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CONTRACTING ORGANIZATION: Duke University

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14. ABSTRACT We have discovered RNA splicing as a novel mechanism underlying tumor aggressiveness and drug resistance in prostate cancer (PCa) in African American (AA) patients. To interrogate further the contribution of RNA splicing to PCa disparities, we have collected blood and tissue specimens of varying Gleason grade from AA and white patients for study. In addition, we have identified single nucleotide polymorphisms (SNPs) predicted to regulate RNA splicing in race-related alternatively spliced genes involved in stemness that associate with race-related PCa risk or PCa survival and genome-wide SNPs predicted to regulate RNA splicing that associate with advanced PCa. Furthermore, we have developed a splice-switching oligonucleotide (SSO) that specifically inhibits expression of the pathogenic androgen receptor (AR)-variant 7 (V7), while maintaining expression of full-length AR, which has therapeutic value. This SSO inhibits proliferation of PCa cells and restores sensitivity to an AR inhibitor. It can be delivered directly to PCa cells without transfection reagent. Ultimately, this study will elucidate further molecular mechanisms underlying PCa in AA men and aid in development of new approaches for prevention and treatment that will mitigate PCa disparities for AAs and improve outcomes for men of all races with aggressive disease.					
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INTRODUCTION: African American (AA) men exhibit 2-fold higher incidence and mortality rates from prostate cancer compared with white men. Although much of this disparity remains after controlling for social determinants of health, very few studies have utilized this population-based difference to identify molecular mechanisms of tumor aggressiveness. The studies proposed here address the urgent need to elucidate the molecular mechanisms underlying the more aggressive prostate cancer biology in AA men. Our objectives are to 1) expand our sample cohort and delineate the relationship between genetic/epigenetic/post-transcriptional factors in AA prostate cancer and Gleason grade and 2) manipulate splicing using novel splice-switching oligonucleotides and determine functional outcomes. Establishing the underlying genetic/epigenetic/post-transcriptional differences between prostate cancer in AA and white patients and the biologic relevance of these differences to tumor biology will identify novel precision biomarkers and/or molecular targets for precision medicine interventions that will have profound implications for the prevention, screening, diagnosis and management of prostate cancer in AA men as well as men of all races with aggressive disease. Specifically, if positive, these genetic/epigenetic/post-transcriptional differences could be developed as prognostic markers, in the context of Gleason grade and other prognostic variables, to delineate patients at greater risk of progressing on active surveillance or through localized therapy. In addition, the causal relationship of these pathways would help to rationalize specifically targeted therapy in selected patients.

KEYWORDS (20 words): Prostate cancer, health disparities among racial groups, molecular mechanisms, differential gene expression, alternative RNA splicing, epigenetic alterations, clinical tumor aggressiveness

ACCOMPLISHMENTS:

What were the major goals of the project?

- Task 1. Validate differentially expressed and spliced candidate genes in AA prostate cancer in an expanded sample cohort and define the relationship between these genes and Gleason grade. Months 1-21. 90% complete (please see progress for Task 1).
- Task 2. Define the biologic significance of differences in *cis*-acting splicing elements of alternatively spliced candidate genes in AA prostate cancer to alternative splicing events specific to AA prostate cancer and define the relationship between these patterns and Gleason grade. Months 21-36. 90% complete (please see progress for Task 2).
- Task 3. Use splice-switching oligonucleotides to delineate the biologic relevance of race-related differentially spliced genes involved in PIK3CD and MET signaling. Months 1-24. 90% complete (please see progress for Task 3).

What was accomplished under these goals?

Progress for Task 1: We have completed obtaining individual patient AA and white prostate cancer tissue specimens and patient-matched blood specimens under our IRB approved GENomics of CANcer DisparitiEs (GENCADE) protocol and capturing annotated data in our accompanying database. For all tissue specimens, we have screened the specimens for tumor content, determined the Gleason grade, isolated cellular DNA and RNA, confirmed adequacy of yield and quality of these nucleic acids for downstream analyses and annotated the specimens. During the remaining no cost extension period, we will conduct and complete analyses of differentially expressed and spliced candidate genes in AA prostate cancer and define the relationship between these genes and Gleason grade.

