Immunology*

Dr. Wilson initially read *Biological Sciences* at the University of Warwick, Coventry, UK and then completed his Ph.D. at the Institute of Molecular Medicine at Oxford University, Oxford, UK under Andrew McMichael, focusing on the host's immune response to HIV and EBV infection. After leaving Oxford University, Dr. Wilson joined the immunology team of Frances Gotch at the Chelsea and Westminster Hospital, Imperial College, London. He continued to work on HIV during his postdoctoral work, turning his attention to the immune responses of long-term nonprogressors. He joined the staff of *Nature Immunology* prior to its launch in 2000.

Robert Winn, M.D.—Director and Lipman Chair in Oncology, Massey Cancer Center; Senior Associate Dean for Cancer Innovation and Professor of Pulmonary Disease and Critical Care Medicine, Virginia Commonwealth University School of Medicine

Dr. Winn oversees an NCI-designated Comprehensive Cancer Center that provides advanced cancer care, conducts groundbreaking research to discover new therapies for cancer, offers high-quality education and training, and engages with the community to make advancements in cancer treatment and prevention equally available to all. He is leading the nation in establishing a 21st-century model of equity for cancer science and care in which the community is informing and partnering with Massey on its research to best address the cancer burden and disparities of those the cancer center serves, with a local focus but global impact. In addition to directing the activities of Massey's 250-plus research members—scientists and physicians from 39 departments in nine colleges and schools at VCU—he also manages a VCU research laboratory. His current basic science research, which has been supported by multiple NIH and Veterans Affairs (VA) Merit Awards, focuses on the molecular mechanisms and novel therapeutic approaches for human models of lung cancer. He has authored or coauthored more than 60 published manuscripts in peer-reviewed academic journals.

Also a pulmonologist, Dr. Winn is committed to community-engaged research centered on eliminating health disparities. He is a Principal Investigator on several community-based projects funded by NIH and NCI, including the All of Us Research Program, an NIH precision medicine initiative. He has received national and international acclaim for his efforts to empower underserved patient populations, improve healthcare delivery, and ensure equal access to cancer care. His previous faculty appointments include

serving as Director of the University of Illinois Cancer Center (UIC) from 2015 to 2019 and as Associate Vice Chancellor of Health Affairs for community-based practice at the University of Illinois Hospital and Health Science System from 2013 to 2019. Prior to joining UIC, he spent 13 years at the University of Colorado Health Sciences Center and School of Medicine in a variety of leadership roles and clinical faculty appointments, including Associate Dean of Admissions and Vice Chair of Career Development/Diversity Inclusion. Moreover, Dr. Winn has nearly 20 years' commitment to Veterans Affairs health services and has held appointments at the Denver VA and Jesse Brown VA in Chicago, where he established the first multidisciplinary pulmonary nodule clinic.

The recipient of numerous awards and honors, Dr. Winn was awarded the NCI Center to Reduce Cancer Health Disparities CURE Program Lifetime Achievement Award. He is a member of the National Cancer Policy Forum of the National Academies of Sciences, Engineering, and Medicine and of several other professional societies. He holds a B.A. from the University of Notre Dame and an M.D. from the University of Michigan Medical School in Ann Arbor. He completed an internship and residency in internal medicine at Rush-Presbyterian-St. Luke's Medical Center in Chicago and a fellowship in pulmonary and critical care medicine at the University of Colorado Health Sciences Center in Denver.

Shane Woodward—Supervisory Grants Management Officer, Office of Grants Administration, NCI

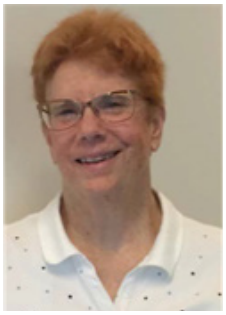
Mr. Woodward is the Supervisory Grants Management Officer of the Grants Management Branch B at NCI. He has served as a Grants Management Specialist, Supervisory Team Leader, and Supervisory Grants Management Officer with NCI. He has managed a large portfolio of highly complex grants, served as a resource and mentor to both senior and junior grants management specialists, provided training for new staff and grantees, and coordinated several large funding initiatives. While he has experience working with all of the Divisions, Offices, and Centers within NCI, he currently is serving as the main liaison for the Division of Cancer Treatment and Diagnosis Small Business Development Center and the Center to Reduce Cancer Health Disparities. Mr. Woodward has been with NCI in Grants Management for over 22 years. He holds both a bachelor's and a master's degree in business administration with a focus on human resource management from West Virginia University.

Speaker Bios

PDW Mock Review Session Bios

Svetlana Kotliarova, Ph.D.—Scientific Review Officer, Center for Scientific Review, NIH

Dr. Kotliarova serves as the Scientific Review Officer for the Chemo/Dietary Prevention (CDP) Study Section, which reviews applications in the general area of dietary and chemopreventive factors and their use in the prevention of cancer. She received her M.S. in biochemistry and molecular biology from the Novosibirsk University in Russia. Her initial research focus was on nucleotide excision repair. After receiving her Ph.D. in human genetics from the University of Tokyo, Japan, Dr. Kotliarova completed postdoctoral training under the Japanese Society for Promotion of Science Fellowship in the Department of Human Genetics of the University of Tokyo. During that time, she identified several ethnic-specific loci on the Y chromosome. She then joined the RIKEN Brain Science Institute as a staff scientist and studied neurodegenerative disorders. There, she developed a novel transgenic model for Huntington's disease (HD) and discovered the degeneration of the hypothalamus in the HD mouse model. Before joining CSR, Dr. Kotliarova pursued brain tumor research in the Neuro-Oncology Branch at NIH's National Cancer Institute, where she was head of the Genomics Core. Her research interests included glioma stem cells, gliomagenesis, genomics, and development of new therapies for brain tumors. She was the first to demonstrate a role of GSK3 in gliomas, and her research is published in highly ranked scientific journals such as *Cancer Research, Clinical Cancer Research, Journal of Biological Chemistry, Human Molecular Genetics, and Cancer Cell.*



Susan A. McCarthy, Ph.D.—Program Director, Division of Cancer Biology, NCI

Dr. McCarthy is an extramural Program Director in the Cancer Immunology, Hematology, and Etiology Branch, DCB. She manages a portfolio of cancer immunology/immunotherapy grants. She received a B.A. in biological sciences and anthropology from Northwestern University in 1976, and M.S. (1980) and Ph.D. (1982) degrees in genetics from the University of Wisconsin. She completed postdoctoral fellowships in immunology at the University of Alberta (1982–1984) and at NCI in the laboratory of Dr. Alfred Singer (1984–1989). She then accepted a faculty position at the University of Pittsburgh in the Department of Surgery, with a co-appointment in the Department of Molecular Genetics and Biochemistry as well as in the Pittsburgh Cancer Institute (1989–2002). She served as the first Director of the Immunology Graduate Training Program at the University of Pittsburgh School of Medicine (1996–2000). Dr. McCarthy returned to NCI in 2002.

Mulualem E. Tilahun, D.V.M., Ph.D.—Program Director, CRCHD, NCI

Dr. Tilahun has been a Program Director in the Diversity Training Branch of CRCHD since August 2019. In this role, he contributes to the grants management of Career Development Mechanisms (K01 - NCI Mentored Research Scientist Development Award to Promote Diversity, K08 - NCI Mentored Clinical Scientist Research Career Development Award to Promote Diversity, and K22 - NCI Transition Career Development Award to Promote Diversity). In addition, he contributes to the grants management of the Comprehensive Partnerships to Advance Cancer Health Equity (CPACHE U54) programs.

Flash Talk List

Flash Talk No. (Poster No.)	Presenter Name (Last, First)	Research Type	Title	Award
1 (47)	Aristizabal, Paula	Behavioral/ Population	Health Literacy in Parents of Children with Cancer: Comparison of Hispanics and non-Hispanic Whites	K08
2	Armaiz-Peña, Guillermo	Basic	Stress Hormones Promote Inflammation, Immunosuppression, and Tumor Growth in Ovarian Cancer	R21
3 (50)	Cespedes Feliciano, Elizabeth	Behavioral/ Population	Automating CT Segmentation to Bring Body Composition into Oncology Practice	K01
4 (9)	de Cubas, Aguirre	Basic	Transposable Elements and Immunogenicity - Understanding Genomic Dark Matter	K01
5	Deh, Kofi	Basic	Increasing the Resolution and Coverage in Hyperpolarized 13C MRI for Improved Metabolic Imaging	DS
6	Jones, Salene	Behavioral/ Population	Improving Identification of Determinants of Evidence-based Practice Implementation	DS
7 (79)	King, Amanda	Clinical	PIONEER: Computational **P**robing of D**I**fferences in Sympt**O**ms and Fu**N**ction of Div**E**rs**E** Brain Tumo**R** Populations	iCURE
8	Shimoda, Michiko	Basic	KSHV Uses Viral IL-6, a Human IL-6 Homolog, To Exploit Monocyte Inflammatory Response	DS
9	Moore, Jade	Translational	Modeling TNBC as a Function of Obesity in African American Women	DS
10 (63)	Perez, Lilian	Behavioral/ Population	Church Factors Across the Social, Physical, and Organizational Environment Associated with Latinos' Physical Activity	DS

Flash Talk List

Flash Talk No. (Poster No.)	Presenter Name (Last, First)	Research Type	Title	Award
11	Perusina Lanfranca, Mirna	Basic	Role of Pro-Inflammatory Cytokines on Expression of Homing Receptor Ligands in Tumor-Associated Endothelial Cells	DS
12 (38)	Rhie, Suhn Kyong	Basic	Identifying Key Oncogenic Transcription Factors and Enhancers Using TENET2.0	K01
13	Riggins, Karen	Basic/ Translational	Epigenetics in Early Onset Colorectal Cancer	DS
14 (68)	Sly, Jamilia	Behavioral/ Population	Smartphone Ownership and Use Among Older Adult New York City Housing Authority Residents	K01
15	Soler, Montserrat	Behavioral/ Population	Provider Acceptability of Innovative Ablative Treatments for High-Grade Cervical Pre-Cancer	DS
16	Zamora, Anthony	Translational	Biological Validation of Candidate Myeloma Driver Genes	DS

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Basic Cancer Research Abstracts			
1	Adeegbe, Dennis	Moffitt Cancer Center	Investigating the Therapeutic Potential of Histone Deacetylase and Bromodomain Inhibition in Non-Small Cell Lung Cancer (K22)
2	Adewunmi, Oluwatoyosi	Baylor College of Medicine	LncRNA MALAT1 as a Potential Therapeutic Target in Triple Negative Breast Cancer (Diversity Supplement)
3	Baker, Francine	National Cancer Institute	Patterns of Epstein-Barr Virus Specific Antibodies in Carriers of IFNL4-dG (iCURE)
4	Bauer, Kylynda	National Cancer Institute	Harnessing Neuroimmune Circuitry: Altering Acetylcholine Signaling in HCC (iCURE)
5	Busby, Theodore	National Cancer Institute	A High-Throughput Screen To Identify Epigenetic Factors That Regulate Genome Structure (iCURE)
6	Carlos, Anthony	University of Southern California	Regulation of Cell Surface Semaphorin4D by Endoplasmic Reticulum Chaperone GRP78 in Breast Cancer Cell Models (NCI Diversity Supplement, iCURE)
7	Collins, Christopher	Washington State University	APOBEC3A Regulation by (De) acetylation of Residue Lys30 (Diversity Supplement)
8	Cruz, Anthony	University of Miami	Deconvolution of Tumor Immune Microenvironment in Uveal Melanoma (Diversity Supplement)
9	De cubas, Aguirre	Vanderbilt University Medical Center	Transposable Element Expression and Immunogenicity in Breast Cancer (K01)

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10	Diabate, Mariame	The Ohio State University	Multiplex Analysis of Functional Assays for BRCA1 Function (Diversity Supplement)
11	Dutta, Pranabananda	Charles R. Drew University of Medicine and Science	Targeting PARP1 and CCL2 in Triple Negative Breast Cancer (CPACHE U54)
12	Elhussin, Isra	Tuskegee University	Genomic Analysis of Prostate Cancer: Immune-inflammation Signature in Men of African Ancestry (CPACHE U54)
13	Fenimore, John	National Cancer Institute-Frederick	Metabolic and Structural Muscular Changes Driven by Chronic Disease-Like IFN-G Exposure (iCURE)
14	Fernandez, Daniel	University of Southern Califonia	The Role of WAVE Proteins in HPV16 Endocytosis and Intracellular Trafficking (Diversity Supplement)
15	Garcia, Keith	University of Iowa	TAZ-CAMTA1 and YAP-TFE3 Modulate the TAZ/YAP Transcriptional Program by Recruiting the ATAC Histone Acetyltransferase Complex (Diversity Supplement)
16	Ghidey, Meron	Baylor College of Medicine	The Characterization of Scaffold Attachment Factor B1 as a Tumor Suppressor via Tight Regulation of Cholesterol and Fatty Acid Biosynthesis in Triple Negative Breast Cancer (Diversity Supplement)
17	Gibert, Myron	University of Virginia	Transcribed Ultraconserved Regions (TUCRs): A Bioinformatics Exploration of the Deregulation and Function of an Understudied Class of Molecules in Gliomas (Diversity Supplement)
18	Goncalves, Marcus	Weill Cornell Medicine	Blocking ActRIIB Signaling and Restoring Appetite Reverses Cachexia and Improves Survival in Mice with Lung Cancer (K08)

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19	González-Pons, Maria	University of Puerto Rico Comprehensive Cancer Center	Host Genetic Susceptibility to Gut Microbiota-Driven Colorectal Carcinogenesis (K22)
20	Grant, Garis	National Cancer Institute-Frederick	Characterizing the Mechanism of Degradation of the Mitochondrial Matrix Temperature-Sensitive Protein yah1pts (iCURE)
21	Hamilton, Sasheen	National Cancer Institute	Developing Glypican-3 Specific Nanobodies for the Treatment of Hepatocellular Carcinoma (iCURE)
22	Hao, Qiongyu	Charles R. Drew University of Medicine and Science	Identification of a Novel AKT/MTOR Pathway Inhibitor (CPACHE U54)
23	Hart, Madeleine	Fred Hutchinson Cancer Research Center	Metabolic Adaptations in SDH-Deficient Cancer Cells (Diversity Supplement)
24	Hilliard, Tyvette	University of Notre Dame	The Influence of Generational Obesity on Ovarian Cancer Metastasis (K01)
25	Jones, Dennis	Boston University School of Medicine	Solid Stress Impairs Lymphocyte Infiltration into Lymph Node Metastases (K22)
26	Kisor, Kyle	University of California, San Francisco	pH Dynamics Determining DNA Binding Specificity of FOX Transcription Factors (Diversity Supplement)
27	Landa, Iñigo	Brigham and Women's Hospital	Tert Mutant Promoter Mouse Model as a Novel Tool to Study Telomerase Transcriptional Regulation and Biology in Advanced Thyroid Cancers (K22)
28	LeBanc, Sharonda	North Carolina State University	Dynamic Protein-Nucleic Acid Interactions One Molecule at a Time (K01)

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29	Lima, Santiago	Virginia Commonwealth University	Lipids in the Etiology of Lung Cancer Health Disparities (R21)
30	McDonald, Sierra	University of South Carolina School of Medicine	miR155 Deficiency Reduces Breast Tumor Burden in a Transgenic Breast Cancer Murine Model (Diversity Supplement)
31	Mojekwu, Ogochukwu	Claflin University	Exploring the Role of Forkhead Transcription Factor foxe1 in Craniofacial Defect Using a Zebrafish Model (CURE Diversity Supplement)
32	Oghumu, Steve	The Ohio State University	Host PI3K-gamma Modulates Anti-Tumor Immunity in Poorly Immunogenic Head and Neck Cancer (K01)
33	Ogony, Joshua	Mayo Clinic College of Medicine	Differential Expression of Immune Biomarkers in Parous and Nulliparous Normal Breast Tissue: Implications for Postpartum Breast Cancer (Diversity Supplement)
34	Ojesina, Akinyemi	University of Alabama at Birmingham	Investigating Race-Related Microbial Influences in Triple Negative Breast Cancer (Diversity Supplement)
35	Parker, Dominique	Vanderbilt University	Analyzing the Role of the Non-Canonical NF-κB Pathway in Macrophage Phenotype and Function and Ovarian Cancer Progression (Diversity Supplement)
36	Perez, Minervo	National Cancer Institute-Frederick	Exploiting Collateral Vulnerabilities Created by a Covalent Oncometabolite (iCURE)
37	Perkins, Abbigale	National Cancer Institute	lrhA and rbsD: Two Genes Involved in the Translational Regulation of rpoS (iCURE)

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38	Rhie, Suhn	University of Southern California	Identifying Key Oncogenic Transcription Factors and Enhancers Using TENET 2.0 (K01)
39	Rodriguez, Anaelena	Rhode Island Hospital/Brown University	Mapping Myeloproliferative Neoplasm-Inducing Inflammatory Signaling Networks by Proximity Dependent Labelling with TurboID (Diversity Supplement)
40	Sanchez Hernandez, Evelyn	Loma Linda University	Contribution of the GR-LEDGF/p75 Axis to Prostate Cancer Chemoresistance (Diversity Supplement)
41	Soto-Pantoja, David	Wake Forest School of Medicine Comprehensive Cancer Center	Anti-CD47 Immunotherapy as a Therapeutic Strategy for the Treatment of Breast Cancer Brain Metastasis (R21)
42	Trinh, Bon	Harvard Medical School	Noncoding RNA-Protein Crosstalk in Myeloid Cell Development and Acute Myeloid Leukemia (K01)
43	Wiredu, Akosua	National Cancer Institute	Role of Rab25 in the Regulation of EGFR Activity in Head and Neck Cancer (iCURE)
44	Yang, Suhui	Charles R. Drew University of Medicine and Science	Protein Disulfide Isomerase as a Potential Therapeutic Target for Breast Cancer (CPACHE U54)
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45	Adebola, Adegboyega	University of Kentucky	Willingness of Black Women to Use HPV Self-Collection at Home (K01)
46	Agénor, Madina	Tufts University	Association Between State Medicaid Expansions and Human Papillomavirus Vaccination Among Adolescent and Young Adult U.S. Women by Race/ Ethnicity and Sexual Orientation (K01)

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48	Barrington, Wendy	University of Washington	Essential Elements of Community Well-Being Reported Among Community Health Workers (CHWs) in Washington State (K01)
49	Bethea, Traci	Georgetown Lombardi Comprehensive Cancer Center	Incident Sleep Disturbance Is Associated with Increases in Depressive Symptoms Among Older Breast Cancer Survivors and Non-Cancer Controls During the COVID-19 Pandemic (K01)
50	Cespedes Feliciano, Elizabeth	Kaiser Permanente Northern California	Adipose Tissue Radiodensity Is Associated with Survival After Colorectal Cancer (K01)
51	Costas-Muñiz, Rosario	Memorial Sloan Kettering Cancer Center	International Adaptation of Meaning-Centered Psychotherapy for Latinos: Providers' Views on Pre-Implementation (K08)
52	Duarte, Danielle	National Cancer Institute	Evaluation of Early-Life Pesticide Exposure as a Risk Factor for Thyroid Cancer in the Sister Study Cohort (iCURE)
53	Ezeani, Adaora	National Cancer Institute	Prevalence of Metabolic Syndrome Among Cancer Survivors in the U.S.: NHANES Analysis (iCURE)
54	Felix, Ashley	The Ohio State University	Black and Hispanic Women Are Less Likely Than White Women to Receive Guideline-Concordant Endometrial Cancer Treatment (K01)
55	Henderson, Vida	University of Illinois Cancer Center	Testing a Culturally Targeted Decision Aid To Promote Genetic Counseling Attendance Among African American Women with Hereditary Risk for Breast Cancer (K01)

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56	Issaka, Rachel	Fred Hutchinson Cancer Research Center	Model-Based Estimation of Colorectal Cancer Screening and Outcomes During the COVID-19 Pandemic (K08)
57	Johnson, Cicely	Hunter College Center for Cancer Health Disparities Research	Dietary and Cultural Practices of Blacks in New York City as an Indicator of Colorectal Cancer Screening and Intent (Diversity Supplement)
58	Lorenzatti Hiles, Guadalupe	University of Michigan Medical School	Understanding the Impact of High-Risk Human Papillomavirus on Oropharyngeal Squamous Cell Carcinomas in Taiwan: A Retrospective Cohort Study (Diversity Supplement)
59	Manley, Cherrel	National Cancer Institute	Drinking Water Sources and Water Quality in the Agricultural Health Study (iCURE)
60	Molina, Yamilé	University of Illinois, Chicago	Empowering Latinas to Obtain Breast Cancer Screenings: Comparing Intervention Effects and Mechanisms (K01)
61	Palmer, Nynikka	University of California, San Francisco	Collaborative Engagement of African American Prostate Cancer Survivors to Inform a Peer Navigation Protocol and Training Guide (K01)
62	Parada, Humberto	San Diego State University	Urinary Parabens and Breast Cancer Risk: Modification and Interaction by LINE-1/LUMA Methylation in the Long Island Breast Cancer Study Project (K01)
63	Perez, Lilian	RAND Corporation	Church Factors Across the Social, Physical, and Organizational Environment Associated with Latinos' Physical Activity (Diversity Supplement)
64	Pinheiro, Laura	Weill Cornell Medicine	Diabetes-Related Hospitalizations and Emergency Department Visits Among Cancer Survivors with Diabetes in SEER-Medicare: Disparities by Race (K01)

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65	Ramirez, Susana	University of California, Merced	Values-Based Messaging to Communicate the Social Determinants of Health: A Randomized Controlled Trial of an Ecological Approach to Health Communication (K01)
66	Rodriguez, Natalia	Purdue University	Indiana Healthcare Provider Perspectives on Cervical Cancer Screening Innovations: A Mixed Methods Study (K01)
67	Rogers, Charles	University of Utah	Recruitment of Adult African-American Men for Colorectal Cancer Research: An Instrumental Exploratory Case Study (K01)
68	Sly, Jamilia	Icahn School of Medicine at Mount Sinai	Smartphone Ownership and Use Among Older Adult New York City Housing Authority Residents (K01)
69	Tamí-Maury, Irene	The University of Texas Health Science Center	Comparing Smoking Behavior Between Female-to-Male and Male-to-Female Transgender Adults (K22)
70	Teran-Wodzinski, Patricia	University of South Florida	Validating Nerve Fiber Recovery, Patient-Reported and Functional Outcomes of an Exercise Intervention for Taxane-Induced CIPN (Diversity Supplement)
71	Vilaro, Melissa	University of Florida	Using Technology To Develop a Culturally Tailored Nutrition Risk Intervention To Promote Colorectal Cancer Prevention Among Rural Adults (Diversity Supplement)
72	Young, Corey	National Cancer Institute	An Augmented Eligibility Strategy to Reduce Disparities in USPSTF 2021 Lung Cancer Screening Guidelines (iCURE)
Clinical Cancer Research Abstracts			
73	Acosta, Laura	University of Miami Sylvester Comprehensive Cancer Center	The Impact of Radiotherapy on Acute Skin Toxicities and Quality of Life in Breast Cancer Patients (Diversity Supplement)

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74	Amonoo, Hermioni	Brigham and Women's Hospital	Distress in a Pandemic - The Association of the Coronavirus Disease-2019 (COVID-19) Pandemic with Distress and Quality of Life in Hematopoietic Stem Cell Transplantation (HSCT) (K08)
75	Barajas, Ramon	Oregon Health & Science University	Assessing Glioblastoma Immunotherapy Response with FMISO Hypoxia PET Imaging (K08)
76	Burgess, Crystal	National Cancer Institute	Occurrence of Fractures in Children with Neurofibromatosis Type 1 on the MEK Inhibitor Selumetinib for Inoperable Plexiform Neurofibromas (iCURE)
77	Gerena-González, Valeria	National Cancer Institute	Is Breast Conservation Therapy as Good as Mastectomy 40 Years After Early-Stage Breast Cancer Diagnosis? (iCURE)
78	Gregorio, Sandy	California State University, Los Angeles	Targeting CXCR4 and Thioredoxin Reductase in Small Cell Lung Cancer (Other)
79	King, Amanda	National Cancer Institute	PIONEER: Computational Probing of Differences in Symptoms and Function of Diverse Brain Tumor Populations (iCURE)
80	Nolan, Timiya	The Ohio State University	The Y-AMBIENT Pilot Protocol (K08)
81	Rauh-Hain, Jose	MD Anderson Cancer Center	Outcomes of the First Pregnancy Following Fertility-Sparing Surgery for Early-Stage Cervical Cancer: A Population-Based Study (K08)
82	Samuel-Ryals, Cleo	University of North Carolina-Chapel Hill	Separate and Unequal: Examining the Role of Race and Site of Care on Patient-Reported Outcomes Among Patients with Metastatic Cancer (AFT-39) (K01)

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83	Thompson, Mone't	National Cancer Institute	The Complexities of Germline PARN Variants in Telomere Biology Disorders and the General Population (iCURE)
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84	Ahanonu, Eze	University of Arizona	Accelerating Abdominal T1 Mapping Using Deep Learning (Diversity Supplement)
85	Boyd, Raya	University of Illinois Urbana-Champaign	Poly- and Perfluoroalkyl Substances Alter the Polycomb Pathway and Tumorigenicity of Testicular Germ Cell Tumor Cells (Diversity Supplement)
86	Campos, Alejandro	University of California, San Diego Moores Cancer Center	Stress-Induced ITGB3 Drives Cell Surface Presentation of Integrin αvβ3 in Epithelial Cancer Cells (Diversity Supplement)
87	Daddacha, Waaqo	Medical College of Georgia	Low SAMHD1 Expression Sensitizes Malignant Glioma Cells to DNA-Damaging Therapeutics and Is Associated with Better Outcome in Patient and Xenograft Models (K01)
88	De Oliveira, Satiro	University of California	Engineering Precision Medicine to Increase Graft-Versus-Lymphoma Activity: Hematopoietic Stem Cells Modified with Chimeric Antigen Receptors (K23)
89	Erazo-Oliveras, Alfredo	Texas A&M University	Oncogenic APC Enhances Wnt Signaling by Reshaping Cholesterol-Dependent Plasma Membrane Organization (Diversity Supplement)
90	Forbes, Andre	Weill Cornell Medical College	Identifying Potential Drug Targets Using Patient-Derived, Tissue Specific, Gene Regulatory Networks (Diversity Supplement)
91	Gallant, Kelsey	National Cancer Institute	A High-Throughput Imaging Pipeline for the Quantitative Detection of DNA Damage in Peripheral Blood Mononuclear Cells (iCURE)

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92	Gamble, Dionna	National Cancer Institute	DNA Repair in HLRCC-Associated Renal Cancer: Investigating a Homologous Recombination Defect in FH-Deficient Cells (iCURE)
93	Huang, Xiao	University of California, San Francisco	Precise Control of Immune Modulation Using DNA Scaffold-Mediated Biomaterial Functionalization (CPACHE U54 i3 Center)
94	Kydd, Andre	National Cancer Institute	Epigenomic Landscape of Advanced Bladder Cancer and Rare GU Tumors from Patient Autopsy Samples (iCURE)
95	Leon, Frank	University of Nebraska Medical Center	A Reduction in O-glycan Modification Induces Differentially Glycosylated CD44 to Promote Stemness and Metastasis in Pancreatic Cancer (Diversity Supplement)
96	Liefwalker, Daniel	Oregon Health & Science University	Metabolic Convergence on Lipogenesis in RAS, BCR-ABL, and MYC-Driven Lymphoid Malignancies (K01)
97	Mirazee, Justin	National Cancer Institute	Engineering of Chimeric Antigen Receptors To Enhance Cytotoxicity Against Antigen-Low Leukemias (iCURE)
98	Pitter, Michael	University of Michigan	Peptidyl Arginine Deiminase 4 Is a Key Regulator of Tissue-Resident Peritoneal Macrophage Phenotype in the Tumor Microenvironment (Diversity Supplement)
99	Silva-Fisher, Jessica	Washington University in St. Louis	Long Non-Coding RNA RAMS11: Chromobox 4 Protein Interaction Promotes Metastatic Colorectal Cancer Progression (K22)
100	Taylor, Sherys	National Cancer Institute	Prospective Analysis of Circulating Inflammatory Proteins in Lung Cancer Risk (iCURE)

Basic Cancer Research Poster Abstracts

1 Investigating the Therapeutic Potential of Histone Deacetylase and Bromodomain Inhibition in Non-Small Cell Lung Cancer (K22)

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Introduction/Background: Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths in the United States. Despite the success of immunotherapy in a subset of NSCLC patients, durable treatments that benefit a wide pool of patients remains a clinically unmet need. We previously described the immunomodulatory properties associated with inhibitors of Histone deacetylase 6 and BET Bromodomain proteins in a pre-clinical mouse model of NSCLC. In the present study, we investigated how these drugs impact tumor-associated immune cells at the genomic level.

Methods: Using a Kras and p53 mutant genetically engineered mouse (GEM) model of NSCLC, we performed RNA-sequencing of CD45+ immune cells isolated from lung tumors of the GEM after treatment with the HDAC6 inhibitor ACY241, the pan BET Bromodomain inhibitor JQ1, or the chemotherapy drug Oxaliplatin.

