The 13th National Symposium on Prostate Cancer

And

Dr. Sidney A. McNairy, Jr.
Student Symposium

September 17 – 19, 2023
Thomas W. Cole, Jr., Research Center for Science and Technology
Clark Atlanta University

Sponsored by the National Institute on Minority Health and Health Disparities Research Centers in Minority Institutions (RCMI) and Clark Atlanta University Center of Excellence for Cancer Research and Therapeutic Development
September 18, 2023

Dear Symposium Guests:

Welcome to the 13th National Symposium of the Center for Cancer Research and Therapeutic Development (CCRTD) at Clark Atlanta University (CAU). At Clark Atlanta University, we believe that research and education cannot be decoupled. The research and scholarly activity done at CAU is essential for providing our students with a world-class educational experience and bringing valuable insights to the world. This biennial prostate cancer symposium, attended by world-renowned prostate cancer researchers, clinicians, investigators, and industry leaders, is a testament to the thriving academic environment and vibrant creative community that is the hallmark of CCRTD.

CCRTD continues its mission of serving the African-American community by providing opportunities for high-caliber basic and translational research; training scientists in cancer research; and providing an educational environment for community outreach, prevention, early detection, and treatment of prostate cancer, which disproportionately affects African-American men. This could not have happened without the passionate leadership of Dr. Shafiq Khan, who served diligently in the role of Center Director for eighteen years.

This remarkable symposium brings together the many talents and passions of investigators and clinicians from across the globe devoted to addressing prostate cancer from bench to bedside. We are here to stimulate discussion among scientists, researchers, physicians, and others involved in the battle against prostate cancer and to help reduce the disparity faced by Black men living with this dreadful disease.

The work, training, and education being done at CCRTD and in each of your labs and institutions are critical to moving the needle forward in cancer research, innovation, and care. As you share your work, you plant seeds for a bright future that will reduce health disparity, encourage a more diverse cancer workforce, and lead the way in prostate cancer research.

Sincerely,

George T. French, Jr.
President
Sidney A. McNairy, Jr., Ph.D., D.Sc., L.H.D
Former Member of the Senior Executive Service
Associate Director, NCRR and
Director, Capacity Building Branch, NIGMS
National Institutes of Health

Dr. Sidney A. McNairy, Jr. is an award-winning academician and senior-level federal grants administrator. He received a B.S. degree in Chemistry/Mathematics from LeMoyne-Owen College; he received both the Master’s and Doctorate degrees in biochemistry with minors in both organic chemistry and human physiology from Purdue University. During his graduate studies his research focused on the isolation and chemical/biological characterization of tri-terpenoid glycosides. He has done further studies at Columbia University and the Harvard Kennedy School of Government.

He was a Professor of Chemistry at Southern University in Baton Rouge and Director of the Health Research Center. While there, he was a visiting scientist at Charles Pfizer, Eli Lilly, Standard Oil of California, Centers for Disease Control, and the George C. Marshall Space Flight Space Center. Thereafter, he spent over 25 years at the National Institutes of Health as a member of the Senior Executive Service developing and managing programs that focused on the support for both basic and clinical research. Among his numerous awards are nine honorary doctorate degrees including Clark Atlanta University.
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Dr. Daqing Wu

Symposium Co-Chairs
Dr. Nathan Bowen
Priscilla Bakari

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Dr. Shafiq Khan (Co-Chair)
Priscilla Bakari
Dr. Nathan Bowen
William Fleming
Tony Griffin
Dr. Cimona Hinton
Dr. Teri Platt
Pamela Smith
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Dr. Bekir Cinar
Nicholas Cook
Dr. Shafiq Khan
Dr. Jing Song
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Dr. Silvia Caggia
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   Kofi Khamit-Kush
   Dr. Xin Li

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   Jazzmin Owen
13th National Symposium on Prostate Cancer and Dr. Sidney A. McNairy Jr. Student Symposium

Clark Atlanta University

September 17-19, 2023

Sunday, September 17th, 2023

Opening Reception: 6:00 – 8:00 pm

6:00 – 8:00 pm Omni Atlanta Hotel at CNN Center
100 CNN Center, Atlanta, GA

Monday, September 18th, 2023

Thomas W. Cole, Jr. Center for Science and Technology

7:45 – 8:00 am Gather and Depart from Hotel Lobby for Transport to CAU

8:30 – 9:00 am Breakfast
Cole Boardroom

Opening Ceremony and Keynote Address: 9:00 – 10:30 am

Chair: Dr. Daqing Wu
Co-Chair: Dr. Nathan J. Bowen

9:00 – 9:10 am George T. French, Jr., JD, PhD
President

9:10 – 9:20 am Charlene D. Gilbert, PhD
Provost and Senior Vice President for Academic Affairs

9:20 – 9:30 am Sidney A. McNairy, Jr., PhD, DSc, LHD
Former Associate Director, National Center for Research Resources and Director, Capacity Building Branch, NIGMS, National Institutes of Health

9:30 – 10:15 am Keynote Address
Martin Gleave, MD, FRCSC, FACS
Vancouver Prostate Center
Targeting Drivers of Resistance in Advanced Prostate Cancer: Evolving Towards Precision Oncology

10:15 – 10:30 am Q&A

10:30 – 10:40 am Coffee Break
Cole Boardroom
Monday Morning Session: 10:40 am – 12:10 pm

Chair: Dr. Zhengxin Wang
Co-Chair: Nicholas Cook

10:40 – 11:10 am
Ana Aparicio, MD
MD Anderson Cancer Center
Developing Therapeutic Strategies for Aggressive Variant Prostate Cancers

11:10 – 11:25 am
Q&A

11:25 – 11:55 am
Wendy Short-Bartie, JD
Bristol Myers Squibb
Health Equity: Delivering Innovation to All

11:55 – 12:10 pm
Q&A

Lunch and Poster Session: 12:10 – 2:00 pm

12:10 - 2:00 pm
Lunch
2nd Floor Exhibition Hall

12:10 – 2:00 pm
Poster Session
2nd Floor Hallway

Monday Afternoon Session I: 2:00 – 3:45 pm

Chair: Dr. Shafiq Khan
Co-Chair: Dr. Jing Song

2:00 – 3:00 pm
Research Discussion—Funding Opportunities; What We Need to Significantly Bring Down Prostate Cancer Death Toll (Bench and Bedside)

Funding Opportunity Participants:
2:00-2:30 pm: Rina Das, PhD
NIH/NIMHD (via Zoom)
NIMHD program and funding opportunities

2:30-3:00 pm: Howard R. Soule, PhD
Prostate Cancer Foundation

3:00 – 3:30 pm
Steven P. Balk, MD, PhD
Harvard Medical School/ Beth Israel Deaconess Medical Center
Mechanisms Driving Progression to Castration-Resistant Prostate Cancer

3:30 – 3:45 pm
Q&A

3:45– 3:55 pm
Coffee Break
Cole Boardroom
Monday Afternoon Session II: 3:55 – 6:15 pm

Chair: Dr. Bekir Cinar
Co-Chair: Dr. Silvia Caggia

3:55 – 4:25 pm

Jiaoti Huang, MD
Duke University
Cellular Heterogeneity of Prostate Cancer Contributes to Therapy Resistance and Disease Progression

4:25 – 4:35 pm

Q&A

4:35 – 4:50 pm

Crystal Byrd
Graduate Student
Clark Atlanta University
Infiltrating Bruton’s Tyrosine Kinase Expressed B Cells Effects On Prostate Cancer Migration

4:50 – 5:00 pm

Q&A

5:00 – 6:15 pm

Career Discussion Activities with Speakers and Students
Cole Boardroom (Interested individuals can remain if they would like to connect with the speakers)
Alternative Activity: Tour of CCRTD (Ana Cecilia Millena)

6:15 – 8:30 pm

Dinner
2nd Floor Exhibition Hall

8:30 – 8:45 pm

Gather and Depart from CAU for Transport to Hotel

Tuesday, September 19th, 2023
Thomas W. Cole, Jr. Center for Science and Technology

7:45 – 8:00 am

Gather and Depart from Hotel Lobby for Transport to CAU

8:30 – 9:00 am

Breakfast
Cole Boardroom

Tuesday Morning Session I: 9:00 – 10:30 am

Chair: Dr. Geou-Yarh Liou
Co-Chair: Dr. Teri Platt

9:00 – 9:30 am

Remi M. Adelaiye-Ogala, PhD
University at Buffalo
Kinase Mediated Posttranslational Modification in the Dynamic Interplay of Compensatory Hormone Nuclear Receptors in Treated-Resistant Prostate Cancers

9:30 – 9:45 am

Q&A
9:45 – 10:15 am  Allen C. Gao, MD, PhD  
University of California Davis  
Targeting Aberrant Androgen Signaling Overcoming Treatment Resistance to AR-Targeted Therapy

10:15 – 10:30 am  Q&A

10:30 – 10:45 am  Coffee Break  
Cole Boardroom

Tuesday Morning/Midday Session II: 10:45 am – 12:35 pm

Chair: Dr. Cimona Hinton  
Co-Chair: Dr. Xin Li

10:45 – 11:15 am  Evan T. Keller, DVM, PhD  
University of Michigan  
Bad to the Bone: Prostate Cancer Bone Metastasis

11:15 – 11:30 am  Q&A

11:30 – 12:00 noon  Bamidele A. Adesunloye, MD  
City of Hope Cancer Treatment Centers  
Recent Advances in the Management of Castration-Resistant Prostate Cancer

12:00 – 12:15 pm  Q&A

12:15 – 12:30 pm  Dawel Zong  
Graduate Student  
The University of Georgia  
Encapsulation of Cas13a into Extracellular Vesicles to Target Prostate Cancer Cells

12:30 – 12:35 pm  Q&A

Closing Ceremony and Student Awards: 12:35 – 1:10 pm

12:35 – 12:50 pm  Announcement for Poster Winners (awards, photos, etc.)