Progress for Task 2: As mentioned above, we have completed obtaining individual patient AA and white prostate cancer tissue specimens and patient-matched blood specimens under our IRB approved GENomics of CANcer DisparitiEs (GENCADE) protocol and capturing annotated data in our accompanying database. For all tissue specimens, we have screened the specimens for tumor content, determined the Gleason grade, isolated cellular DNA and RNA, confirmed adequacy of yield and quality of these nucleic acids for downstream analyses and

annotated the specimens. During the remaining no cost extension period, we will conduct and complete analyses of the biological significance of differences in *cis*-acting splicing elements of alternatively spliced genes in AA prostate cancer to alternative splicing events specific to AA prostate cancer and define the relationship between these patterns and Gleason grade.

In addition, as mentioned in our last progress report, we have extended our analyses to identify genome-wide SNPs predicted to regulate RNA splicing and associated with advanced prostate cancer using the database of Genotypes and Phenotypes (dbGaP). We have recently obtained access to the Million Veteran Program dataset and are currently beginning to validate candidate SNPs in splicing regulatory regions that associate with prostate cancer aggressiveness in AA and white Veteran patients by conducting a case-only study using this dataset and a case-control (aggressive versus non-aggressive) analysis. Furthermore, we are currently beginning to mechanistically and functionally interrogate candidate SNPs associated with advanced prostate cancer or prostate cancer survival in population-specific prostate cancer cell lines. We have leveraged the preliminary data we have generated to date to apply for a 2019 DoD Prostate Cancer Research Program Idea Development Award.

Progress for Task 3: While we continue to work through challenges we have encountered in designing and testing splice-switching oligonucleotides (SSOs) targeting *PIK3CD* and *MET* and as mentioned in our last progress report, we have focused on further assessment of the mechanism and function of a SSO we have developed targeting an oncogenic RNA splice variant we identified for study in the alternative approach section of our original proposal, the androgen receptor (AR)-variant 7 (V7). We have now designed and synthesized the AR-V7 SSO using morpholino oligonucleotide technology, which replaces the ribose sugar moieties with methylenemorpholine rings and replaces the anionic phosphates of RNA with non-ionic phosphorodiamidate linkages. Using this morpholino oligonucleotide, we have been able to directly deliver the AR-V7 SSO to the nucleus of population-specific prostate cancer cells without transfection reagent and such cells similarly exhibit a decrease in AR-V7 at the RNA and protein level and maintenance of expression of full length AR at the RNA and protein level. During the remaining no cost extension period, we will evaluate the therapeutic efficacy of the AR-V7 SSO *in vivo* using prostate cancer xenograft models.

In parallel to the work being done in the context of this grant and as mentioned in our last progress report, we have established and have now completed characterization of a prostate cancer patient-derived explant from a patient of 90% West African ancestry by transferring the primary human tumor directly into an immunodeficient mouse. This model is the first such model established from a patient of African ancestry and will provide an invaluable tool to study the molecular mechanisms underlying race-related aggressive prostate cancer and predict the efficacy of existing and novel therapeutic agents. During the remaining no cost extension period, we will be submitting a manuscript reporting these findings to *The American Journal of Pathology*.

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

This project provided training and professional development for Jennifer A. Freedman, PhD, Co-investigator and Bonnie LaCroix, Lab Research Analyst II. Dr. Freedman has expanded her expertise in performing all aspects of translational research by writing the GENCADE IRB protocol, designing the GENCADE REDCaP database, creating the GENCADE IRB-approved patient handout and collaborating with members of the Genitourinary Oncology clinical research team to implement the GENCADE Study. In addition, this project gave her an opportunity to collaborate with molecular epidemiologists to identify variants of genes predicted to regulate RNA splicing that associate with racial disparities in prostate cancer, prostate cancer survival and advanced prostate cancer. Moreover, Dr. Freedman has gained additional expertise in the design of SSOs and assessment of their functional effects on splicing and prostate cancer cell biology and prostate cancer *in vivo*. Furthermore, she continues to increase her knowledge regarding development of prostate cancer models from AA patients and prostate cancer health disparities among racial groups. Finally, this project has provided an opportunity for Dr. Freedman to develop further her skills in scientific management and mentoring of members of the Genitourinary Oncology Laboratory, including the Lab Research Analyst II working on this project. Mrs. LaCroix has expanded her technical molecular biology expertise in assessing the effects of SSOs on splicing and prostate cancer cell

biology and prostate cancer *in vivo* and her knowledge of prostate cancer health disparities among racial groups. Work was presented at a number of national scientific meetings in 2019, please see the products section below.