Results: We identified immune-related genes and pathways that are differentially regulated under these drug treatments. In in vivo studies, tumor growth was significantly delayed in lung tumor-bearing mice treated with the combination of the two drugs relative to monotherapy. Furthermore, the immunogenic cell death elicited by Oxaliplatin, a chemotherapy drug synergized with ACY241 to potentiate a robust anti-tumor response in treated mice. Immune profiling of the tumor microenvironment under these treatment conditions reveal immune enhancing phenotypic changes that is consistent with the observed disease outcomes. Finally, functional assessments of the tumor associated CD8+ T cells conducted in ex-vivo stimulation assays suggest that the combination of ACY241 and JQ1 or ACY241 and Oxaliplatin evoke increased effector T cell function that likely facilitates enhanced anti-tumor immunity.

Conclusion: Collectively, our findings provide proof of concept for the therapeutic potential of select epigenetics-regulating agents and provides rationale for their clinic clinical testing as promising drugs for the treatment of NSCLC

Funding: This work was supported by National Cancer Institute grant 1K22CA222669-01.

2 LncRNA MALAT1 as a Potential Therapeutic Target in Triple Negative Breast Cancer (Diversity Supplement)

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Introduction/Background: In the United States 1 in 8 women will develop metastatic breast cancer within their lifetime, accounting for nearly 30% of cancer diagnoses annually. Although improvements have been made in early diagnoses and treatment, the heterogeneity of breast cancer often makes treatment of the disease a challenge. Triple negative breast cancer (TNBC) patients will often acquire resistance to existing treatment options, emphasizing the need for new breast cancer therapies. A novel therapeutic approach is the inhibition of the long noncoding RNA (lncRNA), metastasis-associated lung adenocarcinoma transcript (MALAT1). MALAT1, has been associated with the cancer progression of liver, gastric and lung cancer, and has been shown to be upregulated almost four-fold in breast cancer. Targeting MALAT1 is now possible using an antisense oligonucleotide (ASO). Our goal is to assess the therapeutic benefit of using a MALAT1 ASO in TNBC tumor models and as well as the advantage of using a MALAT1 ASO in combination with checkpoint inhibition and/or chemotherapy.

Methods: Treatment studies using the MALAT1 ASO were performed in our Trp53-null syngeneic mouse model which closely mirrors the heterogeneity found in the human disease. After treatment flow analysis as well as immunohistochemistry was performed to determine any changes in the tumor microenvironment with MALAT1 inhibition

Results: Using a MALAT1 ASO we have been able to significantly knockdown MALAT1 RNA expression and have observed a delay in primary tumor growth as well as alterations to the tumor microenvironment. With MALAT1 inhibition we have seen a decrease in immune suppressive macrophages and neutrophils as well as increase in tumor killing immune cells.

Conclusion: The inhibition of MALAT1 delays primary tumor growth and decreases the immunosuppressive tumor microenvironment found in TNBC. These results highlight the potential of using a MALAT1 ASO as a therapeutic option in combination with existing therapies to improve patient outcome.

Funding: This work was supported by National Cancer Institute R01 CA16303-42A1: Hormonal Regulation of Breast Cancer and 5T32GM088129-08: National Institutes of Health T32 Training Grant.

3 Patterns of Epstein-Barr Virus Specific Antibodies in Carriers of IFNL4-dG (iCURE)

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Introduction/Background: IFNL4 is a genetically controlled type-III interferon that is created by a dinucleotide variant dG/TT. Only carriers of the dG allele can produce this protein. The derived human-only IFNL4-TT allele creates a frameshift that eliminates the production of IFNL4. The IFNL4-dG allele is associated with reduced spontaneous, and treatment-induced hepatitis C viral clearance. Inexplicably, the frequency of dG allele is highest in sub-Sahara Africa. Interestingly, endemic Burkitt lymphoma (eBL), a childhood cancer common in Africa that is etiologically linked to Epstein-Barr virus (EBV) infection, shares similar geographic distribution as dG alleles. Although over 95% of the general population are EBV positive, <1% progress to BL. We hypothesize that IFNL4 influence immune response to EBV infection. This study examines the potential association of IFNL4 genotypes with humoral immunity to EBV and potential links to endemic Burkitts lymphoma.

Methods: Serum was analyzed for 202 EBV epitopes via protein microarray that measured anti-EBV IgA and IgG antibodies. Serum was also used to genotype for IFNL4 using Taqman genotyping assay. Antibody levels were log-10 transformed to achieve normal distribution for linear regression analysis that used age and sex as co-variates.

Results: Data analysis shows pattern of decrease production of anti-EBV IgA antibody per copy of IFNL4-dG allele. No clear pattern observed for anti-EBV IgG antibodies.

Conclusion: Results suggest poor EBV control at the mucosal level for carriers of IFNL4-dG. Preliminary results represent the first reported patterns of association between IFNL4 genotypes and anti-EBV IgA and IgG antibodies in African children in Ghana.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

4 Harnessing Neuroimmune Circuitry: Altering Acetylcholine Signaling in HCC (iCURE)

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Introduction/Background: Hepatocellular carcinoma (HCC) remains a significant cause of cancer-related deaths. Both HCC mortality and incidence is projected to drastically increase in the following decades. Highly immunosuppressive, HCC tumors respond poorly to established immunotherapies and novel approaches are needed to alter the HCC immune landscape. Recent studies have revealed profound neuroimmune interactions in the context of cancer. How, and to what extent, the nervous system informs hepatic immunology and HCC remains largely unexplored. Within the liver, the hepatic vagus nerve facilitates liver-brain interactions via release of acetylcholine. We hypothesize that modulating acetylcholine signaling will impact HCC outcomes via neuroimmune modulation. Here, we assess hepatic immune profiles and tumor growth in an HCC mouse model following vagal disruption.

Methods: Female C57BL/6 mice (10-12 weeks old) underwent a hepatic vagotomy (HV) or sham vagotomy (SV). After three weeks, immune profiles from liver and spleen tissues were assessed via flow cytometry. To induce orthotopic tumors, a subset of HV and SV mice received intrahepatic injections (2.5x105 RIL-175 cells). Fluorescent in vivo imaging tracked tumor growth.

Results: HV and SV mice exhibit comparable hepatic phenotypes and immune profiles. HV Treg populations exhibit tissue-specific alteration of CTLA-4+ expression, a T cell exhaustion marker. Hepatic, but not splenic, CD4+ and CD8+ T cells exhibit increased median fluorescent intensity of PD1 and CD69, potentially indicative of increased activation. Pilot studies reported a transient, but not significant, increase of RIL-175 tumors in HV mice.

Conclusion: HV does not significantly shape immune profiles but may impact lymphocyte function. Further work is needed to determine the impact of acetylcholine disruption in HCC. We anticipate that this work will not only further understanding of the liver-brain axis, but also identify nerve-dependent approaches to modulate HCC progression and immunotherapy responses.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

5 A High-Throughput Screen To Identify Epigenetic Factors That Regulate Genome Structure (iCURE)

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Introduction/Background: Chromatin structure is important for genome function and is regulated by epigenetic factors, histone modifications and architectural proteins. The genome is organized into loops and topologically associated domains (TADs), which are formed by the ATP-dependent cohesin complex and maintained by binding of the architectural protein CTCF at domain boundaries. We hypothesize that, in addition to CTCF and cohesin, other factors contribute to the regulation of chromatin domains in healthy and carcinoma cells. Gaining insight into the mechanisms that regulate and coordinate the functions of the known architectural chromatin proteins to mediate the dynamic organization of the genome has the potential to answer fundamental questions about genome organization and its role in certain diseases.

Methods: To identify potential regulators of chromatin domain organization, we are depleting a panel of 826 epigenetic factors in colorectal carcinoma cells in a screen to assay for structural changes in the organization of the Myc TAD. CRISPR-Cas9 mediated gene deletions of each target are generated followed by DNA fluorescence in situ hybridization to visualize TAD organization at the single cell level. Using high-throughput imaging we assess changes in TAD structure induced by the loss of each factor.

Results: We have established a workflow for efficient and reproducible determination of TAD structure. CRISPR deletion of control genes, including subunits of the cohesin complex, has been achieved in HCT116 carcinoma cells as well as visualization of the TAD borders flanking the Myc genomic region using DNA FISH probes.

Conclusion: Our high-throughput imaging approach enables unbiased identification of novel factors and pathways previously uncharacterized for their roles in regulating genome organization. Future experiments will determine how these factors contribute to the genomic structure around the Myc TAD in carcinoma cells.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

6 Regulation of Cell Surface Semaphorin4D by Endoplasmic Reticulum Chaperone GRP78 in Breast Cancer Cell Models (NCI Diversity Supplement, iCURE)

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Introduction/Background: Localization of endoplasmic reticulum (ER) chaperones to the cell surface is an adaptive mechanism for cells to expand the functionality of these proteins in response to stress by activating cell surface signaling pathways associated with cell survival and signaling. In cancer, cell-surface ER chaperones regulate oncogenic signaling pathways, proliferation and cell adhesion through interactions with other cell surface proteins. The emerging role of peripheral cell surface GRP78 (csGRP78), traditionally regarded as an ER luminal chaperone, as a multifunctional co-receptor for many different types of cell surface proteins presents novel opportunities for therapeutic interventions. One such cell surface protein interacting with GRP78 is Semaphorin4D (Sema4D). Sema4D was originally discovered as a cell surface cleavable ligand and neuronal axon guidance cue that mobilizes the actin cytoskeleton to facilitate neuronal growth cone homing during development. In cancer, cell surface Sema4D expression is pro-metastatic and pro-angiogenic. Sema4D has been shown to be highly expressed in the breast cancer and epidemiological studies have demonstrated that Sema4D expression in breast cancer patients confers a poor prognosis and high probability of metastatic organotropism.

Methods: In this study, we use a combination of imaging and molecular biology approaches.

Results: Our recent advances have preliminarily identified a critical role for GRP78 in regulating cell surface levels of Semaphorin4D (Sema4D). We show that Sema4D forms a protein-protein interaction with GRP78 both intracellularly and on the cell surface and siRNA knockdown of GRP78 reduces cell surface levels of Sema4D without affecting total levels. Whether GRP78 regulates ectodomain shedding, cleavage, or membrane trafficking of Sema4D remains an area for further investigation.

Conclusion: Since csGRP78 may interact with and facilitate many of the functions of Sema4D, understanding the conditions by which GRP78 contributes to surface expression of Sema4D and its downstream effects may lead to: A) novel therapeutics that abrogate the effects of Sema4D in cancer and B) elucidation of novel mechanisms by which Sema4D trafficking in cancer is regulated by GRP78

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7 APOBEC3A Regulation by (De)acetylation of Residue Lys30 (Diversity Supplement)

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Introduction/Background: APOBEC-signature mutations are the second-most prevalent among signatures defined in the COSMIC cancer database, contributing significantly to the mutation load in several cancer types. Recently APOBEC3A (A3A) was identified as the primary source of APOBEC mutations in breast cancer (BRCA). While correlations between A3A expression and APOBEC mutations in BRCA tumors suggest transcriptional regulation occurs, outliers suggest post-transcriptional regulation is also important. Tandem mass spectrometry (MS/MS) analysis of recombinant A3A purified from HEK293T showed 9% of A3A to be acetylated at Lys30. We hypothesize that A3A Lys30 acetylation regulates deaminase activity in cells and that dysregulation of this process contributes to increased APOBEC activity in BRCA tumors.

Methods: We purified strep-tagged A3A from HEK293T cells by affinity chromatography followed by MS/MS analysis for phosphorylation and acetylation, and for interactors. To determine the effects of Lys30 modifications, we introduced K30Q and K30R mutations to A3A, mimicking acetylation (A3A-K30Ac) and deacetylation, respectively, and will compare activities of these variants to wild-type A3A in HEK293T. We will determine whether HAT1 regulates A3A activity via cytidine deaminase activity (CDA) assays following incubation of A3A with purified HAT1. To determine whether histone deacetylases (HDAC/SIRT) are involved in A3A regulation, we will treat A3A-expressing HEK293T cells with sodium butyrate (NaBu) or nicotinamide, then measure A3A activity. Once we have identified/validated HAT1 and SIRT1 as cellular A3A modifiers, we will knock down their expression via shRNAs in BT474 (APOBEC-mutated BRCA cell line).

Results: We have identified SIRT1 and HAT1 as A3A-specific interactors by MS/MS. In preliminary CDA assays, mimicking A3A acetylation resulted in a ~3-fold decrease in activity, compared with our deacetylated A3A mutant. Treatment of HEK293T with NaBu had no effect on A3A activity.

Conclusion: Our results suggest that A3A-Lys30 acetylation attenuates deaminase activity in cells. This may be a regulatory mechanism by which cells restrict off-target A3A activity.

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8 Deconvolution of Tumor Immune Microenvironment in Uveal Melanoma (Diversity Supplement)

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Introduction/Background: Uveal melanoma (UM) is the most common primary eye cancer and remains uniformly fatal. In contrast to cutaneous melanoma, UM is an immunologically "cold" tumor that is poorly responsive to immunotherapy. The purpose of this study was to bioinformatically deconvolute the tumor immune microenvironment (TIM) after stratification for key molecular biomarkers associated.

Methods: RNA-seq data were downloaded from The Cancer Genome Atlas Uveal Melanoma (TCGA-UVM) dataset (n=80). Samples were stratified by gene expression profile (GEP) class 1 versus class 2, PRAME expression (negative versus positive), and LAG3 expression (low versus high). TIM deconvolution was performed using Quantiseq from the Immunedeconv R package.

Results: Class 2 UM were inferred to comprise 2.64-fold fewer CD4+ T cells (p =0.0013), 2.3-fold fewer myeloid dendritic cells (p=0.026), 1.74-fold more M2 macrophages (p=4.37E-9), 2.02-fold more NK cells (p=1.2E-6), and 53-fold more CD8+ T cells (p=0.0007) compared to class 1 UM. PRAME-positive UM contained 1.26-fold more M2 macrophages (p=0.022), 1.39-fold more NK cells (p=0.005), and 2.29-fold fewer CD4+ T cells (p=0.0054) than PRAME-negative UM. LAG3 expression was strongly associated with class 2 UM (p=0.0026), increased M1 (p=0.00057) and M2 macrophages (p=5.6E-6), NK cells (p= 0.016), CD8+ T cells (p=1.77E-11), Tregs (p=2.27E-5), and decreased CD4+ T cells (p=0.0045).

Conclusion: The two strongest predictors of metastasis in UM – class 2 GEP and PRAME expression – are strongly associated with an inhibitory TIM. LAG3, which we recently showed by single cell RNA sequencing to be the predominant T cell exhaustion marker in UM, was associated with an increased global inflammatory signature. The data suggest that a subset of Class 2 Tumors are prime candidates for LAG3 Immune Checkpoint Inhibition. Correlation between key molecular biomarkers and TIM will facilitate the development of targeted immune therapy for patients with UM.

Funding: This work was supported by National Cancer Institute grant R01 CA125970 (J.W.H.), Research to Prevent Blindness, Inc. Senior Scientific Investigator Award (J.W.H.), Melanoma Research Foundation Established Investigator Award (J.W.H.), gift from Dr. Mark J. Daily (J.W.H). Dr. Harbour is the inventor of intellectual property related to prognostic testing in uveal melanoma and receives royalties from its commercialization. He has been a paid consultant for Castle Biosciences, licensee of this intellectual property.

9 Transposable Element Expression and Immunogenicity in Breast Cancer (K01)

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Introduction/Background: Recently, immune checkpoint blockade (ICB) therapy was approved for triple negative breast cancer. In these regards, we found evidence that transposable element (TE) expression is associated with activation of immune checkpoint signaling in several cancer types, including breast cancer. Thus, we hypothesize that TE expression and immunogenicity are related in breast cancer. Here, we quantified and analyzed TE expression in the AURORA-USA breast cancer cohort using RNAseq to understand the role that TE expression has in breast cancer immunogenicity, immune cell composition, and metastatic evolution.

Methods: RNAseq was performed in the AURORA-USA cohort of breast cancer patient samples (N=123 primary and matched metastatic samples). TE and gene expression were independently quantified by aligning sequencing reads to the human genome (Hg38) using STAR-aligner and annotated using RepBase or Gencode. Counts were normalized using DESeq2. Transposable element coexpression modules were defined using a weighted gene coexpression network analysis (WGCNA) and integrated with immunologic features (eg. interferon signaling, antigen presentation and immune cell infiltration) using generalized linear models. For validation, we measured TE expression in 38 breast cancer cell lines using RNAseq data in the Broad Institute Cancer Cell Line Encyclopedia (CCLE).

Results: In total, 1,180 TEs were quantified in both the AURORA-USA cohort and breast cancer CCLE samples. After defining TE coexpression modules using WCGNA and relating those modules to clinical traits, we identified one module associated with the basal subtype, another module associated with luminal subtypes, and two modules associated with immune activation. Further analysis showed significant associations between immune signaling and TE expression modules. We validated the subtype specificity of the respective modules in the breast cancer CCLE dataset.

Conclusion: TE expression can define breast cancer subtypes and is associated with immunogenicity, which can have important implications for guiding patient selection for ICB therapy.

Funding: This work is supported by K01CA245231 and Evelyn H. Lauder Founder's Fund for Metastatic Breast Cancer Research.

10 Multiplex Analysis of Functional Assays for BRCA1 Function (Diversity Supplement)

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Introduction/Background: Variants of uncertain significance (VUS) are a type of missense mutation where association with disease risk is unknown. Single-nucleotide variants are the most frequent type of sequence changes detected in the genome and these are frequently VUS, especially for clinically underserved populations. Due to the lack of genetic information in people of color, they are limited in receiving precise clinical recommendations. The increased reporting from genetic screening of VUS has been biased against clinically underserved communities and further contributes to the large disparities in cancer outcomes for these populations. Thus, methods that classify VUS function can help address disparities in the population data from which we can predict cancer outcomes. These functional-genetics methods produce key information for identifying the mutations that drive disease. In the case of breast and ovarian cancer and the tumor suppressor BRCA1, pathogenic variants have shown loss of function in an assay for homology-directed repair (HDR). We hypothesize that through the functional analysis of BRCA1 VUS, we can understand the genetic diversity of variant function and predict whether a gene variant causes disease.

Methods: To test our hypothesis, we analyzed the results from two HDR-based high-throughput functional assays we developed to compare against existing classifications in clinical variant databases.

Results: Comparison of our functional determinations with known benign or pathogenic variants validated the results of the functional assay.

Conclusion: We infer that novel variants of BRCA1 tested in this assay are a resource for clinicians to evaluate whether a VUS in BRCA1 is associated with breast and ovarian cancer.

Funding: This work was supported by a National Cancer Institute Diversity Supplement.

11 Targeting PARP1 and CCL2 in Triple Negative Breast Cancer (CPACHE U54)

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Introduction/Background: PolyADP ribosylation (PARylation) by the Poly ADP ribosyl Polymerase 1 (PARP1) is a post-translational modification involved in the DNA damage response. Outside of its role in DNA damage repair, PARP1 transcriptionally controls multiple cytokines such as chemokine ligand 2 (CCL2) expression that supports cell invasion. PAPR1 inhibition is a potential therapy option for triple negative breast cancer (TNBC) that lacks targeted therapy. However, low sensitivity and resistance often lead to a suboptimal response. We aim to show that inhibiting PAPR1 and CCL2 pathways can synergistically downregulate cell proliferation and metastasis, particularly in TNBC.

Methods: We employed cellular proliferation assay, Boyden chamber assay, and wound healing assay in TNBC cell lines along with western blotting and qPCR.

Results: We found that PARP1 transcriptionally controls CCL2, which is upregulated in TNBC. PARP1 and NFkB transcription factor localize to CCL2 promoter in a PARP1 dependent manner, since inhibiting PAPR1 downregulates recruitment. Treating breast cancer cells with recombinant CCL2 was able to upregulate EMT markers such as vimentin and reduce E-cadherins. Additionally, CCL2 pathway inhibition reduced cell invasion in Boyden chamber assay. We found that global PARylation levels were upregulated with recombinant CCL2 treatments, indicating crosstalk. Treating breast cancer cells with PAPR1 inhibitors can negatively affect cell proliferation and migration in wound healing assay. However, dual treatment with PARP1 and CCR2 inhibitors was more effective in hindering cell proliferation.

Conclusion: Our results indicate that the crosstalk between PARP1 and CCL2 pathway is critical for maintaining cell proliferation and cellular invasiveness. Thus TNBCs, which show higher expression of CCL2 or CCR2, might be more responsive to a combined therapy with inhibitors of PARP1 and CCR2. In the future, CCR2 and PARP1 knockdown will be carried out with siRNAs to determine cell proliferation effects and conduct transcriptome sequencing.

Funding: This work was supported by grants U54CA143931 and U54MD007598.

12 Genomic Analysis of Prostate Cancer: Immune-inflammation Signature in Men of African Ancestry (CPACHE U54)

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Introduction/Background: African American (AA) men have 2 to 3 times higher prostate cancer mortality rates than European American (EA) men. Prostate cancer (PCa) outcome disparity remains even when controlled for access to care and stage at presentation and allocated to differences in tumor subtypes or gene expression profiles. Furthermore, men of African ancestry from the Caribbean and South America demonstrate incidence and mortality rates similar to AA men, suggesting a possible ancestral basis for some of these expected outcomes. Our hypothesis African ancestry drives aggressive prostate cancer and leads to genetic alterations with upregulation of unique immune-inflammatory signatures in men of African descent. Overall objective understand the relationships between genetic ancestry, immune-inflammatory signature, and distinct tumor biology in AA men of African descent compared to EA men with a focus on strategies that help with prevention and therapeutic intervention.

Methods: RNA sequencing was performed for RNA isolated from macro-dissected FFPE (n=28). The raw reads were aligned to the GRCh38 genome, then gene-level expression was measured from STAR counts. We identify the differential gene expression then performed GSEA to identify specific gene sets that are enriched in AA men. ADMIXTURE was used to generate a quantitative estimate of each individual ancestral composition.

Results: Descriptive statistical analysis of the study population were conducted and stratified by race and pathology stage. Our analyses revealed that interferon-inducible gene sets (ISG15, IFT1, STAT1) were positively enriched, while neutrophil degranulation and Interleukin's gene sets (IL8, CXCL8, IL6, CXCL6) were negatively enriched (p-value 0.05) in AA men. These enriched genes may indicate that immune inflammation signatures play an important role in driving aggressive prostate cancer in AA.

Conclusions: Our study provides new insight into understanding how genetic ancestry and upregulation of unique immune-inflammatory signatures may contribute to PCa racial disparities in AA men cohorts from African ancestry.

Funding: This work was supported by National Institutes of Health U54 grant CA118623 from the National Cancer Institute and U54 grant MD007585-26 from the National Institute on Minority Health and Health Disparities.

13 Metabolic and Structural Muscular Changes Driven by Chronic Disease-Like IFN-G Exposure (iCURE)

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Introduction/Background: Cardiovascular myopathies and fatigue have been associated with chronic inflammatory responses and activated cell-mediated immunity, a promising cancer treatment modality. Using murine models we can explore side effects to cytokines that are integral to these autoimmunity and these therapies. Here we focus on IFN-g, the type 2 interferon, a powerful immunomodulatory cytokine.

Methods: ARE mice have a deletion and replacement with random nucleotides in the 3 prime UTR of the IFN-g gene that serves to remove a regulatory element that is integral at controlling the stability of IFN-g mRNA. We utilize immunohistochemistry, echocardiography, PCR, RNAseq, metabolic assessments and electron microscopy to evaluate the changes caused by this chronic level of IFN-g exposure. We also used various interventions to show what was necessary for the pathology, utilizing antibody blockade of IFN-g, castration interventions and beta receptor antagonists.

Results: We report aberrant cardiovascular activity in the form of androgen dependent stress induced reduced ejection fraction in vivo in male mice with persistent low-level expression of IFN-g with increased cellular and mineral infiltrates into myocardium. Our data demonstrates an increase in glucose uptake and fatigue of ARE mice as well as structural and ultrastructural changes. We note a decrease in the transcripts for and a reversible decrease in function of aerobic respiratory components in the muscle. Furthermore, the in vivo data revealed an increase in factors associated with fatigue, such as lactic acid production and changes in expression of genes associated with an increase in anaerobic respiration in cardiac musculature.

Conclusion: These results indicate that the chronic expression of IFN-g results in a model for male biased heart failure under stress in an activated immune environment. Cytokine-driven changes in cardiac musculature may play a critical role in fatigue-related disease associated with active immunity conditions that may be severely exacerbated by testosterone.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

14 The Role of WAVE Proteins in HPV16 Endocytosis and Intracellular Trafficking (Diversity Supplement)

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Introduction/Background: A central focus of research for our laboratory is in understanding early events of viral pathogenesis that lead to host immune response. In order to heal a wound, basal keratinocytes alternate the distribution of cytoskeletal machinery between migration programs and growth factor-stimulated macropinocytosis. Human papillomavirus type 16 (HPV16), the major pathogen that causes cervical cancer, somehow exploits the process of wound healing to achieve a proficient infection. We do not yet understand how the known cell-surface mediators of HPV16 stimulate localized actin polymerization or what a defined entry mechanism includes for HPV16. As such, the objective of this study is to elucidate the host cell factors that control the actin dynamics necessary for HPV endocytosis. We hypothesize that the HPV16 entry process requires the activation of WAVE proteins to mediate localized actin polymeraztion.

Methods: HeLa cells were used for all assays and used to generate WAVE1 knockout cells. B16-F1 cells were gifts from Bruce Goode. HPV16 Pseudovirions (PsV) were used for infection assays as analyzed by flow cytometry. HPV16 virus-like particles (VLPs) tagged with pHrodamine (pHrodo) dye were used in internalization assays and read using a plate reader. Fluid uptake assays were conducted using pHrodo-labelled VLPs and FITC-Dextran (10,000MW) and imaged using Confocal Microscopy.

Results: Knockout of WAVE1 and WAVE2 significantly reduces the rate of HPV16 infection and internalization in multiple cell types. WAVE1 facilitates late stages intracellular trafficking beyond the golgi apparatus. Additionally, HPV16 induces fluid uptake and colocalizes with macropinosomes.

Conclusions: WAVE1 and WAVE2 contribute significantly to multiple steps of HPV16 infection including internalization and intracellular trafficking. Our data confirms that HPV16 utilizes a macropinocytosis-like endocytic pathway.

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15 TAZ-CAMTA1 and YAP-TFE3 Modulate the TAZ/YAP Transcriptional Program by Recruiting the ATAC Histone Acetyltransferase Complex (Diversity Supplement)

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Introduction/Background: Epithelioid hemangioendothelioma (EHE) is a vascular sarcoma with *WWTR1*(TAZ)-*CAMTA1* (85%) and *YAP1-TFE3* gene fusions (15%). The fusion proteins contain the N-terminus of TAZ and YAP, including their TEAD binding domains, fused in frame to the C-termini of CAMTA1 and TFE3, respectively. The C-termini of CAMTA1 and TFE3 contain transactivating domains as well as other protein-protein interaction domains leading us to hypothesize that the C termini of CAMTA1 and TFE3 interact with novel proteins that potentiate the oncogenic activity of TAZ and YAP.

Methods: BioID mass spectrometry and a subsequent shRNA screen was conducted to identify prey proteins crucial to driving anchorage-independent growth for TAZ-CAMTA1 and YAP-TFE3. An approach combining RNA-Seq, ChIP-Seq, and ATAC-Seq was utilized for TAZ-CAMTA1, YAP-TFE3, and controls.

Results: In vitro studies demonstrated that TC and YT bind to TEAD transcription factors to promote cellular transformation**.** RNA-Seq analysis showed that TC and YT drive a transcriptional program that overlaps partially with the TAZ and YAP transcriptional programs, but also activates a unique set of genes. TC and YT bind to unique sets of genes and demonstrated altered DNA binding properties via ChIP-seq analysis. ATAC-seq indicated that TC and YT promote a more accessible chromatin landscape. BioID mass spectrometry showed the TC and YT interactome was enhanced for epigenetic modifying proteins including the ATAC complex as compared to TAZ and YAP. RNA-seq analysis showed that knockdown of YEATS2 and ZZZ3*,* both members of the histone acetyltransferase Ada2a-containing complex (ATAC), are critical to TC/YT oncogenic transcriptional programs.

Conclusions: Our data showed that the TAZ-CAMTA1 and YAP-TFE3 transcriptional programs alter the TAZ and YAP transcriptional programs by modifying the open chromatin landscape via the ATAC histone acetyltransferase complex. This complex provides a therapeutic target for a sarcoma currently lacking a targeted therapy.

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16 The Characterization of Scaffold Attachment Factor B1 as a Tumor Suppressor via Tight Regulation of Cholesterol and Fatty Acid Biosynthesis in Triple Negative Breast Cancer (Diversity Supplement)

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Introduction/Background: The absence of the scaffold attachment factor B1 (SAFB1) correlates with poor survival in breast cancer (BC) patient data sets, but it's unknown if SAFB1 functions as a tumor suppressor. Sterol regulatory element binding proteins both show marked decrease in fatty acid oxidation (FAO) and cholesterol synthesis when knocked down in vitro, and decreased xenograft growth in vivo colon cancer models. SREBP1c, moderator of fatty acid metabolism, has SAFB1 bind the promoter to enhance transcription. Aggressive tumor phenotype is observed in SREBP2 with enhanced cholesterol biosynthesis by activation of the mevalonate pathway (MVA). We hypothesize that SAFB1 suppresses SREBP2 expression, limiting tumor phenotype.

