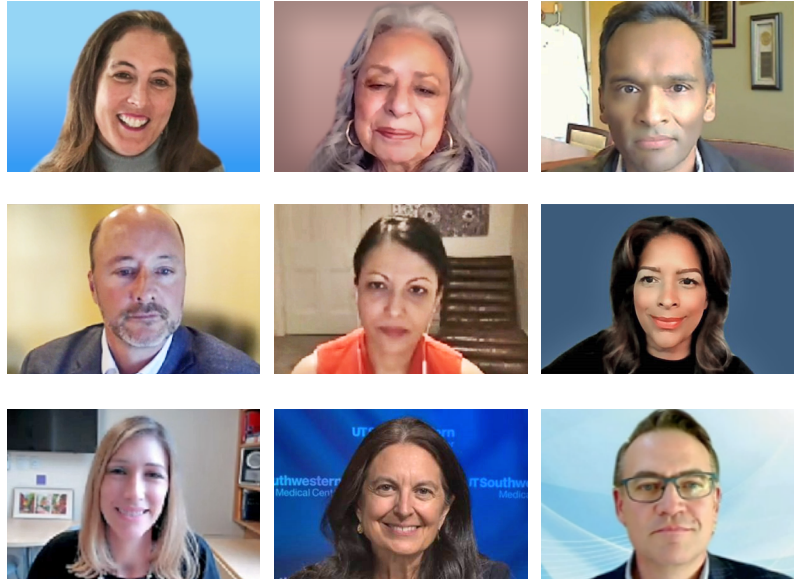


STATE *of the* SCIENCE REPORT



28

Twenty-Eighth Annual
Prostate Cancer Foundation
**SCIENTIFIC
RETREAT**

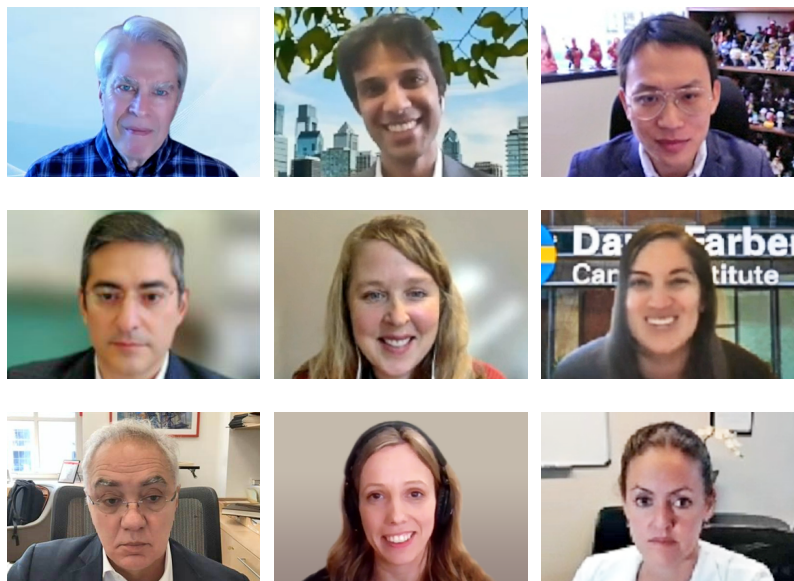
VIRTUAL SCIENTIFIC PROGRAM

Highlights from
the 28th Annual
PCF Scientific Retreat
October 28-29, 2021
November 4-5, 2021

Provided compliments of the
Prostate Cancer Foundation



Prostate Cancer
Foundation
Curing Together.



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Introduction

The 28th Annual Prostate Cancer Foundation (PCF) Scientific Retreat was held virtually over four days, on October 28-29 and November 4-5, 2021. The PCF Scientific Retreat is a leading global scientific conference that focuses on basic, translational, and clinical prostate cancer research. This conference has a legacy of featuring presentations on first-in-field, unpublished, and high impact research, and attendance by investigators from diverse fields who are leading the most impactful research studies in the world on prostate cancer.

The Annual PCF Scientific Retreat is an investment by PCF to foster global knowledge exchange and a collaborative research culture, in order to accelerate research that will ultimately bring an end to death and suffering from prostate cancer. Retreat attendees have been involved in the development of almost every treatment advancement for prostate cancer since the Foundation's inception, and many of them trace critical origins of their work to attendance at a PCF Retreat.

The 28th Annual Scientific Retreat featured the following:

- 52 presentations in the Plenary Session.
- 117 virtual poster presentations.
- 25 different scientific disciplines related to prostate cancer research presented and discussed.
- 53% of speakers presented at a PCF Scientific Retreat for the first time.
- 1,597 individuals from 33 countries registered for the Retreat, including 653 PhDs, 387 MDs, 112 MD/PhDs, 36 PharmDs, 4 PharmD/PhDs, 1 MD/PharmD, 1 DVM, 3 DVM/PhDs, 2 DMDs, 4 DOs, 1 DO/PhD, 8 JDs, 177 with Master's degrees (including MS, MRes, MA, MMed, MPA, MPH, MHA, MBA, Meng, ThM, and MSW degrees), 1 PA, and 2 RNs.
- Retreat registrants included 977 academic researchers or health care professionals, 71 government researchers or health care professionals, 355 biopharmaceutical industry professionals, 35 representatives from non-profit and other professional health care organizations, 4 private practice health care professionals, 2 media and journalism professionals, 65 patients, survivors, caregivers, advocates or other interested members of the general public, and 24 undergraduate and high school students.
- 213 academic institutions, 68 biopharmaceutical companies, and 15 medical research foundations.
- NIH, NCI, Dept. of Defense, and Veterans Affairs research leaders.
- Attendance by 199 PCF Young Investigators, and 206 researchers who have been on a PCF Challenge Award team.
- Attendance by 14 PCF Board of Director members and major donors.
- The 6th Annual PCF Women in Science Forum was held with over 422 attendees.

PCF is the world's leading philanthropic organization funding and accelerating prostate cancer research. The PCF "Global Research Enterprise" currently extends to 28 countries and funds a robust research portfolio. Founded in 1993, PCF has raised over \$912 million and provided funding to more than 2,149 research programs at more than 251 cancer centers and

universities. This includes \$71.3 million awarded to 349 PCF Young Investigators since 2007 and nearly \$235 million to PCF Challenge Award teams since 2008.

We thank the sponsors of the Retreat for their generous support: Advanced Accelerator Applications, Amgen, Bayer, Daiichi Sankyo, Janssen, Lantheus, Pfizer, AstraZeneca, Clovis Oncology, Sanofi Genzyme, Astellas, Bristol-Meyers Squibb, Exact Sciences, Foundation Medicine, Myovant Sciences, Sun Pharma, Merck, Arvinas, Constellation Pharma, Genentech, Dendreon, Essa Pharma, Veru, and MacroGenics.

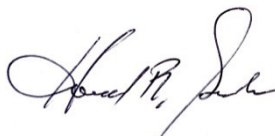
The 2021 State of Science Report was prepared by the Prostate Cancer Foundation to summarize the scientific presentations from the Retreat in a manner accessible to the general public. We hope that global dissemination of this knowledge will aid in advancing understandings of current prostate cancer research, encourage discourse and the exchange of new ideas and information, inspire new research, and stimulate increased support for scientific research. If you have any questions about this Report, please contact Dr. Andrea Miyahira at amiyahira@pcf.org.

All of the presentations and discussions from the 28th Annual Prostate Cancer Foundation (PCF) Scientific Retreat, as well as the PCF Women in Science Forum and the PCF Young Investigator Forum, can be viewed in full here: <https://www.pcf.org/scientific-retreat/28th-annual/video-replays/>.

Yours sincerely,



Charles J. Ryan, MD
President & CEO



Howard R. Soule, PhD
Executive Vice President
& Chief Science Officer
Lori and Michael Milken Chair



Andrea K. Miyahira, PhD
Director, Global Research &
Scientific Communications

Session 1: Dr. Andrew Hruszkewycz Memorial Session on Measuring and Targeting Lineage Plasticity to Prevent Lethal Prostate Cancer

A Tale of Two Evasions: Lineage Plasticity and Tumor Heterogeneity

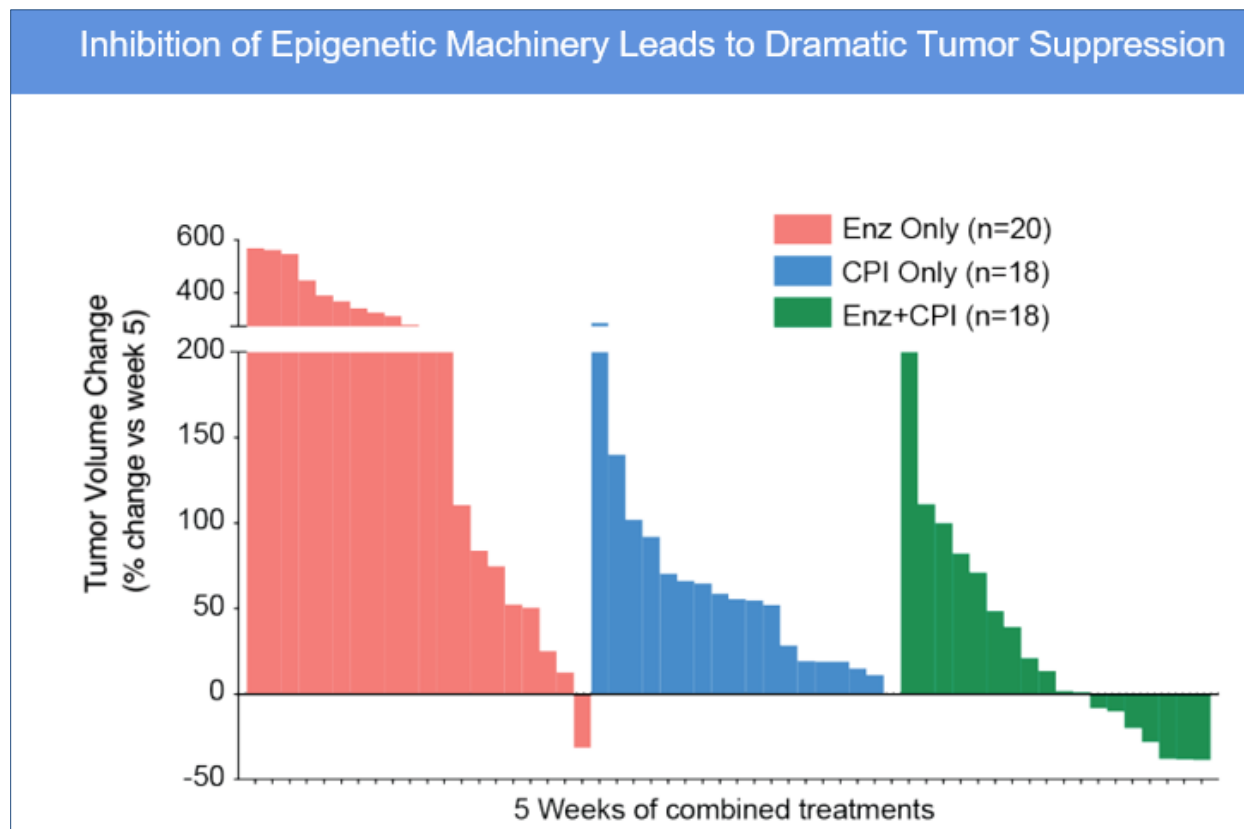
Ping Mu, PhD

UT Southwestern Medical Center at Dallas

- The androgen receptor (AR) is the primary driver of prostate cancer, and for decades has been the primary target of systemic therapy in patients with advanced prostate cancer. Unfortunately, resistance to AR-targeted therapies is nearly inevitable, and patients progress to the castration-resistant prostate cancer (CRPC) disease state.
- Resistance to AR-targeted therapy can occur via several mechanisms and is often accompanied by increased tumor heterogeneity.
- In ~60% of CRPC cases, the AR pathway is partially or fully restored by either AR pathway mutations, expression of constantly active AR variants that are not inhibited by current treatments, mutations that amplify the AR gene, or activation of pathways that bypass but replicate AR activity. The remainder of CRPC cases (up to 40%) are driven by AR-independent mechanisms.
- AR-independent mechanisms include lineage plasticity, in which prostate cancer cells lose luminal epithelial prostate cell features and gain features of other cells that do not require AR for survival, most commonly neuroendocrine cells.
- Lineage plasticity can be driven by mechanisms including combined deletion of the tumor suppressor genes p53 and RB1, which is seen in ~10% of CRPC cases. Tumor cells lacking p53 and RB1 lose typical prostate cell luminal features and take on a stem-cell or multi-lineage phenotype. This state is plastic and highly heterogeneous and can then be driven by selection pressures such as treatments, into AR-independent lineages, including neuroendocrine prostate cancer (NEPC), lineages lacking both AR and neuroendocrine genes (“double-negative”), or others.
- Understanding the biology and origin of lineage plasticity is critical to developing new treatment approaches that can prevent or reverse CRPC.
- Dr. Ping Mu discussed research to identify mechanisms driving lineage plasticity and their relationship with tumor heterogeneity.
- Dr. Mu and colleagues performed a study to screen the 730 most frequently deleted genes in prostate cancer to identify gene-deletions that confer resistance to AR-targeted therapy.
- One of the top genes identified in this screen was CHD1 (Chromodomain Helicase DNA Binding Protein 1). CHD1 is an epigenetic regulator with the function of remodeling chromatin, meaning it controls how tightly wound DNA is, in order to determine which genes a cell can and can't express.
- CHD1 is frequently deleted in prostate cancer, with deletions in 8-20% of cases.
- The correlation between CHD1 levels and clinical benefit was evaluated in a cohort of 56 patients treated with either abiraterone or enzalutamide. Patients with lowest levels of CHD1 develop resistance to these AR-targeted therapies significantly faster compared with patients with highest levels of CHD1.

- In preclinical prostate cancer models, deletion of the CHD1 gene resulted in tumors that were highly resistant to treatment with enzalutamide. CHD1 deletion alone did not lead to more aggressive CRPC tumor growth.
- Interestingly, in CHD1-deleted tumor cells, the normal activity of AR was still inhibited by treatment with enzalutamide. This indicates that in CHD1-deleted cells, an alternate factor maintains tumor growth when AR is inhibited, either due to its increased abundance or increased accessibility to its DNA in the genome.
- Using integrated computational analysis of genome-wide gene expression and epigenetic landscape data, Dr. Mu and team identified 22 candidate enzalutamide-resistance driver genes that were highly upregulated in the CHD1-deleted tumor cells. In a second type of assay using a gene-deletion method called CRISPR, 4 of these genes were confirmed as enzalutamide-resistance driver genes in CHD1-deleted tumor cells: GR, BRN2, TBX2 and NR2F1. Three of these, GR, BRN2 and TBX2, have previously been identified as playing key roles in prostate cancer progression and metastasis, thus validating these methods for identifying prostate cancer driver genes.
- Interestingly, dramatically increased intratumor heterogeneity was observed in expression of these 4 genes in different enzalutamide-resistant CHD1-deleted tumor lines. This heterogeneity increased with increased length of enzalutamide treatment, until each cell line finally committed to express just one of these genes.
- Based on these data, Dr. Mu hypothesizes that loss of CHD1 results in a dysregulated and plastic status of chromatin, which enables the upregulation of different transcriptional programs in different tumor cell subclones. When those heterogeneous subclones are challenged by selection pressure of treatment, they compete with each other until one arises as the dominant subclone driven by one of the driver genes.
- To confirm if similar heterogeneity occurs in patients, gene expression data from 212 CRPC patient tumor samples was evaluated. Patient tumors could be stratified into 5 distinct groups: CHD1-high tumors, and four CHD1-low subtypes, each with high expression of one of the resistance driver genes.
- A panel of CHD1-loss tumors expressing different driver genes were examined for differences in gene expression, and all, no matter which driver gene was expressed, exhibited downregulation of typical prostate luminal genes and upregulation of genes involved in stem cell-like and plasticity phenotypes.
- Using inducible laboratory models, Dr. Mu demonstrated that expression of lineage plasticity genes occurs rapidly following loss of CHD1, and reverts if CHD1 is turned back on again. These data suggest that induction of lineage plastic programs is controlled at the epigenetic level.
- These results suggest that therapeutically targeting the epigenetic machinery may prevent or delay progression to lineage plasticity, enzalutamide-resistance, and CRPC.
- In preclinical mouse models using enzalutamide-resistant CHD1-loss human prostate cancer derived tumors, treatment with enzalutamide was largely ineffective while treatment with the BET inhibitor CPI slowed tumor growth in most mice (**Figure**). However, combination treatment with CPI and enzalutamide dramatically delayed tumor growth (**Figure**; published in *Cancer Cell*. 2020 Apr 13;37(4):584-598.e11.).
- Altogether, tumor heterogeneity is a major driver of treatment resistance, and can be caused by lineage plasticity, which is driven by epigenetic and genetic alterations. These results from Dr. Mu demonstrate the mechanisms by which loss of CHD1 contributes to epigenetic plasticity, and drives upregulation of lineage plastic gene expression programs, enabling prostate cancer cells to develop resistance to AR-targeted therapy and progress to lethal CRPC.

- Targeting the epigenetic machinery has the potential to prevent progression to CRPC and deserves further study.
- In further work, Dr. Mu and colleagues are investigating the molecular details of mechanisms that contribute to tumor heterogeneity, lineage plasticity, and treatment resistance in prostate cancer, to develop innovative therapeutic approaches to prevent or reverse the onset of resistance and tumor progression.



Measuring CRPC Cellular Heterogeneity at the Single Cell Level to Inform Treatment Strategies

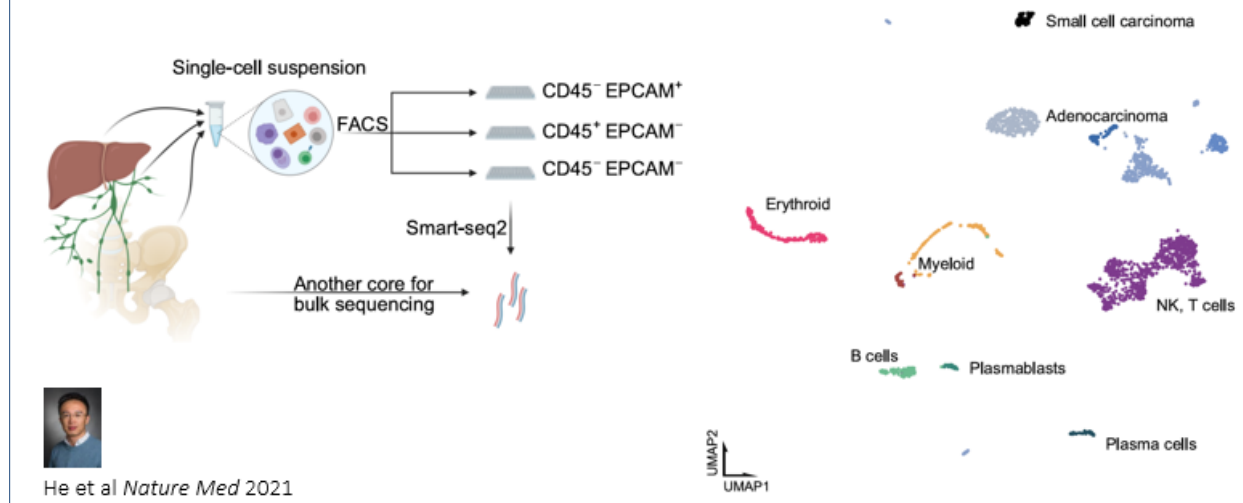
Eliezer Van Allen, MD, PhD
Harvard: Dana-Farber Cancer Institute

- While all prostate cancers originate in prostate cells, the molecular mechanisms that drive their initiation, progression from localized to metastatic disease, and development of treatment resistance, vary.
- One mechanism that contributes to tumor heterogeneity is plasticity, in which cells gain the ability to shift their phenotypes from that of prostate cells to other cell types, such as

neuroendocrine cells. Neuroendocrine prostate cancer (NEPC) is a highly aggressive subset of prostate cancer.

- Dr. Eliezer Van Allen discussed using studies of single cells to identify mechanisms of progression to castration resistant prostate cancer (CRPC) and NEPC, including the role of the immune system.
- These studies aimed to answer questions including identification of the cells that comprise different metastatic niches in CRPC, the transcriptional programs associated with treatment resistance, tumor-extrinsic mechanisms that mediate disease progression, and how the immune system responds to metastases.
- Single cell sequencing analyses were done on CRPC biopsy samples to study gene expression in tumor cells and tumor-infiltrating immune cells (**Figure**).
- TGF-beta was identified as a top gene expression program turned on in tumor cells after treatment with enzalutamide. Upregulation of TGF-beta was validated in tumor pathology studies and pre-clinical models, demonstrating that single cell analyses can be used to identify relevant cancer driving mechanisms.
- Analyses of single cell tumor biopsy data from a patient with NEPC found upregulation of SOX2 and EZH2 genes which are previously known to be involved in NEPC, as well as HOX5, HOX6, and NR1D2 genes which were previously unknown to be involved in NEPC. The HOX5, HOX6, and NR1D2 genes were validated as upregulated in larger NEPC cohorts, demonstrating that single cell studies in single patients can also be used to identify new cancer-associated molecular pathways.
- Single cell immune analyses of pre- and post-enzalutamide biopsies from a single patient found expansion of some T cell clones after enzalutamide. A subset of CRPC patients were also found to have T cell clone expansion after treatment with enzalutamide. Dr. Van Allen hypothesizes that patients exhibiting T cell clone expansion after enzalutamide may benefit from subsequent treatment with immunotherapy.
- In ongoing studies, multiple technologies are being combined to analyze patient tumor and blood samples on deeper levels. These include whole genome, whole exome, and single cell RNA sequencing on serial patient samples collected before, during, and after treatment.
- The Metastatic Prostate Cancer Project is an initiative in which patients can self-enroll and contribute their data and tumor biopsy or surgical samples to research. Serial blood samples are also being collected from patients enrolled. Studies on these samples will help to better understand how tumors and the immune system evolve in patients over time.

Single cell resolution for biological discovery in CRPC metastatic biopsies



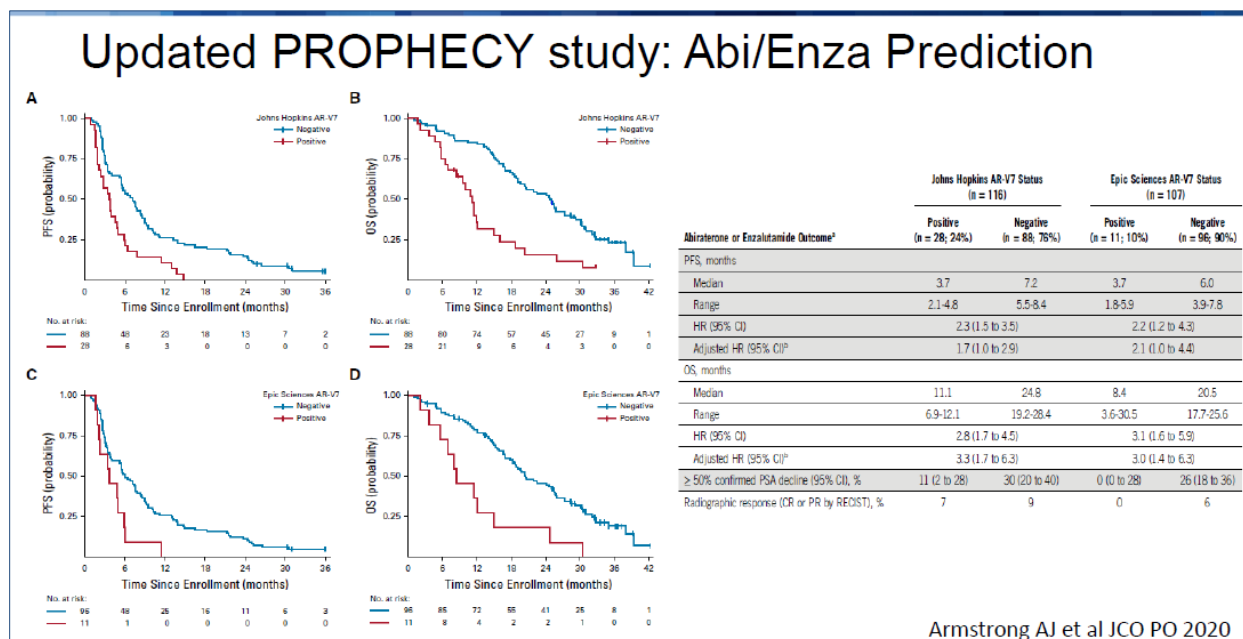
Measuring Lineage Plasticity and Heterogeneity in mCRPC with Liquid Biopsies to Inform Treatment

Andrew Armstrong, MD, ScM
Duke University

- The androgen receptor (AR) is the primary driver of prostate cancer and hence, the primary target of treatment for patients with aggressive and advanced disease. Unfortunately, in many patients, development of resistance to AR-targeted therapy and progression to castration resistant prostate cancer (CRPC) is common and can be driven by various mechanisms. The development of biomarkers to inform treatment selection and treatment resistance for patients with different subtypes of CRPC is critical.
- AR-V7 is an alternate version of AR that is constantly active and cannot be blocked by existing AR-targeted treatments. AR-V7 is upregulated in some CRPC cells and is under study for its role as a biomarker and mechanism of resistance to AR-targeted therapy.
- Several tests have been developed that can detect AR-V7 mRNA (Adnatest) or protein (Epic nuclear test) in circulating tumor cells (CTCs), which are tumor cells that are found in the blood.
- Dr. Andrew Armstrong presented updated results from the PROPHECY clinical trial, which prospectively evaluated AR-V7 CTC tests as biomarkers to guide treatment selection in patients with CRPC who are considering additional AR-targeted therapy vs. taxane chemotherapy or other options.