Our Genitourinary Oncology Laboratory also has three postdoctoral associates who are working on parallel, but related projects and have benefited from exposure to the research conducted in the context of this grant. Dr. Muthana Al Abo is a Syrian scientist who conducted his PhD thesis research and initial postdoctoral research on molecular mechanisms of DNA repair and anti-cancer agents targeting this pathway. Since joining our laboratory, Dr. Al Abo has gained knowledge of cancer health disparities and is applying his technical molecular biology and computational skills to this area. This year he has given poster presentations at national scientific conferences and is currently preparing a manuscript reporting the findings from his computational studies of RNA splicing in solid tumors in AA and white patients. Dr. Tyler Allen is an African American postdoctoral associate who conducted his PhD thesis research on how tumor and stem cells travel through the circulation and exit blood vessels and is highly skilled at molecular biological cancer research. In our laboratory, he is receiving additional training in correlative science, translational cancer research, cancer disparities research, bioinformatics and biostatistics. This year he has given poster presentations at national scientific conferences and has applied for an AACR-Genentech Cancer Health Disparities Research Fellowship and an AACR Minority Scholar in Cancer Research Travel Award. Dr. Sean Piwarski is a Hispanic scientist who conducted his PhD thesis research on how chemical mechanisms in specific toxins work to inhibit cancer metastasis. He has just recently joined our laboratory and is receiving additional training in correlative science, translational cancer research, cancer disparities research, bioinformatics and biostatistics. He is funded by an additional DoD Prostate Cancer Research Program Health Disparity Research Award our team has received focusing on race-related germline genetic variation and response to secondary hormonal therapy in metastatic castration-resistant prostate cancer. In 2019, he attended the 12th AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved and this year he has applied for a Genomic Medicine Research Fellowship.

Finally, Mr. Brendon Patierno, a former Research Technician II in our laboratory established and characterized the prostate cancer patient-derived explant from the patient of West African ancestry mentioned above. During this past year, he began graduate work at The City University of New York in the Molecular Biology PhD program.

How were the results disseminated to communities of interest?

We have undertaken outreach activities to increase participation, including minority participation, in our GENCADE Study. In collaboration with the Duke Cancer Institute's Office of Health Equity and Disparities (OHED), we have approached patients participating in our annual community Men's Health Fair and have designed, produced and implemented use of our GENCADE IRB-approved patient handout. We have also worked with OHED to design and implement a training program called JUST ASK, for all staff participants in GENCADE and other clinical trials, centered on culturally sensitive and competent communications with patients about clinical trials.

In addition, we have broadly disseminated our vision and results through a number of mechanisms. As mentioned above, OHED is engaged in community outreach and programming, including an annual Men's Health Fair in inner city Durham, North Carolina (38% African American), patient navigation and minority accrual to clinical trials. Through these efforts, we shared our vision and results with the public, patients and community practitioners. In addition, we are part of Duke Cancer Institute's Prostate & Urologic Cancer Center. This Center includes translational scientists and clinical investigators from Medical Oncology, Urology and Radiation Oncology. The Center sees prostate cancer patients of all races and ethnicities, places patients onto clinical trials and, as a member of the Department of Defense Prostate Cancer Clinical Trial Consortium, contributes to investigation of novel agents. Thus, we have discussed our vision and results with patients and practitioners through forums, tumor boards and grand rounds. Dr. Patierno, PI of this grant and Deputy Director of the Duke Cancer Institute, Dr. George, as Co-Director of the Duke Prostate & Urologic Cancer Center and additional Duke Cancer Institute leaders regularly reach out to investors and donors. Through these events, we shared our vision and results with such parties. Finally, via our relationships with the Peter Michael Foundation, Prostate Cancer

Foundation, American Cancer Society, American Association for Cancer Research and American Society of Clinical Oncology, Duke Cancer Institute's website, press and social media communications and our Center's website, we continually broadly disseminate our vision and results.