Methods: Knock-down of the SAFB1 gene with silencing RNA across triple negative breast cancer (TNBC) and estrogen receptor positive (ER+) BCs, selected with puromycin. Gene expression measured by quantitative real-time PCR and western blot. Cell viability was assessed with clonogenic and MTT assay. Cholesterol biosynthesis measured by ORO lipid assay. Effect of SAFB1 on mitochondria measured via Seahorse XF Cell Mito Stress Test.

Results: Higher expression of FAO and MVA pathway genes were found with SAFB1 knock downs in the TNBCs exclusively. In functional assays, we observed an increase in proliferation, colony formation and lipid droplets in SAFB1 knock downs of the TNBCs, unchanged in ER+ SAFB1 knock downs.

Conclusions: We found a TNBC-specific feedback loop as SAFB1 loss enhances tumor properties by de-regulating SREBP-mediated fatty acid and cholesterol biosynthesis via FPP byproduct feeding the ETC for increased fatty acid oxidation.

Funding: This work was supported by a National Cancer Institute Diversity Supplement grant.

17 Transcribed Ultraconserved Regions (TUCRs): A Bioinformatics Exploration of the Deregulation and Function of an Understudied Class of Molecules in Gliomas (Diversity Supplement)

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Introduction/Background: Gliomas represent the most common brain tumors. Particularly, glioblastoma (GBM) is the most common and most deadly malignant brain tumor. Most glioma research has focused on protein-coding genes and much less on the non-coding transcripts that make up 98% of cellular RNA. Transcribed Ultra-Conserved Regions (TUCRs) represent an understudied class of molecules that are found 100% conserved across multiple species. These transcripts are highly resistant to variation and are commonly deregulated in cancer, suggesting regulator and functional importance.

Methods: TUCRs were manually annotated using the UCSC Genome Browser. Bedtools was then used to determine TUCR resistance to single nucleotide polymorphisms (SNPs) and to characterize the transcription landscape at TUCR genomic loci. Then, RNA-Seq analysis pipeline was used to identify the absolute (RPKM) and differential expression of TUCRs in GBM and LGG. Multiple methods were then used to characterize TUCR correlation with survival in gliomas. Lastly, GBM and LGG RNA-Seq data was used to generate a list of coregulated genes, which formed the basis for a guilt-by-association analysis to predict biological processes and molecular functions that may be shared by TUCRs and their coregulated genes.

Results: We identified that TUCRs are resistant to variation compared to other RNA classes, are expressed at a level that is comparable to protein coding genes, and are on genomic loci that are amenable to transcription. Of the 481 TUCRs, 197 and 149 are deregulated in GBM and LGG, respectively. Of the TUCRs that are expressed in GBM and LGG, 36 and 167 correlated with survival, respectively. Lastly, we have predicted functions for all 481 individual TUCRs, and TUCRs may be implicated in metabolic processes as a class of molecules in gliomas.

Conclusion: We performed the first analysis of TUCRs in gliomas. Many of these TUCRs are deregulated in gliomas and are correlated with patient outcomes. These results suggest that further research into TUCR biology is warranted.

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18 Blocking ActRIIB Signaling and Restoring Appetite Reverses Cachexia and Improves Survival in Mice with Lung Cancer (K08)

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Introduction/Background: The cancer anorexia-cachexia syndrome (CACS) is a common, debilitating condition with limited therapeutic options. The defining feature of CACS is weight loss, which suggests a state of negative energy balance. It is unclear whether this net reduction in energy is due solely to anorexia or if a combination of anorexia and increased energy expenditure (EE) occurs.

Methods: To address this question, we induced lung cancer in mice and measured changes in food intake, EE, and body composition.

Results: Mice with CACS developed reductions in food intake, spontaneous activity, and EE. There was severe atrophy and markers of metabolic dysfunction in the adipose and skeletal muscle tissues as compared to mice without CACS and pair-fed wild-type mice. We used anamorelin fumarate (Ana), a ghrelin receptor agonist, alone or in combination ActRIIB-Fc, a ligand trap for TGF-β/activin family members, to reverse anorexia and skeletal muscle atrophy, respectively. Ana effectively increased food intake and the combination of drugs increased lean mass, restored spontaneous activity, and improved overall survival.

Conclusion: These beneficial effects were limited to female mice. Our findings suggest that multimodal, gender-specific, therapies are needed to reverse CACS.

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19 Host Genetic Susceptibility to Gut Microbiota-Driven Colorectal Carcinogenesis (K22)

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Introduction/Background: Colorectal cancer (CRC) is the 1st and 2nd leading cause of cancer death in men and women in Puerto Rico and the U.S., respectively. A dynamic balance between the host immune system and the gut bacterial communities is essential to protect colonic tissues against chronic inflammation, which may lead to CRC. The main goal of the proposed study was to investigate if SNPs in the promoter regions of the IL-1β, IL-6 and IL-10, key cytokines that regulate gut inflammation, increase the risk for colorectal adenomas by enriching a subset of the toxin-producing gut microbiota (gene-environment interaction).

Methods: Using a case-control study design, associations between having proinflammatory SNPs and/or bacterial toxins in colonic mucosa or stool were assessed using odds ratios. TaqMan® SNP Genotyping Assays (ThermoFisher Scientific) for IL-1β (rs1143627), IL-6 (rs1800795), and IL-10 (rs1800871) were performed according to the manufacturer's recommendations. The presence of pks, TcPC, GelE, cnf-1, CDT, murB, and usp bacterial toxin genes in tissue and stool were determined using the QuantiTect SYBR Green PCR kit (QIAGEN).

Results: Our preliminary analyses showed that individuals with the IL-1B proinflammatory genotype were 1.5 times as likely to have colorectal adenomas (n=232). Among the bacterial toxin genes studied, USP was detected with a significantly higher frequency among those with colorectal adenomas. Detection of USP in colonic mucosa (n=138) and stool (n=134) was positively associated with having adenomas (OR=6.02; CI 95%= 81- 269.07 and OR=3.02; CI 95%=.88-13.383, respectively).

Conclusion: An evaluation of the association between having pro-inflammatory genotypes, the presence of bacterial toxin genes in stool and tissue, and colorectal adenomas using a larger sample size is warranted and currently underway. This year we established the Human Tissue Engineering Laboratory, where we are generating and biobanking colon organoids for future mechanistic studies.

Funding: This work was supported by National Cancer Institute award #CA226395.

20 Characterizing the Mechanism of Degradation of the Mitochondrial Matrix Temperature-Sensitive Protein yah1pts (iCURE)

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Introduction/Background: Alterations in mitochondrial homeostasis/gene expression are often seen in cancer cells. Specifically, mitochondrial mutations altering cellular metabolism allow cancer cells to grow and proliferate in nutrient-poor microenvironments. While cancer cells benefit from metabolic reprogramming, mitochondrial defects also characterize a host of human disorders and diseases, such as autism and heart failure. Mitochondrial homeostasis is maintained in part by the quality control of mitochondrial proteins, most of which are encoded by the nuclear genome. Recently, a mitochondria-associated degradation (MAD) pathway that facilitates the ubiquitination and degradation of damaged mitochondrial proteins has been elucidated. However, the role of MAD in mitochondrial protein quality control beyond the outer membrane is less understood. Using the tractable model organism, Saccharomyces cerevisiae, we have characterized mitochondrial matrix proteins that function as quality control substrates. One of these a temperature-sensitive form of the yeast mitochondrial ferredoxin, Yah1p, which is required for the formation of iron-sulfur proteins.This study seeks to characterize the mechanisms of degradation of yah1pts, including identifying MAD components involved in its degradation.

Methods: We use protein stability analyses by cycloheximide chase pulse assays, isolation of crude mitochondrial fractions, subcellular fractionation of mitochondria, electrophoretic mobility analyses, and immunoblotting to characterize the localization and degradation of yah1pts protein forms.

Results: We find that a mutated Yah1p (yah1pts) accumulates both as precursor and mature forms of the protein. Both forms of the protein undergo rapid turnover, suggesting their degradation in their respective compartments. Interestingly, in yeast strains lacking resident mitochondrial matrix proteases (yta12Delta, atg3Delta, and pim1Delta) both forms of yah1pts significantly accumulate. Accumulation of the precursor protein is also observed in cytosolic proteasome mutant strains.

Conclusion: The identification and characterization of MAD components involved in the degradation of essential mitochondria proteins, like yah1pts, will be key to providing molecular targets to further study the contributions of mitochondrial homeostasis in human health and disease pathogenesis.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

21 Developing Glypican-3 Specific Nanobodies for the Treatment of Hepatocellular Carcinoma (iCURE)

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Introduction/Background: Glypican-3 (GPC3) is a highly specific diagnostic biomarker for hepatocellular carcinoma (HCC), and is an attractive therapeutic target. Camelids naturally produce nanobodies (Nbs) which have a low molecular weight (15 kDa), low immunogenicity, high stability, and excellent tumor tissue penetration. By coupling them to other agents such as peptides, radioisotopes, and chemotherapeutic drugs, Nbs can be used as tumor-targeted therapeutic agent. We aim to develop a novel HCC targeted therapeutic agent utilizing Nb-specific GPC3.

Methods: A healthy llama was immunized with recombinant human and murine GPC3. Blood was collected from the animal and Nbs genes were cloned into phagemid vectors. Nbs were then displayed on filamentous M13 bacteriophage and subsequently potent binders to GPC3 were identified. We used direct enzyme-linked immunosorbent assay (ELISA) to identify clones specific to both GPC3, which we next sequenced.

Results: Our ELISA demonstrated 11 Nbs (Nb-GPC3 1 - 11) that bound specifically to recombinant murine GPC3. Amino acid sequences of these binders demonstrated 4 unique Nb sequences. Of the 4 unique murine GPC3 Nbs, 1 had specificity to human GPC3.

Conclusion: We successfully identified Nbs specific to murine GPC3 and human GPC3 that could be engineered into HCC selective therapeutic agents. In terms of future directions, we will perform several additional screening cycles to identify additional unique Nbs to both murine and human GPC3. Once we identify 10-20 unique clones, we will validate specificity using cell-free and cell-based binding assays. If successful, we will then optimize the chemistry to conjugate cytotoxic cargo (e.g. chemotherapy, or radioisotope) for therapy studies in preclinical models of HCC.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

22 Identification of a Novel AKT/MTOR Pathway Inhibitor (CPACHE U54)

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Introduction/Background: Aberrant activation of the PI3K/AKT/mTOR pathway promotes the tumor progression and resistance to treatment in human breast cancers. Although first and second generation mTOR inhibitors are currently being used in numerous clinical trials, their role as anticancer agents remains modest. Therefore we hypothesize that comp34 inhibits breast cancer cells growth through inhibition of AKT1 and mTOR expression, via regulating AL354740.1-204 and miR-99 family.

Methods: We perform assays to confirm the regulation of cell proliferation by comp34. For example, Label-Free Cell Counting Kinetic Proliferation Assay, and colony formation assay. Here, we used single-cell RNA fluorescence in situ hybridization (RNA FISH) to survey abundance and cellular localization patterns of AL354740.1-204 in MDA-MB-231 cells. Using combined high-throughput screening of drug and bioinformatics approaches, we will identify a panel of regulatory lncRNAs at upstream of miR-99s.

Results: 1. Comp34 decreased mTOR signaling activity. We analyzed the Akt/mTOR mRNA expression regulated by comp34, MDA-MB-231 cells were treated with comp34, the mRNA and protein of both Akt and mTOR were significantly decreased.
2. miR-99s family involve comp34 induced mTOR signaling alterations. Bioinformatics analysis showed that the 3'-UTR of Akt and mTOR harbored multiple miR-99 family members binding sites.
3. Screening of potential miR-99s family sponges. We observed that the sub-cellular localization of AL354740.1-204 was almost exclusive cytoplasmic localization. Simultaneous abundance analysis of AL354740.1-204 showed that low abundance of AL354740.1-204 was measured in bulk cell populations upon comp34 stimulation.

Conclusion: In view of the malignancy of TNBC associated with metastatic breast cancer, a series of new therapies are needed to improve the prognosis of this refractory breast cancer. We have demonstrate that comp34 presents promising activity as a single agent to inhibit TNBC growth through AL354740.1-204, which functions as a sponge absorbing miR-99s to release the mRNA of AKT1 and mTOR from miR-99s-dependent decay.

Funding: This work was supported in part by National Institutes of Health (NIH), National Institute on Minority Health and Health Disparities U54MD007598, National Cancer Institute (NCI) 1U54CA14393, U56 CA101599-01; Department of Defense Breast Cancer Research Program grant BC043180, NIH National Center for Advancing Translational Sciences Clinical and Translational Science Award UL1TR000124 to JVV; Accelerating Excellence in Translational Science Pilot Grants G0812D05, NIH/NCI SC1CA200517, and 9 SC1GM135050-05 to YW; Accelerating Excellence in Translational Science Pilot Grant G0814C01 to QH; NIH/NIGMS 1SC1GM121202 to PW; and NIH/NCI 1SC2CA235066 to SC.

23 Metabolic Adaptations in SDH-Deficient Cancer Cells (Diversity Supplement)

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Introduction/Background: Cancer cells, characterized by uncontrolled cellular divisions, must alter their metabolism to support rapid cell proliferation by coordinating both catabolic and anabolic processes to continuously balance energy production and biomass replication. One example of this is the tricarboxylic acid (TCA) cycle, a mitochondrial pathway that incorporates several catabolic conversions of the cofactor NAD+ to NADH and is the major anabolic source of aspartate, a key amino acid for proliferating cells. Several components of TCA cycle are implicated in the tumorigenesis of some cancers, including loss of function mutations in succinate dehydrogenase (SDH) that can drive neuroendocrine and renal cancers. However, little is known about how cancers tolerate the loss of SDH activity, which plays a pivotal role in the metabolism of proliferating cells.

Methods: This project utilizes CRISPR/Cas9 technology for generating genetic knockouts, proliferation assays, liquid chromatography mass spectrometry-based metabolomics, and isotope tracing to analyze metabolite contributions for various metabolic pathways.

Results: I have found that SDH-inhibited cells require exogenous aspartate to proliferate. Unlike cells with other respiratory defects, the proliferation and aspartate levels of SDH-inhibited cells are not restored by electron acceptors (molecules that regenerate NAD+ independent of the ETC). Furthermore, additional complex I inhibitors can ameliorate proliferation defects and aspartate limitation caused by SDH deficiency. Using isotopically labelled glucose and glutamine, I have determined that alternative metabolic pathways support aspartate biosynthesis in SDH-deficient cells.

Conclusion: Here, I show that SDH-deficient cells must rewire glucose and glutamine metabolism to noncanonical routes of aspartate biosynthesis in order to optimally proliferate. This research could thereby identify new specific metabolic targets required for SDH mutant cancers.

Funding: This work was supported by a Diversity Supplement for R00CA218679.

24 The Influence of Generational Obesity on Ovarian Cancer Metastasis (K01)

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Introduction/Background: Obesity is a worldwide epidemic associated with many cancer types due to persistent inflammation, hyperglycemia and hyperinsulinemia providing an abundance of nutrients and growth factors to cancer cells resulting in an ideal microenvironment. Maternal obesity often results in an increased risk of offspring developing obesity. Chronic inflammation and immunosuppression found in obese patients have been linked to ovarian cancer (OvCa). OvCa is the most lethal gynecological malignancy among women and approximately 12% of OvCa patients are obese. Poor survival rates are attributable to women presenting with advanced disease with disseminated intraperitoneal (i.p) metastasis at diagnosis. Metastatic tumor cells shed from the primary tumor and preferentially home to the omentum and other peritoneal organs.

Methods: A pre-clinical murine model of generational diet-induced obesity that included maternal cohorts of C57BL/6 mice (dam) with intact host immunity fed either a control diet (CD; 10% fat) or a high-fat diet (HFD; 40% fat) and the resulting offspring fed either diet was utilized to explore diet induced genetic and biophysical modifications.

Results: Body composition analysis revealed differences in weight and lean mass was dependent on offspring diet alone and fat mass was dam diet dependent among CD fed offspring. Additionally, a tumor study was performed using either CD or HFD fed offspring to quantify site-specific metastatic success. Offspring only exposed to a HFD displayed higher omental tumor burden than HFD fed offspring from CD dams suggesting maternal influence. Furthermore, HFD fed mice accumulated more ascites fluid than CD fed mice, however variances were independent of dam diet. Comparison of ascites cytokine expression revealed CXCL13, a dominant chemokine in adipocytes, was significantly increased in mice only exposed to a HFD suggesting an additive effect of both maternal and offspring obesity.

Conclusion: Together, the results suggest maternal obesity or subsequent exposure to a HFD can impact ovarian cancer metastasis.

Funding: This work was supported by National Institutes of Health, National Cancer Institute grant K01CA218305.

25 Solid Stress Impairs Lymphocyte Infiltration into Lymph Node Metastases (K22)

Jones, D.[1], Wang, Z.[1], Chen, I.[2,3], Zhang, S.[4], Banerji, R.[4], Lei, P.[2,3], Zhou, H.[2,3], Xiao, V.[2], Kwong, C.[2], van Wijnbergen, J.[2,3], Pereira, E.[2,3], Vakoc, B.[3,5], Huang, P.[2,3], Nia, H.[4], Padera, T.[2,3]

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Introduction/Background: Metastasis remains the principal cause of cancer mortality. Lymph node metastases are common and indicate poor overall prognosis, likely due to both the metastatic potential of primary tumor cells and the contribution of lymph node metastases to distant metastases. Although antitumor T cells are generated in lymph nodes, metastatic cancer cells are able to grow in this seemingly hostile microenvironment. We hypothesized that lymph node metastases actively suppress anti-tumor repsonses in lymph nodes. The overall goal of our study is to understand how cancer cells avoid immune detection in lymph nodes.

Methods: We obtained patient samples, established a novel ER+ mammary carcinoma (MCa) cell line and employed 4T1 triple negative breast cancer cells to investigate the growth of spontaneous lymphatic metastases. In addition, we developed a lymph node compression apparatus to mimic the compressive forces, known as solid stress, generated by cancer cells in lymph nodes. We used immunofluorescence microscopy, intravital imaging, flow cytometry, and quantitative PCR to characterize the effect of cancer growth on adaptive immune responses in tumor-involved lymph nodes.

Results: Using patient tissue from multiple cancers and preclinical models of spontaneous lymph node metastases, we show that cancer cells disrupt lymphocyte trafficking to lymph nodes, resulting in exclusion of lymphocytes from metastatic lesions. Lymphocyte exclusion from nodal lesions is associated with the presence of solid stress caused by lesion growth. Solid stress reduces the number of functional high endothelial venules in the nodes. Relieving solid stress in the mice increased the presence of lymphocytes in lymph node lesions.

Conclusion: These findings reveal a novel mechanism for the lack of immune response against lymph node metastases and may inform strategies for immunotherapy.

Funding: This work was supported in part by the National Institutes of Health, National Cancer Institute grant K22CA230315 to DJ.

26 pH Dynamics Determining DNA Binding Specificity of FOX Transcription Factors (Diversity Supplement)

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Introduction: Intracellular pH (pHi) is constitutively increased in cancers, which enables tumorigenic behaviors. To understand how pHi enables cancer behaviors our lab bridges protein electrostatics and cell biology to reveal the design principles of endogenous proteins regulated by pHi dynamics. We showed pH-regulated protein-phospholipid and protein-protein binding for cell transformation, proliferation, and migration. However, many cancer behaviors regulated by pHi include changes in gene transcription. My project tests a new idea on pH regulating protein-DNA binding by focusing on titration of a conserved histidine in the DNA-binding domain (DBD) of FOX family transcription factors.

Methods: Structural analysis of nucleotide-histidine distance and alignment of FOX transcription factors were performed in PyMol and UCSF Chimera, respectively. Additionally, K_d values of recombinant GST-FOXM1 DBD with a 6-FAM labeled FOXM1 consensus sequence were determined via fluorescence anisotropy.

Results: Our computational analysis indicates the conserved histidine in the DBD of FOX proteins is spatially aligned and predicts hydrogen bonding to different nucleotides as a function of histidine charge. I confirmed this prediction by showing pH can switch binding preferences to different nucleotides. We found that FOXM1 has increased affinity to a defined consensus sequence at low pH 7.0 (K_d=0.94 ± 0.22 μM; protonated histidine) compared with pH 7.5 (K_d=1.85 ± 0.28 μM; neutral histidine). We also found that binding affinity to the DNA sequence linearly decreases as a function of pH between the cellular range of 7.0-7.6. Lastly, I found that a His287Lys mutant, mimicking a protonated histidine, increased binding affinity at pH 7 (K_d=0.206 μM) and 7.5 (K_d=0.455 μM).

Conclusion: These findings open new directions to understand how gene expression can be regulated by pHi dynamics. These findings have broad significance because transcription factors in other families, including STAT, ETS, and SOX, contain a histidine that forms hydrogen bonds with nucleic acids.

Funding: This work was supported by Diversity Supplement CA197855.

27 Tert Mutant Promoter Mouse Model as a Novel Tool to Study Telomerase Transcriptional Regulation and Biology in Advanced Thyroid Cancers (K22)

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Introduction/Background: Hotspot mutations in the proximal promoter of the telomerase reverse transcriptase (TERT) gene represent the first cross-cancer alteration lying in a gene regulatory region. TERT promoter mutations (TPMs) are enriched in advanced thyroid tumors, metastatic melanomas and gliomas, constituting early markers of disease severity. TPMs enhance TERT transcription, which is typically silenced in adult tissues, reactivating a bone fide cancer protein.

Methods: To study TERT aberrant regulation and its downstream consequences in a biologically accurate model, we generated the first Tert mutant promoter mouse model via CRISPR/Cas9 engineering of the equivalent locus and crossed it with thyroid-specific Braf-mutant mice (TPO-Cre/BrafV600E).

Results: BrafV600E animals develop highly penetrant papillary thyroid tumors (PTC) which hardly ever progress. In contrast, BrafV600E+TertMUT animals showed an increased incidence of poorly differentiated thyroid cancer (PDTC) phenotypes by 20 weeks, mimicking those exhibited by a Tert overexpression transgenic model (BrafV600E+K5-Tert). Tert promoter mutation in mice increased Tert transcription in vitro and in vivo, as reported in patient's tumors carrying TPMs. Braf+Tert animals partially responded to MAPK inhibition (dabrafenib plus trametinib), showing that MAPK remains as an essential pathway in advanced thyroid tumors. Consequences of Tert reactivation in mouse thyroid tumors included unique transcriptomic profiles (compared to Braf alone), suggesting that downstream effects other than telomere-related functions might operate in cancers harboring TPMs.

Conclusion: These cancer models of telomerase reactivation provide an excellent pre-clinical setting to understand the regulatory mechanisms and biological consequences of TPM-positive thyroid cancers and other aggressive tumors, and to eventually explore new treatment strategies.

Funding: This work was supported by National Institutes of Health, National Cancer Institute K22 Career Transition Award 1K22CA 473230381–01A1.

28 Dynamic Protein-Nucleic Acid Interactions One Molecule at a Time (K01)

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Introduction/Background: Single molecule Förster/fluorescence resonance energy transfer (smFRET) is uniquely capable of investigating the molecular mechanisms of biological pathways that involve multiple transient protein-protein and protein-nucleic acid interactions. My poster will focus on the use of smFRET to explore the DNA mismatch repair pathway (MMR), which is a post-replicative system of enzymes that corrects rare mistakes in the genome of all organisms. Failures in the mismatch repair pathway likely initiate tumorigenesis, but currently we lack a fundamental understanding of the MMR process. The molecular mechanism of mismatch repair is critical for revealing how mutants fail to repair and may provide a basis for identifying therapeutic strategies.

Methods: Single molecule Förster/fluorescence resonance energy transfer (smFRET) is uniquely capable of investigating the molecular mechanisms of biological pathways that involve multiple transient protein-protein and protein-nucleic acid interactions. My poster will focus on the use of smFRET to explore the DNA mismatch repair pathway (MMR), which is a post-replicative system of enzymes that corrects rare mistakes in the genome of all organisms. Failures in the mismatch repair pathway likely initiate tumorigenesis, but currently we lack a fundamental understanding of the MMR process. The molecular mechanism of mismatch repair is critical for revealing how mutants fail to repair and may provide a basis for identifying therapeutic strategies.

Results: We utilized a combination of protein and nucleic acid fluorescent labeling strategies to monitor the dynamic interactions involved in the MMR pathway from different vantage points. We connected the measurements via kinetic analyses to reveal coordinated conformational changes in MutS and mismatch DNA that are likely necessary for repair to commence.

Conclusion: We have employed a robust methodology to monitor dynamic protein-nucleic acid interactions using different fluorescent labeling strategies. By connecting the single molecule measurements via kinetic analyses, we can build more comprehensive molecular models of pathways such as MMR that include functional dynamic conformational changes. The approach outlined is broadly applicable to studying the molecular details of many essential biological pathways.

Funding: This work was supported by grant #K01CA218304.

29 Lipids in the Etiology of Lung Cancer Health Disparities (R21)

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Introduction/Background: A goal of our work is to understand if there are molecular differences in the biology of non-small cell lung cancers between African Americans (AA) and non-Hispanic Whites (NHW). Along with other known hallmark alterations, oncogenic transformation is always associated with the reprogramming of lipid metabolism. Enhanced lipid production is essential for tumor development, tumor growth, metastasis, and the regulation of the epithelial-mesenchymal transition (EMT). Sphingolipids like glucosylceramide (GlcCer) and lactosylceramide (LacCer), are also associated with the regulation of EMT. GlcCer alterations also impact clinical outcomes by contributing to chemoresistant phenotypes in tumors and cell-lines, and it is well-established that reducing GlcCer can decrease chemoresistance. Little is known about global lipid metabolism reprogramming in lung cancer tissues of NHW. But more importantly, nothing is known about lipid reprogramming in AA males and AA females. We now have data from AA subjects with LUAD and LSCC, showing significant normal→tumor reprogramming of these and other lipids. But most remarkably, and unexpectedly, we observe race and sex specific alterations in GlcCer, and LacCer levels are differentially associated with outcomes in AA with LUAD.

Methods: Human specimens were analyzed by LC-ESI-MS/MS and clinical patient data were obtained through an honest broker at the VCU biorepository.

Results: 1) Sphingolipids are dramatically altered in the tumors of AA with non-small cell lung cancer. 2) Sphingolipids are strong indicators of lung cancer in AA and NHW. 3) There are significant differences between the normal adjacent uninvolved tissues of AA and NHW with lung cancer. 4) Sphingolipid acyl chain-length is differentially associated with clinical outcomes in AA and NHW with LUAD. 5) Normal→tumor reprogramming of GlcCer acyl chain-length is race- and sex-dependent in LUAD. 6) There are significant differences between the tumor sphingolipids of AA Males and AA Females.

Conclusion: Characterizing the lipid metabolism alterations in AA and NHW may provide some insight that may direct future studies designed to exploit these different molecular tumorigenesis paths.

Funding: This research was supported in part by startup funds and National Institutes of Health, National Cancer Institute grant R21CA232234.

30 miR155 Deficiency Reduces Breast Tumor Burden in a Transgenic Breast Cancer Murine Model (Diversity Supplement)

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Introduction/Background: Deregulated and aberrant expression of microRNAs (miRNAs) have been linked to a variety of disorders such as cancers, autoimmune diseases, and chronic inflammation. Many miRNAs are important regulators of cellular processes involving development, differentiation, and signaling. We investigated whether miR155, a multifunctional miRNA induced by inflammatory cytokines and involved in hematopoiesis, inflammatory disorders, and macrophage activation, has any promise in reducing tumor burden in a transgenic breast cancer model.

Methods: To study the effects of miR155 in breast cancer, our lab developed the first MMTV-PyMT mice deficient for miR155 on a C57BL/6 background. Four-week-old female PyMT (n=12) and PyMT/miR155-/- (n=11) mice were euthanized after 15 weeks. Bodyweights, tumor volume palpations, and tumor number palpations were recorded weekly. Upon euthanizing, mammary glands were excised for RT-PCR, and tumors were counted, measured, and weighed.

Results: PyMT mice deficient in miR155 exhibited reduced tumor volume ($p<0.05$), number ($p<0.05$), and weight ($p<0.05$). Additionally, PyMT/miR155-/- mice displayed reduced tumor volume palpations ($p<0.05$) and tumor number palpations ($p<0.05$). In order to investigate the anti-tumoral effects associated with miR155 deficiency, mammary glands were analyzed to examine inflammatory mediators and macrophage markers within the mammary tumor environment. We demonstrate that miR155 deficiency upregulates suppressor of cytokine signaling 1 (SOCS1) resulting in reduced overall cytokines, and reduced macrophages as indicated by CD68 and Integrin Subunit Alpha X (IGTAX). Mammary glands of miR155-/- mice had reduced pro-inflammatory M1 macrophage cytokines as indicated by reduced interleukin-1-beta (IL-1b), IL-6, and tumor necrosis factor-alpha (TNF-a). Mammary glands of mice deficient in miR155 exhibited even greater inhibition of M2 macrophages, important in reducing inflammation and contributing to tumor growth and immunosuppressive function, as indicated by reduced IL-4, IL-10, IL-13, mannose receptor 1 (Mrc1), and TNF-beta.