12:50 – 1:10 pm  Closing Ceremony

1:10 pm  Boxed Lunch, Networking and Departure
Posters Preview Table
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<td>GLOBAL CHANGES IN RBPS AND MRNA INTERACTIONS DURING PROSTATE CANCER PROGRESSION</td>
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<td>Robin Brice</td>
<td>GATA3 AND E2F6 NEGATIVELY REGULATE WDR77 EXPRESSION IN PROSTATE CANCER CELLS, INHIBITING CELL GROWTH</td>
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<td>Rarnice Johnson</td>
<td>Gai2 PLAYS A VITAL ROLE IN RAC1 DEPENDENT ACTIVATION OF WAVE2 AXIS AND ESSENTIAL FOR CELL MIGRATION IN PROSTATE CANCER CELLS.</td>
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<td>Bethany Smith</td>
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Speakers' Biographical Sketches and Abstracts
Martin Gleave, CM, MD, FRCSC.

Director, Vancouver Prostate Centre/Chief Executive Officer, PC-TRiADD/Distinguished Professor and Head, Department of Urologic Sciences, UBC/BC Leadership Chair in Prostate Cancer Research

Vancouver Prostate Centre, Dept of Urologic Sciences, University of British Columbia

Dr. Gleave is a Distinguished Professor and Chairman of the Department of Urologic Sciences at UBC, and a British Columbia Leadership Chair. He is Co-Founder and Director of the Vancouver Prostate Centre, now a UBC and National Centre of Excellence, publishing > 600 papers with >55,000 citations, an H-Index of 122, and attracting >$120M in research funding. Dr. Gleave is a surgeon-scientist whose research characterizes molecular mechanisms mediating treatment resistance in cancer, and designing co-targeting strategies to improve cancer control. He patented several anti-cancer drugs and founded OncoGenex Pharmaceuticals to develop OGX-011 and OGX-427, inhibitors of cytoprotective chaperones clusterin and Hsp27 which progressed to Phase III and Phase II trials world-wide. OncoGenex was awarded Canadian Biotech Company of the Year in 2010. Dr. Gleave also recently co-founded TRiADD and Sustained Therapeutics.

In 2015, Dr. Gleave was named the Goldenberg Family Chair in Urologic Sciences. In 2018, Dr. Gleave was appointed to the Order of Canada for his leadership role in developing new treatments for prostate cancer and for his research on mechanisms mediating treatment resistance in cancer. In 2020, he was inducted as a Fellow in the National Academy of Inventors.

Dr. Gleave is the recipient of numerous awards, including the 2022 SIU Mostafa M. Elhilali Award, 2018 Dr. Chew Wei Memorial Prize in Cancer Research, the Huggins Medal from the SUO in 2018, the Richard Williams Award from the AUA in 2017, the Barringer Medal from the American Association of GU Surgeons; the Eugene Fuller Award from the American Urological Association in 2013; the Aubrey Tingle Prize from the Michael Smith Foundation for Health Research; and the NCIC William Rawls Award for contributions to cancer control in Canada; He was appointed a Distinguished University Scholar at UBC in 2003 and awarded a BC Leadership Chair in 2005, the 2006 BC Biotech Award for Innovation and Achievement, and the 2007 BC Innovation Council Frontiers in Research Award.
Targeting Drivers of Resistance in Advanced Prostate Cancer: Evolving Towards Precision Oncology

Androgen receptor (AR) pathway inhibitors (ARPI) induce profound and sustained responses in most men with advanced prostate cancer. However, recurrence is inevitable and associated with reactivation of the AR and progression to a castration-resistant prostate cancer (CRPC) phenotype. AR reactivation can occur directly through genomic alterations of AR (amplification, LBD mutations, truncated variants), indirectly via co-factor and co-chaperone deregulation, and supported by stress-driven induction of a myriad of overlapping cellular survival pathways. An unintended consequence of potent ARPI includes stereotypic expansion of heterogeneity of phenotypic states, including cells with heightened plasticity and divergent differentiation that confer resistance to ARPI. Genomic sequencing of metastatic biopsies from SU2C Dream Team studies helped define the molecular landscape of CRPC, prognostic biomarkers, actionable targets, and emergent resistance mechanisms. For example, increased plasticity following ARPI is greater in tumours where RB1 and/or TP53 is inactivated. Detection of DNA repair aberrations like BRCA2 help select patients for PARP inhibitors, while mismatch repair gene defects and microsatellite instability predict for response to PD-L1 immunotherapy.

Despite advances, many challenges persist for precision oncology for prostate cancer, including contributions of tumour heterogeneity, stochastic timing and cooperation of multiple driver gene aberrations, and diverse resistant mechanisms beyond DNA alterations. Indeed, the premise of precision oncology is predicated on detecting actionable genomic alterations and their adaptive evolution during treatment; however, spatial- and temporal-heterogeneity as well as feasibility of bone-metastatic biopsies limits profiling in mCRPC. “Liquid biopsies” using plasma circulating tumor DNA (ctDNA) address some of these challenges, detecting mutations or copy-number changes in most patients that highly correlate with metastatic tissue biopsies, including clinically-actionable alterations in the AR, DNA damage response, CTNNB1, and PI3K genes. Alterations DNA repair, TP53, and RB are negatively prognostic for response duration to ARPI in a phase II crossover trial enrolling 202 patients with mCRPC randomized to ABI followed by ENZA (arm A), or ENZA followed by ABI (arm B). We developed custom targeted ctDNA panels to detect genomic alterations as prognostic biomarkers in metastatic PCa now used in randomized clinical trials (NCT02125357, NCT02254785). ctDNA allows feasible monitoring of drivers of clonal evolution and treatment resistance to enable a precision oncology framework of biomarker-stratified treatments specifically targeting emergent vulnerabilities. Recent developments using new bioinformatic approaches and sequencing panels to study nucleosome footprints in ctDNA can be used to infer mRNA abundance in synchronous metastases. This novel liquid approach has identified treatment-induced changes in AR pathway transcriptional activity and evidence of neuroendocrine (NE) lineage, paving the way to the use of liquid biopsy for rapid and early detection of enhanced plasticity and treatment resistance.

This presentation will review the genomic hallmarks of advanced prostate cancer and disease sub-types that may be susceptible to specific targeted drugs, as well as current challenges confront precision oncology in prostate cancer, including detailed investigation of less common ‘tail’ alterations, contributions and effects of co-occurring lesions, the use of umbrella trials to guide development of more precise, molecularly-driven and combination treatment strategies.
Ana Aparicio, M.D.
Professor, Department of Genitourinary Medical Oncology MD Anderson Cancer Center

Ana Aparicio is a Professor in the Department of Genitourinary Medical Oncology. She specializes in the treatment of advanced prostate cancer. In order to provide a framework for the study of the androgen indifferent prostate cancers, she defined the ‘aggressive variant prostate cancers’ (AVPC, a subset of prostate cancers of heterogeneous morphologies that share the atypical and virulent clinical behavior and molecular features of the histologically defined androgen receptor-negative small cell or poorly differentiated neuroendocrine prostate carcinomas). Her clinical and translational research focuses on understanding and developing novel therapies for this subset, that has limited therapeutic options and a dismal prognosis. Through a series of prospective clinical trials and parallel studies in preclinical models, she defined a molecular signature for the AVPC that has been linked to resistance to androgen signaling inhibitors and to benefit from platinum-based chemotherapies. The importance of this work lies in that it serves as the foundation for a much needed biologically-based, clinically-relevant molecular classification of prostate cancer that will increase the efficiency of clinical and translational research, permit effective and individualized treatment strategies for the lethal variants and spare patients with non-lethal variants the morbidity of unnecessary treatments.