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

During the remaining no cost extension period, we will 1) conduct and complete analyses of differentially expressed and spliced candidate genes in AA prostate cancer and define the relationship between these genes and Gleason grade, 2) conduct and complete analyses of the biological significance of differences in *cis*-acting splicing elements of alternatively spliced genes in AA prostate cancer to alternative splicing events specific to AA prostate cancer and define the relationship between these patterns and Gleason grade and 3) evaluate the therapeutic efficacy of the AR-V7 SSO *in vivo* using prostate cancer xenograft models.

IMPACT:

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

Our publications related to this project to date have discovered alternative RNA splicing as a novel mechanism promoting tumor aggressiveness and drug resistance in prostate cancer in AA patients. In addition, the associations between RNA splicing regulatory variants of stemness-related genes and racial disparities in susceptibility to prostate cancer identify potential novel biomarkers for racial disparities in prostate cancer risk. Moreover, the SNPs of stemness pathway genes predicted to regulate RNA splicing, microRNA and oncogenic signaling that are associated with prostate cancer survival represent potential novel prognostic markers for overall survival of prostate cancer and support a contribution of the stemness pathway to prostate cancer patient outcome.

Our collection of prostate cancer tissue specimens and patient-matched blood specimens from individual AA and white patients contributes to the goal of accumulating racially diverse prostate tumor specimens and will contribute to identification of biologically significant factors driving the clinical aggressiveness of prostate cancer in AA patients. In addition, identification of genome-wide RNA splicing regulatory SNPs that are significantly associated with advanced prostate cancer in white and/or AA populations have the potential to serve as novel molecular targets for development of biomarkers of increased risk of aggressive prostate cancer or therapeutics against aggressive prostate cancer. Moreover, development of the SSO to correct aberrant splicing leading to production of AR-V7 will further our understanding of the contribution of this molecular mechanisms to prostate cancer in AA patients. This SSO has the potential to yield a novel therapeutic modality to combat prostate cancer in AA men as well as men of all races with aggressive disease driven by this mechanism.

Finally, in parallel to the work done in the context of this grant, we will make available to other investigators our prostate cancer patient-derived explant from the patient of African ancestry, after publication.

What was the impact on other disciplines?

In parallel to the work done in the context of this grant, we have identified 25 race-related alternatively spliced genes that also occur in breast, lung and liver cancer. Collaborative work has commenced in these additional solid tumors. For example, we are the first team to identify alternative RNA splicing differences in non-small cell lung cancer (NSCLC) between patients of African and European ancestry. Specifically, in lung squamous cell carcinomas (LUSCs), the number of race-related differentially spliced genes (DSGs) (4,830) far exceeded the number of genes exhibiting race-related differential aggregate gene expression (DEGs) (267) in the same tissues. Among the DSGs, 17% are reported to be oncogenes, tumor suppressor genes and/or drivers and 355 RNA splicing events within DSGs are associated with LUSC survival. Among the DEGs, 6% are reported to be cancer-related and 18 are associated with LUSC survival. A number of the DSGs and DEGs involve therapeutically targetable signaling pathways. Furthermore, we have mined The Cancer Genome Atlas (TCGA) and have identified DSGs and DEGs in additional LUSCs or lung adenocarcinomas (LUADs). A manuscript reporting these findings is in the final stages of preparation for submission to *Clinical Cancer Research*. This work has been leveraged as part of a NIH Feasibility and Planning Studies for Development of Specialized Programs of Research Excellence (SPoREs) to Investigate Cancer Health Disparities P20 application, a DoD Lung Cancer Research Program Idea Development Award application and a NIH Basic Research in Cancer Health Disparities

R01 application. In summary, the RNA splicing-related concepts and targets and the SSO technology developed here have the potential to have broader applicability.

What was the impact on technology transfer?