Conclusion: Given that macrophages are known to promote tumorigenesis, we suggest that the anti-tumor effects of miR155 inhibition are due to its upregulation of SOCS1 and resulting decrease in pro-tumor M2 macrophages.

Funding: This work was supported by R01CA218578-03S1.

31 Exploring the Role of Forkhead Transcription Factor *foxe1* in Craniofacial Defect Using a Zebrafish Model (CURE Diversity Supplement)

Mojekwu, O.

Introduction/Background: Orofacial cleft (cleft lip, cleft palate, or both) is among the most common birth defect; it is caused by genetic and environmental factors and their interactions. Mutations in the gene encoding forkhead transcription factor e1 (*FOXE1*) cause Bamforth-Lazarus syndrome which usually includes orofacial cleft. The *foxe1* gene is also present in zebrafish which develop externally, making it a good model for the study of early development. Facial development is easier to observe in zebrafish as opposed to the mouse, and zebrafish share similar craniofacial anatomy with mice and humans. To understand how the mutations cause birth defects, the Cornell group deleted the promoter of the *foxe1* gene in zebrafish. Homozygous mutants exhibited abnormal craniofacial skeletons, as expected, and usually small retina, which was unexpected. To use the zebrafish mutant in tests of potential therapies, it was essential to accurately and quantitatively describe the craniofacial phenotype using morphometrics.

Methods: Adult heterozygous mutant zebrafish, which have a normal phenotype, were crossed. The mutants were separated from the siblings based on phenotypic appearance. Cartilage was stained with Alcian blue dye at 4.5 dpf, observed under a microscope with 10x magnification and captured using Image-Pro Software. Measurement points were applied around the skeleton. Subsequently, measurements will be taken between significant points. Our plan is ultimately to carry out measurements in 6 siblings and 6 mutant larvae. The data will be analyzed using three software packages: tpsUtil64, tpsDig232, and MorphoJ.

Results: The cartilaginous elements of the embryo's pharyngeal skeleton were observed clearly in the ventral view.

Conclusion: Foxe1 gene is required in the palate morphogenesis in early developmental stages. Orofacial cleft malformation was detected based on Alcian blue imaging. The morphometric description of the mutant achieved here will be useful for measuring, for instance, for the effect of additional mutations, or drugs, to reverse or worsen the phenotype.

Funding: This work is supported by R01 grant DE027983 from the National Institute of Dental and Craniofacial Research.

32 Host PI3K-gamma Modulates Anti-Tumor Immunity in Poorly Immunogenic Head and Neck Cancer (K01)

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Introduction/Background: Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer, with around 650,000 new cases yearly. Gain of function mutations in the PI3K pathway are common in HNSCC, and inhibition of the PI3K p110γ subunit has shown promise in HNSCC treatment. However, given that PI3K p110γ plays an important role in myeloid and lymphoid immune cell function, it is essential to understand how PI3K p110γ inhibition affects the anti-tumor immune response independent of tumor cells.

Methods: To elucidate PI3K p110γ function in HNSCC, we employed an orthotopic mouse model using poorly immunogenic and aggressive cell line MOC2 on Pik3cg-/- mice. Tumor growth and metastasis, and immune cell infiltration to tumor microenvironments were measured. Expression of antitumor and exhaustion biomarkers were compared between wild type and Pik3cg-/- mice.

Results: We observed that wild type and Pik3cg-/- mice displayed similar rates of HNSCC tumor growth and metastasis after 20 days post tumor injection. T-cell infiltration and intrinsic T-cell responses to MOC2 oral tumors were comparable between wild type and Pik3cg-/- mice. Interestingly, the immune response of tumor-bearing Pik3cg-/- mice was marked by increased anti-tumor cytotoxic molecules (IFN-γ, IL-17, PD-1) by T cells, and immune checkpoint marker (PD-L1) expression by myeloid cells compared to tumor bearing wild type mice.

Conclusion: Taken together, our findings demonstrate that inhibition of PI3K p110γ modulates tumor associated immune cells, which likely potentiates HNSCC treatment when used in combination with selective PD-L1 inhibitors.

Funding: This work was supported by National Cancer Institute grant #K01CA207599 and American Cancer Society grant #RSG-19-079-01-TBG.

33 Differential Expression of Immune Biomarkers in Parous and Nulliparous Normal Breast Tissue: Implications for Postpartum Breast Cancer (Diversity Supplement)

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Introduction/Background: Breast cancer risk is increased in parous women in the period immediately following childbirth, peaking at five years after the most recent birth. After weaning or in the absence of lactation, the breast undergoes postpartum involution (PPI), a process characterized by epithelial cell death and tissue remodeling that returns the mammary gland to a baseline state, and has previously been associated with increased inflammation and breast cancer development and progression. We hypothesize that dysregulation of immune components of the breast during remodeling phase of postpartum involution may result in immunosuppressed breast microenvironment that is conducive to tumor development, leading to increased risk for breast cancer in the postpartum period. The objective of this study was to detemine the expression of immune biomarkers associated with increased risk for breast cancer in the postpartum period.

Methods: In this study, we used 725 digitized H&E images of normal breast tissue donated to the Komen Tissue Bank (KTB) by parous and nulliparous women ≤45 years, and breast tissue specimen from 23 women (also from KTB, 13 parous, 10 nulliparous). We assessed the digital images by visual and artificial intelligence (AI) methods to understand involution and immune cell content in parous women, stratified by time since last birth ≤ 5 years and > years as compared with nulliparous women. We assessed RNA expression by NanoString immuno oncology (IO) 360, and immune biomarkers by NanoString GeoMx Digital Spatial Profiling (DSP).

Results: We found that recently parous women (≤5 years of a last birth) had higher numbers of terminal duct lobular units (TDLUs), immune cells, and plasma cells as compared with nulliparous women, and that beyond 5 years of a last birth, TDLU numbers were still higher in parous women, but the immune and plasma cell content of the breast of parous and nulliparous women were not significantly different. Our gene expression analysis revealed differential expression of genes that clustered according to parity status, with interferon stimulated genes; STAT1 and IFITM1, and interferon alpha receptor 1 (IFNAR1), and MHC class II genes (HLA-DMA, HLA-DPA, HLA-DPB1, and HLA-DRA) elevated in parous women. Our DSP analysis revealed that immune biomarkers with immunosuppressive functions, including ARG1, VISTA, CTLA-4, and CD68 were significantly higher in parous women as compared with nulliparous women

Conclusion: Postpartum breast tissue shows sustained alterations associated with increased risk for development of breast cancer in parous women. Lobular tissue is elevated, and profiling of immune microenvironment components reveals elevated expression of immunosuppressive immune biomarkers. Our results provide insight into improved risk assessment and concepts for novel prevention strategies for postpartum breast cancer.

Funding: This work was supported by Supplement/Re-entry grant for R01 CA229811 and Mayo Clinic Cancer Center grant P50 CA15083.

34 Investigating Race-Related Microbial Influences in Triple Negative Breast Cancer (Diversity Supplement)

Ojesina, A.[1], Srinivasasainagendra, V.[1], Van Der Pol, L.[1], Sundaresan, A.[1], Kim, H.G[1], Behring, M.[1], Yates, C.[2], Eltoum, I.E.[1], Shrestha, S.[1], Lefkowitz, E.[1], Tiwari, H.[1], Manne, U.[1]

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Introduction/Background: There are racial differences in the incidence and death rates of triple negative breast cancer (TNBC): African American (AA) women present with more advanced and at younger ages than Caucasians (CA). Disparity is often associated with socioeconomic and biological factors. However the role of microbes in breast cancer is not well understood. The goal of this project is to identify microbial abundance differences in triple-negative breast cancers (TNBCs) between African American and Caucasian patients, using both 16S rDNA and RNA sequencing data.

Methods: Tumor DNA from 27 AA and 16 CA were subjected to 16S rDNA sequencing and analyzed for differences in microbial abundance using weighted Unifrac analyses. RNASeq from the tumors were also subjected Patheq analyses to identify microbes. Bacterial reads were normalized to the number of human reads in each sample (reads per million) and relative abundances were compared between AA and CA patients (t-test false discovery rate FDR<0.05). Bacterial abundance between the two groups at phylum, class, order, family, genus and species levels using t-tests, FDR <0.05).

Results: 16S rRNA analysis revealed that African Americans had higher abundance of Bacteroidetes (FDR=0.0007) and Firmicutes (FDR=0.0305) while Caucasians had higher abundance of Proteobacteria (FDR=0.01). The RNASeq-derived data were largely similar.

Conclusion: Differential bacterial profiles by race suggest that future studies should examine the possible role of breast tumor microbiome in the prognostic disparities observed in TNBC.

Funding: This work was supported by a Diversity Supplement to National Cancer Institute grant #U54CA118948.

35 Analyzing the Role of the Non-Canonical NF-κB Pathway in Macrophage Phenotype and Function and Ovarian Cancer Progression (Diversity Supplement/Re-entry)

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Introduction/Background: Ovarian cancer has a 5-year survival rate of 48.5% and ranks fifth in causes of cancer-related deaths in women. One avenue for new treatments is modulating the tumor microenvironment (TME). One major population in the TME is tumor-associated macrophages (TAMs) that have a pro-tumorigenic (M2) phenotype which can be repolarized towards an anti-tumor (M1) with certain stimuli. We aim to understand and exploit pathways that regulate macrophage phenotype and behavior, including NF-kappaB (NF-κB) signaling. We hypothesize that activating non-canonical NF-κB (nc-NF-κB) pathway in macrophages will worsen tumor progression.

Methods: We are performing co-immunofluorescence on tumor sections. Our *in vivo* studies use doxycycline-inducible transgenic mouse models termed IKFM and ALFM that overexpress cIKKβ (canonical NF-κB) or p52 (nc-NF-κB) specifically in macrophages. Intraperitoneal growth of TBR5 murine ovarian cancer cells is used for tumor progression studies in mice. We have used a luminol derivative, L-012, to analyze reactive oxygen species (ROS) in IKFM and ALFM mice versus control littermates. For statistical analyses, the Mann-Whitney test was used.

Results: Cultured M2 polarized bone marrow derived macrophages express higher levels of nuclear and cytoplasmic p52 in comparison to M1 and unpolarized macrophages. IKFM mice produce significantly more ROS than ALFM when compared to control littermates. In our TBR5 ALFM model, the ALFM mice had lower trending ascites ($P < 0.15$) and significantly reduced tumor weights ($p < 0.01$) in comparison to controls. In a different time course, ALFM mice trended lower with tumor weights and ascites volume ($P < 0.12$ and $P < 0.13$).

Conclusion: Further analyses of *in vivo* samples will be necessary to determine effects of elevated nc-NF-κB on ovarian tumor progression.

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36 Exploiting Collateral Vulnerabilities Created by a Covalent Oncometabolite (iCURE)

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Introduction/Background: Many cancers are fueled by reprogrammed cellular metabolism. A prototypical example occurs in hereditary leiomyomatosis and renal cell carcinoma (HLRCC), a genetic cancer syndrome in which mutations in fumarate hydratase (FH) locus cause accumulation of the oncometabolite fumarate. Fumarate is an electrophilic metabolite that can non-enzymatically modify cysteines, leading to a rare posttranslational modification known as cysteine S-succination.

Methods: The goal of this project is to identify collateral vulnerabilities created by cysteine S-succination in HLRCC, as well as potential chemical leads for their therapeutic targeting. To accomplish this we employed covalent ligand screening to identify a lead, JM-289A-060, that displays FH-dependent toxicity in HLRCC cells.

Results: Global cysteine profiling using liquid chromatography coupled mass spectrometry (LC-MS/MS) allowed the identification targets of JM-289A-060 in an HLRCC cell model, which were validated using a clickable photoaffinity analogue of the lead compound. Finally, we mechanistically explored one of these targets, the tRNA methyltransferase TRMT1, and found overexpression of this protein protected HLRCC cells from FH-dependent cytotoxicity.

Conclusion: Overall, these studies demonstrate the power of covalent ligand screening to identify new therapeutic vulnerabilities in cancer and suggest a novel link between tRNA biology and the TCA cycle in HLRCC.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

37 lrhA and rbsD: Two Genes Involved in the Transcriptional Regulation of rpoS (iCURE)

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Introduction/Background: RpoS is a sigma factor in Escherichia coli and other enterobacteria that accumulates in response to stress or starvation and is important for the cell to survive the stress condition. RpoS accumulation is regulated at multiple levels. RpoS translation is inhibited by a stem loop in the mRNA just before the start codon blocking ribosome entry; for translation to occur, small regulatory RNAs (sRNAs) are needed to open the stem-loop. RpoS is also subject to rapid degradation by an adaptor protein for the ClpXP protease but is stabilized during stress by anti-adaptors.

Methods: In a screen for multicopy negative regulation of an RpoS-mcherry reporter fusion, we identified two genes, lrhA and rbsD. Both appear to down-regulate RpoS by blocking sRNA-mediated translation.

Results: LrhA belongs to the LysR family of transcription factors. Multicopy lrhA was previously identified by Thomas Silhavy (2006) to negatively regulate the translation of RpoS. We show that lrhA from an inducible promoter causes down-regulation of RpoS translation.

RbsD is a ribose pyranase encoded within the rbsDACBK operon; it is involved in the conversion of D-ribose into D-ribose 5-phosphate. The rbsDACBK operon is regulated by the transcriptional regulator rbsR; when the cells are induced with ribose the operon is expressed. We show that when a fragment of the rbs operon containing the promoter, RbsR binding site, and rbsD gene is overexpressed, it titrates the rbsR repressor from the chromosome, allowing rbsD from both the chromosome and the plasmid to be transcribed. The rbsD RNA interferes with the sRNA binding to the rpoS translation inhibitory stem-loop. Induction of the chromosomally encoded rbs operon with ribose is sufficient to reduce RpoS-mCherry expression.

Conclusion: We conclude that lrhA and rbsD likely effect is on translation of RpoS. LrhA likely acts indirectly to repress RpoS and rbsD RNA is likely to directly interact with various sRNAs.

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38 Identifying Key Oncogenic Transcription Factors and Enhancers Using TENET 2.0 (K01)

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Introduction/Background: Transcription factors (TFs) bind to regulatory elements such as promoters and enhancers to control the expression of genes in a given cell. We hypothesize that distinct sets of TFs are activated in each tumor type and bind to tumor-type specific enhancers, leading to carcinogenesis. To identify key TFs and enhancers dysregulated in tumor tissue samples, we have developed an improved version of the Tracing Enhancer Networks using Epigenetic Traits method (TENET 2.0).

Methods: We analyzed DNA methylation, RNA-seq, chromatin immunoprecipitation and sequencing (ChIP-seq), open chromatin, and clinical datasets publicly available in The Cancer Genome Atlas (TCGA), Encyclopedia of DNA Elements (ENCODE), and Gene Expression Omnibus (GEO) databases usng a newly developed bioinformatic tool called TENET 2.0 (https://github.com/suhnrhie/TENET_2.0).

Results: We applied the TENET 2.0 method to breast, prostate, kidney, lung, bladder, and brain tumor and normal datasets and identified key TFs that are associated with tumor-specific enhancers in each tumor type. When we compared the list of identified TFs, we found that most are distinct for each tumor type, but TFs such as FOXM1 were identified in multiple tumor types. To further characterize the relationship between FOXM1 and cancer, we peformed FOXM1 ChIP-seq and siRNA knockdown experiments followed by RNA-seq in breast and lung cancer cell lines. We found that FOXM1 binding sites and genes regulated by FOXM1 are distinct between cancer cell types. We are currently characterizing the effect of FOXM1 inhibitors on the expression of genes regulated by FOXM1.

Conclusion: Identification and characterization of key TFs and associated enhancers in different tumor types provides important insights into the deregulation of cancer epigenomes and transcriptomes, highlighting novel potential targets for clinical intervention.

Funding: This work was supported in part by the National Cancer Institute (K01CA229995, R21CA260082), the University of Southern California (USC) Norris Comprehensive Cancer Center, and USC Keck School of Medicine.

39 Mapping Myeloproliferative Neoplasm-Inducing Inflammatory Signaling Networks by Proximity Dependent Labelling with TurboID (Diversity Supplement)

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Introduction/Background: JAK inhibitors currently used to treat myeloproliferative neoplasms (MPNs) do not show disease-modifying effects and are not curative. This indicates the existence of an alternative signaling pathway contributing to the pathogenesis of MPNs. Abelson interactor adapter protein 1 (Abi-1), a known regulator of actin polymerization-dependent signaling, was recently identified to function as a repressor of STAT3/NF-κB signaling in the bone marrow, and its loss led to development of STAT3/NF-κB-dependent MPN in mice. The objective of this project is to characterize the mechanistic link between Abi-1, STAT3, and NF-κB signaling in order to identify new therapeutic targets for patients with MPNs.

Methods: Abi-1 interactome was established using proximity dependent labelling (PDL) enabled by catalytically enhanced biotin ligase (E. coli-derived BirA* - TurboID) coupled with mass spectrometry. NIH/3T3 cells were transduced with retrovirus encoding TurboID-IRES-GFP (TurboID) or TurboID-linker-Abi-1-IRES-GFP (TurboID-Abi-1), single-cell sorted based on bicistronic GFP expression, and expanded to establish stable cell lines. Three independent PDL experiments were performed followed by lysis, streptavidin pulldown, and label-free quantitative mass spectrometry to identify biotinylated proteins in cell lines expressing TurboID or TurboID-Abi-1.

Results: Two hundred twelve probable Abi-1 interacting proteins were identified, 32 of which are established interactors including Eps8, Vasp and Abl1. Pathway analysis of probable interactors showed significantly enriched pathways including Rho GTPase activation by WASPs and WAVEs as well as Wnt/β-catenin signaling, TNFR1-induced NF-κB signaling, protein trafficking, and centrosome regulation. PDL strategy established for Abi-1 is now being used to determine individual STAT3 and NF-κB interactomes. STAT3, NF-κB, and Abi-1 interactomes will be compared to identify intersections between these signaling networks.

Conclusion: Delineating the common interactome of Abi-1/STAT3/ NF-κB signaling axis using PDL-based approach will aid identification of yet undetermined signaling mechanisms contributing to the pathogenesis of MPNs and uncover new potential therapeutic targets for these blood cancers.

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40 Contribution of the GR-LEDGF/p75 Axis to Prostate Cancer Chemoresistance (Diversity Supplement)

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Introduction/Background: Prostate cancer (PCa) is the second leading cause of cancer deaths in the US, disproportionally affecting African American (AA) men. Glucocorticoids (GCs) are administered to PCa patients and have been implicated in therapy resistance. This may be critical to AA men with PCa since they have elevated endogenous GCs levels compared to Caucasian American (CA) men. GCs bind to the glucocorticoid receptor (GR) to exert their actions and the GR-mediated mechanisms of chemoresistance are unknown, as well as its possible contribution to PCa mortality disparities. Our group demonstrated that GCs upregulate the chemoresistance-associated protein LEDGF/p75 in PCa cells and identified consensus GR binding sites in the promoter region of this protein. We hypothesize that GR transcriptionally regulates and interacts with LEDGF/p75 to enhance chemoresistance in PCa cells.

Methods: Pharmacological and genetic inhibition of GR was performed to determine their effects on LEDGF/p75 expression. Immunoprecipitation studies were performed to determine the interaction between these proteins in PCa cells. LEDGF/p75 silencing was performed to assess its effects on GR expression. Additionally, the expression of LEDGF/p75 and GR was evaluated in AA and CA prostate tissue microarrays (TMAs) by immunohistochemistry.

Results: GR inhibition decreased LEDGF/p75 expression. GR and LEDGF/p75 co-immunoprecipitated in docetaxel (DTX)-sensitive and -resistant PCa cells. LEDGF/p75 silencing did not alter GR expression. Immunohistochemistry data of GR and LEDGF/p75 expression in normal and tumor prostate tissues is currently being analyzed.

Conclusion: These studies use a mechanistic approach to evaluate the potential contribution of the GR-LEDGF/p75 axis to PCa chemoresistance. Evaluating the co-expression of these proteins in racially diverse PCa tissues may also reveal race-related differential expression, providing insights into the potential contribution of this axis to PCa chemoresistance and mortality disparities.

Funding: This work was supported by National Institutes of Health (NIH), National Cancer Institute grant and Administrative Diversity Supplement (3R21CA226654-01), NIH National Institute on Minority Health and Health Disparities grant P20MD006988, and NIH National Institute of General Medical Sciences grant R25GM060507.

41 Anti-CD47 Immunotherapy as a Therapeutic Strategy for the Treatment of Breast Cancer Brain Metastasis (R21)

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Introduction/Background: Triple-negative breast cancer (TNBC) is a highly aggressive subtype of breast cancer characterized by the lack of druggable targets and an incidence of brain metastasis from the primary site of approximately 35%. There is no standard treatment for managing brain metastasis associated with TNBC; therefore, new strategies are urgently needed to overcome disease mortality.

Methods: We stained patient biopsies with antibodies against CD47. We tested anti-CD47 immunotherapies in syngeneic models of orthotopic triple-negative breast cancer. Gene expression analysis of tumors was carried out by RNA-sequencing. Immunohistochemical analysis was used to determine tumor immune infiltrating populations.

Results: Overexpression of CD47 is implicated in tumor progression due to bypassing innate and adaptive immune surveillance. Analysis of gene expression database shows that CD47 expression is significantly elevated in invasive breast cancer when compared with primary. Our immune staining against CD47 in patient biopsies shows a fivefold increase in expression in metastatic brain tumors compared with the primary lesions. Therefore, targeting CD47 may be a new immunotherapeutic strategy to treat metastatic brain breast cancer. Anti-CD47 treatment of mice bearing brain metastatic 4T1br3 orthotopic tumors showed reduced tumor volume and tumor weight by over 50% compared with control mice. Furthermore, in a model of intracardial brain metastasis, absence of CD47 was associated with a 60% increase in survival compared with control mice. RNA sequencing of tumors indicated that CD47 blockade is associated with a reduction in genes linked to TCA cycle regulation, extracellular matrix organization. Furthermore, in vitro CD47 targeting enhanced the cell-mediated cytotoxicity of microglia against brain-metastatic breast cancer cells.

Conclusion: Our data suggest that CD47 blockade may influence both tumor and innate immune cells to limit brain metastatic breast cancer growth and enhance survival.

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42 Noncoding RNA-Protein Crosstalk in Myeloid Cell Development and Acute Myeloid Leukemia (K01)

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Introduction/Background: The underlying mechanism of how ubiquitous transcription factors regulate cell type-specific gene induction in myeloid cell development and interruptions caused by their chimeric derivatives in leukemia is poorly understood. In this study, we investigated the role of RNAs in myeloid gene regulation mediated by transcription factor RUNX1 and oncogenic fusion protein RUNX1-ETO, which is derived from the fusion between *RUNX1* and *ETO1* genes in t(8;21) leukemia.

Methods: We assessed RNA profiles in primary cells, leukemia patient samples, and cell lines by RNA-seq and RT-qPCR analyses. To overexpress and deplete RNAs, we employed CRISPR/dCas9-VP64, CRISPR/Cas9, and shRNA technologies. We examined cell growth and differentiation by Edu incorporation assay and Fluorescence-Activated Cell Sorting (FACS) analyses. Furthermore, we measured interaction between an enhancer, called the upstream regulatory element (URE), and promoter of the myeloid master regulator gene *PU.1* by chromosome conformation capture (3C) assay.

Results: We identified a novel long noncoding RNA originating from the URE of *PU.1* locus that we named *LOUP.* We demonstrated that *LOUP* is a myeloid-specific and polyadenylated long noncoding RNA that

induces myeloid differentiation and inhibits cell growth. *LOUP* acts as a transcriptional inducer of *PU.1* by promoting the formation of a chromatin loop that is required for *PU.1* induction. In t(8;21) leukemia, RUNX1-ETO inhibits chromatin accessibility at the *LOUP* locus, leading to reductions in *LOUP* and *PU.1* expression.

Conclusion: Myeloid-specific long noncoding RNA *LOUP* induces myeloid differentiation and inhibits cell growth. It mediates opposing effects of RUNX1 and RUNX1-ETO in regulation of *PU.1* expression. Because therapeutically targeting RUNX1, RUNX1-ETO, and PU.1 remain a technical challenge, our findings raise the possibility that RNAs like *LOUP* might represent alternative targets for therapeutic development.

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43 Role of Rab25 in the Regulation of EGFR Activity in Head and Neck Cancer (iCURE)

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Introduction/Background: Rab25 is a member of the small GTPase family and highly expressed in epithelial cells, but its role differs across different tissues. Rab25 has also been implicated in tumor invasion and metastasis. A previous study discovered that downregulation of Rab25 results in increased activation of EGFR in head and neck cancer. However, the mechanism is unknown. Therefore, this study seeks to elucidate the mechanism by which Rab25/EGFR signaling axis modulates cancer progression and investigate which downstream pathways to EGFR are affected.

Methods: We cultured human squamous carcinoma cell lines derived and immortalized from head and neck tumors in vitro and used CRISPR/Cas9 knock-out technology to generate cells lacking Rab25. The Rab25-depleted cell lines will be used to measure EGFR activity using western blot or immunofluorescence to measure phosphorylated EGFR in cell culture and orthotopic models. We will perform next-gene sequencing to determine which genes are altered by Rab25 downregulation. Furthermore, we will evaluate the resistance of Rab25-deficient tumors to EGFR therapy by stimulating EGFR in the presence of EGFR-inhibitors.

Results: We used CRISPR/Cas9 technology to delete the Rab25 gene by co-expressing an endonuclease, Cas9 fused to a fluorescent marker, GFP, and a gRNA homologous to our targeted DNA. After obtaining our plasmid constructs, we have been unsuccessful with introducing it into our target cells' genome. We are working with two large plasmids, and co-transfecting it with the packing plasmid, pPACKH1, has been difficult.

Conclusion: This project will investigate the role of the Rab25/EGFR signaling axis in tumor progression. Our findings will aid in identifying what pathways to target during chemotherapy and other cancer treatments.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

44 Protein Disulfide Isomerase as a Potential Therapeutic Target for Breast Cancer (CPACHE U54)

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Introduction/Background: Cancer cells require increased protein synthesis and cause to endoplasmic reticulum (ER) stress by activating the unfolded protein response (UPR) which is mediated by ER chaperones. Protein disulfide isomerase (PDI), ER chaperone, is essential for rapid proliferation and the selective blockade of PDI results in apoptosis, thus making PDI as a potential target for cancer research. This study aims to understand how PDI signaling impacts on breast cancer progression and on areas of breast cancer health disparities.

Methods: The Cancer Genome Atlas (TCGA) datasets were obtained and analyzed from two resources, cBioPortal and Xena browser. The mRNA expression of PDI (P4HB) in various cancers, PDI isoforms in different breast cancer subtypes and different ethnic groups were determined. Also, the expression levels of PDI isoforms of the in-house breast cancer patient samples were evaluated and compared with the analysis of TCGA data.

Results: Among 21 PDI isoforms, P4HB, PDIA3, PDIA4 and PDIA6 levels are highly expressed in breast cancers compared to normal tissue. Their expression levels are higher in Basal-like and HER2-enriched subtypes rather than Luminal A and B. Interestingly, in HER2-enriched subtype, the proteins are more expressed in black/African American (AA) among other ethnicities while Basal-like subtype does not show the significant difference. The data is supported by the preliminary result of the in-house patient samples that the expression of P4HB, PDIA3 and PDIA6 are higher in AA than in Hispanic patients.

Conclusion: TCGA data and the preliminary results support the hypothesis of PDI being highly expressed in breast cancer, especially for more aggressive subtypes and for Black/AA. This finding, in part, could suggest that PDI may be closely associated with triple negative breast cancer (TNBC) which is more common in black/AA, and PDI as potential therapeutic target in breast cancer where exist health disparities.

Funding: This work was supported by the National Institutes of Health, National Institute on Minority Health and Health Disparities under award #U54D007598–AXIS center.

Behavioral Cancer Research Poster Abstracts

45 Willingness of Black Women To Use HPV Self-Collection at Home (K01)

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Introduction/Background: Cervical cancer is preventable and treatable if detected early through regular screening. Human papillomavirus (HPV) testing offers better reassurance of low cancer risk and reliable identification of cervical precancer and cancer. HPV self-collection is an emerging HPV testing method. However, there is a lack of information regarding willingness to use HPV self-collection among black women. The purpose of this study was to examine among black women predictors of willingness to use HPV self-collection.

Methods: We conducted a cross-sectional 85-item survey with community-dwelling women. Data included sociodemographics and HPV and HPV testing knowledge. Logistic regression evaluated predictors of willingness to use self-collection.