Developing Therapeutic Strategies for Aggressive Variant Prostate Cancers

A subset of prostate cancers responds poorly to existing androgen signaling inhibitors (so-called ‘androgen-indifferent’ tumors). They remain with limited treatment options and a dismal prognosis, largely due to the absence of biomarkers that can identify them to enable the development of therapies specific to their underlying biology. The ‘aggressive variant prostate cancers’ (AVPC) were defined as a group of tumors of heterogeneous morphologies that share clinical features with the small cell or poorly differentiated neuroendocrine prostate carcinomas (NEPC), to provide a framework for the development of biomarkers and therapies specific to the androgen indifferent prostate cancers. Novel biomarkers and therapeutic strategies that are emerging for the androgen indifferent prostate cancers will be discussed.
Wendy Short Bartie, JD
Senior Vice President/Chief of Staff Bristol-Myers Squibb

Wendy Short Bartie - A compassionate and strategic leader, her career journey has taken many turns, but her path has always been clear – the commitment to help people - first as a lawyer/public defender, and then as a pharmaceutical industry professional, continuing to act as a voice for those with unmet needs and unequal access. Prior to joining BMS, Wendy was Vice President and Head of Commercial Operations for US Oncology at Merck. In this capacity, Wendy was responsible for leading the Sales, Key Accounts, Market Access, Pricing and Policy organizations within the US Business Unit. Previously, Wendy served as Associate Vice-President of Global Marketing for Genitourinary Cancers (GU), including renal cell carcinoma, prostate cancer and bladder cancer and as the Global Disease Lead for Women’s Cancer. Prior to joining Merck, Wendy held a range of commercial roles with increasing responsibility in sales, business analytics and marketing in cardiovascular neuroscience, osteoporosis, lung cancer, supportive care and chronic myeloid leukemia at various companies including Novartis, Heron Therapeutics, Johnson and Johnson, Pharmacia and Abbott Labs. Prior to her career in pharma, Wendy was a Public Defender in Washington, DC and Bronx, New York. Wendy received her Bachelor of Arts from Clark Atlanta University and her Juris Doctor from Loyola University Chicago, School of Law. Wendy is an HBA Rising Star and was recognized by HBA as a Luminary in 2020 and 2023.

Health Equity: Delivering Innovation to All

The past few decades have evidenced some of the best innovation in the war on cancer. Yet communities of color, which often have the poorest outcomes, are not able to readily access innovation. The purpose of the discussion is to take a look at the disparate outcomes for Black people with cancer and to discuss solution for ensuring access to treatment and resources that can save lives.
Dr. Rina Das serves as Director of the Division of Integrative Biological and Behavioral Sciences at NIMHD. In her current role, she works with the Division of Integrative Biological and Behavioral Sciences team on promoting research to understand and address the various factors that play a role in health disparities among different underserved populations. She lends her expertise to a wide array of NIMHD programs that seek to improve minority health and health disparities, including translational sciences, cancer health disparities, research on the intersection of biological and social sciences, social epigenomics, sleep health disparities, liver disease disparities, and immigrant health. She has led programs on liver disease and cancer disparities, lung cancer disparities among other programs in cancer research. Prior to joining NIMHD, Dr. Das served as a program director at the Center to Reduce Cancer Health Disparities at the National Cancer Institute. She managed programs on cancer health disparities research that focused on community-based interventions among various racial/ethnic minority populations, the role biological factors play in cancer disparities, and grants that enable training to improve diversity in the research workforce. Dr. Das also served as a scientific review officer at the National Heart, Lung, and Blood Institute.
Howard R. Soule, Ph.D.
Executive Vice President & Chief Science Officer Prostate Cancer Foundation

Howard R. Soule, PhD, since 1997 and as Chief Science Officer, coordinates global academic, government and biopharmaceutical sector research activity and is responsible for the implementation of the Prostate Cancer Foundation global research strategies. He is also a member of the Department of Defense Prostate Cancer Research Program Integration Panel. Dr. Soule has been with the Foundation for over 20 years. Dr. Soule received a PhD from Baylor College of Medicine in Virology and Epidemiology and was a Post-Doctoral Fellow in Immunology and Vascular Biology at the Scripps Research Institute.
Stephen Balk, M.D., Ph.D.

Physician at Beth Israel Deaconess Medical Center
Professor of Medicine at Harvard Medical School
Co-director of the Prostate Program and Prostate SPORE at the Dana Farber/Harvard Cancer Center

Steven Balk, M.D., Ph.D., is a Staff Physician at Beth Israel Deaconess Medical Center, Professor of Medicine at Harvard Medical School, and co-director of the Prostate Program and Prostate SPORE at the Dana Farber/Harvard Cancer Center. Dr. Balk’s laboratory conducts basic and translational research in cancer biology, with a primary interest in prostate cancer. A major focus has been on the androgen receptor (AR), a steroid hormone receptor that is critical for most prostate cancers. His lab first established the role of AR mutations and of intratumoral androgen synthesis as mechanisms of resistance to AR targeted therapies, and the lab is currently focused on mechanism of resistance to available AR antagonists. A long-term objective is to improve upon current androgen deprivation therapies to more fully ablate AR activity, and identify and target further vulnerabilities.

Mechanisms Driving Progression to Castration-Resistant Prostate Cancer

Prostate cancer that recurs after androgen deprivation therapy (castration-resistant prostate cancer, CRPC) is in most cases still dependent on androgen receptor (AR). AR in these tumors can be further suppressed by agents such as abiraterone or AR antagonists, but patients still invariably progress. A subset become AR independent, but the majority continue to have high levels of AR activity. Mechanisms contributing to this activity include amplification of the AR gene, mutations in the AR ligand binding domain, increased intratumoral androgen synthesis, and activation of multiple signaling pathways may directly or indirectly enhance AR activity. Finally, increasing evidence indicates that expression of AR splice variants that are constitutively active due to deletion of the ligand binding domain contribute to persistent AR activity. These mechanisms that drive resistance to AR targeted therapies and possible therapeutic approaches will be discussed.
Jiaoti Huang, M.D., PhD.

Department Chair of Pathology/Professor Duke University

Dr. Huang earned his medical degree from China, and PhD from NYU. He was a postdoc at NYU and Yale, did residency in Pathology at NYU and fellowship at Memorial Sloan-Kettering Cancer Center. He was on faculty at the University of Rochester and UCLA. He is currently Distinguished University Professor, Johnston and West Endowed Chair, and Chairman of the Department of Pathology at Duke University.

Dr. Huang is a practicing pathologist with clinical expertise in genitourinary tumors. His research laboratory investigates the molecular mechanisms, biomarkers and novel therapies for prostate cancer. Dr. Huang has published over 300 manuscripts. His research lab has been continuously funded by federal agencies and many private foundations including NCI, DOD, Prostate Cancer Foundation, American Cancer Society, AACR, Mike Slive Foundation and Stand Up to Cancer.

**Cellular Heterogeneity of Prostate Cancer Contributes to Therapy Resistance and Disease Progression**

Prostate cancer (PCa) is composed of luminal type cancer cells expressing androgen receptor (AR) and a minor component of AR negative neuroendocrine (NE) cells. Hormonal therapy targeting AR inhibits luminal cells to cause tumor regression but the NE cells are spared, leading to therapy resistance and tumor progression. Thus, targeting NE cells is critical to achieving sustained disease control.

We discovered that NE cells express a cell surface cytokine receptor CXCR2 which plays a critical role in NE cell function. Targeting CXCR2 in combination with AR inhibition achieves superior therapeutic efficacy but leukopenia is an undesired side effect. We further discovered that oncofetal protein glycopican-3 (GPC3) is also specifically expressed by NE cells and targeting GPC3 can inhibit NE cells without harming normal cells. Thus, targeting heterogeneous populations of PCa will benefit patients who have exhausted currently available treatment options.
Remi M. Adelaiye-Ogala, Ph.D.
Assistant Professor, Division of Hematology and Oncology in the Department of Medicine, Adjunct Research Assistant Professor, Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo

Dr. Remi Adelaiye-Ogala is an Assistant Professor in the Division of Hematology and Oncology in the Department of Medicine and an Adjunct Research Assistant Professor in the Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo. She earned her BSc in Biochemistry at the State University of New York, at Fredonia, New York, and her Ph.D. in Cancer Pathology at the Roswell Park Cancer Institute Division, University at Buffalo. Afterward, Dr. Adelaiye-Ogala pursued her postdoctoral training at the National Cancer Institute, NIH, Bethesda, MD, in cancer biology, epigenetics, and genomics.

Dr. Adelaiye-Ogala’s research is focused on investigating mechanistic determinants of therapeutic resistance in genitourinary cancers and developing optimal therapeutic strategies for durable clinical outcomes. Her research group engages in basic and translational research in genitourinary cancers, emphasizing molecular regulation of signaling pathways in prostate and renal cancers and therapeutic strategies to overcome drug resistance mediated by genetic and epigenetic mechanisms. She has expertise in state-of-the-art multi-omics assays, drug screens, and the development/maintenance of patient-derived xenografts models to evaluate the efficacy of novel pipeline agents in 3D organoid cultures and animal models. Dr. Adelaiye-Ogala’s team leverages information from multi-omics assays and drug screens with established human cell lines and patient-derived xenograft models to identify optimal therapeutic strategies to manage the disease better. Throughout her research trajectory, Dr. Adelaiye-Ogala’s expertise and contributions in epigenetics, genomics, and cancer biology and meticulously evaluating novel and optimal treatment modalities in preclinical settings have led to numerous impactful publications, awards, and grants. In addition, she serves as a reviewer on NIH grants, foundation awards, and several journals.