1. Along with our qualified collaborator, a US Patent Application has been filed regarding alternative splicing variants of genes associated with prostate cancer risk and survival (US 2014/0364483 A1).
2. Freedman, Jennifer, Patierno, Brendon, LaCroix, Bonnie, Robinson, Timothy, Sullenger, Bruce, George, Daniel and Patierno, Steven. Splice-switching oligonucleotides and methods of use. PCT/US16/60549, expiration date 2036.
3. Freedman, Jennifer, Wang, Yanru, Liu, Hongliang, Wei, Qingyi, George, Daniel and Patierno, Steven. 2016. Biomarkers for the identification of prostate cancer and methods of use. 15/344,222, filed November 4, 2016. Patent Pending.

What was the impact on society beyond science and technology?

The outreach activities we have undertaken to increase participation, including minority participation, in our GENCADE Study and our physician-patient informed decision-making and informed consent process in our GENCADE Study will improve public knowledge regarding prostate cancer, prostate cancer health disparities among racial groups and clinical research. In collaboration with Duke Cancer Institute's OHED we have helped devise a curriculum to train clinicians and other staff participants in clinical trials on culturally sensitive and competent communications with minority patients regarding clinical trials. In addition, we have improved public knowledge by broadly disseminating our vision and results through community outreach and programming, the Duke Prostate & Urologic Cancer Center at our institution, investors and donors at our institution, the Peter Michael Foundation, the Prostate Cancer Foundation, the American Cancer Society, the American Association for Cancer Research, the American Society of Clinical Oncology, the website at our institution and press and social media communications.

CHANGES/PROBLEMS:

Changes in approach and reasons for change.

Nothing to report.

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

We have an extension without funds for a period of 12 months. This extension does not involve a change in our approved objectives or scope of our project. Rather, it enables us to complete our approved interrogation of differentially expressed and spliced candidate genes in prostate cancer in AA and white patients and determination of the relationship between these genes and Gleason grade. We were granted this extension because our qualified collaborator and his colleague were unable to complete their portion of collection of prostate cancer tissue specimens and patient-matched blood specimens from AA and white patients because of serious non-compliance in their research with human subjects. This extension has enabled us to complete collection of the number of prostate cancer tissue specimens and patient-matched blood specimens from AA and white patients in our original grant and is enabling us to complete the downstream analyses using these specimens.

Changes that had a significant impact on expenditures.

Nothing to report.

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

Nothing to report.

PRODUCTS:

Publications, conference papers, and presentations.

Peer-reviewed publications:

1. Robinson T.J.* , J.A. Freedman* , M. Al Abo, A.E. Deveaux, B. LaCroix, B.M. Patierno, D.J. George and S.R. Patierno. 2019. Alternative RNA splicing as a potential major source of untapped molecular targets in precision oncology and cancer disparities. *Clinical Cancer Research* doi: 10.1158/1078-0432.CCR-18-2445. *contributed equally as co-first authors. PMID: 30755441

Conference presentations:

1. Patierno S. R., Spliceomics: Alternative RNA splicing as a source of ancestry-related molecular targets in precision oncology and cancer disparities. AACR Annual Meeting. Atlanta, Georgia. March 2019. Plenary presentation.
2. Al Abo M., D. J. George, J. A. Freedman and S. R. Patierno. Ancestry-related differentially spliced and expressed genes in prostate cancer. AACR Annual Meeting. Atlanta, Georgia. March 2019. Poster presentation.
3. Al Abo M., A. Jiang, D. J. George, Z. Wang, S. R. Patierno and J. A. Freedman. Race-related LMO7 exon skipping enhances prostate tumor invasion. 12th AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved. San Francisco, California. September 2019. Poster presentation.
4. Allen T., G. Lipton, A. B. Sibley, P. Healy, B. Patierno, B. Lacroix, S. R. Patierno, K. Owzar, T. Hyslop, D. J. George and J. A. Freedman. Race-related genetic variation and response to secondary hormonal therapy in metastatic castration-resistant prostate cancer. 12th AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved. San Francisco, California. September 2019. Poster presentation.
5. LaCroix, B. L., D. J. George, J.A. Freedman and S.R. Patierno. Race-related RNA splicing dysregulation of PI3Kd signaling: a therapeutic target for aggressive prostate cancer. 12th AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved. San Francisco, California. September 2019. Poster presentation.
6. Allen T., G. Lipton, A. B. Sibley, P. Healy, B. Patierno, B. Lacroix, S. R. Patierno, K. Owzar, T. Hyslop, D. J. George and J. A. Freedman. Race-related genetic variation and response to secondary hormonal therapy in metastatic castration-resistant prostate cancer. Duke Cancer Institute Annual Retreat. Durham, North Carolina. October 2019. Poster presentation.
7. Al Abo M., A. Jiang, D. J. George, Z. Wang, S. R. Patierno and J. A. Freedman. Race-related LMO7 exon skipping enhances prostate tumor invasion. 26th Annual Prostate Cancer Foundation Scientific Retreat. Carlsbad, California. October 2019. Poster presentation.