Results: On average, women (N=91) were 38.2±12.6 years old. The majority (80%) were insured, over half (57%) had a primary healthcare provider, and almost two-thirds (65%) were African immigrants. Eighty-four percent had ever had a Pap test, 36% had ever had an HPV test, while 67% indicated willingness to self-collect. Compared with the uninsured, women who were insured were 90% less likely to be willing to self-collect (OR=0.10, 95% CI=0.02 – 0.64, p=.015). Women who were likely to accept a Pap test recommendation were 10 times more likely to be willing to self-collect (OR=10.41, 95% CI=2.27 - 47.81, p=.003) compared with those who were unlikely. The most common concerns about completing HPV self-collection were worry about proper collection (34%) and pain (23%).

Conclusion: Healthcare providers have an important role in recommending cervical cancer screening, including HPV tests. HPV self-collection may be a promising strategy to reach uninsured and underinsured black women. Interventions should provide education on how to properly self-collect samples for HPV testing and address concerns related to pain.

Funding: The study was supported by University of Kentucky startup funds.

46 Association Between State Medicaid Expansions and Human Papillomavirus Vaccination Among Adolescent and Young Adult U.S. Women by Race/Ethnicity and Sexual Orientation (K01)

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Introduction/Background: Although some racial/ethnic and sexual minority U.S. women are more likely to acquire human papillomavirus (HPV) than white and heterosexual women, respectively, many face notable barriers to HPV vaccination. State Medicaid expansions, which were widely implemented in and after 2014 as part of the Affordable Care Act (ACA) and extended insurance coverage among low-income populations, improved coverage and preventive health services use among racial/ethnic and sexual minority women and had a positive impact on HPV vaccination among U.S. adolescents.

Methods: Using National Survey of Family Growth data (2011-2017), we examined the associations between state Medicaid expansions passed in 2014-2016 and HPV vaccination initiation among U.S. women aged 15-24 years living at or below 138% of the federal poverty level (FPL; N=2,408), overall and by race/ethnicity and sexual orientation. We used linear probability difference-in-difference models with state and year fixed effects and time period indicators relative to state-specific onset of Medicaid expansion to assess these associations in the third year post-expansion. We then used linear probability difference-in-difference-in-differences models to ascertain whether associations varied by race/ethnicity and sexual orientation.

Results: We found a positive association between state Medicaid expansions and HPV vaccination initiation among U.S. women aged 15-44 years living at or below 138% FPL in the third year post-expansion (difference-in-differences estimate: 20.5 percentage points; p=0.073). Among all racial/ethnic groups, Black women had the largest increase in HPV vaccination initiation in year 3 post-expansion (difference-in-differences estimate: 41.1 percentage points; p=0.019). Further, among all sexual orientation groups, lesbian women had the largest increase in HPV vaccine uptake three years post-expansion (difference-in-differences estimate: 63.4 percentage points; p=0.008).

Conclusion: Among low-income adolescent and young adult U.S. women, state Medicaid expansions had the greatest positive impact on HPV vaccination initiation among Black women and lesbian women three years post-expansion. Additional research with larger samples of racial/ethnic, sexual, and other minority women is needed to identify the differential impact of health policy changes on HPV vaccination among U.S. girls and women.

Funding: This research was supported by grant 1K01CA234226-01 (PI: Agénor M).

47 Health Literacy in Parents of Children with Cancer: Comparison of Hispanics and non-Hispanic Whites (K08)

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Introduction/Background: Health literacy (HL) is the ability to process health-related information to function effectively in the healthcare environment. Individuals with limited HL have higher healthcare utilization and poorer health status. Parents of children with cancer must process complex information about the disease to effectively navigate the healthcare system. Research on HL in the pediatric cancer setting is lacking. We assessed HL in Hispanic and non-Hispanic white (NHW) parents of children with cancer.

Methods: Sixty-one parents of children (0-17 y/o) with cancer at Rady Children's Hospital-San Diego were enrolled. To assess HL, we used the English or Spanish form of the 1) Short-form of the Test of Functional Health Literacy Assessment(s-TOFHLA), 2) Newest Vital Sign (NVS), 3) Parental Health Literacy Activities Test (PHLAT), 4) Rapid Estimate of Adult Literacy in Medicine (REALM) or Short Assessment of Health Literacy for Spanish Adults (SAHLSA-50), and 5) Brief Health Literacy Screen (BHLS). Two-sample t-tests, univariate/multivariate linear regression, and Pearson-correlation analyses were used for statistical analysis.

Results: Hispanic parents had significantly lower HL, as measured by the NVS, than NHWs ($p<0.001$). In parents, lower HL levels (measured by the NVS and S-TOFHLA) were significantly associated with older age ($p<0.001$), lower education level ($p<0.001$), informal employment ($p<0.006$), and Spanish language ($p<0.001$). Additionally, S-TOFHLA was significantly correlated with NVS ($p<0.001$), PHLAT ($p<0.001$), and REALM ($p<0.021$).

Conclusion: We show significant differences in HL levels between Hispanic and NHW parents of children with cancer. NVS was correlated with s-TOFLHA and could serve as a rapid assessment of HL in the clinical setting for parents. Cancer treatment is complex, involving intensive treatments, clinical trials, and requiring advanced parental knowledge about the disease. By identifying parents with limited HL, we can help them navigate cancer therapy. Future research should test culture and language-appropriate interventions, including the systematic use of teach-back, pictorial instruction, and patient navigation, to improve HL and, ultimately, cancer care in underserved children.

Funding: This research is supported by grant K08CA230306.

48 Essential Elements of Community Well-Being Reported Among Community Health Workers (CHWs) in Washington State (K01)

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Introduction/Background: Community well-being is an increasingly salient construct for communities, organizations, and public health systems to monitor the impact of policy strategies to reduce health disparities. Yet, evaluation of its definition and measurement across diverse populations is lacking. Indices of community well-being may include variables from large population-based datasets, which often lack representation. Given their work, community health workers (CHWs) may provide insight as to the relevance of proposed indices for the communities they serve.

Methods: CHWs were recruited from a public health department and from a state-wide CHW network and were invited to a 60-minute interview about the CHW role, barriers to community health, and definitions of community well-being within the COVID-19 pandemic environment. A total of 24 interviews were conducted via Zoom using a semi-structured interview guide and thematic analysis of transcripts was completed.

Results: CHWs were diverse in terms of racial/ethnic background as well as geographic location and setting. A total of 61 quotations relating to well-being were extracted. CHWs of color and White CHWs reported that meeting basic needs (i.e., access to housing, transportation, employment, healthcare, and food security) was essential to community well-being. Additionally, CHWs of color reported that the ability to work, cultural or spiritual ties, economic stability, and a "sense of ease and safety" were also important contributors. CHWs from rural and suburban areas reported that meeting basic needs and absence of sickness was most important to community well-being; these themes were similarly endorsed among urban CHWs.

Conclusion: All themes identified by CHWs for community well-being are related to the absence of structural barriers. Indicators of meeting basic needs may be most salient to definitions of community well-being across most cultural groups and geographic settings.

Funding: This work was supported by a mentored career development award from the National Cancer Institute (K01 CA229996).

49 Incident Sleep Disturbance Is Associated with Increases in Depressive Symptoms Among Older Breast Cancer Survivors and Non-Cancer Controls During the COVID-19 Pandemic (K01)

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Introduction/Background: Several studies have reported increases in the prevalence of sleep disturbance during the COVID-19 pandemic. No research to date using longitudinal data has tested how this has impacted the mental health of older women. We hypothesized that women experiencing a new sleep disturbance during the pandemic would have worsening depressive symptoms and that the association may differ between breast cancer survivors than controls.

Methods: Prior to and during the pandemic, women enrolled in the Thinking and Living with Cancer Study, a longitudinal study of older breast cancer survivors and matched non-cancer controls, completed the Center for Epidemiological Studies-Depression (CES-D) scale. A single CES-D item on restless sleep served as the measure of sleep disturbance; the CES-D score without the restless sleep item was used to measure depressive symptoms. Multivariable linear regression models (adjusted for age, case status, county-level COVID-19 mortality rate, and number of months between surveys) examined whether incident sleep disturbance during the pandemic was related to increasing depressive symptoms from the most recent pre-pandemic survey to the pandemic survey and whether there was a multiplicative interaction by case-control status.

Results: Participants included 242 breast cancer survivors and 158 controls; 10% and 13.5% experienced incident sleep disturbance during the pandemic, respectively. There were no case-control differences in change in sleep disturbance ($p=0.24$) or mean change in depressive symptoms ($p=0.19$). Depressive symptoms significantly increased during the pandemic among participants with incident sleep disturbance ($N=44$, $\beta=8.16$, $p<0.01$), relative to participants with no sleep disturbance ($N=248$). No interaction between change in sleep disturbance and case status was present (p-interaction=0.69).

Conclusion: Consistent with our hypothesis, new experiences of sleep disturbance during the COVID-19 pandemic may be negatively impacting women's mental health as indicated by an increase in depressive symptoms. Breast cancer survivors were not more vulnerable to the effect than matched peers.

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50 Adipose Tissue Radiodensity Is Associated with Survival After Colorectal Cancer (K01 CA226155)

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Introduction/Background: Adipose radiodensity may have prognostic importance for colorectal cancer (CRC) survival. Lower radiodensity is indicative of larger adipocytes, while higher radiodensity may represent adipocyte atrophy, inflammation or edema. We investigated associations of adipose radiodensity and longitudinal changes in adipose radiodensity with mortality among patients with nonmetastatic CRC.

Methods: In 3,023 patients with stage I-III CRC, radiodensity of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) was quantified from diagnostic computed tomography images. 1,775 patients had follow-up images available. Cox proportional hazards models and restricted cubic splines were used to examine the risk of death associated with at-diagnosis values of, and longitudinal changes in, VAT and SAT radiodensity, adjusting for potential confounders including body size and comorbidities.

Results: VAT and SAT radiodensity were linearly associated with total all-cause mortality: the hazard ratio (HR) and 95% Confidence Interval (95%CI) for death per standard deviation (SD) increase was 1.21 (1.11, -1.32) for VAT radiodensity and 1.18 (1.11, -1.26) for SAT radiodensity. Changes in adipose radiodensity had a curvilinear association with risk of death: the HR for an increase in VAT radiodensity of at least 1SD was 1.54 (1.23, 1.90) while the HR for a decrease of at least 1SD was non-significant at 1.11 (0.84, 1.47) compared with maintaining radiodensity within 1SD of baseline. Similarly, increases (HR=1.88; 95%CI:1.48, 2.40) and but not decreases (HR=1.20; 95%CI: 0.90, 1.54) in SAT radiodensity significantly increased the risk of death compared with no change in radiodensity.

Conclusion: Adipose tissue radiodensity is a novel risk factor for total mortality in patients with non-metastatic after CRC that is independent of body mass index and changes in body weight.

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51 International Adaptation of Meaning-Centered Psychotherapy for Latinos: Providers' Views on Pre-Implementation (K08 CA234397)

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Introduction/Background: This qualitative study aims to identify facilitators of and barriers to the implementation of Meaning-Centered Psychotherapy (MCP) by providers of mental health services to Latinos in the U.S. and Latin America using the Practical, Robust Implementation and Sustainability Model (PRISM). This information will be used to increase usability and acceptability of MCP for Latino patients with cancer and their providers in Latin America and the U.S.

Methods: A total of 14 Latino cancer patient mental health providers completed in-depth semistructured interviews. Participants were recruited from 9 countries and 12 different sites. They provided feedback about barriers and facilitators of implementation of MCP at the patient, provider, and clinic levels in their clinical setting. The qualitative data from the interviews was coded according to PRISM domains. Three analysts independently coded the transcripts; discrepancies between analysts were resolved through discussion and consensus.

Results: Providers identified clinic environment, intervention characteristics, and patient- and provider-level barriers and facilitators. Based on PRISM, themes were: clinic environment (protected time for training and supervision), intervention characteristics (adapt the intervention using more simple language, include more visual aids, include more collectivistic/family-oriented content), patient (develop materials for the identification and screening of patients, provide educational materials, increase motivation and knowledge about psychotherapy, assess commitment to psychotherapy, adapt for the inpatient vs. outpatient setting), provider (receive interactive/participatory training, educational materials, ongoing supervision, have flexibility of delivering the intervention in a less structured manner, theoretical framework of the provider) and external environment (work at policy level to integrate services for oncology patients).

Conclusion: The qualitative data revealed barriers to and potential facilitators of this psychotherapeutic intervention at an international scale. Cultural, contextual, as well as healthcare systems factors illustrated the importance of examining pre-implementation needs prior to implementing a trial, especially in low-resource settings.

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52 Evaluation of Early-Life Pesticide Exposure as a Risk Factor for Thyroid Cancer in the Sister Study Cohort (iCURE)

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Introduction/Background: The thyroid gland may be particularly susceptible to carcinogenic exposures during childhood. No studies have evaluated childhood residential pesticide exposure and risk of adult thyroid cancer.

Methods: In the Sister Study cohort (n=50,884 women across the US, aged 35-75 years at enrollment in 2003-2009), we assessed whether any childhood residence (≤18 years of age) for at least 1 year was on a farm or the longest-lived residence (≤14 years of age) was on or near a farm, and by farm type and pesticide application. We evaluated incident malignant thyroid cancers from enrollment through 2018 (n=246) using Cox regression to estimate hazard ratios (HR) and 95% confidence intervals (CI). In secondary analyses, we expanded to include prevalent thyroid cancers diagnosed between age 18 and enrollment (n=502) and estimated odds ratios (OR) and CIs with logistic regression. Models were adjusted for age, race/ethnicity, and smoking.

Results: Neither any childhood farm residence (n=57 exposed cases) or longest childhood residence on/near a farm (n=80) were associated with thyroid cancer risk. However, ever living on a farm during childhood (≤18 years) with non-orchard fruit crops (e.g., berries, grapes) (HR=1.7, CI:1.0-2.9, n=34) and orchard fruit crops (HR=1.8, CI:1.1-3.2, n=35) was significantly associated with elevated risk of developing thyroid cancer during follow-up. In analyses including prevalent cases, having the longest childhood residence regularly treated with pesticides was significantly and positively associated with thyroid cancer (OR=1.4, CI:1.0-1.9, n=65).

Conclusion: In this first study to evaluate exposures during this critical window, we found evidence that early-life pesticide exposures are associated with increased risk of thyroid cancer. The findings for fruit crops, which are almost all treated with fungicides, supports prior studies suggesting a link between fungicides and thyroid cancer. Future studies to evaluate pesticide-specific residential use and proximity to application sites are warranted.

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53 Prevalence of Metabolic Syndrome Among Cancer Survivors in the U.S.: NHANES Analysis (iCURE)

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Introduction/Background: The purpose of this study was to determine the prevalence of metabolic syndrome (MetS) in cancer survivors (CS) compared to participants without a self-reported history of cancer with (CD) and without (HI) a chronic disease diagnosis.

Methods: Using National Health and Nutrition Examination Survey (NHANES) data from 2015 to 2018 (n=18248), the prevalence of metabolic syndrome (MetS) was evaluated among participants 20 years and older. MEtS was defined based on the National Cholesterol Education Program's Adult Treatment Panel III. Weighted data were used to estimate the unadjusted prevalence of metabolic syndrome, stratified by cancer site, sex, and race/ethnicity. Chi-square test and logistic regression was used to assess group comparisons and associations, respectively.

Results: Prevalence of MetS was higher among CD (68%) and CS (67.9%) participants compared to HI (55.3%). Overall, Hispanic participants demonstrated the lowest prevalence of MetS compared to non-Hispanic blacks (NHB) and non-Hispanic whites (NHW) in the CD, CS, and HI groups ($p<0.001$). Compared with HI individuals, the odds of meeting MetS criteria was higher among CD (OR 1.73; 1.5 – 1.99) and CS (OR 1.70; 1.34 – 2.16). Among cancer survivors, females had lower odds of having MetS compared to males (OR 0.64; 0.45 – 0.91), but there were no statistically significant associations by race/ethnicity. Compared to HI, the odds of MetS was higher among prostate and colorectal cancer survivors ($p<0.05$).

Conclusions: MetS was more prevalent among CS group than in CD or HI group, and prostate cancer survivors demonstrated higher odds of meeting MetS criteria compared to other cancer survivors. With an aging US population and increase in chronic diseases, strategies to improve prevention of comorbidities and consistent care needs to be developed to support cancer survivors.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

54 Black and Hispanic Women Are Less Likely Than White Women to Receive Guideline-Concordant Endometrial Cancer Treatment (K01)

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Introduction/Background: Differences in receipt of guideline-concordant treatment might underlie well-established racial disparities in endometrial cancer mortality.

Methods: We defined receipt of guideline-concordant treatment using the National Comprehensive Cancer Network guidelines. Multivariable logistic regression models were used to compute odds ratios (ORs) and 95% confidence intervals (CIs) for associations between race and guideline-concordant treatment. We used multivariable Cox proportional hazards regression models to estimate hazards ratios (HRs) and 95% CIs for relationships between guideline-concordant treatment and overall survival in the overall study population and stratified by race/ethnicity.

Results: This analysis included 89,319 women diagnosed with an invasive, endometrioid endometrial cancer between 2004 and 2014. Overall, 74.7% of the cohort received guideline-concordant treatment (n = 66,699). In multivariable-adjusted models, non-Hispanic black (OR=0.92, 95% CI=0.86-0.98) and Hispanic women (OR=0.90, 95% CI=0.83-0.97) had lower odds of receiving guideline-concordant treatment compared with non-Hispanic white women, while Asian/Pacific Islander women had a higher odds of receiving guideline-concordant treatment (OR=1.11, 95% CI=1.00-1.23). Lack of guideline-concordant treatment was associated with lower overall survival in the overall study population (HR=1.12, 95% CI=1.08-1.15) but was not significantly associated with overall survival among non-Hispanic black (HR=1.09, 95% CI=0.98-1.21), Hispanic (HR=0.92, 95% CI=0.78-1.09), or Asian/Pacific Islander (HR=0.90, 95% CI=0.70-1.16) women.

Conclusion: Non-Hispanic black and Hispanic women were less likely than non-Hispanic white women to receive guideline-concordant treatment, while Asian/Pacific Islander women more commonly received treatment in line with guidelines. Furthermore, overall survival was worse among those not receiving guideline-concordant treatment, although low power may have had an impact on the race-stratified models. Future studies should evaluate reasons underlying disparate endometrial cancer treatment.

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55 Testing a Culturally Targeted Decision Aid To Promote Genetic Counseling Attendance Among African American Women with Hereditary Risk for Breast Cancer (K01)

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Introduction/Background: Carriers of hereditary genetic mutations have up to an 85% risk of developing breast cancer compared to 12% in the general population. Overall uptake of genetic services is generally low, particularly among high-risk African American (AA) women, who carry a disproportionate burden of breast cancer mortality. Further, although testing close relatives of individuals who test positive for a pathogenic variant might curtail breast cancer disparities attributable to hereditary risk, it is unclear how counseled or tested individuals influence their social and familial networks. The objective of this research is to test the effectiveness of a culturally targeted decision aid video (previously developed by our research team) on promoting genetic counseling attendance among AA women determined to be at high risk for breast cancer through cancer genetic risk assessment at a federally qualified health center.

Methods: Patients (n=106) will be randomized to one of two arms to receive pretest, view decision aid video or genetic counseling brochure, and posttest. Both arms will be facilitated by a patient navigator. Outcome measures are genetic counseling attendance and psychosocial factors (knowledge, intrinsic motivation, risk perception, and distress). Multivariable logistic regression will be used to estimate odds of each outcome comparing both arms. This study will also compare impact of intervention exposures on diffusion of knowledge about genetic counseling through social network analysis.

Results: Data collection was delayed due to COVID-19 clinical restrictions. Study recruitment will begin August 1, 2021.

Conclusion: It is expected that the culturally targeted decision aid will increase genetic counseling attendance and diffusion of knowledge about genetic risks and counseling among social networks of study participants. The intervention could have broad translational application, which will facilitate its uptake in clinical care settings to promote genetic risk education and service utilization among AA women at high risk for breast cancer.

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56 Model-Based Estimation of Colorectal Cancer Screening and Outcomes During the COVID-19 Pandemic (K08)

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Introduction/Background: Coronavirus-19 (COVID-19) has decreased colorectal cancer screenings. The study objective was to estimate the degree to which expanding fecal immunochemical test-based colorectal cancer screening participation during the COVID-19 pandemic is associated with clinical outcomes.

Methods: A previously developed simulation model was adopted to estimate how much COVID-19 may have contributed to colorectal cancer outcomes. This model included the US population estimated to have completed colorectal cancer screening pre-COVID-19 according to the American Cancer Society. The model was designed to estimate colorectal cancer outcomes between 2020 and 2023. This analysis was completed between July and December 2020. The exposure of interest were adults screened for colorectal cancer and colorectal cancer cases detected by stage. The outcomes of interest were estimates of colorectal cancer outcomes across four scenarios: 1) 9 months of 50% colorectal cancer screenings followed by 21 months of 75% colorectal cancer screenings; 2) 18 months of 50% screening followed by 12 months of 75% screening; 3) scenario 1 with increased use of fecal immunochemical tests; and 4) scenario 2 with increased use of fecal immunochemical tests.

Results: In our simulation model, COVID-19-related reductions in care utilization resulted in 1,176,942 to 2,014,164 fewer colorectal cancer screenings, 8,346 to 12,894 fewer colorectal cancer diagnoses, and 6,113 to 9,301 fewer early-stage colorectal cancer diagnoses between 2020 and 2023. With an abbreviated period of reduced colorectal cancer screenings, increasing fecal immunochemical test use was associated with an estimated 588,844 colorectal cancer screenings and 2,836 colorectal cancer diagnoses, of which 1,953 (69%) were early stage. In the event of a prolonged period of reduced colorectal cancer screenings, increasing fecal immunochemical test use was associated with an additional 655,825 colorectal cancer screenings and 2,715 colorectal cancer diagnoses of which 1,944 (71.6%) were early stage.

Conclusion: These results suggests that increased use of fecal immunochemical tests during the COVID-19 pandemic was associated with increased colorectal cancer screening participation and more colorectal cancer diagnoses at earlier stages. If our estimates are borne out in real-world clinical practice, increasing fecal immunochemical test-based colorectal cancer screening participation during the COVID-19 pandemic could mitigate the consequences of reduced screening rates during the pandemic for colorectal cancer outcomes.

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57 Dietary and Cultural Practices of Blacks in New York City as an Indicator of Colorectal Cancer Screening and Intent (Diversity Supplement)

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Introduction/Background: Colorectal cancer (CRC) is the third most common cancer diagnosed in men and women in the United States, and African Americans have the highest incidence and mortality of all the racial groups. This study examined dietary habits and practices of blacks as a predictor for CRC screening and addresses the relationship between dietary habits and screening behavior and intent. This research is timely as the recommended age for CRC screening was lowered to 45 years of age.

Methods: Survey data were collected on dietary habits and screening behavior (most recent exam and intent to screen within a year) from 500 black individuals in New York City.

Results:
- Females are more intended to screen once eligible than males.
- African Americans are less intended to screen than African or Caribbean blacks.
- Individuals with a more frequent intake of water and other juices are more intended to screen once eligible.
- African Americans have lower screening behaviors than African or Caribbean blacks.

Conclusion: African Americans have lower screening behaviors than Africans or Caribbeans, which highlights the necessity to increase screening awareness and opportunities in African American communities. Healthy eating behaviors were significant for screening intention within the next year, aligning with theoretical frameworks hypothesizing that individuals who practice healthy behaviors will adopt other healthy behaviors such as screening. As women illustrated an intake of more fruit, vegetables, tea, and water, it may also be critical to combine health education around CRC screening and healthy eating when working with men.

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58 Understanding the Impact of High-Risk Human Papillomavirus on Oropharyngeal Squamous Cell Carcinomas in Taiwan: A Retrospective Cohort Study (Diversity Supplement)

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Introduction/Background: Human papillomavirus (HPV)-driven oropharyngeal squamous cell carcinoma (OPSCC) is increasing globally. In Taiwan, HPV-positive OPSCC is obscured by tobacco, alcohol, and betel quid use. We investigated the role of high-risk HPV (hrHPV) in a large retrospective Taiwan OPSCC cohort.

Methods: A cohort of 541 OPSCCs treated at Chang Gung Memorial Hospital from 1998-2016 was studied. Formalin-fixed, paraffin-embedded tissue was used for p16 staining (a surrogate marker for HPV) and testing for HPV DNA presence and type by Multiplex HPV PCR-MassArray. Prognostic outcomes were analyzed between clinical variables and HPV status.

Results: The cohort consisted of 507 men (94%) and 34 women (6%). Most used tobacco (81%), alcohol (51%), and betel quid (65%). p16 and HPV DNA were strongly correlated ($F < 0.0001$). HPV16 was present in 82.8%, and HPV58 in 7.5% of HPV-positive tumors. HPV was associated with higher age (55.5 vs. 52.7 years, $p = 0.004$), lower T-stage ($p = 0.008$) better OS (hazard ratio [HR] 0.58 [95% CI 0.42-0.81], $p = 0.001$), and disease-free survival (DFS) (HR 0.54 [95% CI 0.40-0.73], $p < 0.0001$). Alcohol was strongly associated with recurrence and death (OS: HR 2.06 [95% CI 1.54-2.74], $p < 0.0001$; DFS: HR 1.72 [95% CI 1.33-2.24], $p < 0.0001$). OS and DFS in HPV-positive cases decreased for alcohol users ($p < 0.0001$). Obscured by the strong alcohol effect, predictive associations were not found for tobacco or betel quid.

Conclusions: As with HPV-positive OPSCC globally, HPV is an increasingly important etiological factor in Taiwanese OPSCC. HPV-positive OPSCC has considerable survival benefit, but that this is reduced by alcohol, tobacco, and betel quid use. hrHPV is a cancer risk factor in males and females. Vaccinating both sexes with a multivalent vaccine including HPV58, combined with alcohol and tobacco cessation policies will be effective cancer-prevention public health strategies in Taiwan.

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59 Drinking Water Sources and Water Quality in the Agricultural Health Study (iCURE)

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Introduction/Background: Drinking water contaminants have been associated with adverse health effects. However, little is known about exposures in agricultural communities where farm practices and private well use may enhance exposures.

Methods: We used questionnaire data from the Agricultural Health Study (AHS), a cohort of licensed pesticide applicators and their spouses in Iowa (IA) and North Carolina (NC), to ascertain drinking water source at enrollment (1993-1997). For users of public water supplies (PWS), we linked participants' geocoded addresses to contaminant monitoring data, including five haloacetic acids (HAA5), total trihalomethanes (TTHM), and nitrate-nitrogen (NO_3-N). We estimated private well nitrate levels using random forest models that included well depth, soil characteristics, nitrogen inputs, and other relevant predictive variables.

Results: We assigned drinking water source for 84% (N=74,919) of participants. Approximately 70% of IA and 75% of NC participants used private wells; 27% in IA and 21% in NC used PWS. Median PWS nitrate concentrations (mg/L NO_3-N) were higher in IA (0.9, interquartile range (IQR):0.2-3.1) than NC (0.5, IQR:0.5-0.5), while median concentrations of HAA5 (µg/L) and TTHM (µg/L) were higher in NC (HAA5: 11.7, IQR:4.9-33.3; TTHM: 37.7, IQR:10.6-54.7) than IA (HAA5: 4.3, IQR:3.0-10.8; TTHM: 13.0, IQR:3.7-32.4). Private well nitrate concentrations in IA (1.5, IQR:0.8-4.9) and NC (1.9, IQR:1.4-2.5) were higher than in PWS. More private wells in IA (12%) had levels exceeding the 10mg/L NO_3-N regulatory limit than NC (<1%).

Conclusion: This exposure assessment will be used in future analyses of the health effects of drinking water contaminants in the Agricultural Health Study cohort.

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60 Empowering Latinas to Obtain Breast Cancer Screenings: Comparing Intervention Effects and Mechanisms (K01CA193918)

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Introduction/Background: Multiple approaches have been used to improve early breast cancer (BC) detection among Latinas, including educational interventions and empowerment related interventions, wherein a subset of the population is trained to share information with other members of the priority population. Little is known about these approaches' relative efficacy and underlying mechanisms.

Methods: This quasi-experimental trial is situated in two lower-income Latino communities in Chicago. Eligibility criteria include: 1) age of 52-74; 2) no mammogram within past 2 years; 3) no previous breast cancer diagnosis; and, 4) no prior health volunteerism experience. Women are assigned to a cohort and participate in a three-week intervention (education: BC, diet, physical activity; empowerment: BC, sharing information with networks, health volunteerism). Participants who want mammograms are navigated to free/low-cost services. Data collected at baseline, post-intervention, and six-month follow-up include survey data on demographics, psychosocial mechanisms (community involvement, knowledge, self-efficacy, norms), and BC screening data (verified by study navigation records).

Results: Our sample is 145 women (69 education; 76 empowerment). Empowerment participants were more likely to obtain BC screening (72% vs. 48%; OR = 2.79, 95%CI [1.27, 6.11], p =.01), after adjusting for age, insurance status, and baseline BC screening intention. With regard to potential mechanisms, empowerment participants exhibited greater sustained knowledge gains across 6 months relative to education participants (n=110, baseline: p=0.24; post-intervention: ps ≤ 0.004), which was associated with greater odds of mammography uptake (n=110, p= 0.03).

Conclusions: Empowerment approaches may be particularly effective in promoting mammography among non-adherent Latinas. Preliminary evidence suggests that sustained knowledge gains may be the "active ingredient" underlying intervention effects. Limitations concern generalizability due a non-probability based sample, and limited ability for causal inferences due to a lack of randomization.