- The PROPHECY trial enrolled 120 patients with metastatic CRPC (mCRPC) who were candidates for receiving abiraterone or enzalutamide, and had not had prior taxane chemotherapy. AR-V7 CTC tests were performed on samples from before and after treatment with abiraterone or enzalutamide, and after taxane chemotherapy in patients who went on to receive taxanes after abiraterone or enzalutamide. In addition, studies were done on samples from patients in this trial to identify other biomarkers of treatment resistance.
- Patients who had AR-V7-positive CTCs by either test were found to have significantly poorer overall survival and progression free survival compared with patients with AR-V7-negative CTCs. This demonstrates that AR-V7-positive CTCs are a biomarker of poorer patient outcomes and poor response to frontline AR-targeted therapies.
- Heterogeneity in the expression of AR-V7 in tumors cells within patients was observed. Many patients with AR-V7-positive CTCs also had AR-V7-negative CTCs. Furthermore, a subset of patients with only AR-V7-negative CTCs had poor outcomes on AR-targeted therapy, suggesting other mechanisms of treatment resistance are involved and other biomarkers are needed.
- Results from PROPHECY demonstrated that patients with AR-V7-positive CTCs were significantly less likely to benefit from treatment with abiraterone or enzalutamide compared with patients with AR-V7-negative CTCs (**Figure**), while similar benefit was seen with taxane chemotherapy for both groups. These results demonstrate that the AR-V7 CTC test can help to inform treatment decisions between AR-targeted therapy and taxane chemotherapy for patients with mCRPC.
- AR-targeted therapy has recently become FDA-approved for use earlier in prostate cancer disease history. This has resulted in increasing numbers of mCRPC patients that are AR-V7-negative due to the development of lineage-plasticity, NEPC, and other AR-independent mechanisms of CRPC, that drive treatment resistance to AR-targeted therapy.
- Loss/mutation of the tumor suppressor genes RB1 and TP53 are seen in the most aggressive and rapidly lethal subsets. The development of biomarker tests to identify these patients is critical.
- Dr. Armstrong and colleagues compared genomic sequencing results from CTCs vs. circulating tumor DNA using matched blood samples from 140 patients on the PROPHECY trial. CTCs were often better indicators than circulating tumor DNA for identifying important CRPC driver mutations such as MYC-N oncogene amplification, RB-loss, and PTEN-loss.
- This discordance in results from CTCs vs. circulating tumor DNA has been observed by other groups, and is likely due to CTCs representing live, treatment-resistant tumor cell populations that survived the therapy, while circulating tumor DNA may have largely come from tumor cells that have died.
- MYC-N-amplification and PTEN-loss in CTCs were found to be strongly associated with shorter progression free survival in mCRPC patients.
- To identify biomarkers for guiding treatment decisions about AR-targeted therapy in AR-V7-negative patients, a study was done comparing genomic alterations in CTCs from patients who responded to abiraterone or enzalutamide for over a year (responders) vs. patients who progressed on either of these treatments within 3 months (non-responders).
- CTC mutations in TP53, PTEN, BRD4, WNT, DNA repair, epigenetic regulators, AR signaling, and lineage plasticity pathways (such as CHD1 loss) were associated with poor clinical outcomes in patients with AR-V7-negative mCRPC treated with abiraterone or enzalutamide. These alterations are well known to contribute to AR-targeted therapy resistance.

- CHD1-loss was a top alteration associated with abiraterone/enzalutamide resistance and with poor survival. CHD1 is a regulator of lineage plasticity, and alterations in CHD1 are associated with various AR-independent treatment resistance mechanisms.
- CTCs can also be used to study tumor phenotype (cell appearance and function). For instance, CTC assays to diagnose NEPC are being developed. NEPC cells are often very small, circular, and may or may not express AR.
- Patients with NEPC phenotype CTCs had poorer overall survival. These findings were performed using patient samples from the PROPHECY trial and validated in a second patient cohort.
- These findings demonstrated that in AR-V7 negative patients, NEPC CTC phenotyping may help to identify patients likely to have poor responses to abiraterone or enzalutamide, and may benefit from alternative combination approaches or clinical trials.
- Dr. Himisha Beltran and colleagues have developed a genomic-methylation test using circulating tumor DNA that can identify patients with NEPC. This test evaluates for genomic alterations in genes including *AR*, *RB1*, *TP53*, and *CYLD*, plus methylation alterations on 20 genomic sites.
- Overall, these studies demonstrate that measuring lineage plasticity in patients has challenges, as this is a dynamic state of tumor evolution in response to treatment. Better understandings of the different mechanisms of AR-independent CRPC will enable the development of improved biomarkers and precision medicines for patients with aggressive subtypes of CRPC.



Targeting Transformed Neuroendocrine Cells to Overcome Treatment Resistance

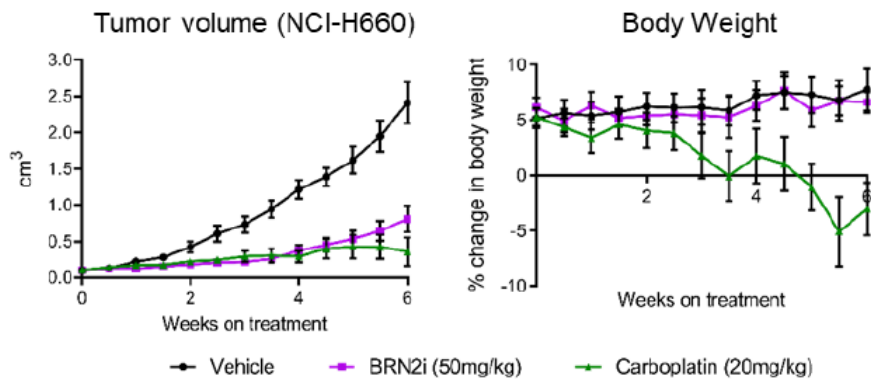
Amina Zoubeidi, PhD

Vancouver Prostate Centre, Canada

- The development of treatment resistance is a major problem in oncology. Prostate cancer for instance, is driven and reliant on the androgen receptor (AR). Thus, treatments that target AR are usually highly effective, yet after some time, patients often develop resistance and progress to castration resistant prostate cancer (CRPC).
- Various mechanisms can drive treatment resistance in prostate cancer.
- These include genomic mechanisms, in which a population of cancer cells gain new mutations that enable therapy-resistance, and expand in numbers after treatment.
- Non-genomic mechanisms of treatment resistance are driven by epigenetic and gene expression alterations. Cancer cells can then gain lineage plasticity and trans-differentiate into alternate cell types, such as neuroendocrine cells, that do not rely on AR. This state is dynamic and reversible.
- Dr. Amina Zoubeidi discussed mechanisms that drive development of neuroendocrine prostate cancer (NEPC), an aggressive subtype of CRPC characterized by cancer cells that have lost prostate cell features and gained neuroendocrine cell features.
- NEPC is resistant to AR-targeted therapy. Still, AR remains expressed in some NEPC cases. The role of AR in these NEPC subsets is unclear.
- AR is a transcription factor that is activated by androgens. Once activated, AR binds to gene control regions to activate expression of certain genes and repress expression of others. The DNA sequence that AR can specifically bind to is called the “AR response element” (ARE).
- Dr. Zoubeidi and colleagues compared the activity of AR in CRPC vs NEPC models. AR bound to a slightly overlapping but larger number of gene sites in NEPC compared with CRPC.
- AR-binding sites that were unique in NEPC included stem cell and neuronal cell genes. The sites that AR bound to on these genes did not have typical ARE sequences but instead were near stem cell and neuronal transcription factor sites. The new set of genes bound by AR in NEPC was found to promote a “lineage infidelity” phenotype.
- Epigenetic regulation is a major mechanism that controls and maintains cell identity. Epigenetic regulators control the 3D structure of DNA to determine which areas of the genome are open and can be accessed by transcription factors, and which are tightly wound up and inaccessible.
- Many of the genes uniquely bound by AR in NEPC were found to be closed in CRPC but open in NEPC, due to epigenetic alterations. Such genes included *GATA4*, *FOXA*, *LHX1*, *NeuroD1*, *OCT4*, and *ASCL1*.
- AR was also found to drive expression of an expanded gene set including neuronal genes after AR-targeted therapy in newly diagnosed patients that received a 3-month course of neoadjuvant enzalutamide, followed by prostatectomy.
- Studies were performed to characterize epigenetic landscape changes in CRPC models in response to enzalutamide treatment.

- An increase was observed in the number of open DNA regions from ~2,700 regions before enzalutamide treatment, to ~26,000 regions after 10 days of enzalutamide.
- Before treatment, a very small fraction of open DNA regions was found in gene promoters, while after treatment, many open gene promoter regions were found.
- These studies demonstrate that enzalutamide treatment redirected DNA accessibility from conventional AR-driven gene expression programs to that of stem cell plasticity and neuronal processes.
- For example, the conventional AR-regulated gene PSA was highly upregulated in typical CRPC cells but repressed in NEPC cells, while expression of the developmental gene WNT5A and neuronal transcription factor BRN2 were low in CRPC and high in NEPC.
- BRN2 is a master transcription factor that controls neuronal differentiation during development. Expression of BRN2 is sufficient to drive neuronal differentiation in embryonic stem cells and fibroblasts. BRN2 is also highly expressed in other cancers with neuronal phenotypes such as small cell lung cancer.
- High expression of BRN2 was confirmed in additional clinical NEPC datasets.
- BRN2 is a special type of transcription factor called a pioneer factor, which is able to bind to both open and closed DNA regions. This ability is likely critical to its ability to drive NEPC.
- BRN2 was found to drive NEPC growth in preclinical models, while turning off expression of BRN2 slowed NEPC tumor growth and decreased neuronal gene expression.
- Dr. Zoubeidi and colleagues determined the 3D structure of the BRN2 DNA binding domain and used this structure to screen for small molecules able to bind and inhibit BRN2.
- A candidate BRN2-inhibitor was identified which strongly bound and inhibited the functions of BRN2. Treatment of NEPC cells with the inhibitor prevented their growth.
- Similar alterations in gene expression patterns were observed between cells with a genetic deletion of BRN2 and cells treated with the BRN2-inhibitor, demonstrating specificity of the inhibitor for BRN2.
- The BRN2-inhibitor was found to inhibit BRN2 by preventing its ability to bind to DNA.
- The BRN2-inhibitor was able to inhibit growth of NEPC tumors in mice (**Figure**). NEPC tumors treated with the BRN2-inhibitor downregulated neuronal gene programs.
- No obvious toxicity was seen in mice treated with the BRN2-inhibitor, suggesting safety (**Figure**). In contrast, treatment with the chemotherapy carboplatin (which is the current standard treatment for NEPC) similarly prevented NEPC tumor growth in mice, but also resulted in toxicity as exhibited by significant body weight loss (**Figure**).
- Altogether, these studies demonstrate that enzalutamide resistance can be conferred by upregulation of neuronal pathways and transdifferentiation to NEPC, a phenomenon driven by BRN2 and epigenetic changes. BRN2 is a promising target for treatment of NEPC. Further preclinical development of a novel BRN2-inhibitor is underway.

BRN2i vs. Carboplatin (Standard of Care)



Session 2: Therapeutic Degraders as a New Class of Prostate Cancer Treatments

Targeting Enhancer Addiction in Prostate Cancer by Impeding Chromatin Accessibility

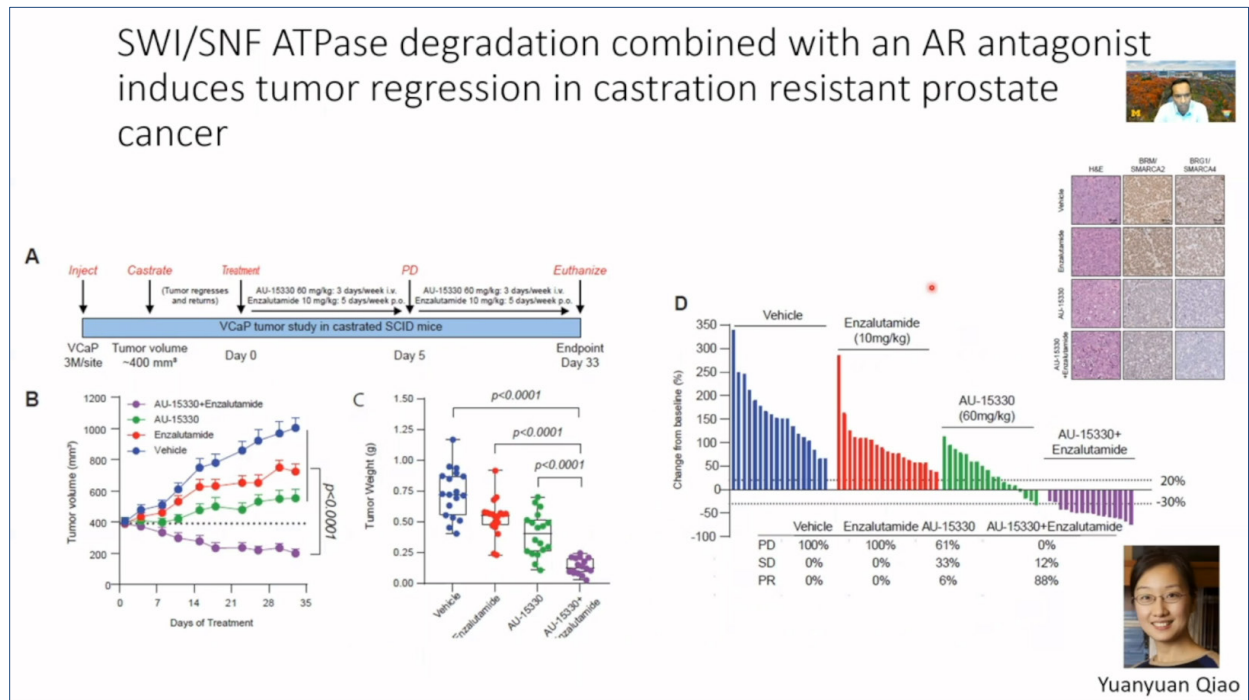
Arul M. Chinnaiyan, MD, PhD

University of Michigan, Michigan Center for Translational Pathology

- Gene expression is a tightly regulated process that is controlled on several levels in cells.
- Genes are encoded on chromosomes, which are arranged and compressed in 3D to enable the expression vs. repression of various genes in different cell types.
- Gene expression requires relaxation/unwinding of the DNA surrounding that gene (“chromatin remodeling”), and the recruitment of transcription factors, which are proteins that recognize specific gene regions (promoters and enhancers) and bring in the transcriptional machinery to transcribe mRNA from the gene’s DNA.
- In prostate cancer, the oncogenic transcription factors that drive expression of growth and survival genes include the androgen receptor (AR), FOXA1, ERG, MYC, and HOXB13.
- Dr. Arul Chinnaiyan discussed studies to block the activity of these transcription factors by preventing chromatin remodeling as a novel therapeutic approach in prostate cancer.
- A study was performed to identify proteins that interact with AR, FOXA1, and ERG. The SWI/SNF chromatin remodeling complex was found to interact with all three.
- SWI/SNF is a multi-protein complex that functions to remodel chromatin. The ATP (energy) required for function of the complex is created by the subunits SMARCA2 and SMARCA4.
- Interestingly, SWI/SNF complex proteins are mutated in ~20% of various cancers, though rarely mutated in prostate cancer.
- PROTACs are small molecule inhibitors with two arms: one binds a target protein and the other binds an E3 ligase, an enzyme that tags proteins to be degraded by the proteasome. This causes the target protein to be degraded, significantly reducing its levels in cells.
- An experimental PROTAC targeting SMARCA2 and SMARCA4 was tested in a series of 65 human-derived normal and cancer cell lines from 14 different lineages.
- The SMARCA2/4-targeted PROTAC inhibited the growth of several AR-dependent prostate cancer cell lines and some multiple myeloma cell lines. Growth of benign prostate cells and other types of cancers and normal cells were unaffected by the SMARCA2/4-targeted PROTAC. This indicates that only cancers dependent on AR and certain other transcription factors are sensitive to treatment with the SMARCA2/4-targeted PROTAC.
- The SMARCA2/4-targeted PROTAC caused degradation of SMARCA2 and SMARCA4 proteins in cell lines regardless of whether or not cell growth was inhibited.
- Epigenetic sequencing studies found that treatment of prostate cancer cells with the SMARCA2/4-targeted PROTAC caused significant compaction of chromatin, while a BRD4-targeted PROTAC did not have this effect. BRD4 is another chromatin remodeling protein that has been investigated as a therapeutic target for cancer treatment.
- Chromatin regions that were compacted by SMARCA2/4-targeting included enhancer regions regulated by prostate cancer oncogenes FOXA, ETS, and AR, while regions that remained unaffected were mostly promoter regions. Further studies found that DNA-binding

by AR, FOXA1, and ERG was significantly reduced after SMARCA2/4-targeting treatment. The expression of genes regulated by AR, FOXA1, and ERG were also lost.

- A method (Hi-ChIP) to evaluate the 3D interactions between promoter and enhancer sites on the AR gene found that these interactions were lost after SMARCA2/4-targeting treatment.
- The SMARCA2/4-targeted PROTAC was tested in mouse models and was found to slow the growth of AR-expressing castration-resistant prostate tumors (**Figure**). Further, the SMARCA2/4-targeted PROTAC synergized with enzalutamide and caused significant tumor regression (**Figure**), an effect that has never been seen with any other treatment in this highly aggressive model.
- Importantly, no toxicity was seen in mice treated with the SMARCA2/4-targeted PROTAC. While previously developed BRD4-inhibitors can cause significant toxicities to goblet cells and germ cells, no toxicity to these cell types was seen with the SMARCA2/4-targeted PROTAC.
- Overall, these data demonstrate that the SWI/SNF chromatin remodeling complex is required for the oncogenic prostate cancer transcription factors AR, FOXA1, and ERG to drive expression of tumor growth and survival genes. This complex, and specifically the enzymatic subunits SMARCA2/4, represent highly promising new therapeutic targets in prostate cancer.



Session 3: PSMA Theranostics: The New Age of Prostate Cancer Imaging and Treatment

LuPSMA: The Newest Treatment Class for Advanced Prostate Cancer

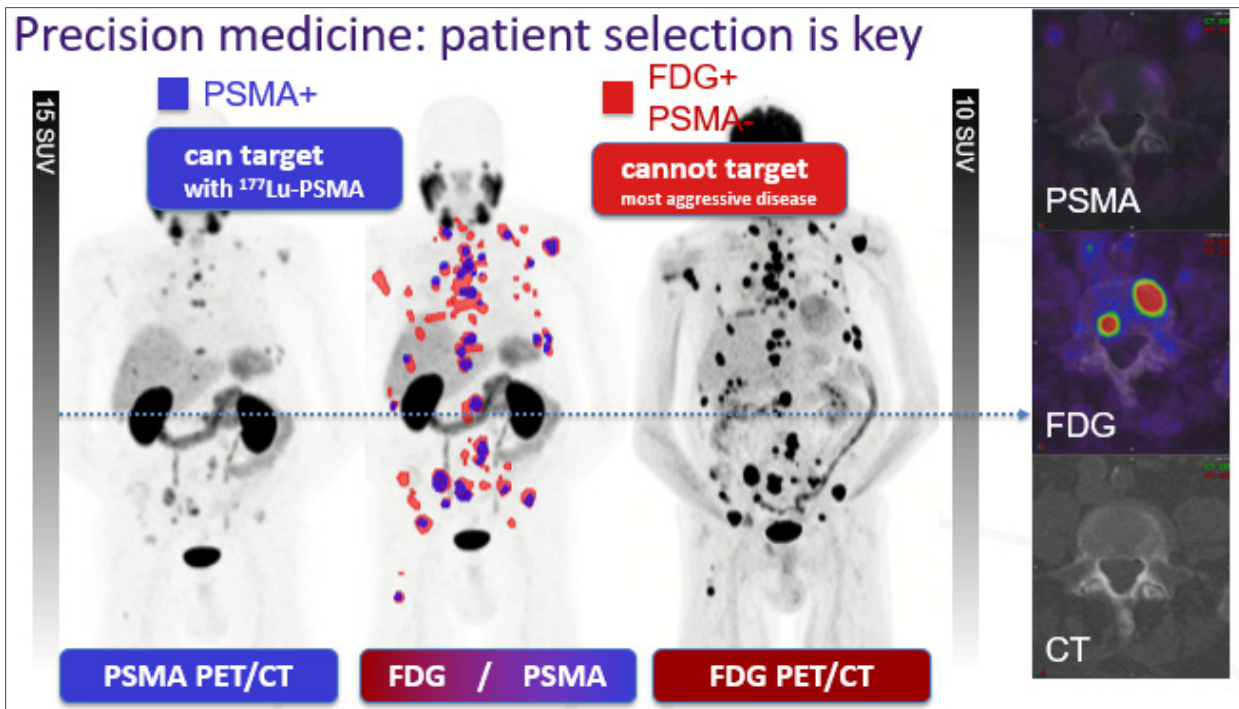
Michael Hofman, MBBS

Peter MacCallum Cancer Centre; Prostate Cancer Theranostics and Imaging Centre of Excellence (ProSTIC), Australia

- PSMA is a protein present on the surface of most prostate cancer cells and is a highly promising target for imaging and treatment of prostate cancer.
- Over the past ten years, the field of PSMA “theranostics” (therapy + diagnostics) has rapidly evolved from using PSMA-targeted agents for diagnostics with PET imaging, to treatment with radioligand therapy.
- Dr. Michael Hofman discussed the evolving field of PSMA theranostics, and research done at Peter MacCallum Cancer Centre.
- Dr. Hofman leads ProSTIC (Prostate Cancer Theranostics and Imaging Centre of Excellence), a program launched by PCF at the Peter MacCallum Cancer Centre to perform new theranostics and imaging clinical trials, perform discovery research, and provide education and leadership to the global community on the clinical use of PSMA theranostics.
- PSMA theranostics is performed using PSMA-targeted small molecules that are attached to radioactive isotopes. For PET imaging, the radioisotopes used (such as 18-Fluorine or 68-Gallium) can be detected by PET scanners but have no therapeutic (cell damaging) activity. For radioligand therapy, the radioisotopes used (such as 177-Lutetium) emit high-energy beta and/or alpha particles that kill the targeted prostate cancer cells by damaging their DNA.
- The first patient was imaged with PSMA PET imaging at Peter MacCallum Cancer Centre in 2014.
- In 2020, the ProPSMA study was published. This trial, led by Dr. Hofman, compared the performance of ⁶⁸Ga-PSMA-11 PSMA PET imaging vs. standard imaging (CT + bone scans) in patients with newly diagnosed prostate cancer. PSMA PET demonstrated higher accuracy (92% vs. 65%), a greater likelihood to change treatment decisions (28% vs. 15%), and fewer uncertain results (7% vs. 23%) compared with CT + bone scans.
- In 2020 and 2021, the FDA approved two PSMA PET imaging agents for use in prostate cancer diagnosis and patient management: ⁶⁸Ga-PSMA-11 and ¹⁸F-DCFPyL (Pylarify®).
- ¹⁷⁷Lu-PSMA-617 is a PSMA-targeted radioligand therapy that has been tested in two randomized trials thus far in patients with metastatic castration-resistant prostate cancer (mCRPC): TheraP and VISION.
- The randomized Phase 2 TheraP trial tested ¹⁷⁷Lu-PSMA-617 vs. cabazitaxel in 200 patients with mCRPC. PSA reductions ≥50% occurred in significantly more patients who received ¹⁷⁷Lu-PSMA-617 vs. cabazitaxel (66% vs. 37%). In addition, significantly more patients who received ¹⁷⁷Lu-PSMA-617 vs. cabazitaxel experienced tumor shrinkage on scans (49% vs. 24%).
- The randomized Phase 3 VISION trial tested ¹⁷⁷Lu-PSMA-617 + standard of care vs. standard of care alone in over 800 patients with mCRPC. Overall survival was significantly longer among patients who received ¹⁷⁷Lu-PSMA-617 vs. standard of care alone (a median

of 15.3 months vs. 11.3 months), representing a 38% reduction in risk of death. These results are anticipated to lead to FDA-approval for ¹⁷⁷Lu-PSMA-617 in the near future.