Website(s) or other Internet site(s).

Nothing to report.

Technologies or techniques.

We have developed a SSO to correct aberrant splicing leading to production of AR-V7 and, once complete, we plan to submit the research data for publication making our scientific discovery open to the scientific community. In addition, in parallel to the work being done in the context of this grant, we have established and characterized a prostate cancer patient-derived explant from a patient of West African ancestry. We are in the final stages of preparation of a manuscript and will be submitting the research data for publication making our scientific discovery open to the scientific community and, upon publication, we will provide our model to the community.

Inventions, patent applications, and/or licenses.

1. Along with our qualified collaborator, a US Patent Application has been filed regarding alternative splicing variants of genes associated with prostate cancer risk and survival (US 2014/0364483 A1).
2. Freedman, Jennifer, Patierno, Brendon, LaCroix, Bonnie, Robinson, Timothy, Sullenger, Bruce, George, Daniel and Patierno, Steven. Splice-switching oligonucleotides and methods of use. PCT/US16/60549, expiration date 2036.

3. Freedman, Jennifer, Wang, Yanru, Liu, Hongliang, Wei, Qingyi, George, Daniel and Patierno, Steven. 2016. Biomarkers for the identification of prostate cancer and methods of use. 15/344,222, filed November 4, 2016. Patent Pending.

Other products.

Nothing to report.

PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project?

Name:	Steven Patierno, PhD, PI
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	No change
Contribution to Project:	Provided senior level oversight and direction of research, oversaw the GENCADE study
Funding Support	P30CA014236-42 See attached other support/ DOD

Name:	Daniel J George, MD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	No change
Contribution to Project:	Oversaw the GENCADE study, contributed to oversight and direction of research
Funding Support	See attached other support/ DOD

Name:	Jennifer A Freedman, PhD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.1
Contribution to Project:	Oversaw collection of GENCADE specimens in collaboration with the Genitourinary Oncology clinical research team, identified variation in cis-acting splicing regulatory sequences of race-related alternatively spliced genes that associates with prostate cancer risk, aggressiveness and survival, assessed function of splice-switching oligonucleotides targeting AR-V7, managed and mentored Research Analyst II, Bonnie LaCroix, oversaw establishment of new models of African American prostate cancer
Funding Support	See attached other support/ DOD

Name:	Yuan Wu
Project Role:	Biostatistician
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	No change

Contribution to Project:	Statistical plan for GENCADE study
Funding Support	

ABSTRACT (approximately 200 words):

We have discovered RNA splicing as a novel mechanism underlying tumor aggressiveness and drug resistance in prostate cancer (PCa) in African American (AA) patients. To interrogate further the contribution of RNA splicing to PCa disparities, we have collected blood and tissue specimens of varying Gleason grade from AA and white patients for study. In addition, we have identified single nucleotide polymorphisms (SNPs) predicted to regulate RNA splicing in race-related alternatively spliced genes involved in stemness that associate with race-related PCa risk or PCa survival and genome-wide SNPs predicted to regulate RNA splicing that associate with advanced PCa. Furthermore, we have developed a splice-switching oligonucleotide (SSO) that specifically inhibits expression of the pathogenic androgen receptor (AR)-variant 7 (V7), while maintaining expression of full-length AR, which has therapeutic value. This SSO inhibits proliferation of PCa cells and restores sensitivity to an AR inhibitor. It can be delivered directly to PCa cells without transfection reagent. Ultimately, this study will elucidate further molecular mechanisms underlying PCa in AA men and aid in development of new approaches for prevention and treatment that will mitigate PCa disparities for AAs and improve outcomes for men of all races with aggressive disease.