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61 Collaborative Engagement of African American Prostate Cancer Survivors to Inform a Peer Navigation Protocol and Training Guide (K01)

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Introduction/Background: Prostate cancer (PCa) and its treatment present daunting communication and decision-making challenges for patients and providers. African American men bear the greatest burden of PCa given the excess incidence and mortality, and disparities in quality of care. Peer navigation is a viable and culturally congruent intervention that offers promise to improve cancer care quality and health outcomes for vulnerable populations. Building upon phase I of our research, we present preliminary work on collaborative engagement of a PCa survivor advisory board to inform development of a peer navigation protocol and training guide.

Methods: We invited members from our PCa support group and phase I participants to join an advisory board aimed to inform 1) interpretation of phase I results; 2) gaps in PCa care and opportunities for intervention; 3) review of navigation models; 4) development of a peer navigation protocol and training guide; and 5) implementation. We will also evaluate board members' overall experience.

Results: Five African American PCa survivors accepted our invitation; and we have conducted three of eight advisory board meetings. Meeting agendas are structured to build rapport, elicit feedback and insights on study results, provide space for survivors to share personal experiences, and offer suggestions for change. Each agenda includes introductions with an icebreaker, an inspiring quote for grounding, set/recap ground rules, presentation of study results, time for reflections and feedback, and appreciations. Key themes from phase I results include communication challenges in diagnosis delivery, explaining biopsy results, discussion of treatment options and side effects, patients' fears/concerns, and resources used/needed. Future meetings will present data on navigation models, and guide discussions on protocol and training guide development.

Conclusion: This collaborative engagement of African American PCa survivors offers key lessons on valuing and leveraging stakeholders' expertise and time for intervention development, sharing decision-making, and fostering genuine community engagement.

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62 Urinary Parabens and Breast Cancer Risk: Modification and Interaction by LINE-1/ LUMA Methylation in the Long Island Breast Cancer Study Project (K01)

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Introduction/Background: Parabens, ubiquitous endocrine disrupting chemicals used in personal care products, may interact with DNA methylation status to impact breast cancer (BC) risk. We examined whether global DNA methylation modifies or interacts with paraben levels to impact BC risk and whether paraben levels are associated with tumor gene-specific promoter methylation in 12 BC-related genes.

Methods: Participants included 708 cases and 598 controls from the population-based Long Island Breast Cancer Study Project. Levels of methyl-/propyl-/butyl-parabens and sum-parabens were measured in spot urine samples, creatinine-corrected, and dichotomized at the 80th percentiles. Global DNA methylation status (methylated vs. unmethylated) was measured in peripheral blood using LINE-1 and LUMA. Among 509 cases, the promoter methylation status of 12 BC-related genes was measured in tumor samples. For effect measure modification, we used logistic regression to estimate covariate-adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the associations between paraben levels and BC stratified by LINE-1/LUMA methylation status. For additive interactions, we used logistic regression to estimate aORs and CIs for the joint associations between paraben levels and LINE-1/LUMA methylation status and BC. To examine outcome heterogeneity, we used multinomial logistic regression to estimate aORs and CIs for the associations between paraben levels and gene-specific promoter methylation status (unmethylated cases vs. controls; methylated cases vs. controls).

Results: Propylparaben levels >80th (vs. ≤80th) percentile were associated with a 50% increase in the odds of having a methylated APC promoter than being a control (aOR=1.50, 95%CI=1.02-2.20), but not with having an unmethylated APC promoter than being a control (aOR=0.94, 95%CI=0.63-1.42). LINE-1/LUMA did not modify the associations between parabens and BC and did not interact with parabens to increase BC risk.

Conclusion: Exposure to parabens may increase the risk of BC with methylated promoter regions of APC, a tumor suppressor gene and regulator of the WNT signaling pathway.

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63 Church Factors Across the Social, Physical, and Organizational Environment Associated with Latinos' Physical Activity (Diversity Supplement)

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Introduction/Background: Religiosity is related to favorable health, yet despite Latinos' high church attendance, they report low leisure-time physical activity (LTPA), which contributes to chronic conditions, including some cancers. There is growing interest in promoting physical activity (PA) through churches+ but there is limited understanding of the modifiable targets in the church environment that may help increase PA among churchgoing Latinos. This study investigated how multilevel factors across the church social, physical (nearby parks), and organizational environment are associated with PA and park use among a sample of churchgoing Latino adults.

Methods: We used baseline data from 364 Latinos (78% female, mean age=50 years) participating in an ongoing faith-based intervention in Los Angeles, CA. Participants completed questionnaires in 2019 that assessed LTPA, visits to the park near one's church, park-based PA, socio-demographics, and the following multilevel factors: church PA social support and social norms; perceived quality and concerns (e.g., crime) about the park near one's church; and church PA programming. Logistic regression models examined associations of the multilevel factors with meeting PA recommendations (yes/no), use of the park near one's church (any/none), and park-based PA (yes/no), adjusting for sociodemographics and church affiliation.

Results: Overall, 31% of the sample met the PA recommendations, 55% reported any use of the park near one's church, and 67% reported park-based PA. Park quality (OR=2.06, 95% CI: 1.55-2.75) and park concerns (OR=1.19, 95% CI: 1.05-1.34) were positively associated with using the park near one's church, controlling for the social and organizational factors. Higher church PA programming was positively associated with park-based PA (OR=1.15, 95% CI: 1.00-1.31), accounting for the social and park factors.

Conclusion: Findings suggest that increasing PA programming in churches and addressing perceived barriers (e.g., park conditions) may be important targets for multilevel faith-based interventions aimed to improve Latinos' physical activity, particularly in parks.

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64 Diabetes-Related Hospitalizations and Emergency Department Visits Among Cancer Survivors with Diabetes in SEER-Medicare: Disparities by Race (K01)

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Introduction/Background: Black individuals and Hispanics with diabetes receive less diabetes care than their white counterparts in the 12 months after a cancer diagnosis. Less diabetes care may lead to worse outcomes including hospitalization and emergency department (ED) use related to diabetes. We sought to determine if blacks and Hispanics with diabetes and cancer are at increased risk of diabetes-related hospitalizations and ED visits compared with white individuals with diabetes and cancer.

Methods: Using data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry linked to Medicare fee-for-service claims from 2006-2014, we included beneficiaries 66+ years diagnosed with incident non-metastatic breast, prostate, or colorectal cancer between 2007-2012 who also had diabetes. Given that less recommended diabetes care may have a delayed impact on outcomes, our study's primary outcomes were diabetes-related hospitalizations or ED visits 366-731 days after cancer diagnosis. Using Fine-Gray sub-distribution hazard models we examined if the risk of diabetes-related hospitalization or ED visits was higher for racial/ethnic minorities compared with non-Hispanic whites, adjusting for potential confounders and considering death as a competing risk.

Results: We included 40,059 beneficiaries with diabetes and cancer with mean age 75.5 (SD 6.3), 45.6% of whom were women and 28.9% of whom were non-white. Overall, 3847 (9.6%) had a diabetes-related hospitalization or ED visit 366-731 days after their cancer diagnosis. Overall, blacks (13.4%) were hospitalized or visited the ED more than non-Hispanic whites (9.1%, $p<0.0001$). Adjusting for potential confounders, blacks (aHR 1.33; 95% CI 1.22-1.45) and Hispanics (aHR 1.14; 95% 1.01-1.29) had higher risk of any hospitalization or ED visit compared with non-Hispanic whites.

Conclusion: Black and Hispanic individuals with diabetes and breast, prostate, and colorectal cancer were at increased risk for diabetes-related hospitalizations and ED visits in the second year after their cancer diagnosis compared to non-Hispanic whites even after accounting for demographics and cancer characteristics.

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65 Values-Based Messaging to Communicate the Social Determinants of Health: A Randomized Controlled Trial of an Ecological Approach to Health Communication (K01)

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Introduction/Background: The high rates of sugary beverage consumption among Latinos are a leading modifiable risk cancer for cancers that disproportionately influence Latinos. Reducing sugary beverage consumption is thus a critical public health priority. Sugary beverage consumption is powerfully influenced by social context, including targeted advertising and marketing, yet health promotion approaches focus on individual behavior, ignoring the social determinants of health. Social justice-based empowerment approaches lend themselves to messaging about social determinants consistent with an ecological approach to health. Moreover, recent research has suggested that values-based appeals may increase receptivity to and engagement with messages, which then improve literacy and empowerment. We thus sought to test the efficacy of messages invoking social justice, standing up to exploitative authority, and familism, three values held strongly by young adult Latinos. We hypothesized that values-based, social determinants messages would be more effective than traditional fear-based, individual messaging.

Methods: An unbalanced randomized controlled clinical trial conducted online with Mexican-American women aged 18-29. The control condition (N=73) received a typical fear-based appeal about the individual harms of obesity. Participants randomized to the experimental condition (N=360) saw one of five values-based messages.

Results: Consistent with hypotheses, the values-based messages communicating an ecological model of public health were more effective than the traditional fear appeal individual behavior message: Participants were more receptive to ($p<.001$) and accepting of ($p<.01$) values-based messages relative to control. Values-based messages increased SSB media literacy ($p<.05$) and the perceived efficacy of civic actions such as boycotting SSB ($p<.05$) and using social media to advocate about SDOH and sugar ($p<.001$). Values-based messages appear to work by engendering identification ($p<.001$) and activating social justice values ($p<.05$).

Conclusion: An ecological approach to health communication holds considerable promise for cancer and chronic disease prevention and may be especially useful for addressing disparities.

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66 Indiana Healthcare Provider Perspectives on Cervical Cancer Screening Innovations: A Mixed Methods Study (K01)

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Introduction/Background: Despite being a preventable and treatable disease, cervical cancer will be diagnosed in over 14,000 US women and kill over 4,000 in 2021. This is largely attributable to disparities in healthcare access. The state of Indiana failed to meet any of the Healthy People 2020 objectives related to cervical cancer, with marked disparities affecting Hispanic women in particular: screening coverage (target: 93%, Indiana: 81%), incidence rate (target: 7.3 new cases/100,000 females, Indiana: 8.2 and 11.7 among Hispanic females), and death rate (target: 2.2/100,000 females, Indiana: 2.5 and 3.3 among Hispanic females). Innovations such as point-of-care testing, patient self-sampling, and community health worker interventions, have led to increased cervical cancer screening coverage among immigrant and racial minority groups in other contexts. This study aims to understand provider perspectives on barriers to cervical cancer screening in Indiana, acceptability of innovative alternative strategies for under-screened groups, and factors associated with adoption of such innovations.

Methods: Semi-structured interviews were conducted with Indiana healthcare providers who conduct cervical cancer screening, including OB/GYN, family medicine, nurse practitioners, and gynecologic oncologists (n=16).

Results: Qualitative content analysis revealed multilevel barriers and challenges to current screening methods including sociocultural factors such as health literacy, mistrust of healthcare institutions because of undocumented status, provider workloads and gender-based comfort levels conducting Pap smears, delayed lab results and inability to follow-up in-person with patients upon receipt of results. Participants expressed varying levels of acceptability and willingness to adopt alternative screening strategies like patient self-sampling or point-of-care testing, and revealed numerous attributes of such innovations that would be necessary for their adoption.

Conclusion: Qualitative findings informed the development of an online survey instrument distributed to Indiana providers in June 2021 that will provide quantitative insight into provider practices, awareness and attitudes towards screening innovations, key attributes, and adoption factors to inform future context-specific interventions.

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67 Recruitment of Adult African-American Men for Colorectal Cancer Research: An Instrumental Exploratory Case Study (K01)

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Introduction/Background: Racial and ethnic minorities remain underrepresented in research and clinical trials. Better understanding of the components of effective minority recruitment into research studies is critical to understanding and reducing health disparities. Research on recruitment strategies for cancer-specific research—including colorectal cancer (CRC)—among African-American men is limited. We present an instrumental exploratory case study examining fruitful and ineffective strategies for recruiting African-American men into focus groups centered on identifying barriers to and facilitators of CRC screening completion.

Methods: The parent qualitative study was designed to explore the social determinants of CRC screening uptake among African-American men aged 45 to 75. Recruitment procedures made use of community-based participatory research strategies combined with built community relationships, including trusted community member partnerships, culturally tailored marketing materials, and incentives.

Results: Community involvement and culturally tailored marketing materials facilitated recruitment. Barriers to recruitment included limited access to public spaces, transportation difficulties, and medical mistrust leading to participation hesitancy.

Conclusion: The use of strategies such as prioritizing community relationship building, using culturally tailored marketing materials, and partnering with community leaders and gatekeepers, and can successfully overcome barriers to the recruitment of African-American men into medical research studies. To improve participation and recruitment rates among racial and ethnic minorities in cancer-focused research studies, future researchers and clinical trial investigators should broaden recruitment, strengthen community ties, offer incentives, and employ multi-faceted approaches to address specific deterrents such as medical mistrust and economic barriers.

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68 Smartphone Ownership and Use Among Older Adult New York City Housing Authority Residents (K01)

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Introduction/Background: Health disparities, such as for colorectal, breast and lung cancer, are generally worse for New York City (NYC) public housing residents compared to the rest of the population. Extensive research has proven mobile health interventions effective for improving health outcomes. However, little research is available about the use of smartphones specifically among older adult, public housing residents. The objective of this study was to assess how minority and bilingual NYC public housing residents 50 years and older access and use mobile technology.

Methods: Anonymous cross-sectional surveys (N=184) were administered to long-term, NYC public housing residents (50 years and older). Sociodemographic questions (e.g., age, gender, income), and a brief survey assessing technology use and access were included. Smartphone ownership, Internet access, frequency of app use, and app use were evaluated.

Results: The majority of public housing participants were female (80.3%), non-Hispanic black/African American (61.8%) and completed the survey in English (85.6%) versus Spanish. Seventy-five percent (N=139) of participants reported that they owned a smartphone. Compared with non-smartphone owners, smartphone owners had more years of education (p=0.04). Among smartphone users (N=139), 69.1% reported having an unlimited internet/data plan; 75% reported using smartphone apps "sometimes/often." Texting was most used (91.1%), followed by music (76.4%) and email (75.6%). Racial/ethnic differences in app use were not statistically significant.

Conclusion: This study contributes to the literature on smartphone and app use among older adult, public housing residents and suggests racial/ethnic group differences in app use. Researchers should consider promoting and developing interventions for populations of low-income adults over 50 years that include text and email applications.

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69 Comparing Smoking Behavior Between Female-to-Male and Male-to-Female Transgender Adults (K22)

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Introduction/Background: The transgender population is considered a minority within the sexual and gender minority (SGM) groups, and they face greater challenges than those who self-identify as lesbian, men having sex with men, or bisexual individuals. While most of the published literature evaluates cigarette smoking among lesbians, men having sex with men (MSM), and bisexual adults, research on smoking among transgender populations is limited. Our objective was to investigate whether there are differences in terms of smoking behavioral patterns based on gender identity in this vulnerable group.

Methods: Data were collected using a cross-sectional survey distributed among transgender individuals attending the Houston Pride Festival and those seeking care at a local transgender health clinic. Relevant variables were compared between female-to-male (FTM) and male-to-female (MTF) transgender individuals using $\chi 2$, Fisher's exact, and two-sample t-tests, when appropriate. Gender identity was used to predict current smoking status using logistic regression, adjusting for other sociodemographic determinants.

Results: The study sample (N=132) comprised 72 MTF (54.5%) and 60 FTM (45.5%) transgender individuals. Mean age of participants was 31.8 years. The sample was racially and ethnically diverse: 45.8% Caucasian, 25.2% Hispanic/Latino, 16.8% African American, and 12.2% other. Current smoking prevalence was 26.7% and 13.9% among FTM and MTF individuals, respectively. Transgender individuals were more likely to self-report current smoking if they were FTM (OR=3.76; 95% CI: 1.17–12.06; p=0.026) or were insured (OR=4.49; 95% CI: 1.53–13.18; p=0.006).

Conclusion: This study reports on important findings by examining intragroup differences in smoking behavior among the transgender population. However, further research is needed for tailoring smoking prevention and cessation interventions for transgender subgroups.

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70 Validating Nerve Fiber Recovery, Patient-Reported and Functional Outcomes of an Exercise Intervention for Taxane-Induced CIPN (Diversity Supplement)

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Introduction/Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a significant dose-limiting toxicity of breast cancer treatment with chemotherapy. CIPN can affect nerves and muscles leading to loss of sensation in hands and feet, difficutly walking, and muscle weakness. The sensory and motor neuron dysfunction accompanying taxane chemotherapy results in impaire physical functioning and increase risk of falls. The overall objective of this Administrative Supplement to Promote Diversity is to capitalize on the parent study (NCIR01CA229681-01A1), wich is a randomized controlled trial to test the efficacy of a 16-week gait and balance training plus resistance exercise compared with an educational attention control condition in decreasing the severity of peripheral neuropathy symptoms in 312 patients who completed a taxane-containing chemotherapy regimen for breast cancer. The specific aims of the Administrative Supplement Study are to: 1) compare the effectiveness of nerve conduction (parent grant) and intraepidermal nerve fiber density (IENFD) (supplement) in predicting nerve recovery and 2) determine the minimal clinically important difference (MCID) in changes in patient-reported (FACT-Taxane Questionnaire), nerve conduction, and functional five-times sit-to-stand (STS) tests in 30 women assigned to both the physical activity and control groups.

Methods: Participants will complete the FACT-Taxane Questionnaire and STS test. The IENFD will be assessed using a 3-mm punch skin biopsy performed at the lateral malleolus of the most affected extremity. The statistical analysis will compute the sample characteristics, correlation between the measurements, and compare the effectiveness of measures in capturing the pre-and-post change and the overall effect in the outcome. The anchor-based method will be used to calculate the MCID of measures.

Results: Currently,10 women have completed the baseline assessment. Skin biopsy (7 in left ankle) showed mean (SD) IENFD 1.93 (1.75) mm. The STS showed 15.94 (4.91) sec.

Conclusion: Understanding the sensitivity of nerve testing and important clinical changes in patient-reported symptoms are needed in patients with CIPN.

Funding: This work was supported by the National Cancer Institute of the National Institutes of Health under Award Number R01CA229681-01A1.

71 Using Technology To Develop a Culturally Tailored Nutrition Risk Intervention To Promote Colorectal Cancer Prevention Among Rural Adults (Diversity Supplement)

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Introduction/Background: Colorectal cancer (CRC) is a leading cause of mortality among U.S. adults. Despite strong evidence that alcohol, red and processed meats increase CRC risk, many rural adults are not aware of these modifiable nutrition risk factors. Interactive health technologies may improve risk perceptions and promote screening. We describe the user-centered development process to create an animated virtual health assistant (VHA) that delivers personalized nutrition risk information via a web-based intervention.

Methods: Between January 2020 and April 2021, black and white adults (50-73 years old) from the rural southeastern U.S. tested an interactive prototype of a VHA-delivered intervention. Focus groups were recorded, and comments were transcribed verbatim. Participant feedback was incorporated into prototype adaptations using a Virtual Interviewer Platform and Ink scripting language.

Results: Overall, 35 participants informed adaptations to three sequential prototypes (V1, V2, and V3). In the first two focus groups participants (n=14) identified preferred alcohol and meat graphics and completed a storyboard activity to draft messages (e.g., what does the VHA say to communicate CRC risk related to alcohol?). Researchers then created prototype V1 and continued testing and adapting (V1 tested with n=11; V2 tested with n=10) resulting in V3. Between V1 and V2, researchers updated content in 14 categories which included adaptations to enhance accuracy of personalized alcohol feedback, perceptions of VHA rapport, and options for multiple conversational pathways (e.g., users can choose to “skip” or “learn more” about certain topics). Updates from V2 to V3 enhanced VHA dialogue to clarify risk messages and improve perceptions of personalization (e.g., providing specific meat/alcohol alternatives).

Conclusion: The user-centered approach facilitated efficient adaptations to improve the cultural relevancy of a nutrition risk module promoting CRC screening. This work demonstrates successful engagement of older, rural adults, at average risk for CRC in cancer-related research using technology.

Funding: This work was supported by National Institutes of Health, National Cancer Institute Award #3R01CA207689-032S

72 An Augmented Eligibility Strategy to Reduce Disparities in USPSTF 2021 Lung Cancer Screening Guidelines (iCURE)

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Introduction/Background: Previous U.S. lung cancer screening guidelines may have induced health disparities because they did not account for race/ethnicity, gender, or socioeconomic status. 2021 U.S. Preventive Services Task Force (USPSTF) lung cancer screening guidelines lowered the recommended age range from 55-80 to 50-80 and lowered pack year eligibility to ≥20, in part so that more minorities would be eligible. Here, we examine if also incorporating ever-smokers selected via the Life-Years From Screening CT (LYFS-CT) individualized prediction-model reduces racial/ethnic disparities in lung cancer screening eligibly.

Methods: Using data from the U.S.-representative 2015 National Health Interview Survey, we modeled the performance of NLST-like screening in ever-smokers eligible by USPSTF 2013 guidelines, USPSTF 2021 guidelines and an augmented USPSTF 2021+LYFS-CT approach that additionally includes all individuals with ≥12 days of life-gained from screening. We calculated the number eligible for screening proportion of gainable life-years gained and the disparities (absolute difference) in preventable deaths and life-years gainable between races/ethnicities.

Results: Eligibility increased by similar proportions for minorities (97.1%) and whites (78.3%) under USPSTF 2021 guidelines. However, the relative disparity in percent of life-years gainable (difference vs. white Americans) from USPSTF 2013 to USPSTF 2021 increased for all minorities (African Americans: 15% to 16%; Hispanic Americans: 24% to 27%; Asian Americans: 13% to 19%). In contrast, the additional inclusion of 3.5 million high benefit individuals by LYFS-CT virtually eliminated the disparities for African Americans (16% to 1%), slightly reduced disparities for Hispanic Americans (27% to 24%) and disparities for Asian American did not change (19%).

Conclusion: USPSTF 2021 guidelines increased the number of eligible minorities versus USPSTF 2013 but may inadvertently increase racial/ethnic disparities for minorities. Augmenting current USPSTF 2021 guidelines to include ineligible people with high predicted benefit from screening, regardless of race/ethnicity, may reduce or even eliminate disparities.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

Clinical Cancer Research Poster Abstracts

73 The Impact of Radiotherapy on Acute Skin Toxicities and Quality of Life in Breast Cpancer Patients (Diversity Supplement)

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Introduction/Background: Radiotherapy (RT) in breast cancer treatment has contributed to improved cancer outcomes. However, some breast cancer patients treated with adjuvant RT develop acute skin toxicities that impact quality of life (QOL); we aim to assess both patient reported RT-related symptoms and clinician-reported skin toxicities related to RT.

Methods: We evaluated 386 breast cancer patients who reported RT-related QOL issues that affected them during and after RT using a questionnaire. Clinicians also reported skin toxicity at the end of RT using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Patient reported outcomes (PROs) were evaluated using Chi-square analyses. PROs and clinician-reported outcomes (CROs) were dichotomized into "high" and "low" categories for comparison and the percent agreement and Kappa coefficient were calculated to evaluate concordance.

Results: Respondents self-identifed as non-Hispanic white (n=56), Hispanic White (n=249), and black (n=81). At RT completion, erythema was the most commonly reported symptom; 87% of the study population reported to being affected by it. Hyperpigmentation was the second most commonly reported symptom with 86% of respondents reporting being bothered by this symptom during RT. At the group level, there was a fair agreement between PROs and CROs (% agreement= 61.1%, Kappa coefficient=0.224).

Conclusion: Erythema and hyperpigmentation were the most commonly reported symptoms that bothered breast cancer patients during their course of RT. Identifying the skin toxicites that most affect patients during treatment can improve management by targeting intervention efforts. Fair agreement in skin toxicity severity observed, points to the potential need of including PRO questionnaires in clinics which can be used to identify patients who are experiencing a high skin toxicity severity. Our findings highlight the need for a more comprehensive RT-related symptom assessment and support the development of a new tool to include both PROs and CROs.

Funding: The study was supported by National Cancer Institute grants R01CA135288, R21 CA234880, and R21 CA234880-01A1S1 (to JJH).

74 Distress in a Pandemic—The Association of the Coronavirus Disease-2019 (COVID-19) Pandemic with Distress and Quality of Life in Hematopoietic Stem Cell Transplantation (HSCT) (K08)

Amonoo, H.[1, 2, 3], Topping, C.[4], Clay, M.[4], Reynolds, M.[4], Rice, J.[4], Harnedy, L.[4], Longley, R.[4], LeBlanc, T.[5], Greer, J.[3,4], Chen, Y.[3,4], DeFilipp, Z.[3,4], Lee, S.[6], Temel, J.[3,4], El-Jawahri, A.[3,4]

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Introduction/Background: The global coronavirus disease 2019 (COVID-19) pandemic has drastically disrupted cancer care, potentially exacerbating patients' distress levels. Patients undergoing HSCT may be especially vulnerable to this pandemic stress. However, the associations of the COVID-19 pandemic with distress, fatigue, and quality of life (QOL) are not well understood in this population.

Methods: In a cross-sectional analysis of data from 205 patients undergoing HSCT enrolled in a supportive care trial, we compared baseline pre-HSCT distress (depression, anxiety, and posttraumatic stress disorder [PTSD]) symptoms, fatigue, and QOL between enrollees pre- (i.e., 03/2019-01/2020) and during (i.e., 03/2020-01/2021) the COVID-19 pandemic. We used linear regression models adjusting for sociodemographics and cancer diagnosis to examine the associations between enrollment period and patient-reported outcomes. We used semi-structured qualitative interviews in 20 allogeneic HSCT recipients who were ≥3-months post-HSCT to understand the impact of the COVID-19 pandemic on their recovery post-HSCT.

Results: Prior to COVID-19, 124 participants enrolled, while 81 participants enrolled during the pandemic. The cohorts had similar baseline demographics and disease risk factors. In multivariate regression models, enrollment during COVID-19 was not associated with pre-HSCT symptoms of depression, anxiety, PTSD, fatigue, or QOL impairment. COVID-19-era participants reported themes of negative (e.g., increased isolation) and positive (e.g., engagement with meaningful activities) implications of the pandemic on HSCT recovery.

Conclusion: We found no differences in pre-HSCT distress, fatigue or QOL in patients undergoing HSCT prior to or during the COVID-19 pandemic. Patients in early recovery post-HSCT, however, report both negative and positive implications of the COVID-19 pandemic on their lives.

Funding: This work was supported by the National Cancer Institute through grant K08CA251654 (to Dr. Amonoo). Dr. El-Jawahri is a scholar in clinical research for the Leukemia & Lymphoma Society.

75 Assessing Glioblastoma Immunotherapy Response with FMISO Hypoxia PET Imaging (K08)

Barajas, J.[1,2,3], Mallak, N.[1], Link, J.[1,4], Krohn, K.[1,4], Brown, A.[1], Thurston, B.[4], Mittra, E.[1], Raslan, A.[5], Dogan, A.[5], Woltjier, R.[6], Murphy, B.[7], Chandra, R.[7], Rooney, E.[2], Fu, R.[8], Thomas, C.[7], Jaboin, J.[7], Neuwelt, E.[9,10,11], Ambady, P.[9,10]

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Introduction/Background: Glioblastoma hypoxia directly contributes to poor clinical outcomes by reducing chemoradiotherapy efficacy. 18F-fluoromisonidazole (FMISO) positron emission tomography (PET) defines regions of hypoxia. The use of checkpoint inhibition is actively being investigated in brain tumors. Our hypothesis is that the presence of a hypoxic tumor burden as defined by FMISO PET/MRI is capable of defining glioblastoma therapeutic failure.

Methods: Three patients with newly diagnosed glioblastoma were recruited into our clinical trial (NCT03649880). All patients underwent maximal safe resection followed by Stupp protocol temozolomide based chemoradiotherapy augmented with concurrent pembrolizumab immunotherapy (NCT03347617). FMISO PET and MRI were performed at the time of first presumed disease progression as defined by iRANO criteria. 3.7 MBq/kg (0.1 mCi/kg; up to 10mCi) of FMISO was administered intravenously 90 minutes prior to emission PET imaging of the brain. The hypoxic volume was defined as 1.2x of mean cerebral uptake. Relative standard uptake values (rSUV) were defined as the ratio of T2 hyperintense lesion and right cerebellum values. The hypoxic tumor burden was the ratio of the hypoxic volume to enhancing volume. Clinical diagnosis was confirmed through surgical biopsy or follow-up MRI.

Results: The one patient with recurrent glioblastoma demonstrated marked elevated rSUV of 1.46 and hypoxic tumor burden of 1.53 . The two patients with neuroinflammation as an etiology for the growing enhancing volume by MRI was found to have a rSUV of 0.91 and 0.98, and hypoxic tumor burden of 0.12 and 0, respectively.

Funding: This work was supported by grant 1K08CA237809.