Outside of her scientific contributions, she mentors several undergraduate, graduate, and medical students from represented and underrepresented groups within and outside her academic institution. In addition, she serves on the Clinical and Translational Science Institute (CTSI) K Scholar Program, the University of Buffalo Leadership Team, co-leads University at Buffalo,
Kinase Mediated Posttranslational Modification in the Dynamic Interplay of Compensatory Hormone Nuclear Receptors in Treatment-Resistant Prostate Cancers

Prostate Cancer remains the most common cancer in men and the second leading cause of cancer-related deaths in the US. The androgen receptor (AR) signaling axis is critical for prostate cancer pathogenesis and all subsequent phases of disease progression. Although initial success with androgen deprivation therapy and AR-targeted agents such as enzalutamide or abiraterone, most patients inevitably relapse due to therapeutic resistance. An evolving concept that contributes to our understanding of resistance to androgen deprivation therapy (ADT) or androgen receptor (AR) antagonists in advanced prostate cancer is the ability of cells to evade AR blockade and turn on compensatory hormone receptor signaling for survival. Preclinical and clinical studies by us and others have demonstrated that induction of glucocorticoid receptor expression confers resistance to AR-targeted therapy. Elegant studies by others in the field have shown that posttranslational modifications on nuclear hormone receptors can amplify or alter their canonical activity to favor cancer cell survival or drug resistance. One such PTM is phosphorylation. Finally, our group has found that the inhibition of oncogenic kinases blocks the induction of these hormone receptor signaling and halts their activity, consequently re-sensitizing treatment-resistant disease to AR-targeted therapy.
Dr. Gao is currently the Ralph deVere White Endowed Professor, Director of Urologic Research, Department of Urology and UC Davis Comprehensive Cancer Center at University of California at Davis. Dr. Gao received his Ph.D. in Molecular Biology at The University of Texas MD Anderson Cancer Center Houston, TX and his MD at Sichuan Medical College, China. He completed a postdoctoral fellowship in the Department of Urology and Oncology at Johns Hopkins University School of Medicine, Baltimore, MD. Dr. Gao served as an Assistant Professor of Urology (1998-2002) at University of Pittsburgh, Associate Professor and Professor (2002-2007) of Medicine and Pharmacology at Roswell Park Cancer Institute and SUNY at Buffalo, New York prior to relocating to the University of California at Davis in 2007. Dr. Gao served as President (2018-2019) of Society of Basic Urologic Research (SBUR). Dr. Gao also serves on the Editorial Board of several journals including Prostate, American J of Pathology, PLOS One, and American J of Clinical and Experimental Urology.

Dr. Gao’s research focuses on understanding the molecular changes associated with progression and treatment resistance to prostate cancer. Particular emphasis includes microRNAs, aberrant androgen receptor activation by cytokines and transcriptional factors such as Stat3 and NF-kB, targeting cell signaling pathways (AR, IL-6 and Stat3), mechanisms of drug resistance, targets and drug discovery, and experimental therapy in prostate cancer. Dr. Gao’s lab discovered novel inhibitors of androgen receptor variants (AR-V7) and enzymes of intracrine androgen synthesis such as AKR1C3, and identified several novel resistance mechanisms to enzalutamide/abiraterone/taxanes/PARPi including AR variants, NF-kB/p52, IL-6/Stat3, intracrine androgens/AKR1C3, and ABCB1. Dr. Gao has published over 130 peer-reviewed articles in prostate cancer. His research findings have translated into several clinical trials for treating advanced prostate cancer.
Targeting Aberrant Androgen Signaling Overcoming Treatment Resistance to AR-Targeted Therapy

Currently the approved therapies for CRPC include systemic drugs (docetaxel and cabazitaxel) and agents that target androgen signaling. Over time, however, all patients inevitably develop resistance to treatment and their disease will continue to progress. In this talk, I will present several key mechanisms that give rise to treatment resistance to anti-androgens including expression of constitutively active variants of the androgen receptor, such as AR-V7; and intracrine androgens and overexpression of androgen synthesis enzymes like AKR1C3. Treatment strategies are being developed to target these pathways and reintroduce drug sensitivity. By better understanding the mechanisms by which drug resistance develops, improved treatment strategies will be made possible.
Evan T. Keller, D.V.M., PhD.
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Dr. Keller is the Richard and Susan Rogel Professor of Oncology and serves as Director of the Single Cell Spatial Analysis Program; Director of Research Cores Office, and Associate Director of the Rogel Cancer Center Shared Resources. Dr. Keller obtained a Doctor of Veterinary Medicine (D.V.M.) (University of California, Davis) and Ph.D. in Developmental Biology (University of Wisconsin, Madison). He is Board Certified in the American College of Veterinary Internal Medicine (Oncology). Dr. Keller has published more than 250 publications and his research focus is on the tumor microenvironment. His work extends from basic through clinical studies.

Bad to the Bone: Prostate Cancer Bone Metastasis

The skeleton is the most prevalent metastatic site in men with hormone-refractory prostate cancer (PCA). PCA bone metastatic lesions are painful, resulting in diminished quality of life. It is well-recognized that PCAs establish and thrive in the skeleton due to cross-talk between the bone microenvironment and tumor cells. In this presentation, we will discuss mechanisms through which the tumor microenvironment is altered by the tumor to enhance progression of bone metastases. For example, primary PCa tumors have been shown to educate the bone microenvironment through exosomes, resulting in progression of bone metastases. Additionally, tumor growth in bone induces pressure that results in mechano-transduction which promotes metastatic growth in a positive feedback cycle. Understanding the mechanisms that contribute to localization and progression of PCa growth in bone will help towards developing therapies to prevent or diminish prostate cancer metastasis.
Dr. Bamidele Adesunloye is a genitourinary medical oncologist at City of Hope, Atlanta. He received his MD degree from the University of Ilorin in Nigeria. He completed internal medicine training and a Master of Science program at Morehouse School of Medicine in Atlanta. He then went on to complete fellowship training in medical oncology and hematology at the National Institutes of Health in Bethesda, Maryland. Dr Adesunloye has authored several book chapters and multiple journal articles. He has served on numerous boards and committees, including the National Cancer Institute Central Institutional Review Board. Dr Adesunloye served as a faculty member at Morehouse School of Medicine and Indiana University School of Medicine, Lafayette. He has been recognized with several awards and honors.

Recent Advances in the Management of Castration Resistant Prostate Cancer (CRPC)

The discovery of the link between androgenic steroids and prostate cancer by Charles Huggins and Clarence Hodges ushered in an era of androgen deprivation therapy in the management of prostate cancer. The unexpected consequence of this therapeutic intervention is the evolution of the castration resistant phenotype of prostate cancer (CRPC). Although synonymously referred to as hormone refractory prostate cancer, this phenotype is still driven by a ligand-activated androgen receptor, and it has a substantial amount of residual intracellular androgen. These characteristics were exploited in the development of the first and second generations of androgen receptor pathway signaling inhibitors. Multiple other pathways have been targeted in drug development, leading to an unprecedented drug approval by the United States Food and Drug Administration (FDA) in the past two decades.
Poster Abstracts
THERAPEUTIC POTENTIAL OF STATINS IN COMBATTING ADVANCED STAGE METASTATIC PROSTATE CANCER (MPCA)

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Prostate cancer (PCa) ranks as the second leading cause of cancer-related deaths among men in the United States. The early stage of prostate cancer, known as adenocarcinoma, can be effectively managed with conventional treatments such as chemotherapy, radiation therapy, surgery, and androgen deprivation therapy (ADT). Advanced stages, notably castration-resistant prostate cancer (CRPC) and neuroendocrine prostate cancer (NEPC) pose formidable therapeutic challenges. These challenges arise from a fundamental shift in androgen dependency as prostate cancer cells progress from early to advanced metastatic stages, such as NEPC. This study focuses on investigating the therapeutic potential of statins, specifically in combating the most aggressive form of prostate cancer, NEPC. Statins are a class of drugs used daily by millions worldwide to help lower blood cholesterol and prevent cardiovascular (CV) disease. Previous research has suggested that statin users exhibit a reduced risk of advanced and fatal prostate cancer. We conducted an extensive investigation into the cytotoxic effects of various statins, including Fluvastatin, Rosuvastatin, Simvastatin, Lovastatin, Atorvastatin, Mevastatin, Pravastatin, and Pitavastatin across three prostate cancer cell lines representing three stages of the disease (adenocarcinoma, CRPC, and NEPC). Our findings reveal that within adenocarcinoma cell line models (LNCap and ARCap), none of the statins significantly affected cell survival. In the intermediate-stage of prostate cancer (CRPC), as represented by DU145, C4-2, and CWR22Rv1 cell lines, a modest sensitivity to Pitavastatin, Fluvastatin, and Simvastatin was observed, particularly within the CWR model. However, NEPC models (PC3 and LNCap-Trpo2) displayed pronounced cytotoxic responses, with Pitavastatin, Fluvastatin, Simvastatin, and Lovastatin being the most potent. Interestingly, Atorvastatin and Rosuvastatin, known for their high HMGCR affinity and cholesterol-reducing capabilities, were less efficacious than their counterparts. These observations suggest that some statins exhibit selective toxicity against aggressive NEPC cell line models. The potential optimization of statin derivatives may offer considerable therapeutic benefits for NEPC patients, highlighting the clinical merit of these drugs and supporting their consideration for clinical repurposing. These findings provide a foundation for developing enhanced therapeutic approaches targeting aggressive prostate cancer variants.