- The TheraP and VISION trials also demonstrated that ¹⁷⁷Lu-PSMA-617 is a well-tolerated treatment. Radiation from ¹⁷⁷Lu-PSMA-617 is only able to travel ~1mm through tissues, thus damage to surrounding tissues is limited. Adverse effects of note include dry mouth (mostly Grades 1-2, affecting 39-60% of patients), nausea (mostly Grades 1-2, affecting 34-40% of patients), and anemia and thrombocytopenia (mostly Grades 1-2 affecting 9-19% of patients, with ~10% of patients experiencing Grades 3-4).
- Compared with cabazitaxel, patients treated with ¹⁷⁷Lu-PSMA-617 experienced fewer side effects, including less frequent diarrhea, fatigue, hair loss, urinary symptoms, dizziness, skin rash, pain in hands and feet, and insomnia.
- Importantly, the VISION trial demonstrated significantly better quality of life measures in patients who received ¹⁷⁷Lu-PSMA-617 vs. standard of care alone. These include a significant delay in worsening pain (median of 14.3 vs. 2.9 months).
- Despite the ~4-month average improvement in overall survival with ¹⁷⁷Lu-PSMA-617, the treatment is not curative. Investigations into ways to improve the treatment further include using PET imaging and artificial intelligence (AI) algorithms to deliver patient-specific doses, testing different radioisotopes that may have better tumor-killing capacity, and developing more potent combination treatment strategies.
- Patient selection is also key, as not all patients benefit from treatment with ¹⁷⁷Lu-PSMA-617. Both VISION and TheraP required patients to have positive PSMA PET imaging (although the specific requirements were different). Additionally, TheraP used FDG PET imaging alongside PSMA PET imaging to screen patients, and required all detectable tumors (by either scan type) to express PSMA, for a patient to be eligible for the trial. This is because tumors that do not express PSMA would not be targeted by ¹⁷⁷Lu-PSMA-617, and patients with such tumors would be less likely to benefit from the treatment (**Figure**).
- The levels of FDG PET and PSMA PET intensity may also be a biomarker for predicting which patients may or may not benefit with ¹⁷⁷Lu-PSMA-617. In a multicenter study of 270 patients treated with ¹⁷⁷Lu-PSMA-617, brighter FDG PET images were associated with less benefit while brighter PSMA PET were associated with greater benefit. This is likely because FDG PET imaging indicates faster growing tumors, while PSMA PET imaging indicates tumors that can be targeted with ¹⁷⁷Lu-PSMA-617.
- Hofman and team have also used imaging to measure how much radiation dose actually makes it to tumor sites with ¹⁷⁷Lu-PSMA-617, and have found a threshold of dose, below which, patients rarely respond to the treatment. Why the dose of radiation that gets to tumors can differ despite patients receiving the same amount of ¹⁷⁷Lu-PSMA-617, is unclear.
- Studies are also investigating the efficacy of ¹⁷⁷Lu-PSMA-617 when used earlier in the disease course. Ongoing trials are testing ¹⁷⁷Lu-PSMA-617 in patients with hormone-sensitive metastatic prostate cancer or with localized prostate cancer prior to surgery.



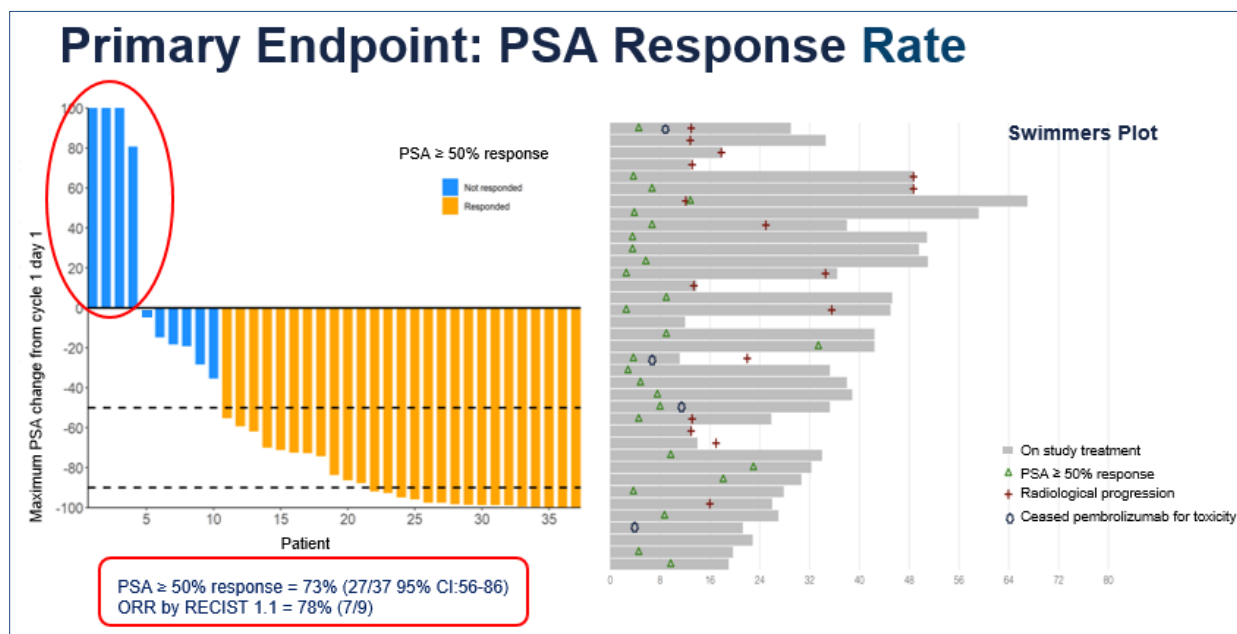
Results from the PRINCE Trial: Testing the Combination of LuPSMA with Pembrolizumab in mCRPC

Shahneen Sandhu, MBBS
Peter MacCallum Cancer Centre, Australia

- Immunotherapy activates a patient's own immune system to fight their cancer. Immunotherapies such as pembrolizumab, have been highly effective in many cancer types, but have not yet been optimized for prostate cancer. Prostate cancer is considered "immunologically cold," meaning it typically does not activate immune responses. New strategies are needed for immunotherapy to be effective in prostate cancer.
- Radiation therapy can cause cancer cells to die in a way that alerts the immune system, and thus may synergize with immunotherapy. Various forms of radiation treatment are being studied for their potential to synergize with immunotherapy.
- ^{177}Lu -PSMA-617 (LuPSMA) radioligand therapy is a systemically delivered form of prostate cancer-targeted radiation.
- The TheraP and VISION trials (discussed in more detail by Dr. Hofman, above) demonstrated that LuPSMA can significantly improve radiographic progression free survival (rPFS) and overall survival in patients with metastatic castration-resistant prostate cancer (mCRPC). However, patients treated with LuPSMA eventually progress and further optimization remains needed.

- Dr. Shahneen Sandhu discussed the potential for combining immunotherapy with LuPSMA for the treatment of prostate cancer.
- Dr. Sandhu hypothesized that LuPSMA, which enables systemic and targeted delivery of beta particle-emitting radiation to PSMA-expressing prostate cancer lesions, will potentially release tumor-associated antigens from multiple sites and facilitate immune recognition.
- Dr. Sandhu and team led the single-arm Phase 1/2 PRINCE trial, which tested the combination of LuPSMA (6 cycles, every 6 weeks) with the immunotherapy pembrolizumab (up to 35 cycles, every 3 weeks) in 37 patients with mCRPC, who had previously progressed on abiraterone, enzalutamide or apalutamide. To be eligible, patients were required to have positive PSMA PET scans, and no tumors detectable on FDG PET scans that were PSMA-negative.
- Treatment-related adverse events (TEAEs) were consistent with those of single agent LuPSMA and pembrolizumab. These included Grade 1-2 xerostomia (dry mouth), fatigue, nausea, rash, and pruritis. Hematological toxicities (anemia, thrombocytopenia, and neutropenia) were largely Grade 1-2 and manageable.
- Immune-related adverse events were also primarily Grade 1-2 including rash, pruritis, myalgia, arthralgia, and electrolyte abnormalities. However, several patients experienced more severe (grade 2-3) and co-occurring immune-related adverse events, including colitis, mucosal pemphigus, ocular myasthenia gravis, optic neuritis, and myocarditis.
- There were no Grade 4 or 5 TEAEs. Four patients discontinued pembrolizumab due to toxicities and none discontinued LuPSMA due to toxicities.
- Overall, PSA \geq 50% declines occurred in 73% (27/37) of patients (**Figure**).
- Tumor shrinkage was seen in 7 of 9 patients with measurable disease on scans, representing an overall response rate (ORR) of 78%.
- At 24 weeks, the median radiographic progression free-survival (rPFS, the time from trial enrollment until tumors grow on scans) was 65%, and PSA progression-free survival was 68%.
- At the time of this presentation, 23 patients were still receiving treatment.
- Despite stringent patient selection criteria, some patients experienced no benefit from the treatment. More research is needed to better understand the mechanisms of primary treatment resistance.
- Blood samples were collected at baseline, every 12 weeks, and at the time of radiographic progression. Tumor biopsy samples were collected at baseline, week 3-4, and at the time of radiographic progression. These samples are being studied to understand the biological effects of the combination and identify biomarkers that can predict response and resistance.
- Circulating tumor cells (CTCs) are tumor cells released into the bloodstream that can be detected and studied using blood draws. A reduction in CTC numbers is considered a promising biomarker of treatment response. 18 of 29 evaluated patients had detectable numbers of PSMA-expressing CTCs at baseline. At 12 weeks, 15 of 18 (83%) had decreases in CTC numbers and 11 of 18 (61%) had zero detectable CTCs. 11 patients had zero detectable PSMA-expressing CTCs at baseline, all of whom continued having zero detectable CTCs at 12 weeks. Additional analyses are ongoing.
- Two cases were highlighted that were instructive of the types of responses and resistance seen with this treatment combination.
- One case was an 81-year old man who previously progressed on abiraterone, and experienced a complete PSA response lasting over 60 weeks, a significant decrease in tumor volume on scans, and a 100% CTC response at 12 weeks.

- In a second case, a 70-year old man who previously progressed on enzalutamide and docetaxel, at first had an excellent PSA response, dropping from 245 at baseline to 4.28 at 24 weeks, as well as corresponding significant reductions in tumor volume on scans and CTC numbers. However, between weeks 36 to 48, he developed treatment resistance and experienced rapid and significant tumor growth on scans, a rise in PSA levels, and rising CTC numbers. Evaluation of CTCs found that multiple tumor clones were contributing to treatment resistance.
- CTCs are being used to study PSMA expression on single tumor cells. Many patients had both PSMA-positive and PSMA-negative tumor cells, highlighting the heterogeneity in PSMA expression on prostate cancer cells.
- Overall, results from the PRINCE trial demonstrate significant promise for the combination of LuPSMA with pembrolizumab. Follow-up is ongoing to determine the impact of the combination on rPFS and overall survival. Biomarker analysis is also ongoing to understand the effects of LuPSMA and pembrolizumab on the tumor microenvironment and to define predictors of response and resistance.



Targeting Micro-Metastatic Disease with Auger or Alpha Emitters

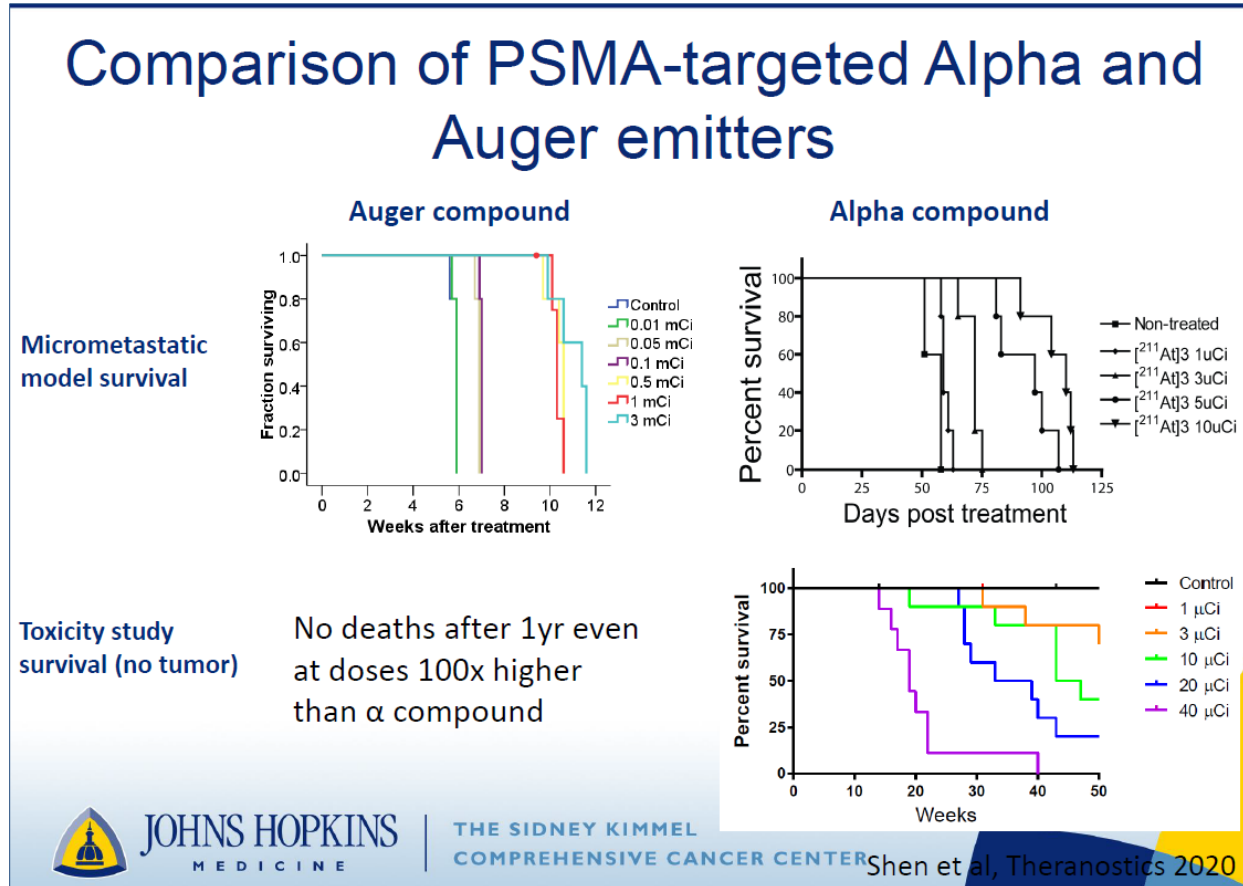
Ana Kiess, MD, PhD
Johns Hopkins University

- Radioligand therapy is an emerging treatment class that typically consists of alpha or beta particle-emitting radioisotopes attached to tumor targeting molecules. The tumor-targeting molecule brings the radioisotope into contact with tumor cells, where the emitted radiation kills the tumor cell.

- ^{177}Lu -PSMA-617 (LuPSMA) is a promising treatment for prostate cancer that uses the beta particle emitter ^{177}Lu -Lutetium attached to a PSMA-targeted molecule which targets prostate cancer cells. While highly effective and likely soon to be FDA-approved for patients with metastatic castration-resistant prostate cancer (mCRPC), this treatment is not curative and strategies for further improvement are being studied.
- Dr. Ana Kiess discussed the potential for using Alpha or Auger emitters for radioligand therapy, particularly to target micro-metastatic prostate cancer.
- Alpha emitters are radioisotopes that emit Alpha particles (and often a series of Alpha particles) when they decay. Alpha emitters with therapeutic potential include ^{225}Ac -Actinium, ^{227}Th -Thorium, ^{223}Ra -Radium, and others.
- Auger emitters (pronounced “oh-jhay”) decay by emitting low energy electrons. Auger emitters with therapeutic potential include ^{125}I -Iodine.
- Alpha, Beta, and Auger particles have different properties that affect their therapeutic potential. Alpha and Auger particles have a shorter range and emit higher energy than Beta particles, and thus have the potential for increased anti-tumor activity with decreased toxicity, especially for micro-metastatic disease.
- The alpha emitting PSMA-targeted radioligand therapy ^{225}Ac -PSMA-617 has been used to treat mCRPC patients in Germany and other countries, and some deep responses have been reported. While controlled trials have yet to be conducted, bone marrow toxicity with ^{225}Ac -PSMA-617 appears to be less than ^{177}Lu -PSMA-617, but high-grade xerostomia has been observed above certain doses.
- Dr. Martin Pomper and colleagues at Johns Hopkins University have developed PSMA-targeted small molecules labeled with either the Auger emitter ^{125}I or the Alpha emitter ^{211}At .
- In preclinical mouse models of prostate cancer, a single dose of the Alpha emitter ^{211}At -PSMA-6 improved survival.
- A micro-metastatic prostate cancer mouse model has been developed, in which mice are injected with prostate cancer cells that form micro-metastases in liver, kidney, and bone after 1 week and detectable lesions after 2-3 weeks. Treatment of these mice with ^{211}At -PSMA-6 also improved survival in a dose-dependent fashion.
- Using a special camera that can visualize radiation, the location of the ^{211}At -PSMA-6 treatment in the mice was determined 1 hour after administration. High uptake was seen in PSMA-expressing tumors. However, high uptake was also seen in the kidneys, which was especially high in kidney proximal tubules. The team thus investigated the long-term toxicity of this treatment in mice.
- Severe kidney toxicity was seen ~4 months after treatment with higher doses of ^{211}At -PSMA-6, or appeared later with lower doses. Only with very low doses was no kidney toxicity observed.
- Treatment with the PSMA-targeted Auger emitter ^{125}I -DCIBzL also extended survival in various mouse prostate cancer models including the micro-metastatic model. However, unlike the Alpha emitter, no short or long-term kidney toxicity was seen in mice treated with ^{125}I -DCIBzL.
- Together, these data demonstrate that Alpha and Auger emitting PSMA-targeted radioligand therapies both have anti-tumor efficacy in mouse prostate cancer models (**Figure**). However, at therapeutic doses, the Auger emitter caused no kidney toxicity and no deaths of mice, while the Alpha emitter caused eventual lethal kidney toxicity (**Figure**).
- The higher toxicity of Alpha vs Auger PSMA-targeted radioligand therapy in kidneys may be partly explained by the significantly higher uptake of the Alpha agent in kidney, but also may

be due to ability of the Auger agent to arrive at the cell nucleus in prostate cancer cells but not kidney cells.

- These studies demonstrate promise for Auger-emitting PSMA-targeted radioligand therapy for the treatment of prostate cancer. More studies are needed to evaluate the anti-tumor potential and toxicities of Alpha and Auger PSMA-targeted radioligand therapies.



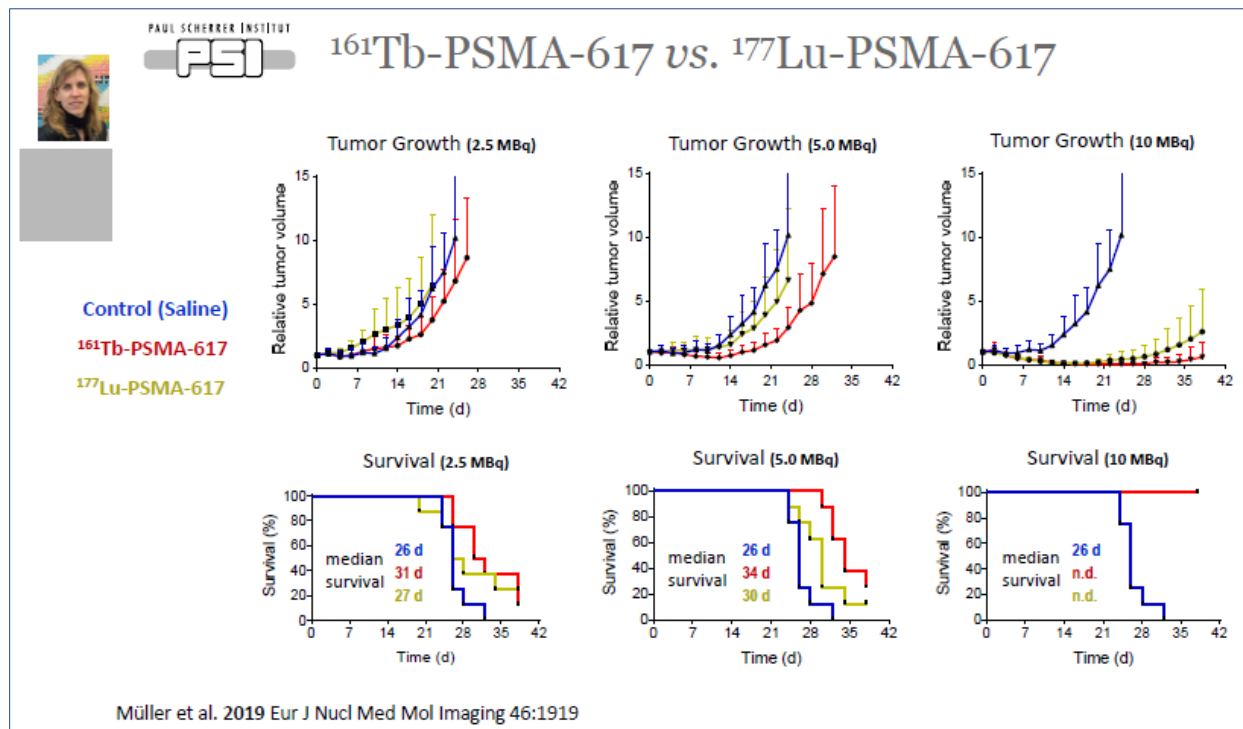
The Four Sisters of Terbium: PET & SPECT Imaging and Targeted Alpha- & Beta-Therapy

Cristina Müller, PhD, PD
Paul Scherrer Institute, Switzerland

- Radionuclides are tumor-targeting small molecules attached to radioisotopes that can be used for imaging or treatment of cancer. Whether the agent is used for therapy or imaging depends on the type of radioisotope attached. Typically, the radioisotope is ideal either for imaging or therapy, which is based on the type(s) of radioactivity emitted during its radioactive decay process.

- For instance, PET imaging requires positron-emission and SPECT imaging requires gamma-emission. Cancer therapy requires the emission of more powerful alpha or beta particles, or Auger electrons, which damage DNA and can kill the targeted cell.
- Dr. Cristina Müller discussed the development of radionuclides using next-generation Terbium isotopes which have properties that may be better for imaging and treatment.
- There are four Terbium “sister” isotopes that may be used for various theranostics purposes: Terbium-152 (PET imaging), Terbium-155 (SPECT imaging), Terbium-149 (alpha-emitting radionuclide therapy), and Terbium-161 (beta-emitting radionuclide therapy).
- A study was done to compare the properties of Lutetium-177 with Terbium-161 for beta-emitting radionuclide therapy. The half-lives and beta particle energy emission levels of these isotopes are very similar. They both also emit gamma radiation and can be used for SPECT imaging. The primary difference is that Terbium-161 also emits a substantial number of conversion and Auger electrons, which have therapeutic potential for the treatment of micro-metastatic cancer (discussed in detail by Dr. Ana Kiess, above).
- In a theoretical dose calculation study by Champion et al., smaller targets (representing micro-metastatic tumors) were predicted to absorb larger amounts of radiation from Terbium-161 compared with Lutetium-177 and other next-generation beta-emitting radioisotopes Copper-67 and Scandium-47.
- Terbium-161 is produced via radiation of Gadolinium-160, in a process that is similar to the production of Lutetium-177. A means of Terbium-161 production has been established at the Paul Scherrer Institute in Switzerland, with potential production planned at sites around the world.
- Lutetium-177 (^{177}Lu) and Terbium-161 (^{161}Tb) were used to label the PSMA-targeted small molecule PSMA-617, and their production and preclinical properties was compared. ^{177}Lu -PSMA-617 and ^{161}Tb -PSMA-617 were both produced efficiently with high purity.
- ^{177}Lu -PSMA-617 and ^{161}Tb -PSMA-617 exhibited similar targeting of PSMA-positive prostate cancer cells and no targeting of PSMA-negative prostate cancer cells.
- In mice, ^{177}Lu -PSMA-617 and ^{161}Tb -PSMA-617 exhibited equivalent pharmacokinetic profiles, including uptake levels and kinetics in PSMA-positive tumors, PSMA-negative tumors, and non-tumor organs. Thus, Lutetium-177 and Terbium-177 are interchangeable without affecting the tissue distribution of the targeting agent (PSMA-617).
- SPECT imaging was performed on mice with prostate cancer after injection of ^{161}Tb -PSMA-617. Despite the lower energy of the emitted gamma-radiation of Terbium-161 as compared to Lutetium-177, SPECT imaging was readily achieved, demonstrating accumulation of the agent in PSMA-positive tumors but not PSMA-negative tumors.
- Other studies using human phantoms have demonstrated that SPECT with Terbium-161 is feasible in clinical settings and can be performed in humans using low-energy-high-resolution (LEHR) collimators. SPECT with ^{177}Lu -PSMA-617 can be performed using medium-energy-general-purpose (MEGP) collimators.
- Importantly, in preclinical studies with ^{177}Lu -PSMA-617 vs. ^{161}Tb -PSMA-617, it was found that ^{161}Tb -PSMA-617 had stronger efficacy against PSMA-positive prostate cancer cells when applied at the same activity level. Both agents had no/minimal effects against PSMA-negative prostate cancer cells. ^{161}Tb -PSMA-617 also outperformed ^{177}Lu -PSMA-617 in the treatment of prostate cancer in PC-3 PIP tumor mice (**Figure**).
- Terbium-152, Terbium-155, and Terbium-149 are more difficult to produce than Terbium-161. However, PSMA-617 labeled with these radioisotopes are being produced and studied.