76 Occurrence of Fractures in Children with Neurofibromatosis Type 1 on the MEK Inhibitor Selumetinib for Inoperable Plexiform Neurofibromas (iCURE)

Burgess, C.[1], Baldwin, A.[2], Dombi, E.[1], Fisher, M.[3], Weiss, B.[4], Kim, A.[5], Bornhorst, M.[5], Dufek, A.[1], Derdak, J.[1], Whitcomb, P.[1], McHugh, K.[1], Widemann, B.[1], Gross, A.[1]

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Introduction/Background: Neurofibromatosis type 1 (NF1) is associated with an increased risk of tumor formation and bone abnormalities (Ferner et. al, 2007). One study has shown that 22% of children with NF1 will have at least one fracture. Pre-clinical data indicate that plexiform neurofibromas (PN) may have a local impact on bone health and that treatment with MEK inhibitors (MEKi) may have an impact on bone formation (George-Abraham et. al, 2013). To better understand the relationship between MEKi and bone health in NF1 patients, we evaluated the incidence of fractures in children enrolled on the Phase 1/2 Study of Selumetinib for Inoperable PN (NCT01362803).

Methods: We reviewed adverse events and the electronic medical record to document any fractures which occurred between the start of drug treatment and our cutoff date. We determined if PN were located near the fracture site for each of the fractures. We also reviewed the patients' alkaline phosphatase, calcium, and vitamin D levels and dual-energy x-ray absorptiometry (DEXA) scans.

Results: Seventeen of the 99 subjects (17.2%) had at least one fracture during selumetinib treatment. There were a total of 23 fractures. Median age at time of fracture was 11 years old and median selumetinib cycle number (1 cycle = 28 days) was 51.5 (range 2, 96). Four of the fractures were discovered as incidental findings on restaging MRI. DEXA scans were obtained before fracture in 9 of the 17 subjects. Ten of the 23 (43.5%) fractures occurred in bones adjacent to a known PN. There were no clinically significant abnormalities in any of the bone health indicator measurements.

Conclusion: Approximately 17% of subjects receiving selumetinib had a fracture of which nearly half occurred in bones adjacent to a known PN. The impact of selumetinib on bone health in NF1 remains unclear. Further studies are needed to determine the long-term effects of selumetinib on fracture risk and healing.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

77 Is Breast Conservation Therapy as Good as Mastectomy 40 Years After Early-Stage Breast Cancer Diagnosis? (iCURE)

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Introduction/Background: Between 1979 and 1987, National Cancer Institute protocol 79-C-0111 randomized 237 women with pathologically confirmed invasive breast tumors 5 cm or less to receive either breast conservation therapy (BCT) or modified radical mastectomy (MRM), with overall survival as the primary endpoint. Both arms of the trial received axillary dissection. Node-positive patients were treated with doxorubicin and cyclophosphamide. BCT patients had radiation to the whole breast followed by a cavity boost. Objective of the study is: Does BCT versus MRM remain equivalent after more than 20 years?

Methods: After median follow-up of 25 years, we performed additional analysis at a median follow-up of 30.9 years to determine patterns which could suggest risk factors for delayed cancer recurrence of all types in long-term survivors of early-stage breast cancer. A chart review was conducted on all patients with a new cancer diagnosis (including recurrent breast) 25-30 years after their original breast cancer diagnosis.

Results: 9.78% of the cohort were documented to have a cancer recurrence between years 25 and 30. 60.0% of recurrent patients had received prior BCT. However, 28.6% of recurrences were non-breast cancer in origin while 71.4% of recurrences were breast cancer in origin. 42.8% of the women had a BMI greater than or equal to 27.

Conclusion: These data suggest that there may be a significant proportion of women with history of early-stage breast cancer who are at risk for late cancer recurrences. Therefore, yearly monitoring with mammograms and physical exams are suggested for long-term breast cancer survivors. Genetic testing is pending on the recurrent patient cohort.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

78 Targeting CXCR4 and Thioredoxin Reductase in Small Cell Lung Cancer (Other)

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Introduction/Background: Patients are dying from a type of incurable cancer, small cell lung cancer (SCLC) which has a five-year life expectancy of 27%. A new therapeutic approach is needed to increase the life expectancy of SCLC patients. These tumors highly expressed G protein coupled receptors, C-X-C chemokine receptor 4 (CXCR4). 177Lutium-pentixather (177Lu-pent) targets these receptors and therefore could be used as treatment of SCLC. Auranofin (Aur), an inhibitor of hydroperoxide metabolism, increases oxidative stress in cancer cells and might selectively enhance 177Lu-pent therapeutic efficacy. We hypothesized that CXCR4 would serve as a radionucleotide target and inhibition of hydroperoxide detoxification will enhance the response to this radionucleotide therapy.

Methods: Clonogenic survival analysis was performed on two SCLC lines in vitro using 1 μM Aur and 177Lu-pent (1 and 10 μCi). A mouse SCLC xenograft model using 25 μCi/g 177Lu-pent +/- 4 mg/kg Aur injections was used to evaluate toxicity and efficacy in vivo. Western blots of tumor lysates were performed to look for damage markers γH2AX and PCNA.

Results: Clonogenic survival analysis demonstrated a more than additive enhancement of cell death when Aur was combined with 177Lu-pent. Also, it was found that 177Lu-pent treatment extended overall survival compared to the control mice however adding Aur did not further enhance survival. Mice treated with 177Lu-pent and 177Lu-pent+Aur had increased PCNA compared to control tumors, indicating the treatments resulted in DNA damage to the tumor cells. No significant changes were shown in serum BUN or creatinine in treatment groups vs control mice.

Conclusion: These data support the clinical evaluation of the safety and efficacy of 177Lu-pent alone and in combination Aur in SCLC in humans.

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79 PIONEER: Computational Probing of DIfferences in SymptOms and FuNction of DivErsE Brain TumoR Populations (iCURE)

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Introduction/Background: Primary brain tumor (PBT) patients are highly symptomatic, but data to date has been based in primarily white cohorts. This study aimed to apply a network-based computational approach to identify symptom co-occurrence patterns and compare pivotal symptoms across diverse ethnoracial groups in a PBT population.

Methods: Two institutional cohorts of PBT patients (Neuro-Oncology Branch Natural History Study and MD Anderson Cancer Center) were merged and included clinical characteristics and symptom severity measured with the MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT) instrument. The Symptom COnsensUs NeTworks portal was used to identify within each ethnoracial group communities of patients sharing similar symptom co-occurrence patterns, generate community-level symptom networks, and prioritize symptoms according to their centrality in the network.

Results: The sample of 1,128 patients (58% male, median age 48, 66% high-grade gliomas, 69% good KPS [90-100]) was comprised of 82% White, 5% African American (AA), 7% Hispanic, and 5% Asian. For mild-severe symptom severity (1-10), fatigue was a central symptom across all ethnoracial communities, particularly for Whites and Hispanics. Sleep disturbance was common for Asians and AAs, while distress was more central for AAs and Hispanics. All groups had at least one cognitive symptom in the top five most central symptoms. At the moderate-severe level (5-10), fatigue remained central for most communities, though to a lesser degree for Asians. Weakness was a central symptom for Asians and AAs, while pain was central for all non-White patient communities, both of which were not seen in lower severity networks.

Conclusion: While there were similarities in symptom networks across ethnoracial groups, differences in pivotal symptoms suggest that other factors contribute to their illness experiences. Future exploration of socioeconomic and cultural factors that might contribute to minority symptom burden is warranted and may allow development of interventions to improve clinical outcomes in these groups.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

80 The Y-AMBIENT Pilot Protocol (K08)

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Introduction/Background: Young African American (AA) survivors report poorer quality of life (QOL), and face more negative social determinants of health (e.g., low socioeconomic status, limited access to care, discrimination) than young White survivors. Yet, there are no published interventions that comprehensively address QOL (i.e., physical, psychological, social and spiritual well-being) in young AA survivors. This study is aimed at evaluating processes and preliminary outcomes of a targeted QOL intervention (Y-AMBIENT) vs. control in young AA survivors in treatment for early (I-II) & late (III) stage breast cancer.

Methods: We will conduct a two-arm, pilot randomized controlled trial to evaluate feasibility, acceptability, and preliminary health-related outcomes of Y-AMBIENT vs. an attention control (enhanced usual care). We will recruit 40 young AA survivors who have completed primary breast cancer treatment (n=20 per group and equal representation of those with a history of early and late-stage breast cancer within). We will measure feasibility via study recruitment and retention (i.e., study enrollment and study contact completion) and protocol acceptability with satisfaction, usefulness, use of strategies via our Topical Concern and Strategy Sheet. We will triangulate qualitative and quantitative responses from each study contact to (a) identify participants' perceptions of its acceptability, (b) willingness to participate in aspects of the protocol (participant burden), and (c) use of self-management strategies. At baseline, two-, and five-months, we will examine health-related outcomes (i.e., QOL, spiritual well-being, self-efficacy, and social support) within and between groups using descriptive and multiple-effects modeling techniques.

Results: The project is ongoing.

Conclusions: We expect this study will provide valuable feedback to scale-up the Y-AMBIENT intervention for a large efficacy trial.

Funding: This research is supported by the National Cancer Institute of the National Institutes of Health under award number K08CA245208.

81 Outcomes of the First Pregnancy Following Fertility-Sparing Surgery for Early-Stage Cervical Cancer: A Population-Based Study (K08)

Rauh-Hain, J.[1], Nitecki, R.[1], Floyd, J.[2], Lamiman, K.[3], Clapp, M.[4], Fu, S.[5], Jorgensen, K.[6], Melamed, A.[7], Brady, P.[8], Kaimal A.[4], del Carmen, M.[9], Woodard, T.[1], Meyer, L.[1], Giordano, S.[5,10], Ramirez, P.[1]

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Introduction/Background: Observational studies have demonstrated that more than a third of cervical cancer survivors who ultimately conceive will deliver prematurely. However, the available data are limited as they are derived from case series and systematic reviews of case series with few pregnancies. Our objective was to evaluate outcomes of the first pregnancy after fertility-sparing surgery in patients with early-stage cervical cancer.

Methods: We performed a population-based study of women 18-45 years old with a history of stage I cervical cancer reported to the 2000-2012 California Cancer Registry. Data were linked to the California Office of Statewide Health Planning and Development birth and discharge data sets. We included patients with cervical cancer who conceived ≥3 months after fertility-sparing surgery. The primary outcome was preterm birth. Secondary outcomes included growth restriction, neonatal morbidity, fetal demise, cesarean delivery, and severe maternal morbidity. We used propensity scores to match similar women from two groups in a 1:2 ratio of cases to controls: population controls without cancer and cervical cancer controls (women who delivered before their cervical cancer diagnosis). Wald statistics and logistic regressions were used to evaluate outcomes.

Results: Of 4,087 patients with cervical cancer, 107 conceived following fertility-sparing surgery (conization/LEEP). Squamous cell carcinoma was the most common histology (63.2%) followed by adenocarcinoma (30.8%). Cases had higher odds of preterm birth before 37 weeks compared to both control groups (21.5% vs 9.3%, OR 2.66, 95% CI 1.38-5.10; 21.5% vs 12.7%, OR 1.88, 95% CI 1.01-3.57), but not preterm birth before 32 weeks. Neonatal morbidity was more common among the cases relative to cervical cancer controls (OR 15.9% vs 6.9%, 2.53, 95% CI 1.16-5.54). There were no differences in rates of growth restriction, fetal demise, cesarean delivery, and maternal morbidity.

Conclusion: In a population-based cohort, patients who conceived after surgery for cervical cancer had higher odds of preterm delivery compared to controls.

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82 Separate and Unequal: Examining the Role of Race and Site of Care on Patient-Reported Outcomes Among Patients with Metastatic Cancer (AFT-39) (K01)

Samuel-Ryals, C.[1], Mbah, O.[1], Elkins, W.[1], Charlot, M.[1], Deal, A.[1], Dueck, A.[2], Ginos, B.[2], Jansen, J.[1], Schrag, D.[3], Spears, P.[1], Stover, A.[1], Basch, E.[1]

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Introduction/Background: Hospital racial composition of patients has been linked to disparities in cancer care quality and outcomes, but questions regarding whether oncology practice racial composition mediates racial disparities in cancer outcomes remain. Using 2017-2020 data from the Patient-Reported Outcomes to Enhance Cancer Treatment (PRO-TECT) trial (ClinicalTrials.gov NCT03249090), we examined racial disparities in PROs among patients with metastatic cancer, and whether oncology practice racial composition accounted for observed disparities.

Methods: Our sample included 1100 patients (n=190 Black; n=910 White) from 52 community oncology practices across the U.S. Practice-reported racial composition was dichotomized as black patient population >20% vs. ≤20%. Patient-reported outcome metrics included pain, appetite loss, fatigue, nausea, dyspnea, insomnia, constipation, diarrhea, and financial burden, measured using the EORTC Quality of Life Core Questionnaire (QLQ-C30). We estimated multilevel linear mixed models predicting each PRO as a function of patient race, adjusting for clinical and sociodemographic factors, followed by further adjustment for practice racial composition.

Results: Across all practices, black patients reported worse pain (β=5.7, 95% CI:2.0-9.4), nausea (β=2.9, 95% CI:0.9-4.9) and financial burden (β=7.1, 95%CI:3.5-10.7), but less fatigue (β=-=-3.4, 95%CI:-6.8 - -0.1) and diarrhea (β=-4.8, 95%CI:-7.7- -1.9) when compared with whites. Regardless of race, patients receiving care at practices with >20% black patients reported more pain (β=5.0, 95% CI:0.5-9.4), appetite loss (β=8.5, 95% CI:4.3-12.6), and fatigue (β=4.6, 95% CI:0.5-8.7), than patients receiving care at practices comprised of ≤20% black patients.

Conclusion: Racial disparities in PROs were observed among patients treated at US community oncology practices. Practice racial composition was associated with multiple PROs, regardless of patient race, but racial disparities in PROs were not explained by practice racial composition. These findings suggest that identifying and addressing the needs of practices serving a disproportionate share of black patents may be one effective strategy to mitigate practice-level disparities in cancer outcomes.

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83 The Complexities of Germline PARN Variants in Telomere Biology Disorders and the General Population (iCURE)

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Introduction/Background: PARN encodes poly(A)-specific ribonuclease, a highly conserved 3' exoribonuclease important in regulating the stability and maturation of RNAs; it acts by shortening the mRNA poly(A) tail through deadenylation. Pathogenic germline variants in PARN result in reduced levels of TERC by altering its stability and accelerating its degradation. Autosomal dominant and recessive inheritance of rare PARN variants have been identified in telomere biology disorders (TBDs) including dyskeratosis congenita (DC), Hoyeraal-Hreidarsson syndrome (HH), and familial pulmonary fibrosis.

Methods: To better understand the full scope of germline PARN variation in disease, we conducted a comprehensive literature review, curated PARN variants, and assessed evolutionary conservation. The Genome Aggregation Database (gnomAD, N=141,456) was used to identify rare variation (MAF <0.01) in healthy populations. Evolutionary conservation metrics were evaluated with MEGAX. Variants were deemed deleterious if clinical significance evidence was provided by ClinVar, at least two of three deleterious in silico predictors (missense), or there was at least one deleterious prediction by HSF or SpliceAI (splice-site). All frameshift/nonsense variants were classified as deleterious.

Results: There were 362 unique PARN variants with MAF <0.01 across all gnomAD racial/ethnic groups: 8 splice-site, 12 frameshift, 6 in-frame deletion, 326 missense, and 10 nonsense. Fifty-six gnomAD variants (15.5%) were classified as deleterious and 306 as tolerated. A survey of the TBD literature identified, 66 unique PARN variants reported in TBD patients, including 10 splice-site, 4 intronic, 10 frameshift, 34 missense, 7 nonsense, and 1 synonymous. Our schema classified 40 of the 66 as deleterious and 26 as tolerated. Thirteen of the 34 missense variants (38%) were at highly conserved residues with the same amino acid present in at least four distinct species.

Conclusion: In general, PARN is highly conserved with primarily rare variants across all populations evaluated. Notably, commonly used in silico predictions of variant deleteriousness were not consistent across literature reported TBD-associated PARN variants.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

Translational Cancer Research Poster Abstracts

84 Accelerating Abdominal T1-Mapping Using Deep Learning (Diversity Supplement)

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Introduction/Background: T1-mapping is an MRI technique used to obtain quantitative information on tissue pathology. Application of T1-mapping in the abdomen is useful for identification and characterization of cancerous lesions and pre-cancerous conditions such as liver fibrosis which can lead to hepatocellular carcinoma. For a comprehensive evaluation of the liver and to be able to detect small lesions, high spatial resolution with complete anatomical coverage is needed. Our group recently proposed an inversion recovery radial MRI technique for high resolution T1-mapping within a single breath hold period (BHP), but requires multiple BHPs for full abdominal coverage. We propose an accelerated T1-mapping framework which utilizes deep learning techniques to estimate T1 values using a fraction of the T1 recovery curve (T1RC), allowing for more efficient anatomical coverage while maintaining high spatial resolution.

Methods: Radial views acquired throughout T1 recovery are grouped into inversion time (TI) groups, followed by joint-reconstruction to obtain TI images. Reference T1-maps are produced using a non-linear least square (NLLS) curve fitting method. Datasets simulating shortened T1RC sampling are produced by truncating the number of TI groups, followed by reconstruction to obtain corresponding truncated sets of TI images. Individual Convolutional Neural Networks (CNNs) are trained using each truncated image set to take as input the TI images and produce as output the reference T1-map.

Results: In vivo experiments demonstrate that the proposed framework achieves <6% average estimation error within liver ROIs when using only 25% of the T1RC. Meanwhile NLLS fails to produce reasonable T1 estimates (>100% estimation error) with the same data.

Conclusion: The proposed accelerated T1-mapping framework demonstrates significant improvement in T1 estimation performance over conventional methods while extending slice coverage 4x compared to recent radial T1-mapping techniques.

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85 Poly- and Perfluoroalkyl Substances Alter the Polycomb Pathway and Tumorigenicity of Testicular Germ Cell Tumor Cells (Diversity Supplement)

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Introduction/Background: Poly- and perfluoroalkyl substances (PFAS) are a class of chemicals used since the mid-1900s for various purposes, such as creating water- and oil-repellent surfaces, fire-fighting foams, and food packaging. These chemicals are ubiquitous in the environment because of their persistent and bioaccumulative nature due to the carbon-fluorine bonds characteristic of the chemical class. Several epidemiological and animal studies have suggested an increased risk of several cancers due to high exposure to PFAS, including testicular cancer. Mechanisms of carcinogenicity are not yet understood.

Methods: Testicular cancer cell lines were treated with 10 nM and 5 μM perfluorooctanesulfonic acid (PFOS) for 4 days, followed by RNA-seq and Immunoblot analysis. CD-1 mice were dosed daily with 20 mg/kg of PFOS and hexafluoropropylene oxide dimer acid (GenX) for 15 days. Testes were harvested, and gene expression was analyzed using RNA-seq. A xenograft model was employed to assess the effects of daily dosing of 10 mg/kg PFOS on testicular cancer tumorigenicity.

Results: PFAS treatment increased the polycomb mark histone 3 lysine 27 (H3K27) tri-methylation in testicular cancer cells. Gene set enrichment analysis also revealed PFAS mediated transcriptional changes associated with increased activity of the polycomb pathway. Previous studies determined that alterations in H3K27 methylation through the polycomb repressive complex 2 (PRC2) profoundly affect tumorigenicity and testicular cancer cells' cisplatin sensitivity. Normal testis from CD-1 mice dosed with 20 mg/kg PFOS and GenX also demonstrated transcriptional changes associated with increased methylation of H3K27. Importantly, preliminary xenograft studies revealed that daily treatment of mice with PFOS resulted in increased testicular tumor growth compared to vehicle control.

Conclusion: The data suggest that PFAS may potentially augment testicular cancer tumorigenicity by altering the PRC2, which controls H3K27 methylation. Further research is necessary to confirm this hypothesis to understand the mechanisms in which PFAS affects testicular cancer cells.

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86 Stress-Induced ITGB3 Drives Cell Surface Presentation of Integrin αvβ3 in Epithelial Cancer Cells (Diversity Supplement)

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Introduction/Background: Integrin αvβ3 is a heterodimer cell-surface receptor consisting of integrin αv and integrin β3 units. Integrin αvβ3, while not expressed on resting tissues, is rapidly up regulated during tissue injury and inflammation where it contributes to the tissue remodeling and repair. Similarly, early-stage tumors do not express integrin αvβ3, but its acquired expression is associated with increased tumor progression, metastasis, and drug resistance. Understanding how cancer cells mechanistically up regulate integrin αvβ3 expression remains a critical unanswered biological question.

Methods: Quantitative PCR and western blot analyses were performed to measure mRNA and protein expression, respectively. Flow cytometry was utilized to assess expression of integrin αvβ3 on the cell-surface. Chromatin immunoprecipitation was performed to investigate histone methylation and acetylation status on integrin β3's promoter region.

Results: Here, we report, that cellular stress associated with the tumor microenvironment such as hypoxia, oxidative stress, and nutrient deprivation induce β3 expression leading to increased αvβ3 presentation on the cell-surface of breast, pancreas, and lung cancer cells. Specifically, exposing tumor cells to nutrient stress (e.g. no serum), hypoxia (1% O_2) or hydrogen peroxide (H_2O_2) leads to chromatin remodeling on the β3 promoter resulting in increased mRNA expression and protein synthesis. Furthermore, we identify Signal Transducer and Activator of Transcription 3 (STAT3) as an essential transcription factor for stress mediated induction of β3 expression. Silencing STAT3 expression with RNAi or pharmacological inhibition of STAT3's transcriptional activity prevents stress mediated induction of β3 expression.

Conclusion: We hypothesize that cellular stress leading to STAT3 activation coordinates with chromatin changes on the β3 promoter to drive stress-mediated induction of β3 mRNA expression. By targeting this stress-mediated pathway we hope to identify therapeutic strategies that not only prevent tumor progression but reverse tumor drug resistance.

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87 Low SAMHD1 Expression Sensitizes Malignant Glioma Cells to DNA-Damaging Therapeutics and Is Associated with Better Outcome in Patient and Xenograft Models (KO1)

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Introduction/Background: Malignant glioma is the most commonly diagnosed primary nervous system malignancy, and despite standard aggressive therapy, the patients' prognosis remains siginificantly poor. Therefore, there is an urgency to develop a more efficient therapeutic strategy to improve patient outcome. The standard-of-care treatments for malignant glioma, including radiation therapy (RT) and the chemotherapy drug temozolomide (TMZ), induce cancer cell death by causing DNA double-strand break. However, these treatments are not effective due to resistance. We discovered that SAMHD1, a well-established dNTPase, plays a role in DSB repair through homologous recombination.

Methods: The Cancer Genome Atlas data set was analyzed for SAMHD1 expression and association to patient outcome. A patient-derived cells data set from HGCC was used to assess SAMHD1 expression, cell proliferation, and survival in xenograft models. Cell sensitivity to therapeutic agents was evaluated by AlmarBlue-based cell viability assay. Cellular DNA damage response was assessed through immunofluorescence assay. VLPs were generated using a two-vector system packaged in 293 cells. Cellular dNTP pool was measured using HIV-1 RT-based primer extension.

Results: Exposing glioblastoma cells to virus-like particles (VLP) packaging viral protein X (VLP(+Vpx)) enhances the malignant glioma cells' sensitivity to DNA damaging agents. (VLP(+Vpx)) induced dose-dependent delayed cell growth, and combined with RT or TMZ, resulted in improved sensitivity. Brain tumors from glioblastoma patients exhibit significantly higher SAMHD1 levels. Patient-derived cells with lower SAMHD1 levels show reduced proliferation rate and resulted in a better outcome in a mouse xenograft. Low SAMHD1 levels are associated with better outcomes in patients with glioblastoma.

Conclusion: Our finding shows SAMHD1 importance for malignant glioma carcinogenesis and that it could be a plausible therapeutic target. Moreover, our finding provides a proof of concept for using virally encoded Vpx as a therapeutic tool to improve the efficacy of TMZ and RT in glioblastoma.

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88 Engineering Precision Medicine to Increase Graft-Versus-Lymphoma Activity: Hematopoietic Stem Cells Modified with Chimeric Antigen Receptors (K23)

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Introduction/Background: Refractory or recurrent B-lineage hematological malignancies have less than 50% of chance of cure. Therapy with FDA-approved autologous T-cells expressing chimeric antigen receptors (CAR) have led to remissions in chemotherapy-resistant malignancies, but effector cells do not persist, limiting efficacy. Our hypothesis is the modification of hematopoietic stem cells (HSC) with anti-CD19 CAR will lead to persistent generation of multilineage target-specific immune cells, enhancing graft-versus-cancer activity and leading to anti-tumor memory.

Methods: We generated CD28- and 4-1BB-costimulated CD19-specific CAR using lentiviral vectors for modification of human HSC for assessment in humanized NSG. Cells were harvested from bone marrows, spleens, thymus and peripheral blood for evaluation by flow cytometry and ddPCR. Mouse cohorts received challenge with injections of lymphoma cell lines.

Results: Gene modification of HSC with CAR did not impair differentiation or proliferation in humanized mice, and led to CAR-expressing progeny in myeloid, NK and T-cells. Humanized NSG engrafted with CAR-modified HSC presented similar humanization rates to non-modified HSC, with CAR-expressing cells present in all tissues up to 44 weeks post-transplant, similar in both CAR constructs. Animals engrafted with CAR-modified HSC did not present increased autoimmunity or inflammation. T-cells were higher in humanized mice with CAR-modified HSC in comparison to mice engrafted with non-modified HSC. CAR-modified HSC led to development of T-cell effector memory and T-cell central memory phenotypes. Mice engrafted with CAR-modified HSC presented tumor growth inhibition and survival advantage against lymphoma cells, with no difference between both constructs (62.5% for CD28-costimulated CAR and 66.6% for 41BB-costimulated CAR, p=0.69).

Conclusion: CAR modification of HSC for cancer immunotherapy is feasible and continuously generates multilineage CAR-bearing immune cells. This approach can augment the anti-lymphoma activity in autologous HSC recipients, and offers alternative therapeutic approach for patients with no available sources for allogeneic transplantation, benefiting ethnic minorities.

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89 Oncogenic APC Enhances Wnt Signaling by Reshaping Cholesterol-Dependent Plasma Membrane Organization (Diversity Supplement)

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Background: Wnt signaling has been linked to ~90% of all colorectal cancer (CRC) cases. Markedly, the majority (>80%) of sporadic CRC cases display mutations in Apc. Loss of APC function causes aberrant stabilization of β-catenin, a crucial step in CRC initiation. Attempts towards "drugging" this pathway still pose multiple hurdles. Consequently, there is an urgent need for novel insights associated with the Wnt pathway in order to develop novel therapeutic approaches. With respect to Wnt signaling activation, LRP5/6 and Frizzled require plasma membrane (PM) raft localization and nanoclustering for efficient signaling. Interestingly, various effectors that disrupt rafts, alter LRP5/6-Frizzled clustering, leading to reduced β-catenin stabilization.

Methods: We examined the effect of oncogenic APC (oAPC) on PM lipid/protein-carried interactions of Wnt-associated effectors in a CRC mouse model and cell lines utilizing high resolution microscopy, e.g., FLIM-FRET and STORM, measured the level of key biochemical effectors using fluorescence microscopy and determined Wnt signaling activation using Wnt reporter assays.

Results: We show for the first time, that oAPC increases the levels of PM cholesterol, a major component of rafts known to selectively activate Wnt signaling, in the intestinal epithelium including the cells of origin of CRC, Lgr5+ stem cells. Moreover, oAPC altered colonocyte raft organization. We also demonstrate that oAPC increased LRP6-Fzd7 nanoclustering as well as their interactions with key lipid/protein, leading to enhanced Wnt signaling activation. Finally, we elucidated that cholesterol alone modulates Wnt receptor clustering and signaling activation.

Conclusion: Collectively, these findings indicate that oAPC can perturb cholesterol homeostasis in colonocytes, thereby altering raft domain structure, LRP6-Frizzled7 nanoassemblies and downstream Wnt signaling. This knowledge will serve as foundation to develop new drug targets and chemopreventive strategies against CRC.

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90 Identifying Potential Drug Targets Using Patient-Derived, Tissue Specific, Gene Regulatory Networks (Diversity Supplement to R01CA218668)

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Introduction/Background: Recent developments in sequencing have allowed consortiums like ENCODE and ROADMAP to probe the epigenome of normal and cancer cell lines. Applying these approaches in a broad fashion to patient data has been difficult but a pioneering The Cancer Genome Atlas (TCGA) study using ATAC-Seq, an assay for probing open chromatin and thus regulatory regions, provides an opportunity to analyze cancer patient epigenomes for key regulators and drug targets.

Methods: Utilizing this dataset, we identify regulatory targets of open chromatin regions from ATAC-Seq and RNA-Seq across 371 patients on a patient-specific basis. We subsequently utilize transcription factor (TF) footprinting to identify regions bound by 850 TFs &TF-families in each patient which identifies TF target genes for every patient. Using a combination of network metrics and TF abundance, we identify a set of TFs with greater predicted importance in each patient relative to others and clusters of similar patients. After clustering the patient samples, we assign cell lines from the Achilles/DepMap project to the closest representative patient cluster. Codependency is then used to identify genes most highly correlated with the set of critical TFs for each cluster, We then utilize the Drug Interaction Database to identify compounds that target each gene set in this set. We prioritize codependent gene pairs using TF-activity, pan-cancer dependency, and inferred toxicity of targeting drugs.