GATA3 AND E2F6 NEGATIVELY REGULATE WDR77 EXPRESSION IN PROSTATE CANCER CELLS, INHIBITING CELL GROWTH

Center for Cancer Research and Therapeutic Development, Clark Atlanta University, Atlanta Georgia.

Prostate cancer is one of the most prevalent cancers among men worldwide, and its development is closely linked to aberrant androgen receptor (AR) signaling. The WD repeat domain 77 (WDR77) protein p44, an AR-interacting protein, plays a critical role in prostate gland development and maintenance. However, dysregulation of WDR77 expression has been associated with prostate tumorigenesis. In this study, we aimed...
to investigate the regulatory roles of two transcription factors, GATA 3 and E2F6, on WDR77 expression in prostate cancer. We observed that GATA 3 and E2F6 mRNA and protein expression levels increased during prostate development, while WDR77 expression decreased. Co-expression analysis revealed a negative correlation between GATA 3 and WDR77 in prostate cancer. To further investigate their regulatory roles, we transiently transfected GATA 3 and E2F6 into prostate cancer cells, which resulted in a dose-dependent reduction of WDR77 expression and cell viability. Subsequent chromatin immunoprecipitation and gel shift assays confirmed the binding of GATA 3 and E2F6 to the WDR77 promoter. Luciferase assays demonstrated that GATA 3 and E2F6 repress WDR77 promoter activity by binding to specific sites in the promoter region. Taken together, our findings indicate that GATA 3 and E2F6 negatively regulate WDR77 expression in prostate cancer cells, leading to the inhibition of cell growth. These results provide valuable insights into the molecular mechanisms governing WDR77 expression in prostate cancer and offer potential therapeutic targets for the treatment of this prevalent disease.

INfiltrating Bruton’s Tyrosine Kinase Expressed B Cells Effects on Prostate Cancer Migration

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Prostate cancer is the most common type of cancer found in senior males in the United States. Although prostate cancer grows slowly within the prostate glands, because of a lack of efficient treatments at the appropriate timing, cancer cells eventually become aggressive and metastatic. Many factors support the progression of this cancer, such as external signaling factors received from surrounding cells, such as B cells. As a part of the adaptive immune system, B cells play a role in the production of antibodies in the immune system. The maturation of B cells is due to the activation of a non-receptor kinase, Bruton’s Tyrosine Kinase (BTK). Preliminary data from our lab showed that infiltrating B cells expressing BTK were at a higher density near cancer cells in prostate cancer tissues. Upon this finding, we hypothesize that BTK-expressed B cells will support the progression of prostate cancer cells through BTK signaling. In this study, we overexpressed BTK in B cells to study the migration of prostate cancer cells through a co-culture system. We also evaluated the secretion factors of the BTK-B cells and studied the effects of those secretion factors on the migration of our prostate cell lines. Our findings showed an increase in migration of prostate cancer cells when they were co-cultured with BTK-B cells, and when they were treated with the recombinant proteins targeting those secretion factors. Our overall findings from this project would reveal key elements of the signaling pathways of BTK-B cells to promote prostate cancer migration.

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CHEMOTHERAPY INCUCES PROSTATE CANCER CELL MIGRATION, WHICH IS BLOCKED BY INHIBITORS OF Ga2 PROTEIN.

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Chemotherapy is normally the first line of treatment in cancer patients. Depending on the cancer types and the stages of the disease, this strategy can be effective and curative. However, the development of distant metastases is quite common in cancer patients. Recent studies have shown that chemotherapy can induce the cancer cells to escape from death and migrate to distant sites to form metastasis in several cancer types. However, not much is known about the effects of chemotherapy on metastasis in prostate cancer patients. In this study we evaluated the effects of several chemotherapeutic drugs, such as taxanes (docetaxel), anti-androgens (enzalutamide and bicalutamide) and histone deacetylase (HDAC) inhibitors (SAHA and SBI-I-19), on cell migration in PC3 and LNCaP prostate cancer cells. We observed that all treatments induced cell migration in LNCaP cells. Similarly, treatment with Docetaxel caused a significant increase in cell migration in androgen receptor (AR)-negative PC3 cells. Previously, we have shown that heterotrimeric G-protein subunit alpha2 (Ga2) is essential for cell migration and invasion in prostate cancer cells and small molecule inhibitors targeting Ga2 inhibit the migratory and invasive behavior of several cancer cell types. In the present study, anti-androgens significantly upregulated the levels of Ga2 protein in LNCaP cells and simultaneous treatments with Ga2 inhibitors blocked prostate cancer cell migration induced by all chemotherapeutic agents. These results show for the first time that chemotherapy may induce prostate cancer cell migration, and a combination treatment with Ga2 inhibitors and chemotherapy could blunt the capability of cancer cells to migrate and form metastasis.

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CHRONIC IL-1 CONFERS NOVEL CONSTITUTIVE P62-KEAP1 INTERACTION

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The tumor microenvironment is replete with inflammatory cytokines that can be anti- or pro-tumorigenic. The inflammatory cytokine, interleukin-1 (IL-1) is elevated in PCa patient tissue and serum and is associated with disease progression and metastasis. However, the molecular mechanism of IL-1 in PCa progression is not fully elucidated. I found that chronic exposure to IL-1 can transform castration-sensitive PCa cells into castration-insensitive PCa cells, suggesting that chronic IL-1 exposure can confer a growth advantage for PCa cells under androgen deprivation therapy (ADT).
To gain insight into how chronic IL-1 might confer a growth advantage under ADT, we performed mass spectrometry and immunoprecipitation (IP) western blot on serum starved PCa cells. Our analyses revealed that chronic IL-1 exposure causes PCa cells to evolve a constitutive p62-KEAP1 interaction. The p62-KEAP1 interaction reportedly promotes NRF2 antioxidant signaling. Therefore, I sought to determine the regulation of NRF2 signaling in our chronic IL-1 induced CRPC cell line models (IL-1 sublines). Despite constitutive p62-KEAP1 binding, the chronic IL-1 sublines do not show elevated canonical NRF2 signaling. However, I discovered constitutive upregulation of select NRF2 antioxidant genes, which I also found to be regulated by serum starvation. Unexpectedly, siRNA silencing suggests that p62 and KEAP1 regulate select NRF2 genes independently under serum starvation conditions. Thus, experiments are underway to determine the significance of this novel regulation in our chronic IL-1 CRPC sublines. I predict that the p62-KEAP1 interaction has a NRF2-independent function under serum starvation conditions. Thus, chronic IL-1 may select for PCa cells that evolve novel roles for p62 and KEAP1 that provide a growth advantage under ADT.

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GLOBAL CHANGES IN RBPS AND MRNA INTERACTIONS DURING PROSTATE CANCER PROGRESSION

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Prostate cancer (PC) is a leading cause of cancer in men in the United States and worldwide, disproportionately affecting men of African ancestry. The etiology and molecular mechanism contributing to lethal human PC remain poorly understood. RNA binding proteins (RBPs) controlled all aspects of RNA biogenesis, and dysregulated RBPs are linked to human diseases, including cancer. However, the global changes in RBP-mRNA interactions during PC progression are unknown. Here, we have investigated the patterns of RBPs and polyA-mRNA interaction in the castration-sensitive LNCaP and castration-resistant C4-2 PC cell lines. Our enhanced-RNA interactome capture assay combined with mass spectroscopy (MS) revealed that LNCaP and C4-2 cells showed distinct RBP-mRNA interaction patterns in steady-state and androgen-treated conditions. Also, we have studied the interaction between Yes-associated protein 1 (YAP1) and nucleophosmin (NPM1) RBP. Androgen increased NPM1 and mRNA interaction, and NPM1 is part of the YAP1 multiprotein complex, as revealed by MS-based proteomics approaches. Our proximity ligation assay showed that androgen hormone signaling regulated the interaction between YAP1 and NPM1. Besides, our GST-pulldown demonstrated that NPM1 binds the proline-rich region domain of YAP1, whereas the WW/SH3 domain of YAP1 mediates the interaction in C4-2 cells. Genetic silencing of NPM1 reduced PC cell growth in culture. Furthermore, the upregulation of NPM1 correlates with prostate adenocarcinoma and metastasis. These observations suggest that changes in RBP and RNA interaction patterns may play a critical role in PC progression and recurrence.