- Terbium-149 may be useful for targeted alpha therapy, as it does not produce daughter isotopes that also emit alpha particles, making it safer than other alpha emitters under study such as Actinium-225.
- Preclinical studies in prostate cancer models have demonstrated promising anti-tumor activity with ^{149}Tb -PSMA-617.
- Terbium-149 also emits positrons, which enables PET imaging. PET imaging could be performed on mouse prostate cancer models treated with ^{149}Tb -PSMA-617. Thus, this agent is attractive for clinical translation; however, the lack of facilities to produce Terbium-149 must first be addressed.
- ^{152}Tb -PSMA-617 and ^{155}Tb -PSMA-617 were produced and studied as diagnostic PET and SPECT imaging agents in mouse prostate cancer models, respectively. These agents have potential for use in combination with long-circulating agents, for delayed imaging, and for dose-planning for the treatment of patients with PSMA-targeted radionuclide therapy.
- Regarding Terbium-152, Terbium-155 and Terbium-149, current ongoing research is focused on production methods and set-up of new facilities. Additional preclinical research is also necessary before these agents can be tested in clinical trials.
- ^{161}Tb is well established in terms of production and studies are underway to determine the advantage of the Auger electron emission for the treatment of metastatic disease. The clinical translation of ^{161}Tb -based PSMA radioligand therapy is planned for the near future.



aPROMISE: An Artificial Intelligence Platform to Assist in Standardizing the Detection, Localization and Quantification of Prostate Cancer in PYLARIFY PSMA Scans

Aseem Anand, PhD

Imaging-Oncology Biomarker, EXINI Diagnostics AB. Sweden (a wholly owned subsidiary of Lantheus Holdings)

- The ability to standardize cancer quantification from imaging scans is crucial for improving patient care and speeding the development of new treatments.
- Quantitative imaging biomarkers are algorithms that automate and standardize determinations of cancer burden from scans. Quantitative imaging biomarkers can be developed for use in several contexts: prognostic (to predict a patient's outcome independent of treatment), predictive (to predict if a patient will or won't respond to a treatment), and response (to measure a patient's response to a treatment).
- Development and validation of biomarkers requires demonstration of repeatability, reproducibility, accuracy, comparisons with current gold-standard and standard-of-care methods, and validation of use in the proper clinical context.
- Dr. Aseem Anand discussed the development of quantitative imaging biomarkers for prostate cancer.
- The automated bone scan index (aBSI) is an artificial intelligence (AI)-based cancer imaging technology using bone scans that has been translated into clinical use.
- aBSI was validated in a prospective Phase 3 trial as an independent prognostic biomarker for overall survival of patients with metastatic castration resistant prostate cancer (mCRPC). This study demonstrated additive value for aBSI with other known prognostic biomarkers such as LDH, hemoglobin, PSA, and albumin, for predicting outcomes. These data also suggested that aBSI may aid in designing and determining patient eligibility for clinical trials.
- In another study, aBSI was demonstrated to be predictive of response to radiation therapy, and to identify patients with newly diagnosed prostate cancer who are likely to benefit from radiation therapy.
- aBSI was selected as the primary endpoint in a prostate cancer clinical trial testing TAS-115, an anti-VEGF therapy, in patients with CRPC.
- PSMA PET is a highly sensitive new imaging method for detecting sites of metastatic prostate cancer. However, standardization of PSMA imaging is limited by poor ability of different readers to quantify metastases in bone.
- Machine learning is being used to develop AI algorithms to automate and standardize PSMA PET imaging.
- Dr. Anand and colleagues are developing a deep-learning based method, aPROMISE, to determine the location and quantify burden of tumors from PSMA PET/CT imaging.
- PyL ACCESS was a program by Progenics that provided free PSMA PET imaging agent to clinicians in exchange for patient images, in order to accelerate research on PSMA PET imaging. PSMA PET + CT images were collected from over 3,000 patients through this program.
- An AI algorithm was developed to automatically identify 52 bones and 12 different organs using the CT images. PSMA PET images are then superimposed over CT images to determine PSMA levels in normal organs. An updated second AI algorithm is then applied to

PSMA PET imaging data to identify tumor lesions, as sites where PSMA uptake is higher than in certain normal (reference) organs. This adaptive algorithm adjusts its comparison of PSMA levels in reference organs vs. tumor, in order to optimally identify primary and metastatic tumor sites while avoiding false-positives. The algorithm also determines a PSMA-index (automated PSMA score) for individual lesions and at the patient level.

- The aPROMISE algorithm was trained on over 500 patient images and the findings were validated by radiologists.
- The OSPREY and CONDOR registrational studies demonstrated the specificity and sensitivity of the PSMA PET imaging agent PYLARIFY® in patients with prostate cancer, and led to its FDA-approval in 2021. The CONDOR data was also used to validate the performance of aPROMISE in detection and quantification of PSMA PET/CT against standard of truth.
- The subsequent PCF-VA study also validated the ability of aPROMISE to detect prostate cancer in Veterans diagnosed with localized high-risk prostate cancer imaged with PSMA PET/CT.
- Ongoing studies are being performed to validate quantitative PSMA index/core as a prognostic biomarker in patients with metastatic prostate cancer, and as a response imaging biomarker in mCRPC patients undergoing treatment with Radium-223. Preliminary results from these studies are promising.
- In conclusion, aPROMISE has undergone rigorous performance valuation, with the objective of providing clinicians with a standardized platform for efficiently, consistently, and accurately quantifying prostate cancer disease, in order to improve patient management and outcomes. Use in specific clinical contexts requires validation studies in the specific clinical setting.
- aPROMISE v1.2.1 is the first AI enabled application to receive clearance for PSMA PET quantification by the FDA in 2021.

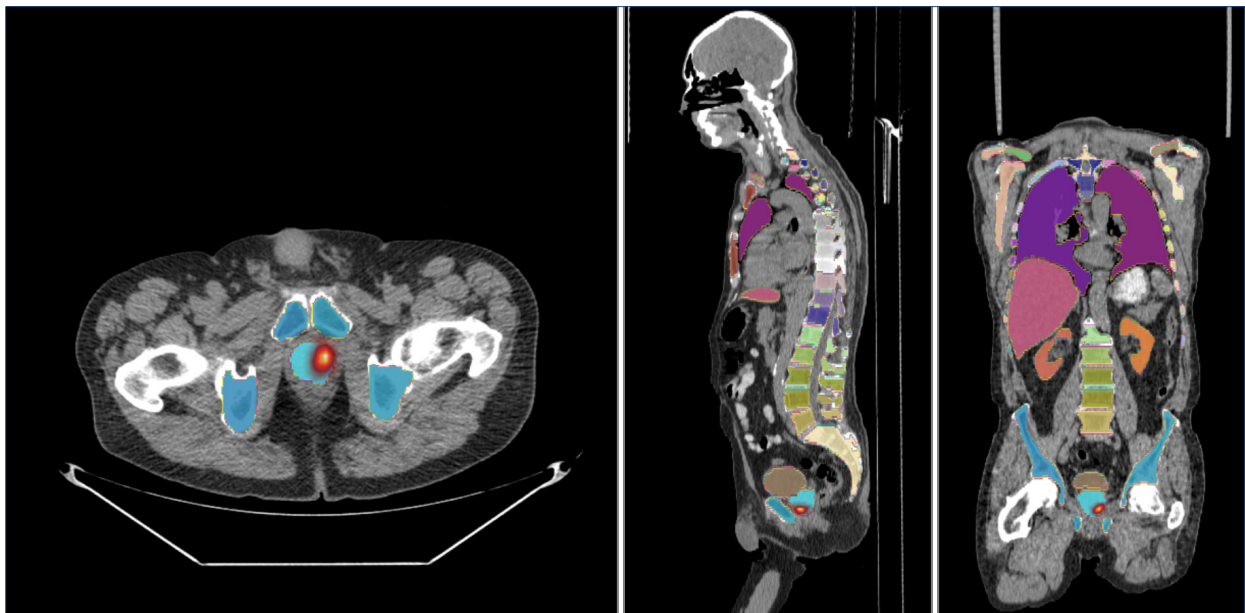


Figure: Deep learning enabled segmentation of anatomical context in low dose CT of PET/CT. Individual color represents the respective segmented organ. The aPROMISE technology enables automated segmentation of reference organs, and anatomical delineation of the disease in the prostate (miT), regional lymph nodes (miN), and distance metastases (miM). The tumor burden is automatically quantified for PSMA expression.

Targeting Fibroblast Activation Protein-alpha (FAP) in Prostate Cancer: Is FAP the Next Theranostic Target after PSMA in Prostate Cancer?

Andy Simmons, PhD
Clovis Oncology

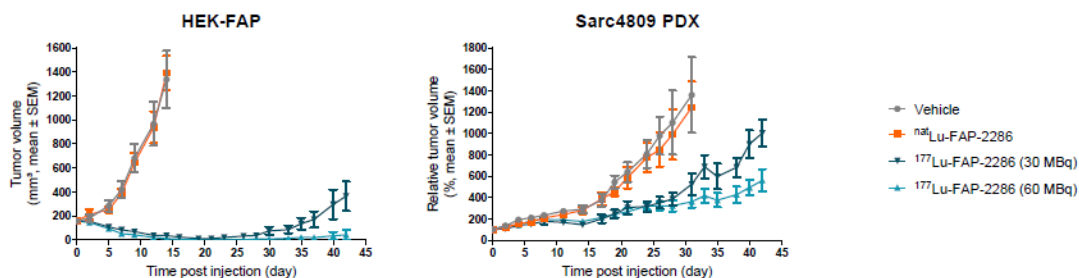
- Targeted radionuclide therapy (TRT) is a new class of treatment designed to target and destroy cancer cells by bringing small doses of radiation directly to cancer cells anywhere they are in the body.
- A protein found in prostate cancer cells called prostate-specific membrane antigen (PSMA) is the most widely studied and validated target for prostate cancer TRTs, and LuPSMA (¹⁷⁷Lu-PSMA-617) is likely to soon receive FDA approval for the treatment of metastatic castration resistant prostate cancer (mCRPC). However, other targets are under study.
- Fibroblasts are a type of connective tissue cell. In many tumor types however, an altered type of fibroblast is often found, called cancer associated fibroblasts. Cancer associated fibroblasts support tumor growth, including promoting growth of tumor blood vessels, metastasis, and therapy resistance.
- Fibroblast activation protein (FAP) is a protein present at high levels on the surface of cancer associated fibroblasts and some tumor cells but is usually not present on normal cells except at sites of tissue remodeling such as wound healing and fibrosis.
- Because FAP is highly and primarily present on cancer associated fibroblasts and tumor cells, it is under investigation as a target for cancer imaging and treatment, including with TRT.
- Dr. Andy Simmons discussed studies evaluating FAP as a tumor imaging and TRT target.
- Studies have demonstrated that FAP is expressed in prostate cancer as well as multiple other solid tumor types.
- A comprehensive pan-tumor assessment was performed to evaluate FAP RNA expression in tumors from The Cancer Genome Atlas (TCGA) dataset. High FAP expression was seen in many tumor types, such as pancreatic, breast, and sarcoma. For prostate cancer, limited expression was seen, however TCGA samples are almost all from primary and not metastatic tumors.
- FAP protein levels were also evaluated in multiple cancer types. Most prostate cancer samples in this small study exhibited low FAP protein levels.
- A series of FAP-targeted small molecules were developed that can be labeled with radioisotopes for diagnostic imaging (such as ⁶⁸Ga) or therapy (such as ¹⁷⁷Lu). Preclinical evaluations found the FAP-targeted molecules were preferentially taken up by tumor cells compared with normal tissues, demonstrating promise for clinical use.
- A study in Germany tested ⁶⁸Ga-FAPI-04 as a PET imaging agent in 80 cancer patients, representing 28 cancer types. Several indications, including patients with sarcoma, esophageal, breast, cholangiocarcinoma, and lung cancer, showed high uptake of ⁶⁸Ga-FAPI-04 by PET.
- 13 prostate cancer patients with PSMA-negative disease were included in this study; all demonstrated intermediate to high tumor uptake levels with FAP PET. Whether FAP PET imaging will work as well in PSMA-positive prostate cancer remains to be determined.
- In a case report of a patient with mCRPC with limited ⁶⁸Ga-PSMA-11 uptake by PET/CT imaging, ⁶⁸Ga-FAPI-04 uptake was observed in lymph node and bone metastases, suggesting the potential for FAP-targeted therapy in PSMA-negative prostate cancer.

- FAP-2286 is a newer FAP-targeted peptide that can be attached to radionuclides and is being developed for imaging and therapeutic use. In preclinical studies, FAP-2286 bound strongly and selectively to FAP and was stable in human plasma.
- ^{177}Lu -FAP-2286 TRT was developed and tested in various mouse cancer models. Treatment of mice with a single dose of ^{177}Lu -FAP-2286 significantly slowed growth of FAP-expressing tumors, with no obvious toxicity (**Figure**).
- ^{177}Lu -FAP-2286 was more effective at blocking tumor growth in these models compared with a different FAP-targeted TRT agent, ^{177}Lu -FAP-46. Imaging studies found that may be because of longer retention times of ^{177}Lu -FAP-2286 in tumor sites.
- A Phase 1/2 clinical trial (LuMIERE; NCT04939610) studying FAP-2286 in multiple solid tumors, including prostate cancer, is ongoing. In this trial, FAP imaging with ^{68}Ga -FAP-2286 is being used to identify patients with FAP-positive tumors who are then treated with the TRT agent ^{177}Lu -FAP-2286.
- A second clinical trial is underway to evaluate the ability of ^{68}Ga -FAP-2286 to detect metastatic cancer in patients with solid tumors.
- Overall, these data demonstrate that FAP is a promising imaging and therapeutic target for multiple cancer types, however additional research is needed to further understand the potential utility in prostate cancer.
- Ongoing studies aim to determine the potential for FAP imaging and therapy in prostate cancer and other cancers, including whether there is a subset of prostate cancer patients with high FAP-expressing tumors who may benefit from FAP TRT. Other questions, such as identification of other clinical factors or biomarkers that correlate with FAP expression, and whether there is overlap between PSMA and FAP expression in prostate cancer, are also being investigated.

Robust Anti-tumor Efficacy of ^{177}Lu -FAP-2286 Observed in FAP-Expressing Tumor Models



- Treatment with a single dose of ^{177}Lu -FAP-2286 demonstrated statistically significant tumor growth inhibition in FAP-expressing cell line and patient derived xenograft (PDX) models
 - No significant body weight loss observed



Female swiss nude mice were subcutaneously implanted with 5×10^6 FAP expressing HEK293 cells, while female NMRI nu/nu mice were implanted with Sarc4809 tumor fragments. A single dose of the indicated treatments was administered by intravenous injection (10 mice per group). Tumor growth and body weight were monitored 3-times weekly. Sarc4809 tumor growth was normalized to the mean tumor volume at the time of injection for each group due to variability in starting tumor volume between the groups.

1. Zboralski D, et al. ESMO Annual Congress 2020, Abstract 571P.

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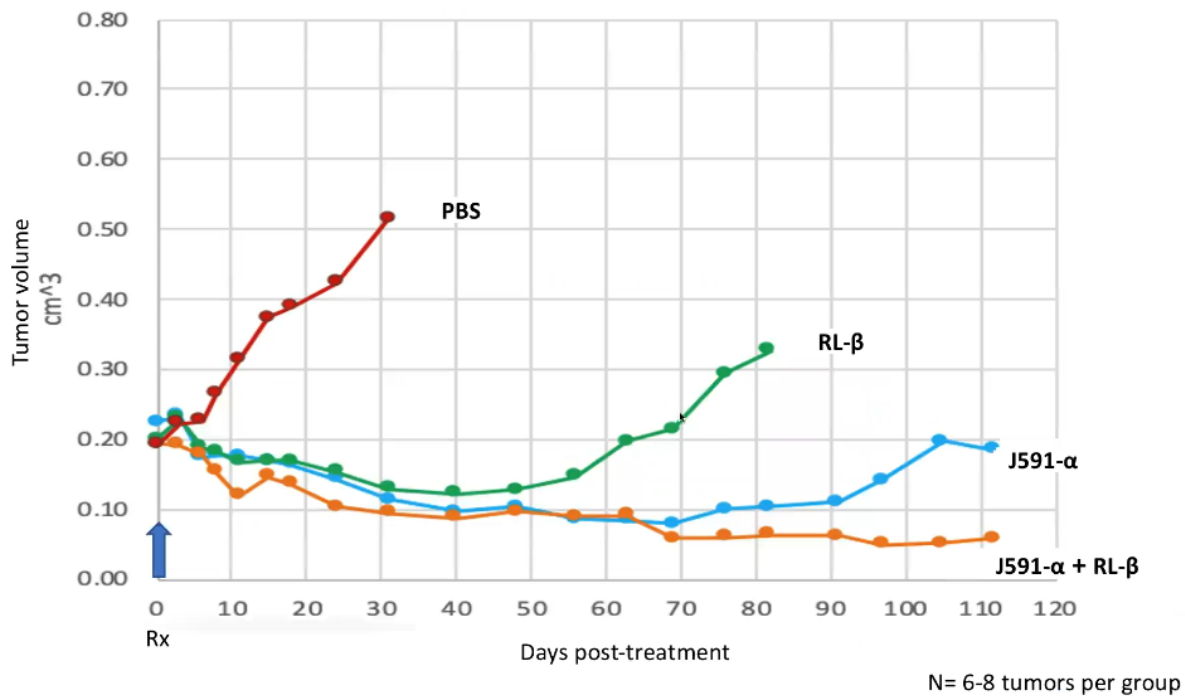
Insights & Future Predictions from 25 Years of PSMA Research

Neil Bander, MD
Weill Cornell Medicine

- Dr. Neil Bander is one of the first researchers to study PSMA in prostate cancer, and pursue targeting it for therapy and diagnostics (“theranostics”) as a way to transform patient care. He discussed the state of PSMA theranostics and predictions for future applications.
- PSMA PET is a highly sensitive new imaging method for detecting sites of metastatic prostate cancer. Ongoing studies have shown promise for PSMA PET in detecting localized prostate cancer as well. This is because PSMA expression levels strongly correlate with Gleason grade, and PSMA levels have been shown to be prognostic for rate of recurrence after localized therapy and risk for developing lethal prostate cancer.
- PSMA PET imaging in diagnostic settings may enable identification of which patients need a biopsy, enable targeted biopsy, provide a non-invasive Gleason score and risk assessment at the time of diagnosis, provide a method to monitor active surveillance patients, may be integrated for planning focal ablation techniques and radiation therapy, and may help to screen high-risk family members.
- Optical imaging with PSMA is under investigation for use in intra-operative surgical settings to help visualize cancer margins and identify tumor-positive lymph nodes that need to be removed.
- Measurable radiographic response assessment has been less applicable in prostate cancer because of the predominance of bone lesions, which are not measurable on conventional imaging. However, validating PSMA PET as a response biomarker could enable faster and more cost-effective drug development and get better drugs to patients faster. This would be applicable for PSMA-targeted treatments as well as other drug classes.
- PSMA-targeted radioligand therapy has been highly promising.
- The VISION trial demonstrated an overall survival benefit with the beta particle-emitting agent ¹⁷⁷Lu-PSMA-617 (LuPSMA), which will likely soon gain FDA approval. ¹⁷⁷Lu-PSMA I&T is another beta particle-emitting agent being tested in a Phase 3 trial (SPLASH).
- Radioligand therapy with alpha particle-emitting agents are also being tested. Alpha particles emit ~1,000-fold higher energy than beta particles, and cause double-stranded DNA breaks, which are irreparable and more likely to cause cell death. In contrast, beta particles primarily cause single-stranded DNA breaks which are more easily repaired by cells. Thus approximately 1 hit on DNA from an alpha particle is estimated to kill a cell, while 1,000 hits on DNA from beta particles would be needed to kill a cell.
- ²²⁵Ac-PSMA-617 is an alpha particle-emitting PSMA-targeted radioligand therapy that has been tested in some patients with very promising results, but unfortunately also caused significant intolerable salivary (xerostomia) and lacrimal (tear) gland toxicity.
- PSMA-617 is a PSMA-targeted small molecule, and in imaging studies has demonstrated uptake in lacrimal and salivary glands, as well as spleen, liver, kidneys, small bowel and bladder, due to urinary excretion.
- PSMA-targeted antibodies have also been developed. Antibodies are approximately 100-fold greater in mass than the small molecule ligands and thus have different pharmacokinetics and bio-distribution compared with small molecules. In imaging studies with antibody agents, no uptake is seen in lacrimal or salivary glands, longer persistence is seen in the vascular system, and excretion is via the liver and GI tract.

- The non-overlapping bio-distributions of PSMA-targeted antibody and small molecule-based radioligand therapies also result in non-overlapping toxicity profiles.
- Dr. Bander and colleagues have developed the PSMA-targeted antibody J591, and are testing this as an alpha particle-emitting radioligand therapy, ^{225}Ac -J591 that avoids the salivary/lacrimal gland toxicity associated with the small molecule radioligands.
- A Phase 1 single ascending dose trial testing ^{225}Ac -J591 has been completed. In this trial, 32 patients were treated with a single dose of ^{225}Ac -J591, in 7 cohorts of increasing dose levels. PSMA PET imaging was not used to select patients for this trial.
- Overall, ^{225}Ac -J591 was found to be well-tolerated, and no maximum tolerated dose was identified. 12 patients had grade 1 xerostomia, but no higher grades were observed, and most cases occurred in patients who had prior ^{177}Lu -PSMA-617.
- PSA $\geq 50\%$ responses occurred in 44% (14/32) of patients, including in 54% (7/13) of patients that have previously been treated with ^{177}Lu -PSMA-617. A trial testing multiple ascending doses is currently underway.
- Additionally, a trial testing the combination of ^{225}Ac -J591 and ^{177}Lu -PSMA-617 has recently been opened. This is feasible because the antibody and small molecule bind to different sites on PSMA, as well as have non-overlapping tissue bio-distributions and toxicities. Thus, combining these treatments is hypothesized to deliver additive doses to the tumor, without additive doses to normal tissue sites, potentially enabling greater efficacy with no increase in toxicity.
- Interestingly, preclinical studies in animal prostate cancer models actually suggest that the efficacy of the combination is not simply additive but synergistic, and can lead to complete tumor regression (**Figure**).
- Another reason these treatments provide a favorable combination is that they have complementary efficacy related to tumor size. Due to the geometry of ^{177}Lu radiation, lesions at or below PET resolution/visibility receive a low, ineffective dose of radiation. As a result, trials of ^{177}Lu -radioligands commonly report progression that is due to “new” (i.e., previously unvisualized) lesions, most often in the bone marrow. However, these small volume lesions are very effectively radiated by ^{225}Ac due to its short, focused emissions range.
- In addition to radioligand-based PSMA targeting agents, other PSMA-targeted treatments are being developed. These include PSMA-targeted antibody-drug conjugates, bispecific antibodies, CAR T cells, and other novel approaches.
- In the future, there will likely be increasing use of dual-targeted PSMA therapeutics with increased efficacy. In addition, earlier use of PSMA-targeted treatments including as neo-adjuvant (pre-surgery) or adjuvant (post-surgery) therapies may offer the potential to cure some high-risk patients in these earlier settings.

In vivo pre-clinical studies Synergy of J591- α + RL- β



Source: Bander Lab, Weill Cornell Medicine

Session 4: Prostate Cancer Disparities

Overview on Prostate Cancer Disparities in African Americans: Lessons from the VA Health System and VANDAAM Study

Kosj Yamoah, MD, PhD
Moffitt Cancer Center

Isla Garraway, MD, PhD
University of California, Los Angeles; VA Greater Los Angeles Healthcare System

- Dr. Kosj Yamoah and Dr. Isla Garraway discussed prostate cancer disparities and studies in the Veterans Health Administration (VA) that aim to determine the factors that contribute to disparities.
- Black men have a significantly higher risk of developing and dying from prostate cancer compared with White men. In 2020, the lifetime risk of developing prostate cancer was 14.8% (1 in 7) in Black men and 10.6% (1 in 9) in White men and the lifetime risk of dying from prostate cancer was 4% (1 in 25) in Black men and 2.2% (1 in 45) in White men.
- Factors that contribute to these disparities are complex, and include access to and quality of medical care, other sociodemographic factors, and biologic factors.
- The increased incidence in Black men appears largely driven by biological factors, while the increase in mortality risk has additional significant contributions from healthcare access and quality.
- Factors that impacts differences in biology include inherited genetics, genomics, epigenetics, immune system differences, environmental and occupational exposures and differences in stress, diet, and metabolism.
- Factors that impact disparities in health care access and quality include structural racism, healthcare system inequalities, health policies, mistrust of the medical system by the African American community, disparities in health insurance, and low socioeconomic status.
- Additional social factors that may impact prostate cancer disparities include education access and quality, neighborhood and built environments, economic stability, and social and community context.
- All of these factors can interact in varying degrees in a complex manner to impact overall prostate cancer disparities.
- Approaches to understand the etiology of prostate cancer disparities include clinical trials that maximize African American accrual and multivariable studies in equal access healthcare systems such as the VA. Such studies will aid in understanding the genomic diversity of prostate cancer and optimize risk classification and treatment responses in African American men.
- Dr. Kosj Yamoah discussed the VanDAAM study, a clinical trial conducted in the Moffitt Cancer Center, James Haley VA Hospital, and Bay Pines VA HealthCare System, from 2018 to 2021. The trial had a unique minority-focused accrual strategy, in which a self-identified African American patient with prostate cancer was first enrolled, followed by enrollment of a clinically matched non-African American patient. Clinical matching was

based on CAPRA scores: a system which considers PSA levels, Gleason Score, T stage, percent of biopsy cores positive for cancer, and age at diagnosis.