Results: We identify a cluster of neuroendocrine-like cancers in lung and stomach adenocarcinoma, a rare disease subtype and expressing high levels of known neuroendocrine markers synaptophysin and PCSK1. Within cancers like breast and colon adenocarcinoma we identify separate ER+ and ER- sample clusters as well as MSI-H samples as separate and featuring different key TFs than MSI-L/MSS clusters.

Conclusion: Our approach identifies known drugs in ER+ breast cancer, Tamoxifen and Fulvestrant, in addition to the novel candidates GMX1777 and EP300 inhibitors as potential therapeutic agents.

Funding: This work was supported by a CURE Diversity Supplement to R01CA218668.

91 A High-Throughput Imaging Pipeline for the Quantitative Detection of DNA Damage in Peripheral Blood Mononuclear Cells (iCURE)

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Introduction/Background: DNA damage is a prominent biomarker in numerous diseases, including cancer and aging. Detection of DNA damage routinely relies on traditional imaging or cytometric methods. However, these methods are not ideally suited for large-scale, longitudinal and population studies that require analysis of large sample sets. We have developed a robust single-cell assay pipeline for detection of DNA damage by high-throughput imaging using the two major DNA damage markers 53BP1 and γH2AX.

Methods: The assay involves the immobilization of purified human peripheral blood mononuclear cells (PBMCs) on 384-well microplates, and the visualization of DNA damage response (DDR) activation using antibodies against the DNA-damage marker γH2AX and the DDR protein 53BP1, which accumulate as foci at sites of DNA damage, and which can be quantified by an automated image analysis pipeline.

Results: We demonstrate sensitive detection of DNA damage in a wide set of freshly isolated and cryopreserved primary human immune cells, including CD4+ and CD8+ T-cells, B-cells, and monocytes with low inter-assay variability.

Conclusion: These results establish a novel high-throughput assay which will be of use for the evaluation of DNA damage in large-scale studies.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

92 DNA Repair in HLRCC-Associated Renal Cancer: Investigating a Homologous Recombination Defect in FH-Deficient Cells (iCURE)

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Introduction/Background: Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is caused by inactivating mutations in the Krebs cycle enzyme fumarate hydratase (FH). Affected individuals develop leiomyomas and are at risk for development of an aggressive form of renal cancer. Elevated fumarate levels in FH-deficient cells are known to cause metabolic reprogramming, and more recently were proposed to cause defects in DNA damage and repair. Previous studies suggest homologous recombination (HR), a major DNA double-strand break repair pathway, is directly or indirectly suppressed in FH-deficient cells. Suppression of this high-fidelity repair pathway can lead to reliance on more error prone repair, such as non-homologous end joining (NHEJ). We are performing whole genome sequencing of HLRCC tumors to characterize potential HR defects as well as other repair defects through somatic mutational signature analysis. Although this repair deficiency is likely not the driver of carcinogenesis, we hypothesize mutation patterns associated with HR deficiency will be present in tumors if the pathway is indeed suppressed.

Methods: We are using whole genome sequencing to identify mutation patterns, previously described in the Catalogue of Somatic Mutations in Cancer (COSMIC) database, in HLRCC tumors. Our analysis will be comparing paired tumor/germline samples from different patients as well as multiple tumors within single patients.

Results: While preliminary data analyzing four HLRCC tumors show no evidence of large-scale genome rearrangements, we have observed some evidence of somatic mutational signatures associated with HR deficiency, as well as additional signatures of both known and unknown etiologies.

Conclusion: Additional tumor genome sequencing is required to achieve robust conclusions. The findings of this study will lead to a better understanding of DNA repair in HLRCC tumors and will identify vulnerabilities that can be targeted therapeutically.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

93 Precise Control of Immune Modulation Using DNA Scaffold-Mediated Biomaterial Functionalization (CPACHE U54 i3 Center)

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Introduction/Background: Synthetic materials displaying multi-modal ligands with exact chemiophysical properties can provide both valuable research tools for immunological studies and promising therapeutic strategies for immune modulation. However, precise chemical conjugation of multiple proteins on biomaterial surfaces is challenging.

Methods: Through DNA hybridization-mediated biomolecule loading, we achieved high density and precise ratiometric control of multiple ligands on biodegradable nano-/micro- particles. This DNA-scaffold method can be adapted to different synthetic and biological surfaces.

Results: We found increasing ratios of anti-CD3 to anti-CD28, 1:5, 1:3, 1:1, 3:1 to 5:1, on microparticles yielded a linear increase of ex vivo expansion of primary human CD4+ and CD8+ T cells until reaching a plateau at 3:1 ratio. For CD8+ T cells, the ratio of 3:1 resulted in the highest percentage of central memory cells, 51.4% vs. 14.4 for 1:5 ratio (n = 5 donors). Particle surface presentation of IL-2 using an anti-IL-2 antibody (in trans to CD3/28 particles) yielded ~3 fold more ex vivo expansion of CD4+ and CD8+ T cells in 14 days when compared to the equivalent dose of soluble IL-2. Using intratumoral injection of microparticles presenting a ligand for a synthetic Notch receptor, we locally induced chimeric antigen receptor (CAR) expression on systemically infused engineered T cells and observed CAR T cell killing of the injected tumors, while sparing the uninjected identical tumors in the contralateral flank.

Conclusion: These results highlight the potential of this platform in achieving better control of therapeutic cell manufacture and local tuning of immunotherapies. Ongoing work is using DNA origami-mediated patterning to dissect spatial requirements of various T-cell activating ligands to better understand critical parameters of T-cell activation with the goal to improve the design of immunotherapies.

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94 Epigenomic Landscape of Advanced Bladder Cancer and Rare GU Tumors from Patient Autopsy Samples (iCURE)

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Introduction/Background: Bladder cancer is the 6th most common type of cancer in the United States, with approximately 84 thousand new cases predicted in 2021. Despite FDA approval of multiple agents for advanced/metastatic bladder cancer in the past 5 years, many patients exhibit short-lived treatment responses and high mortality. Prior genomic studies have revealed high rates of mutation in epigenetic regulators. However, there is a limited understanding of the role of epigenetic dysregulation in disease progression and treatment response in GU tumors. We hypothesize that analysis of the epigenetic landscape will highlight dysregulated pathways, utilizing our autopsy repository of tumor tissue collected from patients with advanced GU cancers.

Methods: Our repository currently consists of 33 patients with urothelial carcinoma and other rare histologies of GU tumors (including bladder adenocarcinoma, small cell carcinoma of the bladder, and renal medullary carcinoma). Tissue chromatin immunoprecipitation/ Next Generation Sequencing (ChIP-Seq) was optimized for FOXA1 using prostate cancer patient-derived xenografts (PDXs) prior to application to autopsy samples. After pathology review of tumor purity and extent of necrosis, ChIP-Seq was performed for H3K27me3, H3K4me3, H3K27Ac. Data processing and analysis was performed with R/Bioconductor (Pipeliner package).

Results: ChIP-Seq performed on PDXs and 2 patients demonstrated the feasibility for generation of ChIP-Seq data of sufficient quality for subsequent analysis. H3K4me3 and H3K27me3 peak patterns at individual genes and by primary component analysis (PCA) are consistent with published TCGA molecular subtypes; super-enhancers identified correlated with previous analysis revealing HER2 amplification.

Conclusion: Epigenomic analysis will continue for additional autopsy patient samples, with potential inclusion of transcription factor targets for ChIP-Seq analysis. These analyses expand molecular profiling beyond treatment-naïve and early stage tumors queried in earlier studies. This epigenomic analysis, paired with subsequent validation and functional studies, will provide greater insight into GU cancer progression and opportunities for therapeutic intervention.

Funding: iCURE

95 A Reduction in O-glycan modification Induces Differentially Glycosylated CD44 to Promote Stemness and Metastasis in Pancreatic Cancer (Diversity Supplement)

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Introduction/Background: Glycans are post-translational modifications (PTMs) largely found on proteins required for normal biological processes and cellular function and shown to be a hallmark of cancer. A loss in C1GALT1 (Core-1 O-glycosyltransferase) was previously shown to enhance the properties of pancreatic cancer (PC). We hypothesize that O-glycan truncation accelerates metastatic properties of increased expression of self-renewal markers and features of pancreatic cancer stem cells (CSCs). This work provides a rationale for future design of glycoprotein targets with a unique PTM pattern to prevent and treat established metastasis and CSCs.

Methods: Human PC cell lines generated for CRISPR/Cas9-mediated knockout of C1GALT1, and tumor-derived PC cells, KPC (KrasG12D/+; Trp53R172H/+; Pdx-1-Cre) and KPCC (KrasG12D/+; Trp53R172H/+; C1galt1loxP/loxP; Pdx-1-Cre) were used in this study. We identified CD44 using an enrichment approach of Tn-antigen glycoproteins and confirmed its phenotype related to CSCs (tumorsphere, ALDH, Side-population) and association with truncated O-glycosylation (lectin enrichment, immunofluorescence). Lastly, a double knockout of C1GALT1 and CD44 in luciferase-positive cells was used for in vivo orthotopic injections into the pancreas of nude mice to assess tumor growth.

Results: Our results identify CD44 as the top differentially glycosylated protein in C1GALT1 KO cells across multiple human PC cells and tumor-derived animal cells. We observed upregulation of CSC self-renewal markers Nanog, KLF4, Sox9, OCT3/4, and other CSC-associated genes in C1GALT1 KO cells, correlating to increased side-population and tumorsphere analyses. By implementing a CRISPR/Cas9 double KO of CD44 and C1GALT, we observed a reduction in Nanog expression, which was reflected in decreased tumorsphere formation. Lastly, we observed decreased tumorigenic and migratory potential using in vivo and in vitro models.

Conclusion: Our findings begin to contextualize the contributions of aberrant glycosylation to accelerate cancer through enhanced characteristics of CSCs. Taken together, our results display a unique vulnerability for the development of effective therapeutic targets of pancreatic CSCs and metastasis.

Funding: R01 CA210637, R01 CA206444, P01 CA217798, U01 CA200466, and U01 CA210240.

96 Metabolic Convergence on Lipogenesis in RAS, BCR-ABL, and MYC-Driven Lymphoid Malignancies (K01)

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Introduction/Background: Metabolic reprogramming is a central feature in many cancer subtypes and a hallmark of cancer. Many therapeutic strategies attempt to exploit this feature, often having unintended side effects on normal metabolic programs and limited efficacy due to integrative nature of metabolic substrate sourcing. Although the initiating oncogenic lesion may vary, tumor cells in lymphoid malignancies often share similar environments and potentially similar metabolic profiles. We examined cells from mouse models of MYC, RAS, and BCR-ABL-driven lymphoid malignancies and find a convergence on de novo lipogenesis. We explore the potential role of MYC in mediating lipogenesis by 13C glucose tracing and untargeted metabolic profiling. Inhibition of lipogenesis leads to cell death both in vitro and in vivo, and does not induce cell death of normal splenocytes.

Methods: We analyzed RNA-seq data sets for common metabolic convergence in lymphoma and leukemia. Using in vitro cell lines derived in from conditional MYC, RAS, and BCR-ABL transgenic murine models and oncogene-driven human cell lines, we determined gene regulation, metabolic profiles, and sensitivity to inhibition of lipogenesis in lymphoid malignancies. We utilize preclinical murine models and transgenic primary model of T-ALL to determine the effect of lipogenesis blockade across BCR-ABL, RAS, and c-MYC-driven lymphoid malignancies.

Results: This study illustrates that de novo lipid biogenesis is a shared feature of several lymphoma subtypes. Using cell lines derived from conditional MYC, RAS, and BCR-ABL transgenic murine models we demonstrate shared responses to inhibition of lipogenesis by the acetyl-coA carboxylase inhibitor 5-(Tetradecloxy)-2-furic Acid (TOFA), and other lipogenesis inhibitors. We performed metabolic tracing studies to confirm the influence of c-MYC and TOFA on lipogenesis. We identify specific cell death responses to TOFA in vitro and in vivo and demonstrate delayed engraftment and progression in vivo in transplanted lymphoma cell lines. We also observe delayed progression of T-ALL in a primary transgenic mouse model upon TOFA administration. In a panel of human cell lines, we demonstrate sensitivity to TOFA treatment as a metabolic liability due to the general convergence on de novo lipogenesis in lymphoid malignancies driven by MYC, RAS, or BCR-ABL. Importantly, cell death was not significantly observed in non-malignant cells in vivo.

Conclusion: These studies suggest that de novo lipogenesis may be a common survival strategy for many lymphoid malignancies and may be a clinically exploitable metabolic liability.

Funding: DFL is/was funded by Tumor Biology Training grant (NIH 5T32CA009151-38), Stanford University (National Cancer Institute); Burroughs Wellcome Fund Postdoctoral Enrichment Award, Burroughs Wellcome Fund; Research Supplement Award (National Cancer Institute), 3U01CA188383-03S1; and the Mentored Research Scientist Development Award (K01) CA234453 (NCI). SS was supported by a Special Fellow Award from the Leukemia and Lymphoma Society and a Scholar award from the American Society of Hematology. Research reported in this publication included work performed in the mass spectrometry core supported by the National Cancer Institute of the National Institutes of Health under grant number P30CA033572. Oregon Health & Science University Shared Resources are supported by the Knight NCI Cancer Center Support Grant 5P30CA069533, RS support: NCI U01 grant CA224012, R01 CA186241, VS is supported by funds from the Brenden-Colson center for Pancreatic Care.

97 Engineering of Chimeric Antigen Receptors To Enhance Cytotoxicity Against Antigen-Low Leukemias (iCURE)

Mirazee, J.[1,2], Achar, S.[3], Su, A.[1], Phadke, I.[1,4], Dede, K.[1], Benzaoui, M.[1,4], Pouzolles, M.[1,4], Morally, J.[1], Altan-Bonnet, G.[3], Taylor, N.[1,4]

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Introduction/Background: Chimeric antigen receptors (CARs), when expressed on human T-cells, enable lysis of tumor cells via binding of CAR extracellular single-chain antibody variable fragment (scFv) to a tumor-associated antigen. The extracellular hinge connects the scFv to intracellular signaling domains, commonly derived from 41BB or CD28. CARs with a CD28 costimulatory domain have increased activation but decreased persistence while CARs with a 41BB costimulatory domain have decreased activation but increased persistence. Importantly, CARs with different hinge, transmembrane and costimulatory domains are able to achieve short-term remissions in patients with CD19+relapsed/refractory B-cell leukemias/lymphomas. However, up to 50% of patients treated with CAR T-cells relapse with antigen-negative or -low leukemia. We hypothesize that modular interactions between scFv, hinge, transmembrane and co-stimulatory domains regulate cytotoxicity against antigen-low leukemia.

Methods: We generated 18 CAR constructs representing all combinations of hinge, transmembrane, and costimulatory domains found in FDA-approved anti-CD19 CARs. Using a high-throughput robotics system, we tested CAR reactivity against leukemia lines expressing varying quantities of CD19.

Results: We found that CARs containing a CD28-derived hinge (28H) were significantly more efficacious at killing CD19-low leukemia than those containing a CD8a-derived hinge (8H), regardless of the costimulatory domain. Notably though, modulating hinges resulted in disparate outcomes in anti-CD22 CARs; in CARs containing the 41BB, but not the CD28, costimulatory domain, an 8H conferred a significantly enhanced ability to kill CD22-low tumors.

Conclusion: All together, these demonstrate a novel role for the CAR hinge domain in regulating responsiveness against antigen-low tumor and will inform future iterations of CAR design for the treatment of relapsed patients.

Funding: The following work was made possible through the generous support of the National Institutes of Health-Johns Hopkins University Graduate Partnerships program, the iCURE program, and the NIH Intramural Program.

98 Peptidyl Arginine Deiminase 4 Is a Key Regulator of Tissue-Resident Peritoneal Macrophage Phenotype in the Tumor Microenvironment (Diversity Supplement)

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Introduction/Background: Tissue-resident macrophages are transcriptionally distinct and this heterogeneity is largely epigenetically driven. Peptidyl arginine deiminase 4 (PAD4) is an epigenetic enzyme that converts arginine residues on protein targets into citrulline, changing the charge of the residue from positive to neutral which has fundamental consequences on protein structure and function. PAD4 citrullinates histones and this is sufficient to decondensing chromatin. PAD4 histone citrullination-mediated modification of chromatin accessibility has major consequences on transcriptional programming. Normally, tissue-resident peritoneal macrophages (TRPMØ) maintain homeostasis and exhibit anti-inflammatory phenotypes. We observe that the loss of PAD4 induces a robust pro-inflammatory phenotypic switch in TRPMØ. We hypothesize that PAD4 serves as a repressor of pro-inflammatory macrophage activities as means to maintain tolerance which characterizes the immune polarization of TRPMØ.

Methods: To study this, we mainly harvest fresh TRPMØ from wild-type and PAD4-KO mice and then determine differences in phenotype by observing protein and mRNA expression. In vitro studies include observing basal differences between fresh WT and KO samples and differences after treatment with activating agents such as lipopolysaccharide (LPS) or interferon-□ (IFN□). In addition, we use cell lines to study the phenomena that we encounter in the primary TRPMØ. In vivo studies are being conducted in which we inoculate WT and PAD4-KO with intraperitoneal tumors and monitor metastasis growth.

Results: We find that tumor growth is reduced in PAD4-deficient mice and that the TRPMØ harvested from the ascites of the PAD4-KO mice are more pro-inflammatory, exhibiting M1-like features.

Conclusion: This suggests that PAD4 activity in TRPMØ contributes to tolerance towards tumor growth and therefore targeting PAD4 may constitute an avenue for antagonizing peritoneal metastasis.

Funding: This work is funded by the NCI Diversity supplement which is apart of the R01 grant of my principal investigator Weiping Zou.

99 Long Non-Coding RNA *RAMS11*:Chromobox 4 Protein Interaction Promotes Metastatic Colorectal Cancer Progression (K22)

Silva-Fisher, J.[1,2], Dang, H.[1,2,3], White, N,[1], Strand, M.[4], Krasnick, B.[4], Rozycki, E.[1], Jeffers, G.[1], Grossman, J.[4], Highkin, M.[1], Tang, C.[1], Cabanski, C.[5], Eteleeb, A.[1], Mudd, J.[4], Goedegebuure, S.[4], Luo, J.[2,6], Mardis, E.[7], Wilson, R.[7], Ley, T.[1,2], Lockhart, A.[8], Fields, R.[2,4], Maher, C.[1,2,3,9]

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Introduction/Background: Colorectal Cancer (CRC) is the most common gastrointestinal malignancy in the U.S. Approximately 50% of patients with CRC develops metastatic disease (mCRC). To date, the mechanisms driving mCRC remain poorly characterized and has focused on the deregulation of protein-coding genes. Here, we focus on the emerging class of long non-coding RNAs (lncRNAs) that are greater than 200 nucleotides in length and have been found serve as critical regulators in metastasis. We hypothesize that lncRNAs can be used as predictive biomarkers and potential therapeutic targets. Our objective is to characterize mCRC lncRNAs and assess their clinical applicability.

Methods: We performed transcriptome sequencing and analysis of matched normal, primary, and distant metastatic CRC patient samples. We compared metastatic samples to normal and primary to identify differentially expressed (DE) lncRNAs. We assessed aggressive phenotypes *in vitro* and *in vivo* of the top DE lncRNA, *RAMS11.* Next, we used an FDA-approved drug high-throughput viability assay to determine biological significance. Further, we assessed RNA protein binding with RNA immunoprecipitation qPCR and RNA pull-down experiments and used chromatin immunoprecipitation qPCR to validate chromatin occupancy.

Results: We identified 148 DE lncRNAs in metastasis, termed RNAs Associated with Metastasis (*RAMS*). We focused our study on *RAMS11* as it was the only lncRNA associated with poor survival. Decreased expression of *RAMS11* in CRISPR knock-out and transient knockdown cell lines mitigates cellular invasion, colony formation, and liver metastasis in mice. Our high-throughput drug panel showed *RAMS11* expression impacted cellular sensitivity to topoisomerase inhibitors, specifically TOP2α. This led to identify that *RAMS11* overexpression increased TOP2α protein expression via binding to Chromobox protein 4 (CBX4*).*

Conclusion: These data highlight the potential of *RAMS11*-dependent CBX4 regulation of *TOP2α* to induce mCRC. Furthermore, our data indicates *RAMS11* as an important biomarker to select mCRC patients that may benefit from topoisomerase inhibitor treatment.

Funding: JSF received funding from a National Cancer Institute Career Transition Award to Promote Diversity K22 (K22CA241329) and Washington University School of Medicine Molecular Oncology Training Grant (T32CA113275). CAM received funding from The Alvin J. Siteman Cancer Center Siteman Investment Program, The Foundation for Barnes-Jewish Hospital Cancer Frontier Fund, National Cancer Institute Cancer Center Support Grant P30 CA091842, and the Barnard Trust.

100 Prospective Analysis of Circulating Inflammatory Proteins in Lung Cancer Risk (iCURE)

Taylor, S.[1], Arauz, R.[1], Zingone, A.[1], Steinwandel, M.[2], Blot, W.[2,3], Ryan, B.[1]

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Introduction/Background: Lung cancer deaths account for more cancer deaths than colon, breast, and prostate cancers combined. While smoking remains the min risk factor for lung cancer, not all smokers will develop lung cancer, creating the need for biomarkers for lung cancer risk. Furthermore, smoking incidence does not affect all populations equally as African American (AA) men experience a higher incidence of lung cancer. We previously found that AAs have an altered inflammatory profile at the time of lung cancer diagnosis using the NCI-UMD case control study. We hypothesized that there would be significantly altered levels of specific inflammatory proteins in patients who developed lung cancer when compared to those who did not. We also hypothesized that there may be unique proteins associated with lung cancer risk in AAs.

Methods: To this end, we measured the levels of 26 inflammatory proteins in the serum of patients enrolled in the PLCO (prostate, lung, colorectal, and ovarian, n = 234) and SCC (Southern Community Cohort, n= 576) case-control prospective studies. We used the Mesoscale Discover multiplex assay to measure proteins associated with inflammation and immunity. Following quality control methods, protein concentrations were categorized into median, and quartiles.

Results: Cox proportional hazard regression modeling to estimate hazard ratios and 95% confidence intervals produced four inflammatory proteins associated with increased risk of lung cancer in both studies independently, and in pooled analysis.

Conclusion: These proteins were associated with pro-inflammatory signaling, and vascular injury, and target multiple cell types including immune, epithelial, and endothelial cells. Our findings demonstrate that circulating inflammatory proteins measured in serum may serve as a biomarker for lung cancer risk. Monitoring these levels in patients at high risk for lung cancer such as smokers or those with familial history of lung cancer may aid in early detection and improved survival.

Funding: This work is supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute (NCI), Center for Cancer Research (CCR), Center to Reduce Cancer Health Disparities (CRCHD) and the Intramural Continuing Umbrella of Research Experiences (iCURE) program.

Mock Review

NCI CRCHD Virtual Mentored Mock Review
Thursday, July 22, 2021
1:00 pm – 5:00 pm
Group #1 (Behavioral/Epigenetics/Health Disparities/Cancer Prevention/Epidemiology)

Meeting Roster
Enhancing Prevention Pathways Toward Tribal Colorectal Health

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Consultants are required to absent themselves from the room during the review of any application if their presence would constitute a conflict of interest.

Mock Review

NCI CRCHD Virtual Mentored Mock Review
Thursday, July 22, 2021
1:00 pm – 5:00 pm
Group #2 (Cancer Immunology/Biology, Breast Cancer)

Meeting Roster
Role of GATA3 in Transcriptional Pathways Suppressing Breast Cancer Metastasis

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Mock Review

NCI CRCHD Virtual Mentored Mock Review
Thursday, July 22, 2021
1:00 pm – 5:00 pm
Group #3 (Immunotherapy, Pancreatic Cancer, Metastasis)

Meeting Roster
Enhancing Immune Therapy in Pancreatic Cancer by Targeting IL-6

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CRCHD Resources

Overview

- Website
- Contact Information and Staff Bios
- Twitter: @NCICRCHD
- LinkedIn: NCI Center to Reduce Cancer Health Disparities (CRCHD)

CRCHD Funding Opportunities

- Administrative Supplements to Support Cancer Disparity Collaborative Research (PA-18-842)
  LeeAnn Bailey, M.B.B.S., M.S., Ph.D.
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- Basic Cancer Research in Cancer Health Disparities (R01 Clinical Trial Not Allowed)
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- Comprehensive Partnerships to Advance Cancer Health Equity (CPACHE) (Collaborative U54 Clinical Trial Optional)
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- Diversity Research Supplements (PA-21-071)
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  Laritza Rodriguez, M.D., Ph.D.
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- Exploratory/Developmental Grants Program for Basic Cancer Research in Cancer Health Disparities (R21 Clinical Trial Not Allowed)
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- Exploratory Grant Award to Promote Workforce Diversity in Basic Cancer Research (R21 Clinical Trial Not Allowed)
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CRCHD Resources

- Feasibility and Planning Studies for Development of Specialized Programs of Research Excellence (SPOREs) to Investigate Cancer Health Disparities (P20 Clinical Trial Optional)
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- Feasibility Studies to Build Collaborative Partnerships in Cancer Research (P20 Clinical Trial Not Allowed)
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- Mechanisms of Disparities in Chronic Liver Diseases and Cancer (R21)

- Mechanisms of Disparities in Chronic Liver Diseases and Cancer (R01)

- Mentored Career Development Awards (K01 Independent Clinical Trial Not Allowed, K01 Clinical Trial Required; K08 No Independent Clinical Trials, K08 Clinical Trial Required)
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- Minority Patient-Derived Xenograft (PDX) Development and Trial Centers (M-PDTCs) (U54)
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- Transition Career Development Award (K22 No Independent Clinical Trials, K22 Clinical Trial Required)
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- Notice of Special Interest in Research on the Health of Sexual and Gender Minority (SGM) Populations (NOT-MD-19-001)
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- Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers

- Research on the Health of Transgender and Gender Nonconforming Populations: R21, R01
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- Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship to Promote Diversity in Health-Related Research (Parent F31-Diversity) (PA-21-052)
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- Support of Competitive Research (SCORE) Research Advancement Award (SC1)
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- Support of Competitive Research (SCORE) Pilot Project Award (SC2)
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NIH Resources and Tools

NIH Grant Application Resources

- NIH Grants and Funding Information: grants.nih.gov/grants/oer.htm
  - Find funding
  - How to apply
  - Explore NIH-funded research (RePORT)
- Center for Scientific Review: public.csr.nih.gov
- Early Stage and Early Established Investigator Policies: grants.nih.gov/policy/early-stage/index.htm

NIH/NCI Training Resources

NCI Resources for Researchers: cancer.gov/research/resources

Extramural

- NIH Extramural Diversity: extramural-diversity.nih.gov
- Center for Cancer Training: cancer.gov/grants-training/training/about
- Continuing Umbrella of Research Experiences (CURE): cancer.gov/about-nci/organization/crchd/diversity-training/cure

Intramural

- Office of Intramural Training and Education: training.nih.gov
- NIH Intramural Research Program: irp.nih.gov
  - NCI Center for Cancer Research: ccr.cancer.gov
  - NCI Division of Cancer Epidemiology and Genetics: dceg.cancer.gov
- Cancer Prevention Fellowship Program: cpfp.cancer.gov
- Intramural Continuing Umbrella of Research Experiences (iCURE): cancer.gov/about-nci/organization/crchd/diversity-training/icure
- Lasker Clinical Research Scholars: nih.gov/research-training/lasker-clinical-research-scholars
- Stadtman Tenure Track Investigators: irp.nih.gov/careers/trans-nih-scientific-recruitments/stadtman-tenure-track-investigators

NIH Grants Process
At-a-Glance

National Institutes of Health Grants Process
At-A-Glance

Planning, Writing, and Submitting

Planning: Applicant should start early, collect preliminary data, and determine internal deadlines.

→ *Writing:* Applicant often begins writing application several months prior to application due date.

→ *Submitting:* Applicant organization submits most applications to NIH through the Federal portal, *Grants.gov*.

Receipt and Referral

1 – 3 Months

Applications compliant with NIH policies are assigned for review by the Division of Receipt and Referral in the Center for Scientific Review (CSR).

→ CSR assigns application to an NIH Institute/Center (IC) and a Scientific Review Group (SRG).

→ Scientific Review Officer (SRO) assigns applications to reviewers and readers.

Peer Review

4 – 8 Months

Initial Level of Review: SRG members review and evaluate applications for scientific merit.

→ *Priority Scores:* Available to Principal Investigator in eRA Commons.

→ *Summary Statement:* Available to Principal Investigator in eRA Commons.

→ *Second Level of Review:* Advisory council/board reviews applications.

Award

9 – 10 Months

*NIH Requests additional information needed *Just-In-Time* for award.

Pre-Award Process: IC grants management staff conducts final administrative review and negotiates award.*

→ *Notification of Award:* Institute/Center issues and sends Notice of Award (NoA) to applicant institution/organization.

→ ***Congratulations! Project period officially begins!***

Post-Award Management

Administrative and fiscal monitoring, reporting, and compliance

Visit: http://grants.nih.gov/grants/grants_process.htm for more about the NIH grants process

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