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PROINFLAMMATORY CYTOKINE CXCL-8 (INTERLEUKIN-8) IS A POTENTIAL DRIVER OF CADMIUM-INDUCED PROSTATE CARCINOGENESIS

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Cadmium (Cd) is a toxic heavy metal ubiquitous in nature and an industrial pollutant. Abnormally high levels of cadmium are found in human prostate tissues. Further, studies on rodents showed cadmium exposure causes liver and prostate cancers. The mechanism of carcinogenesis caused by Cd remains unclear. We previously reported that the chemokine IL-8 drives cancer progression in prostate cancer (PCa) and is a prognostic marker for biochemical-PCa recurrence. The present work tested the hypothesis that chronic cadmium exposure induces upregulation of proinflammatory cytokines, such as IL-8, which could facilitate carcinogenesis and cancer progression. The non-transformed prostate epithelial cell line RWPE-1 was continuously exposed to Cadmium chloride (CdCl₂) for up to one year. The CdCl₂ exposed cultures were analyzed regularly for inflammatory changes and cellular transformation. The studies included changes in cell proliferation by MTT and clonogenic assays. Production of cytokines (IL-8, IL-1β, IL-6, and others), increase in activity of Nuclear Factor-kB (NF-kB), and pro-tumorigenic factors, e.g., VEGF-A and B, Matrix metalloproteinase (MMP) 2 & 9, cellular motility and invasive potential. RWPE-1 cells exposed to CdCl₂ showed increased proliferation starting in four weeks and up to 2-fold by nine weeks. Cyclin D1, B1, and E were also increased. Further, clonogenic growth was enhanced with larger colonies in exposed cells. While un-exposed RWPE-1 cells did not express IL-8, it was the first cytokine to increase, followed by activation of NF-kB (p65-rel), VEGF-A, & B and MMPs. Gene silencing of IL-8 suppressed motility, invasion, and survival activity. Cancer induction in the prostate is an insidious Cd exposure toxicity and lacks preventive measures. These studies may provide a window to explore preventive measures by silencing IL-8 mediated chronic inflammation. Funding: GCC, MCGDF, & DOD-TERP Grant No. TX220325.

A CASE AND CONTROL GENETIC PROFILE OF TISSUE AND SERUM IN AFRICAN AMERICAN MEN

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Prostate cancer is the most common non-cutaneous cancer among men. The relative risk is increased by 2-3-fold in men with 1 or more 1st degree relative with a history of family of prostate cancer. In the United States, African American men have the highest incidence and mortality rate of prostate cancer. Globally, men of African descent are more likely to die from prostate cancer than any other ancestral groups. Studies have shown that tumor subtypes and microenvironment play a significant role in ancestral disparities of prostate cancer survival. We performed Immunohistochemistry (IHC) and RNA seq analysis, and Spatial
transcriptomics on African American tissue and serum samples, with a focus on HMGA2, which has been shown promote EMT, invasion, and metastasis in cancer. Our sample set included 3 benign and 10 prostate cancer tumors from African Americans and Kenyan. IHC markers showed high HMGA2 staining within epithelial cells of the prostate cancer tissue. However, RNA seq results showed HMGA to be non-significantly down-regulated in tumor samples. The most differentially expressed (DE) gene, however, was SNORD116-18. Studies have shown SNORD116-18 expression to be associated with chronic lymphocytic leukemia in distinguishing prognostic groups. This finding may be a pathway of interest for further studies. RNA seq of serum gene set enrichment analysis of the most differentially expressed genes within the serum showed overlap with inflammation pathways gene for upregulated DE genes and Methylation Pathway for downregulated DE genes. We are currently analyzing the data from Spatial transcriptomics.

Further analysis on more samples from African Americans tissue will be used to validate findings.

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Gαi2 PLAYS A VITAL ROLE IN RAC1 DEPENDENT ACTIVATION OF WAVE2 AXIS AND ESSENTIAL FOR CELL MIGRATION IN PROSTATE CANCER CELLS.

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Gαi2 is a heterotrimeric G protein subunit, classified into Gs, Gi/o, Gq, G12 in the form of activated Ga-GTP and Gβγ subunits that are required for signal transduction in response to activation of G-protein coupled receptors (GPCRs). Gαi2 protein is essential for cell migration in prostate cancer cells, in response to both oxytocin and EGF, acting via GPCR and PTKR, respectively. Cell migration is regulated by intracellular proteins; the most important proteins belong to the Rho family of GTPases, such as RhoA, Rac1 and Cdc42. The knockdown of Gαi2 does not cause any reduction in basal Rac1 activity in both PC3 and DU145 cells and had only marginal effects on EGF-induced increase in Rac1 activity, therefore Gαi2 may be involved in the regulation of cell motility and invasion at a step which is independent or downstream of Rac1 activation. We hypothesize, Gαi2 effects are exerted at the level of Rac1-dependent F-actin polymerization and branching. We studied Gαi2 effects on proteins activated by Rac1, specifically Wave2 and Arp 2/3. We transfected PC3 empty vector and PC3 Rac1 constitutively active stable cells with control siRNA or Gαi2 siRNA to knockdown endogenous Gαi2 expression. The western blot analysis showed Rac1 dependent activation of Wave2 and Arp 2/3 are impaired in the absence of Gαi2. Next, we overexpressed constitutively active form of Gαi2 (Gαi2-Q205L) in PC3 parental cell lines. The result showed that when PC3 cells are transfected with Gαi2-Q205L the migration rate in these cells is significantly increased. In the parallel experiment we used a specific Gαi2 inhibitor, which resulted in attenuation of Gαi2-Q205L effects on cell migration in PC3 cells.

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THE ARYL HYDROCARBON RECEPTOR MAY MEDIATE THE DOWNSTREAM TRANSCRIPTION OF GENES RELEVANT TO PROSTATE CANCER PROGRESSION, APOPTOSIS AND LIPID METABOLISM

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The aryl hydrocarbon receptor (AhR) is a nuclear transcription factor and xenobiotic sensor reported to mediate diet-induced obesity and is both upregulated and constitutively active in high-grade prostate cancer. AhR activity has also been reported to contribute to proliferation and potentially disease progression in C4-2 cells (Powell et al. 2015). To determine if the aryl hydrocarbon receptor mediates transcription of genes pertinent to cancer progression, we performed an RNA-seq analysis in C4-2 AhR knockdown cells and the vehicle control. When a fold-change cutoff of ±1.5 and an adjusted p-value (p-adj) <0.05 were used, data analyses revealed several differentially expressed genes (DEGs), i.e. LEPROT, CHAC1/2, GDF11/15, CDKN2, FAS, FASTKD, ATF1/3, CCNL2, and CCNG2 with known functions involving the cell cycle, apoptosis, epigenetic modifications, tumor aggressiveness, and interestingly – lipid metabolism. Recent evidence demonstrates significant changes in the expression profile of many of these genes in response to treatment with chemotherapeutics, specifically bromocriptine (Wu et al 2023). In murine models AhR has been shown to promote diet-induced obesity coupled with metabolic dysregulation leading to obesity, which has been reported to cause malignant behaviors in prostate cancer. Leptin, a pleiotropic obesity-associated adipokine, is significantly overexpressed in mCRPC tissues. Our lab previously reported an integrative bioinformatics analysis using TCGA data (n=498) to explore the role of AHR and leptin receptor (LEPR) in prostate cancer, which revealed AHR and LEPR mRNA expression positively correlate in a subset of prostate cancer patients (P<0.05, Pearson: 0.68, R^2=0.46). We also confirmed AhR inhibits bortezomib and docetaxel -mediated apoptosis of C4-2 cells (data not shown). Further understanding of the potential interactions between metabolism and drug treatment should lead to a better understanding of the complex network of factors influencing prostate cancer progression and lead to more effective therapeutics for patients.

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YAP1 ASSOCIATES WITH THE EPHA3 RECEPTOR TYROSINE KINASE TO PROMOTE PROSTATE CANCER PROGRESSION

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Metastatic prostate cancer is morbid and lethal, and the mechanisms contributing to this deadly disease are largely unknown. The disparity in our knowledge poses a significant barrier to developing effective therapeutics against this disease. Evidence suggests that Ephrin receptor A3 (EPHA3) tyrosine kinase signaling is critical in prostate cancer progression. However, the role and mechanism need to be better
understood. Recently, we have demonstrated that YAP1, in concert with the TEAD1 transcription factor, controls EPHA3 expression downstream of the Hippo pathway. Here, we investigated the relationship between YAP1 and EPHA3 expression in prostate cancer and offered a possible mode of action by which EPHA3 could lead to aggressive prostate cancer behavior. Our comprehensive analysis, encompassing both computational assessments of publicly available data and immunohistochemistry experiments, unveiled a positive correlation between YAP1 and EPHA3 expression within prostate tumor samples. EPHA3 depletion reduced cell growth and increased responsiveness to enzalutamide in castration-resistant prostate cancer C4-2 cells in both 2D and 3D cultures. Mechanistically, EPHA3 depletion reduced the levels of GTP-bound RHOA protein and phospho-ERK1/2, resembling the impact of inhibiting ROCK1/2. EPHA3 depletion also attenuated the EMT transcription factors ZEB1/2 and cancer stem cell marker CD44 while increasing CXCR4 expression. Furthermore, quantitative PCR analysis of ethnically distinct prostate cancer cell lines reveals divergent patterns of Ephrin receptor expression, including EPHA3. Given the regulatory role of YAP1 and EPHA3 in immune cell infiltration within the tumor microenvironment, targeting the YAP1-EPHA3 axis presents a promising avenue for therapeutic intervention in advanced prostate cancer cases and reducing disparities in tumor burdens.

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THE KEY ROLE OF NUDT5 (NUDIX HYDROLASE 5) IN CHEMO-RESISTANT PROSTATE CANCER

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Prostate cancer (PCa) is one of the most common types of cancer in men. Many PCa patients respond well to traditional anti-hormonal or first line treatment; however, many men relapse and begin to demonstrate resistance to these traditional PCa therapies. These resistances are a major obstacle in the clinical management of PCa and other cancers. NUDT5, an enzyme, has been linked to key processes in nucleotide metabolism and cancer. We aimed to unveil role of NUDT5 in PCa, drug resistant PCa.