- Overall, 243 patients (125 African American, 118 non-African American) were enrolled of 276 approached, representing an 88% accrual success rate over three years. Genomic data was obtained from 233 of these patients.
- Ancestral genetic data revealed significant overlap between self-identified race and ancestry proportions. 9% of self-identified African Americans were classified as non-African American based on genetic ancestry data.
- The Decipher genomic classifier test was used to estimate prostate cancer risk, and was compared with risk based on standard NCCN guidelines. 18.2% of NCCN-low risk African American patients were reclassified as high risk based on Decipher scores, while no such reclassification occurred in non-African American patients. Overall, the risk of genomic reclassification was 2 to 5-fold higher in African American men compared with non-African American men (**Figure**).
- This study indicates that current clinical risk stratification strategies are suboptimal in assessing true disease risk in a subset of African American men with early disease presentation and high genomic risk of developing metastasis.
- Targeted accrual of African American men to clinical trials can help to determine the race-specific genomic diversity of prostate cancer to optimize disease stratification and treatment response.
- Dr. Isla Garraway discussed studies in the VA to determine how social determinants interact with biologic determinants to influence prostate cancer incidence, aggressiveness, and clinical outcomes. These studies were done by the RESOLVE PCa (Rate Elements Skewing Outcomes Linked to Veteran Equity in Prostate Cancer) Consortium.
- Prior studies have linked various social determinants of health to prostate cancer aggressiveness and survival. Income levels have been linked to clinical stage at diagnosis and prostate cancer aggressiveness. Socioeconomic status (SES) has been linked to prostate cancer aggressiveness and mortality. Marital status has been linked to the development of metastatic disease. Social support has been linked to prostate cancer aggressiveness, metastasis, and overall survival. Education levels have been linked to overall survival.
- For instance, redlining, a discriminatory practice by the Homeowner's Loan Corporation which gave poor ratings to predominantly Black neighborhoods in the 1930s, continues to have impact, as these neighborhoods display the highest social vulnerability indexes today.
- Other studies have found that people of color in the U.S. are exposed to disproportionately higher levels of air pollution in their neighborhoods, such as PM_{2.5} pollutants, which are fine inhalable particles that are 2.5 micrometers and smaller.
- As the largest equal-access healthcare system in the U.S., the VA offers an opportunity to study factors that contribute to prostate cancer disparities, including the roles of genetics, lifestyle, environmental exposures, and differences in treatment access, quality, and survivorship care. These can also be studied in a geo-coded fashion.
- The PCF-VA Partnership enabled the development of a database of prostate cancer patients (the prostate cancer data core) in the VA. This database was developed by VINCI Investigators through abstraction of structured data from the electronic health record and implementation of newly developed natural language processing tools to compile information on metastatic stage and other clinical and demographic factors.
- Between 2000-2018, approximately 488,984 living patients, and 592,153 deceased patients with prostate cancer were identified in the VA. Of these, 16,618 patients living with

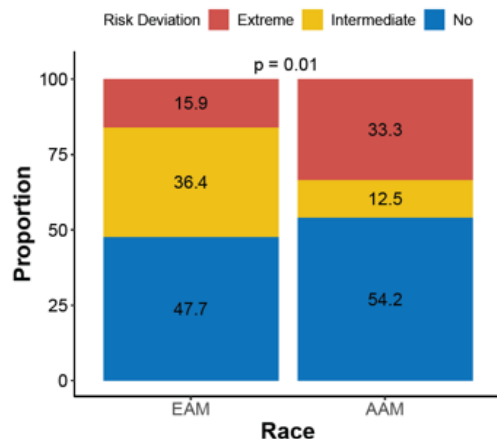
metastatic prostate cancer were identified (includes cases of regional lymph node metastasis as well as distant metastasis).

- Using geocoding, the locations of prostate cancer patients in the VA cohort can be compared with maps of environmental exposures available through the EPA websites and datasets that measure social economic status measures. For instance, maps of daily PM_{2.5} exposure levels across the U.S. may be compared with location densities of patients with metastatic prostate cancer to determine correlations between metastasis incidence rates and exposure to PM_{2.5}.
- These tools will allow multi-dimensional studies on factors that may contribute to prostate cancer incidence and severity, and aid in the creation of complex predictive models, which could allow better understanding of the etiologies of health disparities.
- The PCF-VA Partnership has created collaborative partnerships across the VA and established numerous programs to improve the care of Veterans with prostate cancer. These include the POPCAP program, which is creating infrastructure to improve quality, delivery and access of precision medicine and clinical trials for prostate cancer patients in the VA, and a related PCF-VA Health Disparity Working Group, led by Dr. Kosj Yamoah.
- The PCF-VA Health Disparity Working Group recently reported a study including close to 8 million veterans undergoing routine care in the VA hospitals between 2005-2019.
- To better understand the disparities in prostate cancer incidence, the PCF-VA Health Disparity Working Group performed a study evaluating disparities in prostate cancer diagnostics and biopsies in the VA. Of the nearly 8 Million Veterans undergoing routine care in the VA between 2005-2019, ~259,000 underwent a diagnostic biopsy in the VA and ~137,000 were diagnosed with prostate cancer within the VA health system. This study found no difference in time between the first elevated PSA (>4.0) test result to biopsy, and time from the PSA test to treatment initiation.
- Black Veterans had a ~2-fold higher incidence rate of prostate cancer compared with White Veterans. Black Veterans were also more likely to be younger, have higher PSA levels and more aggressive prostate cancer at diagnosis, and higher rates of metastatic disease at diagnosis.
- Among a sub-cohort of ~92,000 Veterans who had been diagnosed between 2005-2015, with at least 5 years since diagnosis, were evaluated for long-terms outcomes following definitive treatment such as surgery or radiotherapy. Overall, the 10-year cumulative incidence of death from prostate cancer was actually lower in Black compared with White Veterans (4.0% vs. 4.8%). This demonstrates that disparities can be negated with equal health care access and quality.
- Similar to the previous study, Black men treated with radiation therapy or surgery were found to do slightly better than White men, demonstrating that equal access and equal treatment in equivalent patients result in equal outcomes.
- However, despite equal treatment, the ~2-fold higher disparities in incidence led to disproportionately higher numbers of Black Veterans developing metastatic disease and dying from prostate cancer compared with White Veterans (**Figure**).
- Together, these data demonstrate that disparities in the incidence of prostate cancer between Black and White men are a major driver of disparities in metastatic disease and prostate cancer mortality in the VA.
- Ultimately, advancing health equity in prostate cancer will require understanding the dynamic interactions and relative impact of non-genetic and genetic factors on prostate cancer incidence, tumor biology, and clinical outcomes. Understanding the drivers of prostate cancer susceptibility will enable the disaggregation of race from more specific factors that drive prostate cancer disparities.

Risk of genomic reclassification

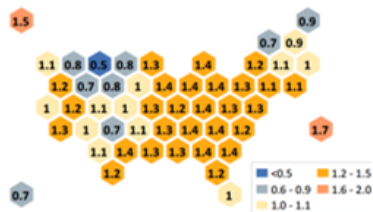
Self-Race		RR (95% CI)	p	Ancestry		RR (95% CI)	p
EAM		1 (Ref)		EUR		1 (Ref)	
AAM		2.23 (1.02 – 4.90)	0.04	AFR		5.26 (1.66 – 16.63)	0.004

Abbreviations: EAM, European American; AAM, African American; RR, Relative Risk; CI, Confidence interval, EUR, European Ancestry; AFR; African Ancestry. Models are adjusted Age at diagnosis.

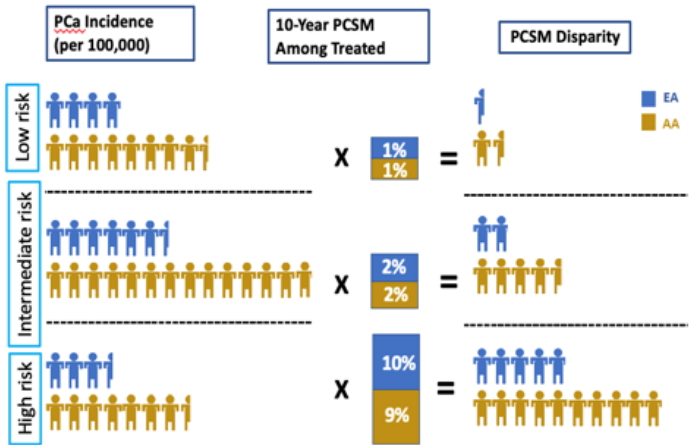
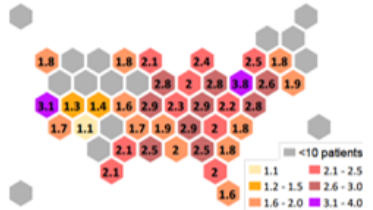


Incidence Level Differences Drive Residual Disparity Following Treatment in VA Cohort

Relative Localized Prostate Cancer Incidence (AAM v. EAM)



Relative De Novo Metastatic PCa Incidence (AAM v. EAM)



Epidemiologic Aspects of Prostate Cancer in Black Men and Men of African Ancestry

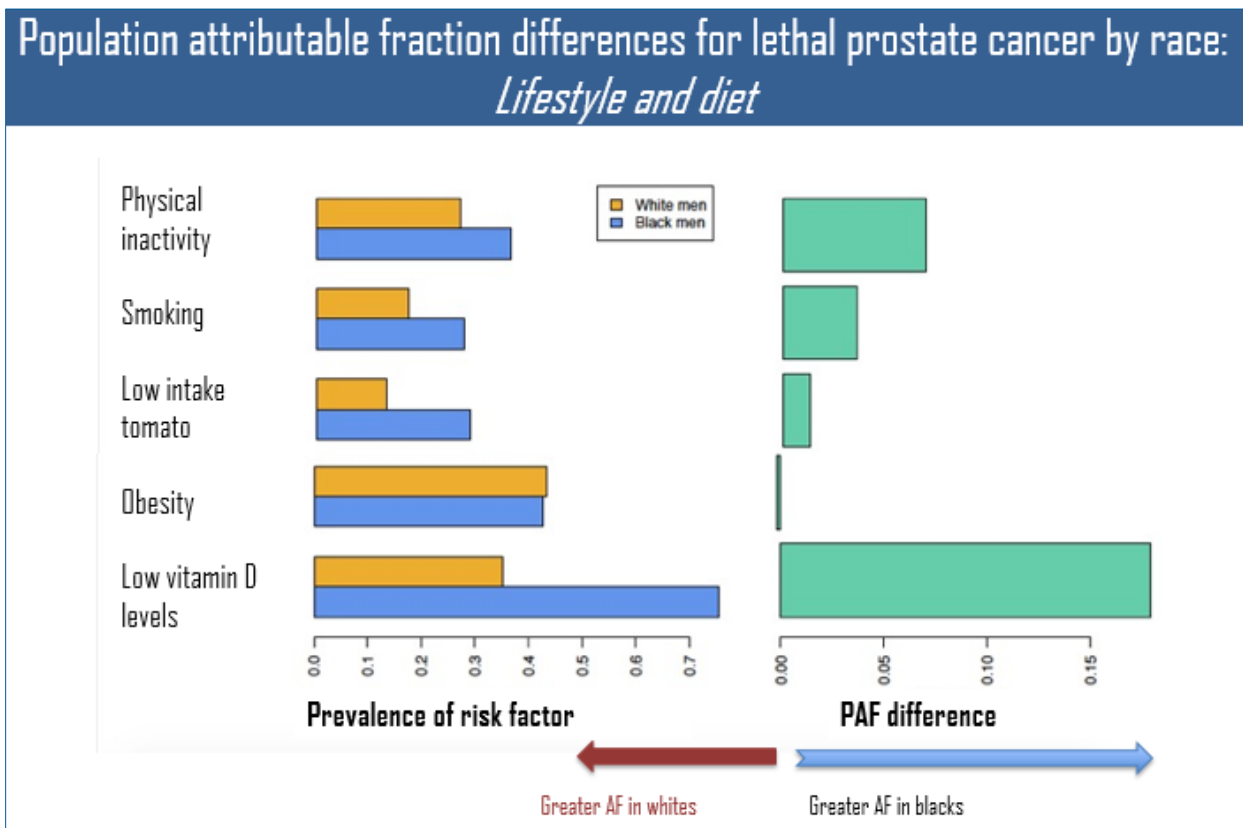
Lorelei Mucci, ScD

Harvard T.H. Chan School of Public Health

- Dr. Lorelei Mucci discussed the epidemiology of prostate cancer disparities.
- In cancer epidemiology, there are 3 main concepts: cancer incidence, cancer mortality, and survival and fatality.
- Cancer incidence is defined as the number of new prostate cancer cases within a specific time period, divided by the total population at risk at the start of the time period. Prostate cancer incidence is driven largely by prostate cancer risk factors in the population as well as the intensity of prostate cancer screening (with PSA testing).
- Cancer mortality is defined as the number of deaths due to prostate cancer within a specific time period, divided by the total population at risk at the start of the time period. Mortality is driven by both prostate cancer prognosis and disease incidence rates.
- Survival and fatality are defined as the number of deaths due to prostate cancer within a specific time period, divided by number of prostate cancer cases at the start of the time period.
- Each year, approximately 1.4 Million men will be newly diagnosed and 375,000 men will die from prostate cancer around the world. The global prostate cancer death rate is estimated to double to 740,000 by 2040.
- Men of African ancestry are disproportionately affected by prostate cancer, and will be disproportionately affected by future increases in these rates. In the U.S., Black men have a 1.6-fold higher incidence rate compared with Non-Hispanic White men, and a 2.9-fold higher incidence rate compared with Asian men. Additionally, Black men have a 2-fold higher rate of mortality from prostate cancer compared with Non-Hispanic White men, and a 4.6-fold higher rate of mortality compared with Asian men. In the past 5 years, nearly 1 Million men of African ancestry were diagnosed with and ~390,000 died from prostate cancer globally.
- Cancer disparities in Black men are seen across many cancer types, including lung and bronchial cancer and colorectal cancer. However, prostate cancer has the greatest racial disparities of any cancer type.
- The highest population rates of non-Hispanic Blacks are in the southeastern U.S., and these areas also experience significantly higher rates of prostate cancer deaths. Globally, the highest rates of prostate cancer deaths occur in Africa and South American countries with higher numbers of people of African ancestry.
- Lifestyle and genetic factors can contribute to prostate cancer disparities. Risk factors for prostate cancer incidence that have been established in both White and Black men include older age, family history for prostate or breast cancer, the presence of cancer risk genes, and taller height. However, Black men are on average ~2.5 years younger at diagnosis compared with White men.
- A polygenic risk score (PRS) has been developed that can identify men at the highest lifetime risk for prostate cancer incidence in men of European ancestry and men of African ancestry. This demonstrates that inherited genetic factors play a strong role in prostate cancer incidence.
- Lifestyle factors associated with increased risk for aggressive and lethal prostate cancer in both Black and White men include obesity, lower Vitamin D levels, low lycopene intake (from

tomatoes), smoking, and low physical activity. Whether the prevalence of these factors differs between Black and White men, and whether they contribute to disparities is an important question.

- The VITAL trial found significantly lower prostate cancer mortality rates in men taking Vitamin D supplements compared with a placebo, including in Black men specifically. Black men tend to have lower baseline Vitamin D levels, and this data suggests that they may benefit from Vitamin D supplementation.
- A study was conducted using data from two large and long-term epidemiology studies, the National Health and Nutrition Examination Study, and the Health Professionals Follow-up Study, to examine what fraction of prostate cancer incidence can be explained by the differences in lifestyle factors in White vs. Black men.
- The study found that Black men had higher rates of physical inactivity, smoking, low tomato intake, and low vitamin D levels compared with White men, while obesity rates were similar (Figure).
- Altogether, these data suggest that differences in inherited genetic factors contribute to higher incidence and mortality among men of African ancestry. However, increasing vitamin D intake, physical activity, and not smoking represent potential opportunities for intervention and prevention to reduce prostate cancer disparities. Additional epidemiologic studies among Black men, particularly on role of contextual factors, are greatly needed.

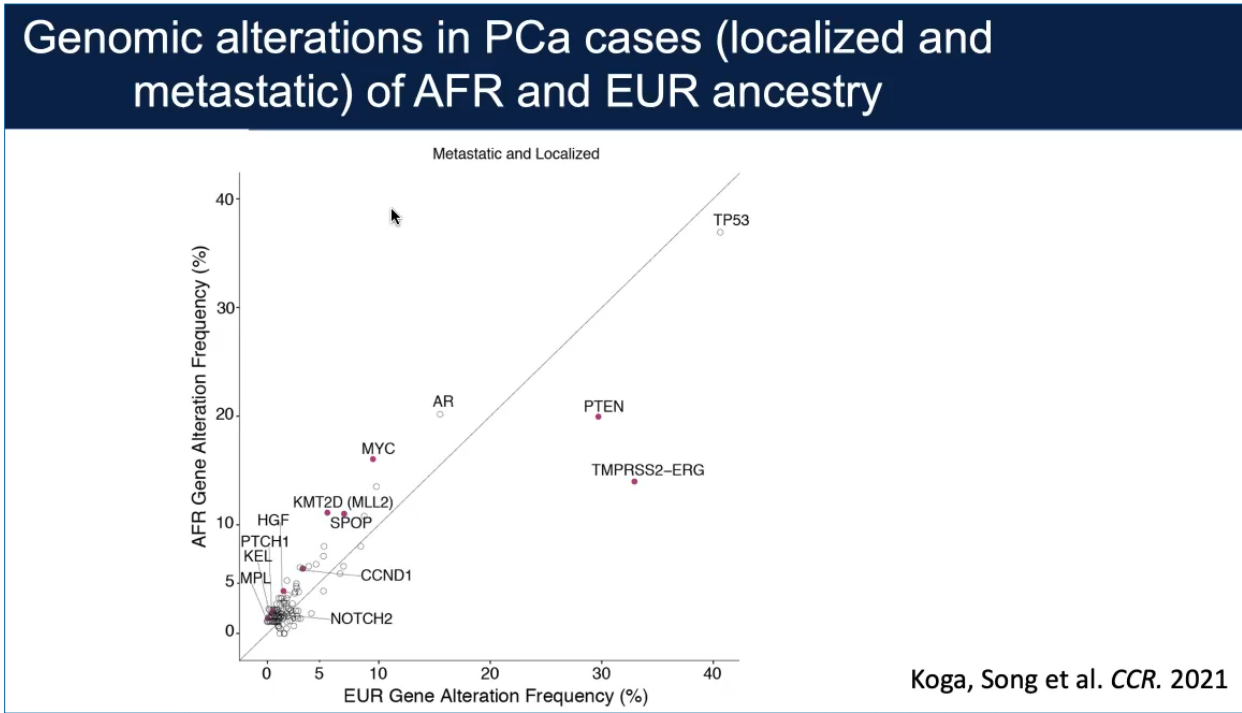


Disparities in Metastatic Prostate Cancer and Opportunities to Exploit Biology to Improve Outcomes

Franklin Huang MD, PhD
University of California, San Francisco

- African American men suffer disproportionately from prostate cancer compared with other racial and ethnic groups. Compared with European American men, African American men are more likely to present with metastatic disease, have a higher risk of death from prostate cancer, and are less likely to be enrolled in clinical trials.
- However, recent data have shown that disparities in prostate cancer outcomes can be mitigated in equal access healthcare systems and clinical trials settings.
- For instance, a prior meta-analysis of prostate cancer clinical trials found that overall survival for Black men was similar or slightly better than White men in clinical trials testing docetaxel or docetaxel-containing regimens.
- More recent clinical trials that prospectively enrolled and compared outcomes in Black vs. White patients treated with androgen-targeted therapies (abiraterone and enzalutamide) also found similar or better outcomes for Black men.
- A retrospective study in the PROCEED prostate cancer registry further found that Black men had longer overall survival than PSA-matched White men following treatment with the immunotherapy Sipuleucel-T.
- It will be critical to understand the mechanisms that underlie improved outcomes for African American patients in clinical trial settings. Another important question is the identification of immuno-biological features of prostate cancer in African American men and how these much inform treatments.
- Dr. Franklin Huang discussed studies examining prostate cancer genomic alterations in a cohort of 3,454 European and African ancestry patients. These included 251 African American and 1,940 European patients with localized prostate cancer, and 185 African American and 1,078 European patients with metastatic prostate cancer.
- Tumor mutations that were more frequent in prostate cancer from European ancestry patients included *TMPRSS2-ERG* fusions and *PTEN*-deletions (**Figure**). Tumor mutations that were more frequent in prostate cancer from African ancestry patients included alterations in the *MYC*, *SPOP*, and *KMT2D* genes (**Figure**).
- Among African ancestry patients, alterations in *AR*, *MYC*, and *RB1* were more frequent in metastatic vs. localized prostate cancer cases.
- The frequency of gene alterations considered “targetable,” as there are treatments available for these patients specifically, were similar in European and African ancestry patients. These include alterations in *ATM*, *BRCA2*, and *MSH2*, as well as rates of tumor mutation burden (TMB) and micro-satellite instability (MSI).
- Unfortunately, including this study, genomic sequencing data has only been reported on for ~220 cases of metastatic prostate cancer from patients of African ancestry, collectively. This is far too few to definitively identify the genomic drivers of metastatic prostate cancer and treatment resistance in African ancestry patients.
- Together, these studies identify potential genomic similarities and differences in prostate cancer in European and African ancestry patients, some of which can inform treatment selection. However much more studies are needed to better understand the factors that contribute to prostate cancer disparities.

- Importantly, treatment in equal access settings can minimize disparities. Thus, more work needs to be done to ensure inclusion in treatment and research settings including clinical trials and genomics studies. Working with the community and patients will be necessary to address some of these issues to improve access and reduce disparities.

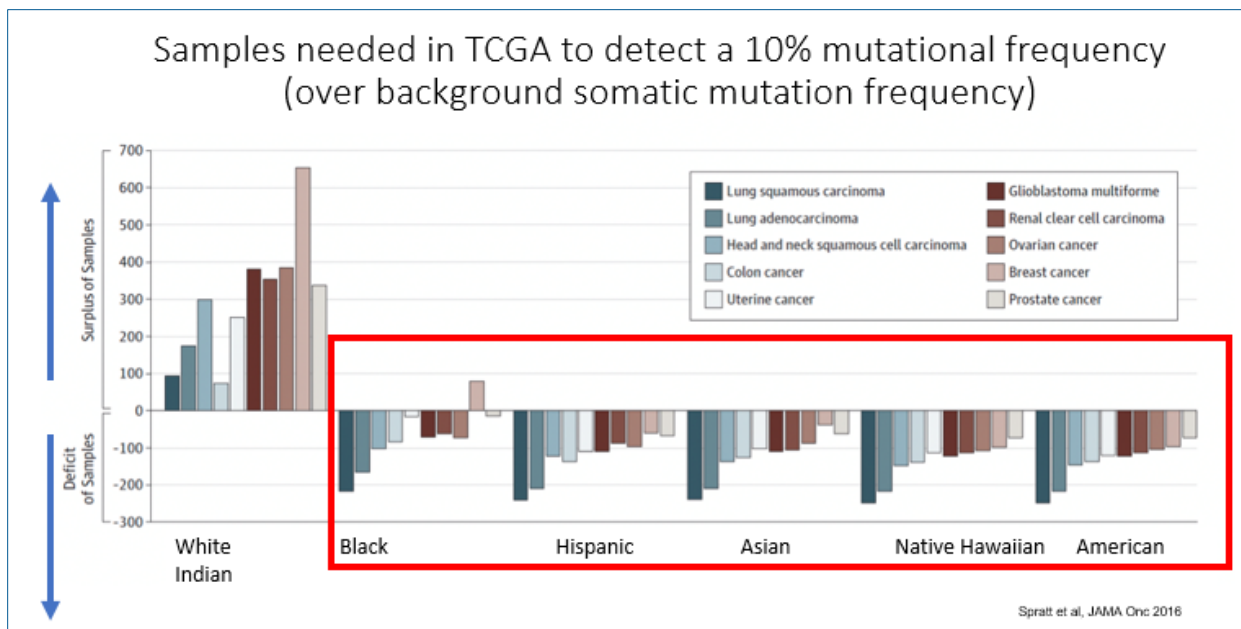


Evidence and Solutions in Access with Equitable Health Care as a Contributor to Prostate Cancer Disparities

Brandon Mahal, MD
 University of Miami

- African American men have a far higher lifetime probability of developing and dying from prostate cancer than Caucasian men.
- In the U.S., there are an estimated 4,800 prostate cancer deaths per year in Black men, representing an excess of ~2,500 deaths compared with White men.
- There are only three well-established risk factors for prostate cancer: age, family history, and race or the impact of racism.
- Self-identified race or ethnicity is a social construct that has many aspects including culture, behavior, environment, and social influences, as well as ancestry and genomic variation, which interact to influence disease prevention, development, treatment and outcomes.