Design: We investigated NUDT5 expression in prostate cancer cell lines C4-2B (androgen-independent), C4-2B TaxR (Resistant to docetaxel), C4-2B MDVR (enzalutamide-resistant) and C4-2B AbiR (abiraterone-resistant) compared with normal/benign prostate epithelial cells BPH1 using Western blot. We also used proteomic analysis with cell lines C4-2B, C4-2B (TaxR), C4-2B (MDVR) and C4-2B AbiR. Each sample was harvested in triplicate and the resulting data analyzed using Perseus. We test docetaxel IC50 with NUDT5 siRNA treated chemo-resist cell line C4-2B TaxR. We also investigated NUDT5 inhibitor TH5427 IC50 in C4-2B TaxR cells. Results: 1. Proteomic analysis found that NUDT5 was upregulated significantly in the one chemo and two Anti-hormone resistant cell lines. Especially, expressed higher in C4-2B-MDVR cells. 2. NUDT5 protein western blot analysis in BPH1 and C4-2B Parental, C4-2B-TaxR, C4-2B-Abiraterone and C4-2B-MDVR found that NUDT5 expression was upregulated. 3. Docetaxel tested in treated C4-2B TaxR cell line with NUDT5 SiRNA. The cells growth suppression was seen in the cell line. The cell growth inhibition followed a dose-dependent fashion. 4. NUDT5 inhibitor TH5427 suppressed c4-2b TaxR cells growth. The cell growth inhibition followed a dose-dependent fashion too. The studies showed that NUDT5 might play a key role in PCa progression towards therapeutic-resistant. That overexpression of NUDT5 promotes PCa progression and could be explored as a new drug target to overcome drug resistance.
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A NOVEL SKP1 INHIBITOR HAS POTENT PRECLINICAL EFFICACY AGAINST METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

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Background: Metastatic, castration-resistant prostate cancer (mCRPC) directly contributes to the mortality and morbidity of prostate cancer. It is imperative to identify new molecular targets and discover effective therapeutic agents against lethal mCRPC.

Methods: We developed a novel small-molecule anticancer compound named GH501. The in vitro cytotoxicity of GH501 was evaluated in the NCI-60 human cancer cell panel and human mCRPC cell lines. Molecular targets of GH501 were investigated using various molecular and cellular approaches. The in vivo efficacy of GH501 against mCRPC was evaluated in clinically-relevant xenograft models.

Results: GH501 effectively inhibited the in vitro proliferation of NCI-60 human cancer cell lines and established mCRPC cell lines at nanomolar potency by inducing cell cycle arrest and apoptosis. Mechanistically, GH501 might bind S-phase kinase-associated protein 1 (Skp1) and disrupt the physical interaction between Skp1 and S-phase kinase-associated protein 2 (Skp2), thereby affecting multiple oncogenic signals implicated in mCRPC progression. As a lead compound, GH501 had excellent preclinical safety. In animal studies, GH501 monotherapy effectively inhibited the skeletal and subcutaneous growth of four mCRPC xenografts with heterogeneous genetic backgrounds.

Conclusion: These results indicate that GH501 is a promising lead compound for the treatment of mCRPC and warrant further preclinical development.

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TARGETING ENDOGLIN AND FGFR3 SIGNALING TO REDUCE ANDROGEN-TARGETED THERAPY RESISTANCE IN PROSTATE CANCER CELLS

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Prostate cancer (PCa) is the second-leading cause of cancer-related death in men. One in six African American (AA) men will develop PCa during their lifetime, as compared to 1:9 of the general American male population. AA men are twice as likely to die from the disease compared to their European American (EA) counterparts. Androgen receptor signaling inhibitors (ARSI, e.g. apalutamide, enzalutamide) have initial therapeutic efficacy, but genetic adaptations present challenges for clinical intervention. Alternative splicing (AS) of fibroblast growth factor receptor 3 (FGFR3) represents a racial disparity where loss of Exon 14 expression was observed in AA PCa patients with lower survival (p = 0.04; n = 550). Normally, FGFR3 Exon 14 is a ‘molecular brake’, where the kinase region regulates FGFR3 signaling. We previously reported that CD105 antagonism (carotuximab) and enzalutamide inhibit AS of androgen receptor to produce AR-V7 splice variant. We also reported that carotuximab decreased prostate tumor growth in mouse models and patients in Phase 2 clinical trial. We hypothesized that carotuximab improves therapeutic response to ARSI for AA patients by regulating full length FGFR3. Apalutamide decreased FGFR3 Exon 14 expression but increased when combined with carotuximab. Inhibition of CD105 and FGFR3 decreased FGFR3 activity and ID1, a downstream CD105 signaling gene. We confirmed that CD105 and FGFR3 interact by immunoprecipitation and Western blot. Finally, we found that targeting splicing factors with siRNA also decreased FGFR3 Exon 14 and lineage plasticity genes. These findings improve the efficacy of existing ARSI therapy by targeting CD105 and FGFR3 signals, revealing a novel crosstalk between both pathways. Overall, our study addresses cancer health disparities by limiting a common splice variant of FGFR3 in AA PCa patients.

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THE KDM5 INHIBITOR PBIT REDUCES PROLIFERATION OF CASTRATION-RESISTANT PROSTATE CANCERS VIA THE INDUCTION OF SENESCENCE

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The compound KDM5 family inhibitor 2-4(4-methylphenyl)-1,2-benzisothiazol-3(2H)-one (PBIT) is an inhibitor of lysine-specific histone demethylases that has been suggested as a potential lead compound for cancer therapy. It has been reported that PBIT suppresses the proliferation of human breast cancer cells. Previous work by our group demonstrated that PBIT also reduces the viability of early-stage prostate cancers. This study aimed to characterize the anti-tumor effects of PBIT within two castration-resistant human prostate cancer cell lines: the androgen receptor (AR) positive C4-2B cells and the PC3 cells, which express little to
no AR. Our group initially demonstrated via quantitative RT-PCR analysis that PC3 and C4-2B cells express varying amounts of KDM5A, KDM5B, and KDM5C, the therapeutic targets of PBIT. Presto Blue assays were next performed to determine whether PBIT alters cell proliferation. Micromolar concentrations of PBIT significantly reduced prostate cancer cell proliferation in a time- and concentration-dependent manner. Data from Cell Death ELISAs suggest that 10 mM PBIT does not significantly induce apoptosis within C4-2B or PC3 cells. However, PBIT did appear to increase the amount of senescence associated beta-galactosidase staining within cells, which is a marker of cellular senescence. Flow cytometry analyses revealed PBIT also altered cell cycle progression. Furthermore, PBIT exposure modified protein levels of the senescence and proliferation markers Lamin B1, Cyclin D1, and p21. Together, these data strongly suggest that the PBIT significantly reduces the proliferation of the more aggressive castration-resistant prostate cancer via cellular senescence.

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GENETICAL ENGINEERING OF CAS9 WITH MYRISTOYLATION FACILITATES ITS TETHERING TO THE CYTOPLASMIC MEMBRANE

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While CRISPR/Cas9 has revolutionized gene editing, delivery into prostate cancer cells as a gene therapy has proved difficult due to its large size and surface charges of the Cas9 protein. Protein N-myristoylation, catalyzed by N-myristoyltransferase 1 (NMT1), is co/post translational modification resulting in the covalent attachment of a myristoyl group to a glycine residue at the N-terminus of the protein. N-myristoylation of Src kinase leads to increased association of Src kinase to the cytoplasmic membrane in addition to charge interactions between basic lysine residues in the N-terminus and the acidic phospholipids of the bilayer. This association results in increased encapsulation of Src kinase into extracellular vesicles (EVs) through EV biogenesis. We have previously demonstrated that fusion of an octapeptide derived from the N-terminus of Src kinase to Cas9 allows recognition as a myristoylation substrate. We hypothesize that the fusion of the octapeptide onto the Cas9 promotes its tethering to the cytoplasmic membrane. Additionally, myristoylation of the genetically modified Cas9 is mediated by NMT1. To test this hypothesis, plasmids expressing Cas9 and genetically modified Cas9 (mCas9) were transfected into HEK293T cells using calcium chloride method. Additionally, mCas9 transfected cells were treated with DDD85464, an NMT1 inhibitor. The cells were fractionated to separate the cytosol and membrane components. Immunoblotting was performed to determine the intracellular location of Cas9 and mCas9. We anticipate that mCas9 should be present more in the membrane than in the cytosol due to the myristoylation, but will be inhibited by DDD85464. This study will reveal the biological mechanism of how myristoylation can be applied to encapsulate Cas9 into EVs, which serve as a vehicle to deliver Cas9 for gene therapy and treatment of prostate cancer.
THE YAP1/TEAD AND NF-KAPPA B TRANSCRIPTION FACTORS MAY COOPERATE TO MEDIATE PROSTATE CANCER PROGRESSION