- While the contributions of biology to prostate cancer disparities remains unclear, the impact of access to care and other social-economic impacts of systemic racism are better defined.
- Studies have found that Black men do as well as or better than Caucasians in clinical trials and equal-access care settings. In a meta-analysis of RTOG randomized controlled clinical trials, Black race was associated with a slightly lower risk of prostate cancer mortality among patients diagnosed with non-metastatic prostate cancer. Similarly, a meta-analysis of Phase 3 clinical trials testing docetaxel regimens found similar or slightly better overall survival in Black vs. White patients with castration-resistant prostate cancer.
- An important avenue toward equalizing health care access, is provision of medical insurance. A study by Mahal and colleagues found that higher rates of Black men who were uninsured and newly diagnosed with intermediate to high-risk prostate cancer did not receive treatment compared with White men (27.8% vs. 15.7%). In newly diagnosed patients with medical insurance, non-treatment rates were reduced but still higher in Black vs. White men (15.5% vs. 10.6%).
- The Affordable Care Act (ACA) eliminated racial disparities in medical coverage, with higher rates of uninsured Black vs non-Black patients in years prior to the ACA (13.9% vs 10.4%), but equivalent rates post-ACA (6.9% vs. 6.2%). This demonstrates that policies that improve access to insurance can reduce health disparities.
- Disparities are also prevalent in genomics studies. For instance, in GWAS studies, Whites are highly overrepresented, comprising ~80% of all study participants despite making up ~16% of the global population.
- Among samples in The Cancer Genome Atlas (TCGA), there is a surplus of samples from White patients, but a deficit in sample numbers needed to detect a 10% mutational frequency over background somatic mutation frequencies for all other races/ethnicities, across all cancer types, except for Black women with breast cancer (**Figure**).
- Ancestry-specific prostate cancer mutations have been identified, including many that are actionable or targetable, some of which are at higher frequency in Black patients. For instance, a study in TCGA found higher frequencies of *TP53* alterations and *SCNA/CCNE1* amplifications and lower frequencies of PI3K pathway alterations in patients of African vs European ancestry.
- Ongoing studies by Dr. Mahal and team are evaluating the rates and timing of comprehensive genomic testing in patients of different races, the association between the timing of genomic testing and overall survival, and the differences in frequencies of prostate cancer gene alterations between Black and White men.
- Solutions to disparities require trans-disciplinary and clinical research in diverse populations, and outreach programs to bring care delivery and cutting-edge science to diverse communities.
- In order to overcome distrust of the medical community, patients and the community must be considered research partners rather than subjects, using transparency, education, acknowledgment of the history of racism, and a diverse oncology workforce.
- For instance, the University of Miami has established a cancer education and prevention initiative which involves community outreach by a multicultural and multi-lingual staff who are integrated with the Cancer center, and serve >30,000 individuals per year.
- Overall, a major contributor to prostate cancer disparities is unequal access to care, although insufficient research on genetic contributions has been done. Solutions must be multi-pronged and rely on research and active engagement of diverse communities.



The Importance of Clinical Trial Diversity & Lessons from the COVID-19 Vaccine Trial

Sandra Amaro, MBA
Pfizer

- Sandra Amaro, Senior Director of Global Clinical Trial Diversity Team Lead at Pfizer, discussed the importance of clinical trial diversity, and lessons from the Pfizer COVID-19 vaccine trial.
- Equitable representation in clinical trials allows understanding of our health needs and the impact of medicines and vaccines. Ensuring diversity of volunteers in clinical trials is crucial to equity and reducing healthcare disparities. Additionally, race, ethnicity, age, and sex can all impact how different people respond to the same medicine or vaccine. Thus, it is imperative to recruit clinical trial participants who represent the communities of the countries in which trials are conducted or are disproportionately impacted by the disease being addressed.
- COVID-19 has a disproportionate impact on communities of color, with higher rates of COVID-19 infections and deaths affecting the Hispanic/Latino(a) and Black/African American communities.
- As part of their effort to achieve equity in clinical trials, Pfizer has implemented a Multicultural Equity Health Collective made up of external stakeholders that include advocacy organizations and legislative representatives. Study toolkits are shared with these

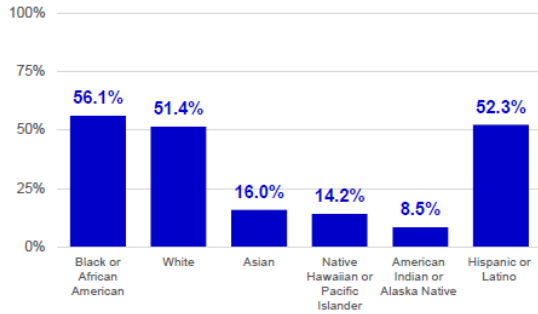
partners to disseminate to communities to inform and educate them about trials and opportunities to participate, in both English and Spanish language.

- Having this Multicultural Equity Health Collective already in place prior to the COVID-19 pandemic played a significant role in Pfizer's ability to rapidly reach diverse volunteers for the COVID-19 clinical trial.
- For example, during the enrollment period on the COVID-19 trial, a Southern California radio station's Strength Thru Unity show featured Dr. Elena Rios of the National Hispanic Medical Association, one of Pfizer's Multicultural Equity Health partners, who discussed the impact of COVID-19 on Americans of Color and the importance of enrollment in the COVID-19 vaccine trial, as well as specifically sharing the trial website URL. Within the next two days, over 1,000 website visitors completed the trial pre-screener through the website and were referred to a San Diego vaccine clinical trial site; ultimately over 90 of these individuals were randomized into the clinical trial. This demonstrates the power that a trusted voice has on influencing medical behaviors in underserved and underrepresented communities.
- A study has recently been published on the baseline diversity and demographic data from Pfizer's U.S. clinical trials conducted from 2011 to 2020. This in-depth analysis of 213 therapeutic clinical pharmacology and vaccine trials with 103,103 participants in the U.S., evaluated overall trial demographics of age, race, ethnicity, sex, and age, and determined the percentage of trials that had racial and ethnic distribution levels at or above U.S. census levels.
- Overall, 56% of trials achieved participant levels at or above U.S. census levels for Black or African Americans, and 53% of trials achieved participant levels at or above U.S. census levels for Hispanic or Latino individuals (**Figure**). However, only 16%, 14%, and 8.5% of trials achieved participant levels at or above census levels for Asian, Native Hawaiian or Pacific Islander, and American Indian or Alaska Native individuals, respectively (**Figure**).
- U.S. Census levels vs. Pfizer Trial participant levels were 76.3% vs. 80.4% for White, 13.4% vs 14.3% for Black or African American, 18.5% vs. 15.9% for Hispanic or Latino, 5.9% vs. 3.1% for Asian, 1.3% vs. 0.6% for American Indian or Alaska Native, and 0.2% vs. 0.2% for Native Hawaiian or Pacific Islander individuals (**Figure**).
- These data have been published in a peer-reviewed medical journal as part of an effort to achieve transparency and contribute to reducing disparities in clinical trials.
- Additional actions being undertaken at Pfizer to achieve diversity in clinical trials include embedding the importance of diversity within the organization, choosing and developing clinical trial site partnerships that ensure diversity in trial enrollment and diversity of site staff, building trust and awareness in communities, addressing practical barriers to trial participation including use of digital tools, and sharing knowledge and transparency in representation on clinical trials with the global community.

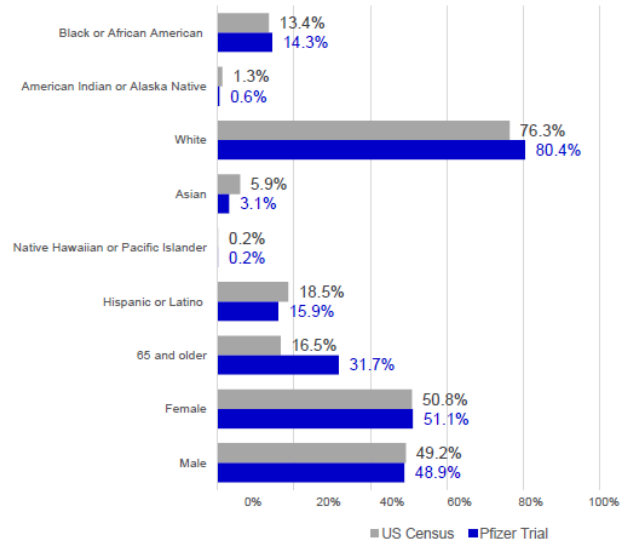
Our Findings

Our analysis of these clinical trials are published in a peer-reviewed journal. By publishing our methodology and data, we are taking steps towards better transparency and raising awareness to ensure equity in our clinical trials.

Percentage of trials with participant levels above census:



Representation in Pfizer Trials vs. US Census Level:*



*Rottas, M., et al. (2021). Demographic Diversity of Participants in Pfizer Sponsored Clinical Trials in the United States. *Contemporary Clinical Trials*, July issue

Confidential 7

Session 5: Prostate Cancer Survivorship

Prostate Cancer Survivorship: New Programs and Strategies

Alicia Morgans, MD, MPH

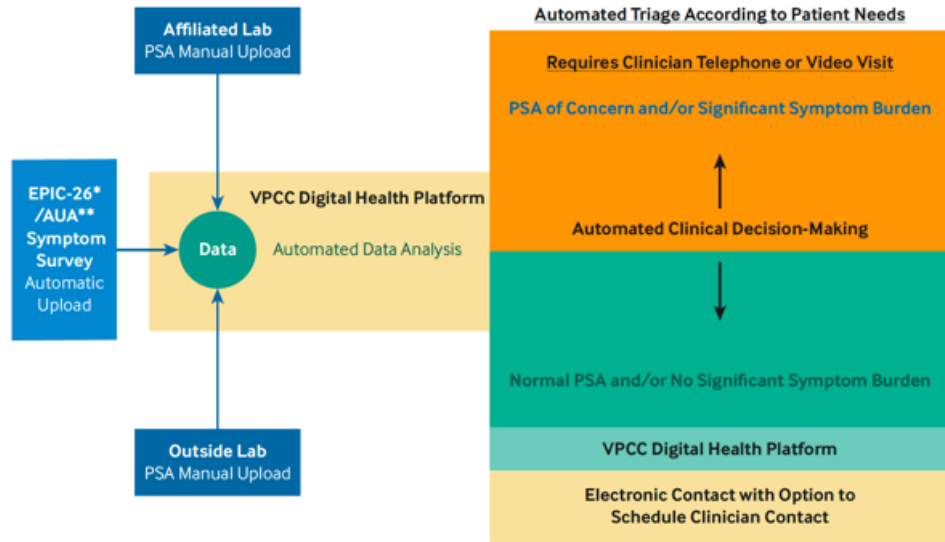
Harvard: Dana-Farber Cancer Institute

- Cancer survivorship is a branch of oncology which cares for the quality of life of cancer patients and survivors.
- Survivorship care begins at diagnosis and continues through the entire continuum of the patient journey, including initial treatment, throughout either ongoing/subsequent treatment or long-term disease remission, and end-of-life care.
- The goal of survivorship research is to test and apply quality-of-life treatment and management for patients in a rigorous way that mirrors the standards for development of anti-cancer treatments.
- Dr. Alicia Morgans discussed new programs and strategies in prostate cancer survivorship. In addition, results from a study testing a new wearable device to reduce hot flashes from prostate cancer hormone therapy were presented.
- The Survivorship Program at the Dana-Farber Cancer Institute (DFCI) includes clinical care, research, education programs, and patient outreach programs. The care team includes nurses and oncologists as well as specialty care by cardio-oncologists, nephrologists, onco-endocrinologists, tobacco counselors, sleep insomnia experts, psychologists, and sexual health experts. Research areas include how to improve survivorship care, the biology of survivorship issues, and prospective clinical trials. Education initiatives include educating medical care providers on how to support patients living with cancer. Bi-directional methods for communication with patients are being developed to better understand and respond to their needs.
- SURECaP is a PCF-initiated working group to improve research on prostate cancer survivorship. This working group has developed a white paper outlining the most important areas for improvement in prostate cancer survivorship research.
- Priority areas for survivorship research identified by the SURECAP working group include determining the subjective patient experience, which includes assessments of quality of life, patient reported outcomes, caregiver-patient interactions, social functioning, financial toxicity, and racial disparities and minority engagement issues.
- In addition, clinical effects need study; these are complications of therapy on cardiovascular and metabolic health, frailty and exercise tolerance, cognitive and psychological health, and skeletal and bone health.
- A better understanding of disease biology that contributes to the survivorship experience is also critical. This includes understanding inflammation and stress response, aging and senescence, and prostate cancer genetics.
- Precision survivorship is the concept of individualizing approaches to survivorship care. The heterogeneity of patient biology, including in genetic polymorphisms, microbiome, and clonal hematopoiesis, can contribute to differing experiences including the risk of long-term complications from treatment, patient reported outcomes, and adverse events. These are a focus of investigation by the SURECaP group.

- Artificial intelligence (AI)-based monitoring measures have been developed to follow patients who are long term survivors not undergoing active therapy, for outcomes and adverse events, as well as identify patients who are candidates for survivorship clinical trials.
- The AI system followed ~1,400 men to ensure PSA testing and patient reported outcome surveys were done every 3 months. The system automatically identified patients with a rising PSA or who developed symptoms, who were immediately referred for a clinician visit for follow-up diagnostics and care (**Figure**). This system provided automated triage according to patients' needs, to improve well visits and free up clinician time for acute care.
- Hot flashes are an adverse side effect that affects up to 80% of men receiving hormone therapy for prostate cancer. Over a quarter of men report hot flashes as the most troubling side effect. These symptoms tend to worsen with longer treatment duration and a younger age at diagnosis, and have a negative impact on sleep and quality of life. Current treatment options are limited.
- A wrist-wearable device (Embr) has been developed that delivers phasic cooling or warming thermal waves to the wrist and can change perception of the environmental temperatures by up to 5° F. This device is controlled by a mobile app, which offers options for personalizing the duration, frequency and intensity of the thermal waves.
- In women with hot flashes caused by menopause, the device was found to reduce hot flash interference, improve control over hot flashes, and improve sleep quality.
- Dr. Morgans conducted a pilot study to assess the ability of this device to manage hot flashes in 50 men with prostate cancer and bothersome hot flashes. Patients used the device for 4 weeks, and were followed on device usage, hot flash interference scores, sleep surveys, and hot flash surveys, temperature symptoms, and perceived efficacy.
- Preliminary results from the first 32 patients who completed this study found that men used the device for 3 hours per day over 8 sessions on average.
- Assessment of daily patient reported feedback surveys found use of the device resulted in a ~22% reduction in the experience of hot flashes over 4 weeks. The device reduced hot flashes in patients treated with different types of hormone therapies (Lupron, abiraterone, and enzalutamide).
- Improvements were also seen in hot flash quantity, bothersome ratings, interference with activities or sleep, and control over interference with activities or sleep.
- A slight improvement was seen in sleep disturbance and sleep related fatigue.
- There was also a trend for improvement seen in hot flash-related temperature symptoms.
- Overall, ~2/3 of patients surveyed felt the device was somewhat to extremely effective at managing hot flashes. The 1/3 of patients who felt the device was only somewhat to not effective tended to use the device less frequently.
- These preliminary results suggest the wrist-wearable device has no adverse effects or tolerability issues and may have efficacy in the management of hot flashes as well as improving hot flash-impacted quality of life measures in men with prostate cancer who experience bothersome hot flashes. This study is ongoing and full results will be presented at a later date.
- The PCF SURECaP group is continuing to conduct innovative studies in priority areas of survivorship research. Future survivorship investigations need to focus on basic biology, the patient experience, and patient-friendly interventions. Adaptable approaches are needed to optimize clinical research, especially in survivorship studies. Non-pharmacologic interventions such as the wrist-wearable device discussed, have the potential to impact multiple quality of life domains, are appealing to patients, and warrant further investigation.

Screening Through Artificial Intelligence

- AI delivered PROs identify men in need of support **and** candidates for survivorship protocols



Dana-Farber Cancer Institute

Updates and Preliminary Results from the PCF-SURECaP Survivorship Working Group Initiatives: COGCaP and ARACOG

Charles J. Ryan, MD

University of Minnesota; Prostate Cancer Foundation

- The PCF-SURECaP initiative is a working group of prostate cancer researchers who are studying prostate cancer survivorship and leading efforts to improve this field of oncology.
- The SURECaP working group has published a white paper on improving research for prostate cancer survivorship. This paper included a framework to integrate analyses of the subjective patient experience, clinical effects, and disease biology, in order to study, evaluate, and describe the prostate cancer survivorship experience.
- Dr. Charles Ryan discussed SURECaP-led clinical trials to evaluate the cognitive effects of androgen deprivation therapy (ADT) on prostate cancer patients.
- ADT is the backbone of treatment for patients with aggressive or advanced prostate cancer. Unfortunately, while some patients experience few side effects, many patients experience a range of side effects including fatigue, weight gain, and depression. ADT may also increase risk for cognitive impairment and dementia. Identifying biological mechanisms and risk

factors for ADT-associated side effects is critical to managing these side effects and improving quality of life in patients.

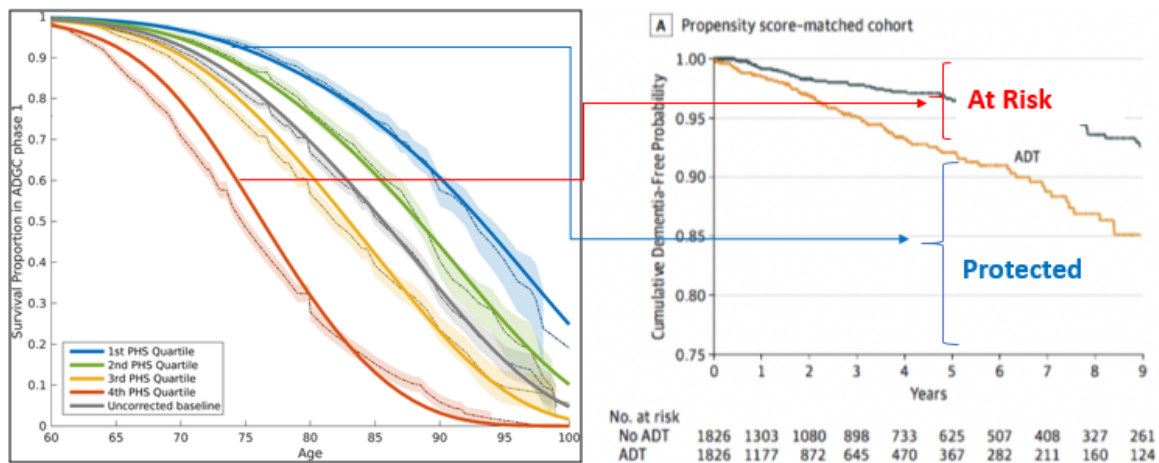
- The androgen receptor (AR), the target of ADT, is expressed and has functions in the brain. These include regulation of memory, executive functions, visual and spatial cognition, neuron protection, and removal of waste products from the brain. Blocking androgens may impair brain functions and could lead to increased accumulation of β -amyloids and increased tau hyperphosphorylation, which are two leading contributors to Alzheimer's disease. Accordingly, low brain testosterone levels have been associated with increased levels of β -amyloids in patients with Alzheimer's disease.
- Androgen levels in the brain steadily decrease with age in men. For instance, at age 80, androgens levels are \sim 1/4th-1/5th of the levels seen at ages 40-50. This may contribute to decreased neural protection and poorer cognitive function in older patients.
- Studies in patients with prostate cancer have documented some cognitive decline after undergoing ADT. In one study, compared with healthy controls, patients treated with ADT for 1 year had a 40% gap for immediate span of attention, a 50% gap for visuo-spatial activity, and a 40% gap for executive function.
- A different study using cognitive performance tests found that while approximately half of patients and controls had poor performance at baseline, controls were able to learn and improve their performance on the test over time, while patients on ADT tended to do worse over time.
- It is important to note that dementia is a different disorder than the cognitive impairment assessed in the two studies above. Dementia is defined as a chronic or persistent disorder of mental processes caused by brain disease or injury and characterized by memory disorders, personality changes, and impaired reasoning.
- Polygenic hazard scores are genetic tests that identify individuals at higher genetic risk for a specific disease. A polygenic hazard score has been developed for Alzheimer's disease.
- Dr. Ryan and colleagues hypothesize that the polygenic hazard score for Alzheimer's disease could also identify men at higher risk for developing cognitive disorders after treatment with ADT, while men with low polygenic hazard scores for Alzheimer's disease had lower risk for cognitive disorders after ADT (**Figure**). These data suggest that genetic factors that modulate risk for Alzheimer's disease also modulate risk for cognitive disorders after ADT, and that this test may help to identify patients at higher risk.
- These studies show that patient characteristics including age, comorbidities, and genetics may impact risk for cognitive disorders after ADT. In addition, drug effects, such as central nervous system (CNS) penetration and drug potency may also impact cognitive side effects.
- Dr. Ryan and Dr. Alicia Morgans are leading clinical trials to evaluate the cognitive effects of different AR-targeted therapies used to treat patients with metastatic castration resistant prostate cancer (mCRPC).
- COGCaP is a trial to evaluate the cognitive effects of abiraterone and enzalutamide in patients with mCRPC without dementia or prior to treatment. Patients on this trial receive abiraterone vs. enzalutamide, and undergo cognitive tests and functional brain scans before, during, and after treatment. These treatments have a different mechanism of action: abiraterone blocks androgen production and does not directly target AR, while enzalutamide directly binds to and inhibits AR. This trial is ongoing and actively enrolling patients.
- ARACOG is another ongoing trial that is comparing the cognitive effects of darolutamide and enzalutamide in patients with mCRPC. Both of these medications bind directly to AR. However, darolutamide is far less able to enter the brain than enzalutamide, and is thus hypothesized to impart lower risk for cognitive decline. Patients on this trial are randomized to receive darolutamide vs. enzalutamide, and undergo cognitive tests and functional brain

scans before, during, and after treatment. Patients on this trial are able to cross-over to the other treatment arm if they display symptoms of cognitive decline.

- Challenges to cognitive trials in oncology include patient self-selection biases, the ability of oncology clinics to perform these tests, and ability of the tests to identify cognitive decline in these patients.
- If successful, these trials will identify cognitive risks associated with different types of hormone therapies for prostate cancer and determine patient risk factors and biomarkers for cognitive decline. These data will help clinicians and patients to make more informed individualized therapy choices, which will lead to better survivorship outcomes. These studies will also inform about the role of AR in cognition, which may be of value to the neuroscience field.

ADT and Dementia: Hypothesis that it arises post ADT in an at risk population

Applying Polygenic Hazard Score to Cognitive Assessment in ADT Treated patients



Desikan RS, et al. (2017) Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score. PLOS Medicine 14(3):



Sleep Dysfunction and Prostate Cancer

Stacy Loeb, MD, MSc, PhD (Hon)

New York University; Manhattan Veterans Affairs Hospital








- Dr. Stacy Loeb discussed the association between sleep dysfunction and prostate cancer.
- Sleep disturbances are common in the general population, with 35% of U.S. adults sleeping under 7 hours per night, 10-30% experiencing insomnia, and 2-30% experiencing obstructive sleep apnea (blockages in upper airway during sleep).
- Sleep disturbances are known to have both mental and physical health consequences, including depression, poorer well-being, increased risk of accidents, hypertension, diabetes, obesity, depression, heart attack, and stroke.
- Night shift work, which disrupts the normal physiological circadian rhythm, has been classified as a Group 2A carcinogen (“probably carcinogenic to humans”), though this is primarily based on data from experimental animal models and limited evidence in humans.
- Mechanisms by which sleep disturbances may contribute to cancer include the circadian system and melatonin acting as potential tumor suppressors, while obstructive sleep apnea may cause hypoxia (low oxygen), which can accelerate tumor progression.
- An analysis of epidemiologic studies on the links between circadian rhythm, sleep loss and prostate cancer risk, found a positive association in 15 of 16 studies, 10 of which reached statistical significance. Findings from these studies included associations between higher prostate cancer incidence in countries with more light at night, with shorter sleep duration, and in shift workers, pilots and other occupations with circadian disruptions.
- Another study identified a link between genes that regulate circadian rhythm and melatonin pathways with prostate cancer risk.
- However, other studies have not found associations between melatonin levels, insufficient sleep, and poor sleep quality with prostate cancer risk.
- Overall, many epidemiological studies have investigated the relationship between sleep or circadian rhythm disturbances with prostate cancer risk, and many, but not all, suggest an association.
- Importantly, there is no mention of sleep in common guidelines for prostate cancer patients, such as the American Cancer Society prostate cancer survivorship guidelines.
- Dr. Loeb and team used a number of methods to study the links between sleep and circadian disruptions and prostate cancer and to identify concerns and unmet needs of patients and their families. These included “social listening,” a method that evaluates social media posts, surveys of patients and caregivers, and systematic reviews of studies in caregivers and patients that included sleep as an endpoint.
- A social listening study that examined posts in an online prostate cancer patient community, found 685 posts about sleep; 86% were posted by patients and 14% were posted by caregivers. Posts about sleep were more common amongst patients with advanced disease than localized disease, and were associated with more negative emotions. Co-existing complaints included pain and hot flashes. 22% of the posts discussed sleeping medications.
- An ongoing systematic review of studies in patients and caregivers suggests that prostate cancer has a substantial impact on sleep, based on subjective and/or objective measures. Sleep disturbances were commonly linked with physical issues such as night sweats, urination, and pain, and psychological issues such as distress, depression and anxiety. Little research was found to evaluate interventions for sleep disturbances in prostate cancer, but

limited data suggested potential benefits from acupuncture, hypnotic therapy, mindfulness-based cognitive therapy, and educational information.