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The complexities in understanding the cellular and molecular basis of aggressive prostate cancer remain a puzzle, urging an in-depth exploration of the underlying mechanisms. Here, we investigated biochemical and functional interactions between the Hippo pathway effector YAP1 and RELA, a critical subunit of the nuclear factor (NF) kappa B, in prostate cancer. Coimmunoprecipitation demonstrated that endogenous YAP1 and RELA form protein complexes. Similarly, proximity ligation assay showed that androgens, combined with SDF1a or RANKL, enhanced interaction between the native YAP1 and RELA protein in the cell. Confocal microscopy demonstrates that combined SDF1a and androgen exposure augmented the YAP1 and RELA colocalization compared to a single-agent treatment. Perturbation of YAP1 function via genetic and pharmacological interventions attenuated the interaction between endogenous TEAD and RELA, suggesting that YAP1 regulates the TEAD and RELA interaction. Promoter-reporter assay showed that silencing YAP1 or TEAD, a key mediator of YAP1 transcription, significantly reduced the NF-Kappa B promoter-reporter activity. Likewise, controlled expression of MST1/STK4, a potent inhibitor of YAP1, suppressed the NF-Kappa B promoter-reporter activity. In tandem, an integrated bioinformatics approach of the existing RELA and YAP/TEAD ChIP-seq data revealed several genes likely coregulated by YAP/TEAD and NF-Kappa B. Furthermore, our computational analysis of the TCGA and Stand Up To Cancer (SU2C) data sets indicated that YAP1/TEAD and NF-kappa B expression correlates in prostate cancer tissues. These findings suggest that cooperative androgen and cytokine signaling controls Hippo/YAP and NF-Kappa B activity, thus contributing to advanced prostate cancer and identifying the YAP-NF Kappa B axis as a potential cancer drug target.

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THE EFFECT OF CHRONIC IL-1 EXPOSURE ON THE IL-1/IL-6 AXIS IN CRPC

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The androgen receptor promotes prostate cancer (PCa) cell proliferation; thus, the first-line therapy is androgen deprivation therapy (ADT). However, patients can develop ADT resistance (i.e., castration-resistant prostate cancer (CRPC)). CRPC patients have a poor prognosis, developing lethal bone metastases. Thus, it is imperative that we fully understand the mechanisms governing CRPC initiation and progression. The PCa tumor microenvironment (TME) contains a milieu of inflammatory cytokines, where chronic inflammation promotes cancer initiation and progression. In kind, our lab discovered that chronic exposure to
the inflammatory cytokine, interleukin-1 (IL-1), can cause castration-sensitive PCa cells to become castration-insensitive. However, it is not known how chronic IL-1 contributes to the tumorigenicity of PCa cells that have already transformed into CRPC.

To investigate the molecular effect of chronic IL-1 exposure on CRPC progression, I chronically exposed the C4-2 CRPC cell line to IL-1 to generate novel sublines. Notably, chronic exposure renders C4-2 cells insensitive to exogenous IL-1 intracellular signaling. Therefore, I explored their molecular response to other inflammatory cytokines, such as interleukin-6 (IL-6). Among its roles, IL-6 is associated with PCa progression, anti-androgen and chemotherapy resistance, and PCa neuroendocrine differentiation. Interestingly, the chronic IL-1 sublines show attenuated response to IL-6. Canonical IL-1 signaling occurs through NF-κB, while canonical IL-6 signaling is mediated by STAT3. Importantly, I observed synergistic intracellular signaling when I co-treated C4-2 cells with IL-1 and IL-6. Taken together, my data suggests that the IL-1 and IL-6 pathways crosstalk, where chronic IL-1 exposure directly attenuates IL-1 intracellular signaling and indirectly affects IL-6 signaling. The cell biological consequences of an attenuated IL-1/IL-6 axis in CRPC cells have yet to be determined; I will use my unique cell line models to elucidate how cells integrate these signals in a complex TME.

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A TREATMENT STRATEGY OF CASTRATION RESISTANT PROSTATE CANCER USING EXTRACELLULAR VESICLES BASED GENE THERAPY

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Prostate cancer is the most commonly diagnosed malignancy in men in the United States. Approximately 10-20% of prostate cancer patients will progress to castration-resistant prostate cancer (CRPC), posing significant challenges for effective treatment. The androgen receptor (AR) signaling remains active in majority of CRPC cases and is considered a key driver in CRPC progression. The CRISPR/Cas9 system provides a genetic approach to target and silence AR signaling by knockout of AR gene. However, an efficient and safe delivery of the CRISPR machinery has yet to be established. To address these issues, we have developed a novel technology that involves in the encapsulation of Cas9/sgRNA the ribonucleoprotein complex (RNP) into extracellular vesicles (EVs) to target the AR gene. For this purpose, Cas9 was genetically modified (mCas9) by fusion with a myristoylation consensus sequence derived from the N-terminus of Src kinase. The fusion led to Cas9 being myristoylated, but retained its gene-editing function. The mCas9/sgRNA-AR complex effectively knocked out both ectopically and/or endogenously expressed AR genes in 293T-AR cells and/or PCa cells. The disruption of the AR was confirmed using the T7 endonuclease assay and Sanger sequencing. Additionally, we conducted a comprehensive characterization of the EVs encapsulating Cas9/sgRNA-AR RNP. These tested EVs had an average diameter of approximately 150 nm and exhibited the typical cup-shaped structure. Moreover, the encapsulated Cas9 protein constituted approximately 0.5% of the total EV protein and displayed resistance to protease digestion. Future investigations will focus on evaluating whether EVs encapsulating mCas9/sgRNA-AR RNP can effectively knock out AR expression in PCa cells. This study has the potential to provide a novel technology to silence AR expression in prostate tumors in vivo.
HMGA2 PROMOTES RESISTANCE TO ENZALUTAMIDE, BUT NOT ALISERTIB IN PROSTATE CANCER CELLS

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High Mobility Group AT-hook 2 (HMGA2), a DNA binding protein acts as a transcriptional regulating factor in gene transcription and facilitates proliferation and epithelial-mesenchymal transition (EMT), which is usually the onset of prostate cancer progression and metastasis. As a second-generation antiandrogen medication, enzalutamide blocks the androgen receptor's (AR) ability to translocate into the nucleus by competitively binding to AR and obstructing androgen binding. Alisertib (MLN8237) is a small molecule inhibitor of Aurora kinase A has been utilized in clinical trials for neuroendocrine cancers and can also inhibit EMT. We aim to investigate the role of HMGA2 in mediating resistance to these two drugs in prostate cancer cells. As cell models, we utilized LNCaP, C4-2B and C4-2B MDVR (enzalutamide resistant) cell lines. We initially performed dose-dependent treatment of C4-2B MDVR cells with enzalutamide (1-30 µM) and alisertib (2.5-40 µM). The higher doses of enzalutamide slightly decreased cell proliferation. However, alisertib treatment indicated a more significant dose-dependent decline in cell growth. Additionally, we treated LNCaP, C4-2B and C4-2B MDVR with 20 µM of enzalutamide and alisertib. A significant growth suppression was observed in LNCaP and C4-2B cell, but not C4-2B MDVR when treated with 20 µM enzalutamide. Immunofluorescent analysis showed that AR remained in the nucleus in C4-2B MDVR cells even after treatment with enzalutamide. Furthermore, transient knockdown of HMGA2 using siRNA in the three cells followed by treatment with 20 µM of enzalutamide and alisertib led to greater decline in C4-2B MDVR proliferation. This suggests that HMGA2 might be involved in mediating resistance to enzalutamide. In conclusion, alisertib is a better candidate for the treatment of prostate cancer expressing HMGA2.

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ENCAPSULATION OF CAS13A INTO EXTRACELLULAR VESICLES TO TARGET PROSTATE CANCER CELLS

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The clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated (Cas) systems protect bacteria and archaea from infections and has been successfully harnessed for gene editing in a variety of specific diseases. The class 2 type VI CRISPR/Cas effector, Cas13a, targets and cleaves RNA to protect bacteria from RNA phages, offering promising potential for therapeutic treatment of various diseases including viral infection and prostate cancer. However, the delivery of CRISPR/Cas13a remains a significant challenge. Protein N-myristoylation is a co/post-translational modification that results in the covalent attachment of the myristoyl-group to a glycine residue at the N-terminus of the target protein. It acts as an
anchor, enabling the target protein to associate with the cytoplasmic membrane and thus governs its intracellular trafficking and activity. Extracellular vesicles (EVs) are secreted vesicles that mediate cell-cell communication. Previous studies have shown that Cas9/sgRNA ribonucleoprotein (RNP) complex can be encapsulated into EVs for treatment of many diseases. To demonstrate if the similar strategy can be used to encapsulate Cas13a/gRNA into EVs, Cas13a was genetically modified by fusion of an octapeptide derived from N-terminus of Src kinase onto its N-terminus. Our results showed that the genetically modified Cas13a was myristoylated and remained its biological function. Next, plasmids expressing mCas13a and gRNA-EGFP were transfected into HEK293t cells expressing GFP mRNA using calcium phosphate method. The results of immunoblotting, RT-qPCR, and Flow cytometry showed that the mCas13a/gRNA-EGFP complex effectively knocked down GFP mRNA and protein levels. In the future, we will focus on whether Cas13a can be encapsulated into EVs. And the encapsulated Cas13a can effectively knock down endogenous and exogenous mRNA including oncogenic or viral genomic RNA in an in vitro model. This study will provide a novel therapeutic strategy to target viral infection and prostate cancer disease.
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