- Dr. Loeb and colleagues conducted a survey of patients with prostate cancer and caregivers. Preliminary data suggest high rates of poor sleep quality and use of sleeping medications in both groups.
- Preliminary data in patients with metastatic prostate cancer enrolled in the IRONMAN registry similarly found a substantial proportion with difficulty falling asleep or who did not feel rested when waking up in the morning.
- Across studies, the overuse of sleep medications is concerning, as many have black box warnings, such as for risk of serious injury caused by sleepwalking.
- The guidelines from the American College of Physicians for managing chronic insomnia recommend cognitive behavioral therapy for insomnia (CBT-I), a structured therapy program that addresses thoughts and behaviors about sleep, as the initial treatment. If CBT-I alone is unsuccessful, then shared-decision-making about adding pharmacologic therapy would be recommended. In addition, treatable secondary causes of insomnia should be considered (e.g., depression, pain, urinary problems, and other sleep disorders like sleep apnea).
- CBT-I is a widely available intervention, including in individual or group therapy, web-based modules/apps, and self-help books. The VA has a CBT-I Coach App available for patients.
- Unfortunately, in urology practice, sleep health is not routinely assessed in patients. Preliminary data from a survey of urologists suggest that most do not assess sleep quality or discuss sleep hygiene recommendations with patients.
- There are guidelines on sleep from the NCCN survivorship guidelines (for survivors of all types of cancer). These outline how to assess for insomnia and secondary causes, and recommend behavioral strategies (sleep hygiene education and CBT-I) as first line treatment strategies, with pharmacologic therapy only considered as a second step if deemed safe.
- Sleep hygiene recommendations include keeping a regular bedtime and wake time, to avoid looking at the clock if awakened, regular physical activity in morning or afternoon, to limit caffeine consumption at night, to avoid big meals and limit fluid within 3 hours of bedtime, to have bright light in the morning and avoid bright light at night, to turn off electronics at night, and to enhance the sleep environment (such as optimizing temperature and comfort) **(Figure)**.
- Additional sleep hygiene recommendations from the NCCN survivorship guidelines include stimulus control, using the bed for sleep and sex only, avoidance of naps, cognitive therapy, and relaxation training such as deep breathing, yoga, and bio-feedback.
- There is a significant link between sleep and fatigue.
- Sleep is also linked to erectile function. Poor sleep may cause hypoxia which is deleterious to erectile tissue, and reduced nocturnal erections during REM sleep, which may be protective. A study in prostate cancer patients who had undergone radical prostatectomy found that obstructive sleep apnea was associated with reduced recovery of erectile function.
- Ongoing observational studies that are evaluating sleep in prostate cancer patients include IRONMAN, the Health Professionals Follow-Up Study, and the recently launched “Eat-Move-Sleep” study at UCSF, which is a Digital Survivorship study examining lifestyle after cancer diagnosis.
- Dr. Loeb and colleagues have recently developed an intervention to improve sleep in patients with prostate cancer and their caregivers, the Sleep Health & Lifestyle Improvement Program (SHIP). A pilot study will soon begin to test the feasibility of this 3-month tailored digital intervention. Sleep and other lifestyle factors will be evaluated before and after the intervention using questionnaires and actigraphy assessments.

- Overall, these studies demonstrate that there is a substantial burden of sleep disturbance among prostate cancer survivors and caregivers, however sleep is inadequately assessed by doctors and sleep medication is overused. Sleep disturbances have a negative effect on overall health and quality of life. Thus, studies to address sleep health in prostate cancer survivorship are greatly needed.

Promote Sleep Hygiene

 <ul style="list-style-type: none"> ✓ Regular bedtime & wake time ✓ Avoid looking at clock if awoken 	 <ul style="list-style-type: none"> ✓ Bright light in morning ✓ Avoid bright light at night
 <ul style="list-style-type: none"> ✓ Regular physical activity in morning/afternoon 	 <ul style="list-style-type: none"> ✓ Turn off electronics at night
 <ul style="list-style-type: none"> ✓ Limit caffeine consumption 	 <ul style="list-style-type: none"> ✓ Enhance the sleep environment (e.g., temperature, comfort)
 <ul style="list-style-type: none"> ✓ Avoid big meals & limit fluid within 3h of bedtime 	

Utilization of an “Exercise is Medicine” Approach to Optimize Treatment and Health Outcomes among Prostate Cancer Survivors

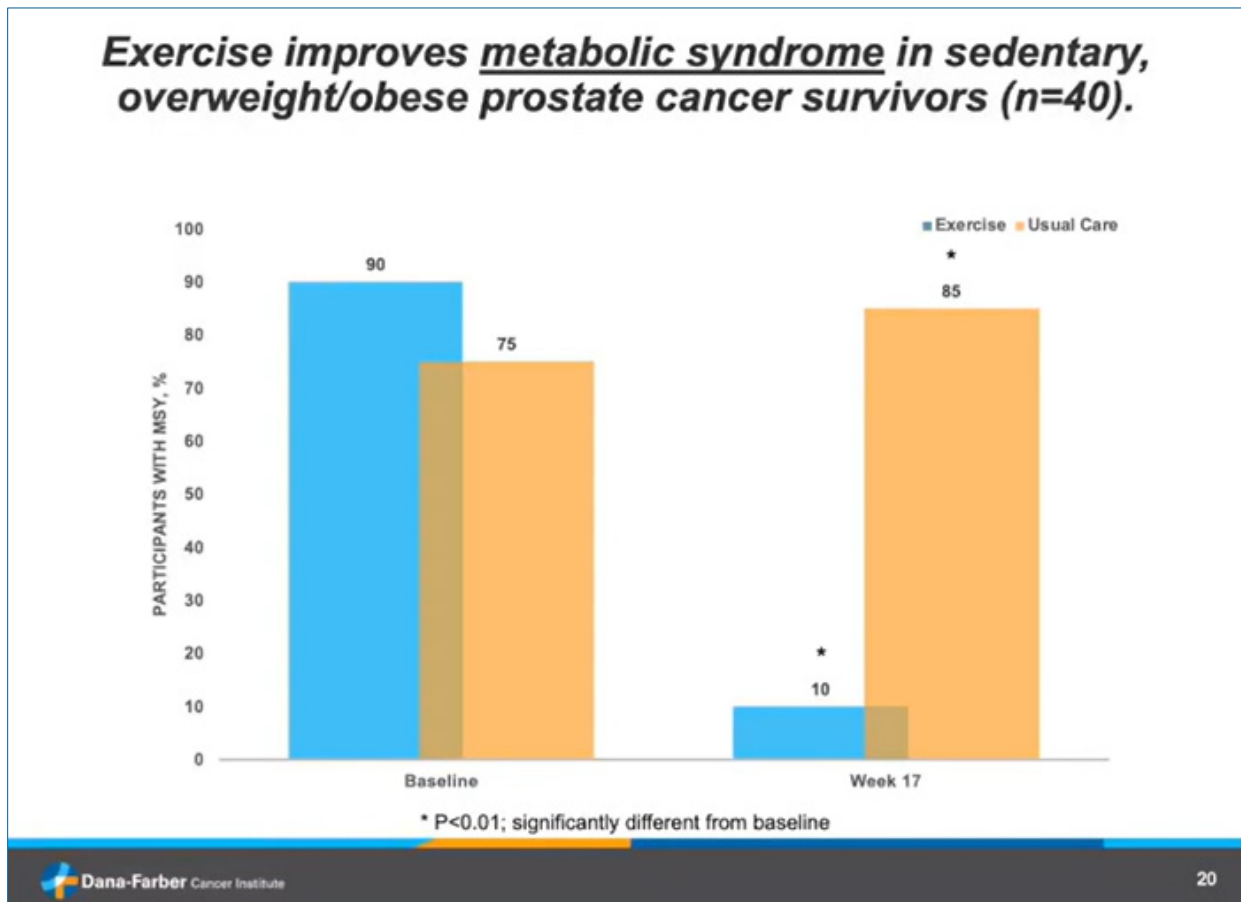
Christina Dieli-Conwright, PhD, MPH
Harvard: Dana-Farber Cancer Institute

- Dr. Christina Dieli-Conwright discussed research on the benefits of exercise in cancer patients.
- Exercise oncology is the utilization of exercise or physical fitness to enhance the lives of people diagnosed with cancer or at risk of developing cancer. This field is over 100 years old and has grown immensely in the past 20 years.

- Exercise oncology has led to the establishment of exercise guidelines for cancer survivors. Current guidelines recommend aerobic activity (30 minutes of moderate intensity physical activity, 3 times per week) plus resistance exercise (30 minutes per session, 2 times per week).
- There is much evidence that engagement in regular exercise elicits multiple benefits among prostate cancer survivors, including improving numerous mental and physical quality of life aspects, and increasing chance of survival. Whether exercise improves treatment efficacy and tolerance for treatment remains understudied and unclear.
- Cancer survivors are at increased risk for mortality and accelerated general health declines due to the side effects from cancer treatments. Unfortunately, ~25% of cancer survivors are physically active, ~65% are overweight or obese, and cancer survivors are at increased risk for comorbidities. Exercise interventions may highly benefit this population and have a greater impact if initiated earlier in the disease journey.
- In prostate cancer patients, androgen deprivation therapy (ADT) is known to lead to reduced lean mass, increased fat, lower physical function, and lower quality of life. ADT is also associated with a ~2-fold increase in risk for metabolic diseases including diabetes and cardiovascular disease. Thus, prostate cancer patients may especially benefit from exercise.
- The Dieli-Conwright Lab, led by Jackie Dawson, PhD, conducted a clinical trial testing the clinical impact of a 12-week periodized resistance training regimen in prostate cancer patients undergoing ADT. Patients underwent 3 months of a 3-times per week, 45-min long, supervised in-person exercise regimen consisting of machine-based total body exercises that progressed in intensity in a periodized fashion.
- This study found that periodized resistance training significantly improved lean mass in patients on ADT, by ~1.1kg of lean muscle mass on average, and significantly reduced the prevalence of sarcopenia (loss of skeletal muscle mass and strength), from 38.5% to 15.4% of patients.
- Periodized resistance training also significantly reduced fat mass while total mass did not change. There was also a trend toward improved physical function including walking speed and speed of time to get up and go. There were significant reductions in waist circumference and triglyceride levels.
- Overall quality of life scores were significantly improved in the exercise group, as well as a trend toward reductions in fatigue and depression.
- Compliancy in this trial was very good, with >90% of patients completing the exercise.
- A follow-up pilot trial, called ACTIVATE, was recently completed in sedentary overweight/obese prostate cancer patients undergoing ADT. This trial incorporated aerobic exercise in addition to resistance training in circuit-based intervals. Outcomes evaluated included changes in cardio-metabolic health, fitness, quality of life, and sarcopenic obesity measures.
- Preliminary results from this study demonstrate a decrease in the percentage of patients with metabolic syndrome from 90% at baseline to 10% at week 17 of the exercise regimen (**Figure**). In contrast, in the group that did not undergo exercise, the percentage of patients with metabolic syndrome increased from 75% at baseline to 85% at week 17 (**Figure**).
- Other studies from members of Dr. Dieli-Conwright's lab include the ERASE trial led by Derek Kang, PhD, which found that cardiorespiratory fitness was significantly improved in prostate cancer patients on active surveillance. In this study, 52 men were randomized to receive usual care vs. aerobic high-intensity interval training for 12 weeks. The trial found improvements in biochemical recurrence (PSA velocity) in patients on the exercise arm.
- In another trial led by Rebekah Wilson, PhD, a combined intervention of exercise and diet modifications were tested and shown to reduce fat mass and improve fitness in obese

patients with prostate cancer undergoing ADT. This trial also found good patient adherence, with 89% of patients attending supervised exercise regimens and 100% attending dietary consultations.

- A recently initiated trial, THRIVE, is testing home-based exercise strategies to improve exercise participation and cardiovascular health in underserved minority patients with prostate, breast or colorectal cancer undergoing chemotherapy. This study will include virtually supervised exercise regimens that the patient does at home. Participants will receive the exercise equipment delivered to their homes.
- Future studies needed in exercise oncology include the development of virtual mechanisms to increase outreach and access, testing more novel exercise modalities, better studies into the effects of exercise on treatment efficacy, skeletal muscle quality and tumor biomarkers, establishing adapted exercise guidelines for patients and survivors, and establishing the ability of exercise in reducing prostate cancer disparities in underrepresented populations.
- Ultimately, these studies aim to improve prostate cancer survivorship with exercise prescription and active lifestyle promotion.



Prostate Cancer Survivorship at the VA: Leveraging Existing Veterans' Data to Improve Cardiovascular and Bone Health

Ravi Parikh, MD, MPP

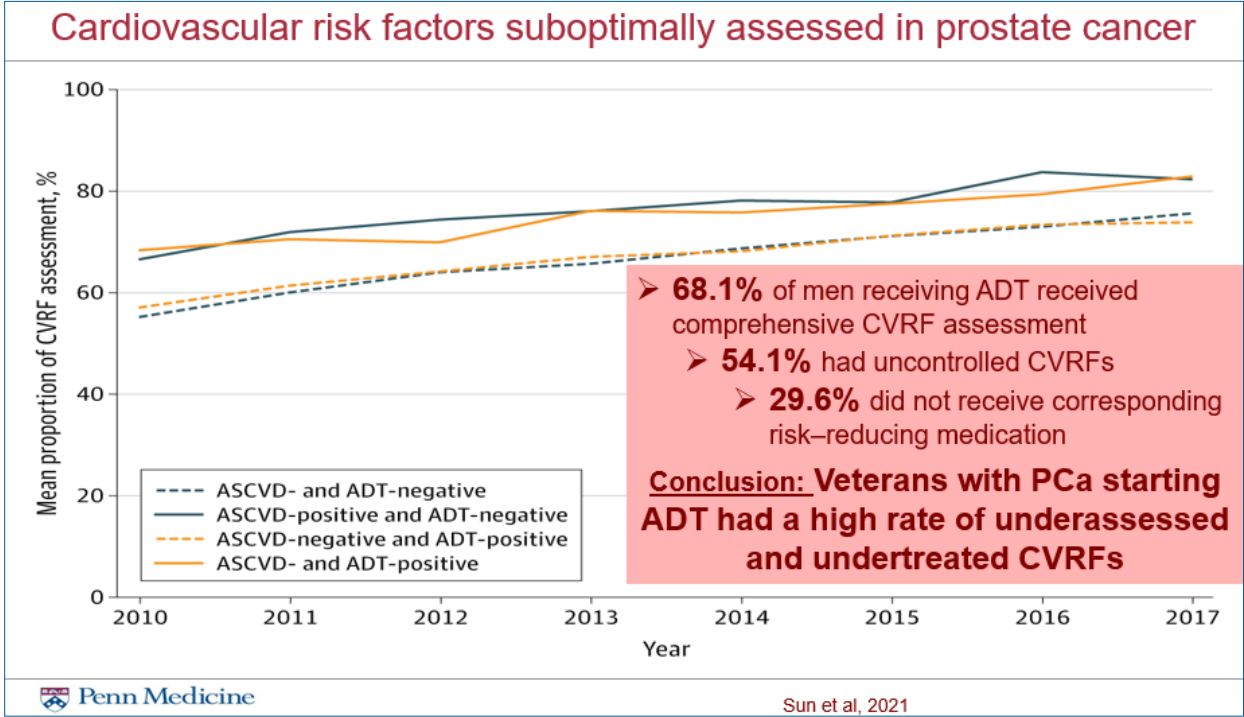
University of Pennsylvania; The Corporal Michael J. Crescenz VA Medical Center

- Androgen deprivation therapy (ADT) is the primary systemic treatment used for patients with high risk localized, recurrent, or advanced prostate cancer.
- There are several types of ADT, which prevent activity of the androgen receptor (AR) via different mechanisms of action. The most common forms of ADT include GnRH agonists (leuprolide, goserelin, triptorelin, histrelin) and GnRH antagonists (degarelix, relugolix), which significantly lower testosterone levels and result in deep anti-cancer responses. These forms of ADT can be combined with newer treatments such as abiraterone, enzalutamide, apalutamide, or darolutamide.
- ADT is used in up to 40% of men with prostate cancer at some point during the course of their treatment, with curative intent for men with localized disease, and with palliative intent for men with advanced or metastatic prostate cancer.
- Although it is associated with excellent cancer control outcomes, the hormonal shifts from ADT cause negative side effects. These include cardiometabolic side effects such as atherogenesis, myocardial infarction, dyslipidemia and diabetes, bone health side effects such as osteopenia and fragility fractures, and other side effects such as sarcopenia, decreased exercise tolerance, hypertension, and potentially mental health-related consequences.
- Dr. Ravi Parikh discussed survivorship research in the VA to improve cardiovascular and bone health in patients with prostate cancer.
- Early intervention is key to reduce these side effects from ADT. However, studies into how to improve these survivorship issues have been limited by insufficient data on long-term follow-up to assess long-term consequences, and on treatment, demographic, and socioeconomic factors. Data infrastructure with high quality data that enables longitudinal survivorship studies is key.
- The VA Corporate Data Warehouse is a high-performance infrastructure that has optimized standardization, consolidation and streamlining of clinical data systems throughout the VA. These data can be curated for research purposes.
- Dr. Parikh and colleagues assembled a data cohort of >150,000 veterans diagnosed with prostate cancer between 2004-2020. This cohort has registry-like curation, and includes longitudinal data on lab tests, imaging, mental health and socioeconomic burden, and cause of death.
- This data cohort is being used for survivorship research projects studying the prevalence of cardiometabolic and bone health consequences of ADT in prostate cancer patients over time.
- One project investigated the assessment and management of cardiovascular risk factors among U.S. Veterans with prostate cancer.
- Cardiovascular risk factors are known to be prevalent and lead to early mortality among men with prostate cancer. ADT exacerbates this risk, and changes in cardiometabolic health can be seen as early as 12-24 weeks after initiation of ADT. This knowledge led the FDA to issue a black box warning in 2010, warning that GnRH agonists increase risk of diabetes

and cardiovascular diseases, and that patients undergoing treatment with GnRH agonists should undergo periodic monitoring of blood glucose and/or hemoglobin A1c levels.

- Dr. Parikh and colleagues investigated how well physicians screen for and manage cardiovascular risk factors prior to initiating treatment with GnRH agonists, in a cohort of >90,000 veterans diagnosed with prostate cancer between 2010-2017. Cardiovascular outcomes including hypertension, dyslipidemia, and impaired glucose tolerance were assessed.
- Overall, cardiovascular risk factors were found to be under-assessed and under-treated in men with prostate cancer. While higher rates of cardiovascular risk factor assessments occurred in men with pre-existing cardiovascular risk factors (such as age, dyslipidemia, smoking), no significant differences in assessments were seen in patients starting ADT vs. those not starting ADT (**Figure**). In other words, ADT initiation played no role in cardiovascular risk factor assessments by physicians. Approximately 68% of patients receiving ADT received comprehensive cardiovascular risk factor assessment. 54% had uncontrolled cardiovascular risk factors, and 30% did not receive corresponding risk-reducing medication.
- In a second project, Dr. Parikh and colleagues investigated biomarker-based approaches to predict bone fracture risk among Veterans with metastatic hormone-sensitive prostate cancer (mHSPC).
- ADT is known to accelerate bone loss and is associated with a 10-20% risk of significant fracture after five years. ADT-associated fractures are a significant survivorship concern, being associated with decreased quality of life and functional status, and increased prostate cancer-related mortality by up to 40%. Anti-resorptive therapy (bisphosphonates, denosumab) which decreases fracture risk and is commonly recommended in patients with very late-stages of disease, is unfortunately not routinely recommended in mHSPC.
- Survivorship guidelines recommend bone mineral density screening and fracture risk assessments be done prior to ADT. Despite this evidence, less than 1/3 of prostate cancer patients in the VA were found to receive bone health screening, including less than half of patients with mHSPC.
- Ways to improve early and opportunistic assessments of bone health are needed. Biomechanical computed tomography (BCT) is an approach that uses routine CT scans to assess bone health. BCT is already available as a Medicare screening benefit for osteoporosis diagnostic testing, but is not yet approved for assessing bone health in prostate cancer patients.
- Most CT scans that patients routinely undergo for baseline and surveillance prostate cancer imaging include the spine or hip regions. BCT can be opportunistically applied to these CT scans, to determine bone strength, bone mineral density, and other measures of fracture risk.
- Dr. Parikh and colleagues used BCT to investigate changes in bone strength and bone density from routine CT scans in 140 patients with mHSPC undergoing ADT. Baseline CT images (taken within 48 weeks prior to ADT initiation) were compared with CT images taken up to 96 weeks after ADT initiation, and at least 48 weeks after the baseline CT.
- Preliminary results from BCT assessments found that after ~1 year of ADT, average bone strength was decreased by 22%, femoral neck T-score decreased by 60%, and hip bone density decreased by 20%. Using data from this information, virtual stress testing could be performed to estimate risk for fractures if a patient were to fall.
- Future studies will investigate type I collagen C-telopeptide (CTX), a marker of bone turnover and future fracture risk in non-prostate cancer populations, as a blood test-based biomarker of fracture risk in Veterans with mHSPC. This study will take advantage of ongoing blood collection studies at the VA.

- Overall, these studies find that cardiovascular and bone health survivorship screening and management are suboptimal among Veterans with prostate cancer.
- Novel imaging-based techniques and blood-based markers of bone turnover may provide better and opportunistic assessment of fracture risk and be integrated as part of routine surveillance and to guide recommendations for anti-resorptive therapy. Studies to test these approaches and interventions to improve prostate cancer survivorship are underway.



Patient Perspective - ADT, Exercise and QoL

Joël Pointon, MPH
 Patient and Advocate

- Mr. Joël Pointon discussed a patient-directed exercise initiative to preserve and improve quality of life in prostate cancer patients on androgen deprivation therapy (ADT).
- Mr. Pointon was diagnosed with prostate cancer in 2019, and was struck by the limited resources available to patients for managing the physical quality of life and mental health consequences of prostate cancer diagnosis and treatment.


- ADT is a life-prolonging treatment, but can cause negative side effects including hot flashes, lethargy, muscle loss, weight gain, decreased bone density, increased blood pressure and glucose levels, and increased risk for cardiac impairment. Pharmacological solutions are available for managing many of these side effects, and exercise (resistance training) is recommended.
- However, resistance training programs appropriate for men with prostate cancer undergoing ADT are limited.
- In partnership with personal trainer Justin Fassio, who has experience working with people with limitations, a core resistance training exercise program was developed for patients undergoing ADT, to do in their own homes with minimal equipment at varying levels of difficulty.
- A website presenting this information as videos, photos and instructions, was created.
- This website also includes a section for a patient support group.
- The possibility to add on the ability for patients to obtain personalized one-on-one training is being considered.
- The largest challenge for this project is to gain support and to develop patient awareness about it, and partnerships with larger well-known prostate cancer organizations are being sought. This would also provide data on use of the website and patient feedback for improvement.
- A recent cancer survivorship survey found that ~2/3 of patients with stage 4 cancer listed exercise as one of their main concerns in their cancer treatment. With an estimated 40% of patients with prostate cancer undergoing ADT, there is an obvious need for exercise programs designed specifically for patients.
- Survivorship programs such as these are critical to improving patient quality of life, and enabling patients to not just survive, but to thrive.
- The exercise website is: www.exrx4adt.com. Questions about this program can be emailed to Rt4adt@gmail.com.

ExRx 4PCS

HOME COMMUNITY FITNESS RESEARCH

POWIR4ADT CORE WORKOUT

GALLERY
CORE EXERCISE GALLERY //


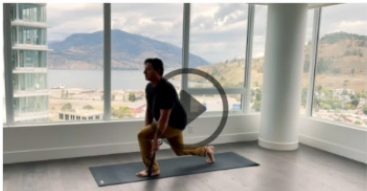


IMPACT
SQUAT JUMP

RESISTANCE + IMPACT
LOWER BODY

These lower body exercises should be performed in sets of 10 one round each. Start with bodyweight only, limiting your range of motion if you feel pain.

Once you've advanced to full range of motion start increasing the resistance using bands or weights. When you first add resistance you can limit your range of motion to begin. Once you are at full range of motion, continue to increase resistance load.

Prevention of Osteoporosis with Impact + Resistance (POWIR)
September 11, 2021

Industry-Presented Webinar:
Exercise as Medicine for Cancer
September 9, 2021

WHAT'S POPULAR

- EXERCISE AS MEDICINE
- EXERCISES
- FITNESS ASSESSMENT
- FITNESS EQUIPMENT
- FUNCTIONAL FITNESS

SPECIAL LECTURE: ADT and CV Risk: Why Relugolix?

Neal Shore, MD
Carolina Urologic Research Center
GenesisCare, US

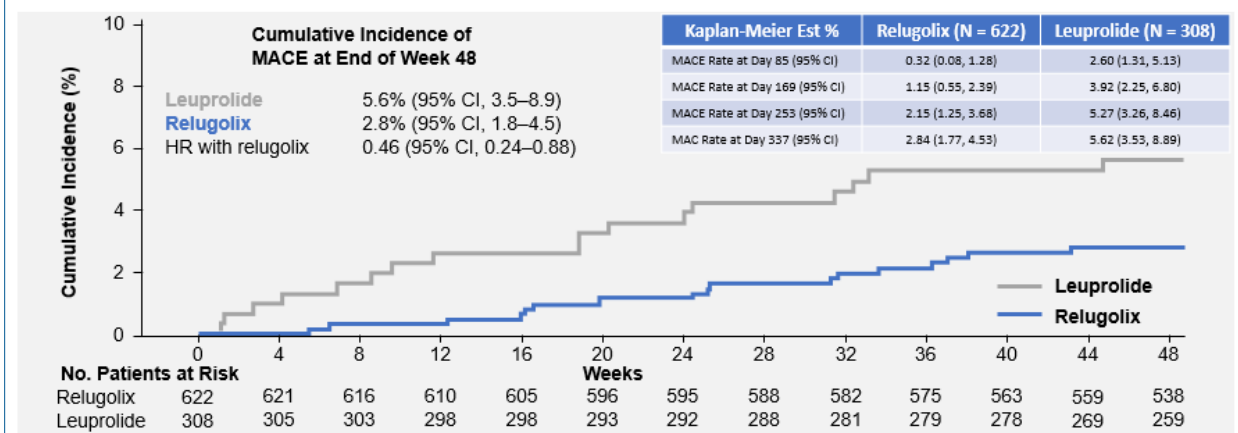
- Hormone suppression has been the primary treatment for aggressive and advanced prostate cancer for decades, as it suppresses the activity of the androgen receptor (AR), the primary driver of prostate cancer.
- Unfortunately, there are long-term and chronic risks associated with ADT, due to the metabolic changes it triggers. These include increased risks for cardiovascular disease, sarcopenic obesity (which is seen in 70% of patients), dyslipidemia, diabetes mellitus, metabolic syndrome, fatigue, and depression.

- Androgen deprivation therapy (ADT) comes in several forms: Luteinizing hormone releasing hormone (LHRH, also called Gonadotropin Releasing Hormone or GnRH) antagonists (such as degarelix) and LHRH agonists (such as leuprolide and goserelin).
- A proposed mechanism by which ADT (specifically LHRH agonists) increases risk for cardiovascular disease, is via stimulating immune cells in atherosclerotic plaques to cause plaques to become unstable and rupture, and create subsequent thrombotic complications.
- Several studies have been done to evaluate the risk of cardiovascular events during treatment with LHRH antagonists vs. LHRH agonists.
- A retrospective analysis evaluated cardiovascular disease risk using data pooled from six randomized prospective Phase 3 trials comparing LHRH agonists with LHRH antagonists, in a total of 2,328 men with prostate cancer. Among the 708 patients who had pre-existing cardiovascular disease, cardiovascular events and deaths during the initial year of treatment were 56% lower with LHRH antagonists vs. LHRH agonists (6.5% vs. 14.7%). There were no differences between incidences of death from any cause or cardiac events among men without pre-existing cardiovascular disease.
- A prospective randomized Phase 2 trial evaluated cardiovascular disease risk with an LHRH antagonist (degarelix) vs. LHRH agonist (3 months depot of leuprolide) in 80 advanced prostate cancer patients with pre-existing cardiovascular disease. New cardiovascular events were observed in 15 patients: 13 (33%) treated with LHRH agonist vs. 2 (5%) treated with LHRH antagonist. A major adverse cardiac and cerebrovascular event (MACCE) was observed in 9 patients: 8 (20.5%) treated with LHRH agonist vs. 1 (2.4%) treated with LHRH antagonist. This represents an 18% absolute risk reduction for MACCE at 12 months with an LHRH antagonist. These data demonstrate lower risk of cardiovascular events for LHRH antagonists vs LHRH agonists in men with pre-existing cardiovascular disease.
- A meta-analysis of randomized controlled clinical trials found that LHRH antagonists were associated with lower all-cause mortality rates and cardiovascular events compared with LHRH agonists. However, ~40% of patients treated with degarelix have injection site reactions, which contributes to a high rate of patients crossing over to receive a LHRH agonist instead.
- An analysis of real-world data from the U.K. also found a lower risk of cardiac events in patients treated with degarelix compared with LHRH agonists.
- A study evaluating data from the FDA Adverse Events Reporting System (FAERS), found that cardiovascular adverse event reporting among prostate cancer patients was higher with LHRH agonists than non-LHRH agonists.
- Another large analysis of cardiovascular toxicities during treatment with ADT also found lower cardiovascular disease risk with LHRH antagonists vs. LHRH agonists. This study also noted that further research is needed in African American populations, due to disparately higher prostate cancer mortality rates and high mortality from cardiovascular disease.
- Altogether, multiple studies have found that cardiovascular disease risk is higher with LHRH agonists vs. LHRH antagonists, specifically in patients with pre-existing cardiovascular disease. However, there are caveats and flaws in many of these prior studies. A prospective study with cardiovascular events as the primary endpoint has yet to be done.
- This suggests that screening for metabolic and cardiovascular risk factors in patients with prostate cancer receiving ADT may be critical to choosing the appropriate ADT and mitigating risk. Additional lifestyle and pharmacological interventions may be recommended, and cardiovascular risk factors should be monitored regularly.
- Relugolix is a new oral LHRH antagonist that received FDA approval for prostate cancer treatment in December, 2020.

- The HERO trial was the pivotal randomized controlled Phase 3 trial that led to FDA approval for relugolix. The trial recruited 934 men with advanced prostate cancer and randomized them 2:1 to receive relugolix (a once-daily pill) vs. leuprolide (given by subcutaneous injection every 3 months). The primary endpoint was sustained castration (defined as testosterone levels below 50ng/dL) from day 29 through 48 weeks of treatment. Secondary endpoints included castration at Day 4 and Day 15, PSA responses, and FSH levels. Cardiovascular events were a pre-specified safety endpoint.
- The majority of patients enrolled had at least one cardiovascular risk factor (lifestyle risk factors, cardiovascular or cerebrovascular risk factors, or a history of major adverse cardiovascular events (MACE)) including 92% of patients on the relugolix arm and 94% of patients on the leuprolide arm. The trial had specifically excluded patients with a history of MACE in the 6 months preceding enrollment. A history of MACE (more than 6 months prior) was present in 13.5% of patients on the relugolix arm and 14.6% of patients on the leuprolide arm.
- The cumulative incidence of new MACE events in the first 48 weeks after trial enrollment was 54% lower in patients treated with relugolix (2.8%) vs. leuprolide (5.6%) (**Figure**). New MACE events were significantly higher with leuprolide in patients that had a history of MACE vs. patients with no history of MACE (17.8% vs. 4.2%). New MACE events with relugolix in patients that had a history of MACE vs. patients with no history of MACE, were 3.6% vs. 2.8%, respectively.
- There were no statistically significant correlations with cardiovascular risk when analyzing for FSH levels, dyslipidemia, HbA1c, weight, BMI, blood pressure, Gleason score, global geographic region, race, ethnicity, testosterone at baseline, prior ADT use, and lifestyle-related risk.
- The PRONOUNCE trial was the first randomized clinical trial designed to prospectively compare the cardiovascular safety of a LHRH antagonist (degarelix) and a LHRH agonist (leuprolide) in prostate cancer patients scheduled to start ADT. No significant differences in MACE were observed at 1 year in patients treated with degarelix (5.5%) vs. leuprolide (4.1%), although the study was terminated prematurely due to insufficient numbers of participants and cardiovascular events. Thus, conclusions on cardiovascular safety between degarelix and leuprolide could not be drawn from this study.
- Finally, a recently published study that retrospectively analyzed real-world claims-based data going back 10 years, also found no significant differences in cardiovascular events in prostate cancer patients treated with a LHRH antagonists vs. LHRH agonists.
- Altogether, well-designed trials to prospectively assess cardiovascular safety and other safety measures as primary endpoints in prostate cancer patients being treated with different types ADT remain needed. Ideal biomarkers and cardiovascular risk assessment tools also remain to be defined.

HERO: Cumulative Incidence of Major Adverse Cardiovascular Events (MACE)^{1,2}

- Kaplan-Meier estimates of the MACE incidence rate were consistent with a 54% lower risk (hazard ratio, 0.46; 95% CI, 0.24 to 0.88) in the relugolix group than in the leuprolide group



Session 6: Predicting Risk of Prostate Cancer with Polygenic Scores

Genetic Risk Prediction for Prostate Cancer

Christopher Haiman, ScD
University of Southern California

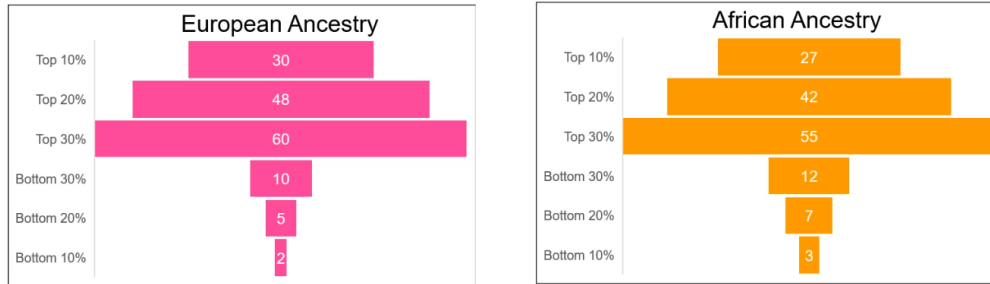
- Genome-wide association studies (GWAS) are studies that look for disease risk genes, using genetic data from large populations of individuals with vs. without the disease in question.
- Dr. Christopher Haiman discussed GWAS studies to identify common genetic risk markers for prostate cancer in multi-ethnic populations.
- A trans-ancestry GWAS meta-analysis, using genetic data from an international consortium of 110,406 patients with prostate cancer and 126,974 controls, identified 269 genetic prostate cancer risk variants. This included 86 newly identified risk variants, and stronger data for 183 previously identified risk variants. Together, the 269 risk variants account for an estimated 40% of familial prostate cancer risk. The prior known 183 risk variants only accounted for approximately 28% of familial prostate cancer risk.
- The 269 risk variants were used to create a “Polygenic Risk Score” (PRS), which is able to stratify the lifetime risk of prostate cancer. Compared with individuals with median PRS scores (average), men with PRS scores >80% have a 2.5-fold increase in risk for prostate cancer, and men with PRS scores >90% have a 4-fold increase in risk for prostate cancer.
- The PRS also had high performance in identifying men at risk for prostate cancer in both White and Black populations. Men with the top 1% of PRS scores had a lifetime risk of prostate cancer of >60% for White men and >50% for Black men.
- The PRS can also identify men with a very low lifetime risk of developing prostate cancer. Men with the lowest 10% of PRS scores have a lifetime risk of under 5% (1 in 20) (vs. 1 in 8 on average in the U.S.).
- The ability of the PRS to stratify men for lifetime prostate cancer risk has now been validated in a number of studies, including in cohorts of men with European or African Ancestries.
- The PRS can also estimate a man’s risk for prostate cancer based on age. This is important because for most men, PSA screening is not recommended until age 55. Thus, the PRS can identify men who may benefit from starting PSA screening at younger ages.
- However, the PRS is unable to distinguish risk for non-aggressive vs. aggressive prostate cancer. This suggests that the genetic risk variants in the PRS play a stronger role in disease development than disease progression.
- Nevertheless, a large percentage of cases with lethal prostate cancer are found to occur in men with the top 10-30% PRS scores, in both White and Black populations (**Figure**). This suggests the PRS is useful in screening approaches to identify men at highest risk for lethal prostate cancer. For instance, 27-30% of lethal prostate cancer cases were found to occur in men with the top 10% of PRS scores, and 55-60% of lethal prostate cancer cases occurred in men with the top 30% of PRS scores (**Figure**). This emphasizes the power of the PRS as a risk stratification tool.
- The relationship between the PRS and rare cancer risk gene variants for prostate cancer was evaluated. In European populations, variants in the *BRCA2*, *ATM*, and *CHEK2* genes are known to increase risk for prostate cancer. In African Ancestry populations, variants in the *BRCA2*, *ATM*, *NBN*, and *PALB2* genes were found to increase risk for prostate cancer.

While the overall risk of prostate cancer in men who carry these risk genes is higher than the general population, their risk was also found to be modified by their PRS score. For instance, in men of European ancestry who carry these risk genes, those with the lowest 10% of PRS scores had an average population risk level for prostate cancer, while those with the highest 10% of PRS scores had an 11-fold increase in risk over men at average risk based on the PRS.

- In ongoing studies to improve the PRS, Haiman and colleagues performed GWAS studies in a much larger trans-ancestry study of ~153,000 prostate cancer cases and ~775,000 controls, and identified over 100 new genetic prostate cancer risk variants. This brings the total number of genetic prostate cancer risk variants identified to ~400. The team is currently testing and validating this newer PRS (based on ~400 risk variants) in additional cohorts.
- Increasing diversity in GWAS studies is critical to addressing cancer disparities. By increasing the numbers of African American men in the GWAS cohorts studied from ~10,000 prostate cancer cases + ~11,000 controls to ~19,000 prostate cancer cases + ~64,000 controls, Haiman and colleagues were able to identify 9 new prostate cancer risk variants, 7 of which are only present or substantially more common in African Ancestry populations.
- *HOXB13* is a gene with a well-established role in prostate cancer susceptibility. Several *HOXB13* prostate cancer risk variants have been identified in European and Asian populations, including one variant that accounts for ~5% of hereditary prostate cancer cases in European men. By increasing the numbers of African Ancestry individuals in GWAS studies, Haiman and colleagues identified a new rare variant in the *HOXB13* gene in African ancestry men that is associated with increased risk for aggressive and metastatic prostate cancer. This variant was found to be specifically present in those with West African ancestry, and was absent in East, South, Central and North African ancestry populations.
- Haiman and colleagues are now performing large exome sequencing studies to identify rare genetic variants that confer risk for aggressive prostate cancer. In a study of 8,361 patients with non-aggressive prostate cancer vs. 9,185 patients with aggressive prostate cancer, no new risk variants for aggressive prostate cancer were identified.
- *BRCA2*, *ATM* and *NBN* are DNA repair genes, a class of genes with known roles in the development and progression of prostate, breast, and other cancer types. An evaluation of variants in a broader group of 23 DNA repair genes found that 17 of these were present at higher frequencies in aggressive vs. non-aggressive prostate cancer (16.4% vs. 8.9% of cases). 5 of these genes were significant: *BRCA2*, *ATM*, *NBN*, *MRE11A* and *SLX4*. Identifying men with “low-risk” prostate cancer who have these genetic variants may inform patient management and treatment selection strategies, as they may have higher risk for progression to aggressive disease.
- This recent work has demonstrated the importance of increasing diversity in GWAS studies. However, the recent large GWAS cohort studied is still comprised of ~78% individuals of European ancestry. Future studies aim to include more representative numbers of other ethnic and racial populations in GWAS analyses. For example, RESPOND is an ongoing initiative led by Haiman, which aims to sequence the genomes of 20,000 men of African ancestry.
- Altogether, these data demonstrate that a PRS score is able to stratify a man’s lifetime genetic risk for prostate cancer, which may help to guide individualized prostate cancer screening strategies. More studies are needed to determine how best to clinically implement this tool, as well as to increase racial and ethnic diversity in GWAS studies, such that PRS tools developed will be equally informative in predicting prostate cancer risk in men of all races and ethnicities.

Genetic Risk-Based Screening

% of prostate cancer cases (and % of lethal disease) within PRS categories



Lifetime risk of developing prostate cancer by PRS

European Ancestry (1 in 8)

- 1 in 2.7 men in Top 10%
- 1 in 3.3 men in Top 20%
- 1 in 4 men in Top 30%
- 1 in 24 in Bottom 30%
- 1 in 32 in Bottom 20%
- 1 in 40 in Bottom 10%

African Ancestry (1 in 6)

- 1 in 2.2 men in Top 10%
- 1 in 2.9 men in Top 20%
- 1 in 3.3 men in Top 30%
- 1 in 15 in Bottom 30%
- 1 in 17 in Bottom 20%
- 1 in 20 in Bottom 10%



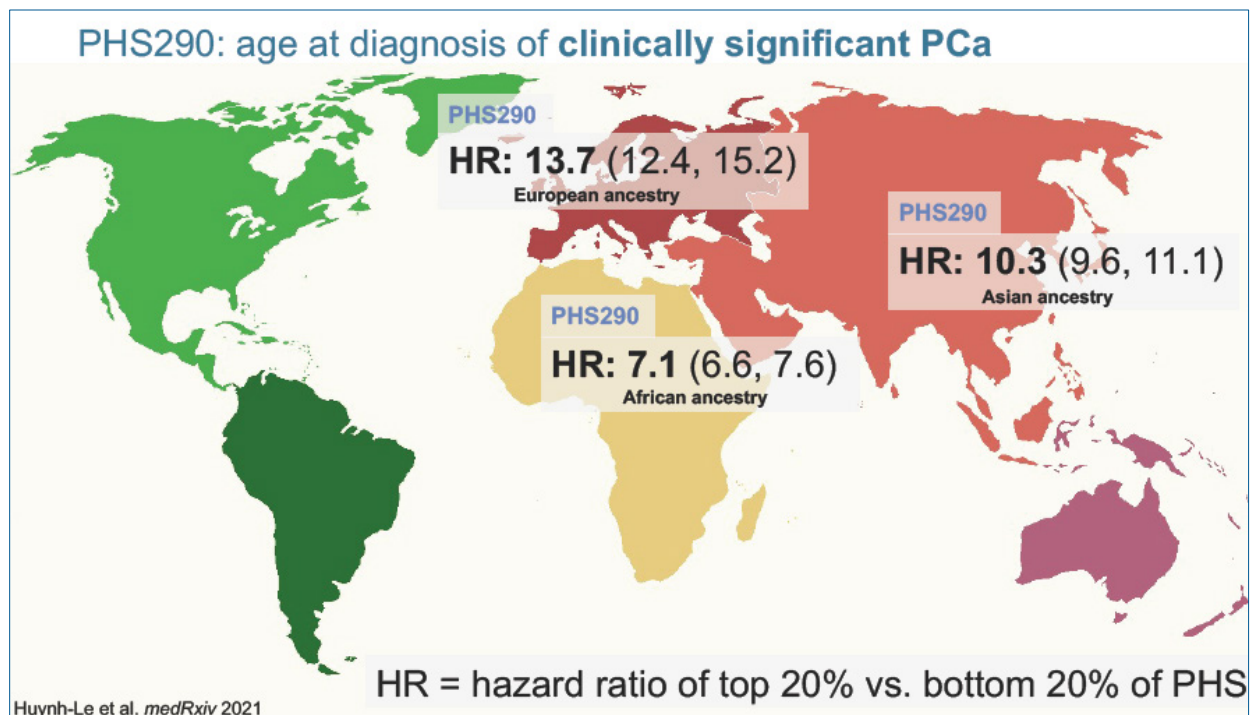
Genetic Risk Stratification for Prostate Cancer: Genomics, Ancestry, and Disparities

Tyler Seibert, MD, PhD
University of California, San Diego

- Early detection of prostate cancer using PSA screening has reduced prostate cancer mortality rates by ~27%. Unfortunately, elevated PSA is not a prostate cancer-specific phenomenon, and PSA screening has led to many false positives, over-diagnosis and overly aggressive treatment of non-aggressive disease.
- Current guidelines on PSA screening encourage shared decision-making between patients and their doctors that consider individual factors, the most important of which are age, family history and race/ethnicity.
- However, whether this approach is reasonable in modern primary care practices, whether family history is a surrogate for genetics, how race, ethnicity, and genetics relate to each other, and whom should be screened and at what age, remain questions.
- Dr. Seibert discussed the development of a “Polygenic Hazard Score,” (PHS) based on genetic prostate cancer risk variants discovered in genome wide association studies (GWAS), as a tool to guide individualized screening for aggressive prostate cancer.

- The PHS is similar in principle to the Polygenic Risk Score (PRS) discussed above by Dr. Haiman, but incorporates an age dependence within a survival analysis framework to account for the possibility that someone who is a “control” may yet someday develop prostate cancer, and that someone who has “low-risk” prostate cancer may someday progress to aggressive disease.
- A PHS was developed using 46 genetic prostate cancer risk variants from a largely European cohort. In a validation study in an independent cohort from the UK, PHS scores were found to have a significant ability to predict age at diagnosis of aggressive cancer, and to improve identification of men at risk for aggressive prostate cancer when added to PSA screening. This demonstrated that individualized prostate cancer screening can be improved when genetic information such as the PHS is used in addition to age, family history, and race/ethnicity.
- Genomics studies that do not incorporate diverse populations will only exacerbate health disparities. Unfortunately, while diversity in GWAS studies has increased over the years, as of 2016 only 19% of participants in GWAS studies were individuals of non-European ancestry. Genetic risk prediction tools developed primarily in Europeans will have weaker performance in other populations.
- The performance of the 46-variant PHS was evaluated in a new multi-ethnic cohort of 80,491 participants, comprised of 71,856 European, 6,253 African, and 2,382 Asian ancestry participants, based on genetic ancestry. In the overall cohort, the PHS performed well in predicting aggressive and lethal prostate cancer. However, compared with individuals in the lowest 20% of PHS scores, individuals in the top 20% PHS scores had an increased risk for clinically significant prostate cancer by 5.6-fold in European, 5.2-fold in Asian, and 2.4-fold in African ancestry populations. This demonstrates the PHS has a decent performance in Asian ancestry populations, but has significant room for improvement in African ancestry populations.
- Studies in an African ancestry dataset were performed, and 3 new genetic risk variants were identified that when added to the PHS, improved its performance in African ancestry populations (from 2.4 to 4.7-fold increased risk for aggressive prostate cancer in individuals in the top 20% vs. bottom 20% of PHS scores).
- However, the relevance of socially-defined ancestry categories in disease risk stratification is unclear. For instance, there are differences in structural racism, disparities in health equity and access, disparities in representation in datasets, possible environmental exposure differences, and genomic differences that may or may not correlate with social categories, which may also contribute to disease risk differences in different races/ethnicities. There is also significant genetic and cultural diversity in African and Asian ancestry groups.
- As an alternative approach to defining genetically similar groups of people, an agnostic artificial intelligence method was used to infer “ancestries” based on genomics data, using the dataset comprised of 71,856 European, 6,253 African, and 2,382 Asian ancestry individuals. The agnostic method identified 2 different inferred ancestral groups and one admixed group. The vast majority of European individuals formed one group, while ~2/3 of African ancestry individuals formed the second group. Nearly all of the Asians and ~1/3 of Africans were grouped into the admixed group.
- The performance of the PHS was tested in these inferred ancestral groups, and was found to strongly perform in the group comprised of mostly Europeans, and nearly as well in the admixed group. However, it again had relatively weak performance in the group comprised mostly of African individuals.
- A new PHS was developed using 290 prostate cancer genetic risk variants identified by combining the 46-variant PHS with the strongest performing variants from the 269-gene PRS score discussed by Dr. Haiman.

- A validation study of the new 290-variant PHS in the multi-ethnic cohort of 80,491 participants found significant improvement compared with the 46-variant PHS. Compared with individuals in the lowest 20% of 290-variant PHS scores, individuals in the top 20% of 290-variant PHS scores had an increased risk for clinically significant prostate cancer by 13.7-fold in European, 10.3-fold in Asian, and 7.1-fold in African ancestry populations **(Figure)**. However, this study suffers from the caveat that this cohort was not an independent dataset, as the data from the same individuals had been used for discovery of the genes in the PHS score.
- A validation study was performed to test the 290-variant PHS score in a completely independent data set, using data from the Million Veteran Program. This cohort includes >580,000 Veterans of whom >68,000 had a prostate cancer diagnosis, and includes harmonized data on race/ethnicity. The 290-variant PHS was significantly able to predict those at highest genetic risk for total, metastatic, and lethal prostate cancer.
- A multivariable model was developed to evaluate risk factors for prostate cancer in this cohort. Family history (having a first-degree relative with prostate cancer) and African ancestry both increased risk by nearly 2-fold, while those in the top 20% of the 290-variant PHS had increased risk by >4-fold.
- Altogether, these data demonstrate the PHS is associated with age at diagnosis of clinically significant / aggressive prostate cancer, age at diagnosis of prostate cancer metastases, and lifetime risk of death from prostate cancer. The new 290-variant PHS is able to stratify risk in men of various genetic ancestries, however more data in non-European ancestry individuals will likely improve this tool further. Finally, prospective studies are needed to validate this tool and help to determine how it may best be utilized in the clinic.



A Healthy Lifestyle in Men with a High Prostate Cancer Polygenic Risk Score

Anna Plym, PhD

Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health

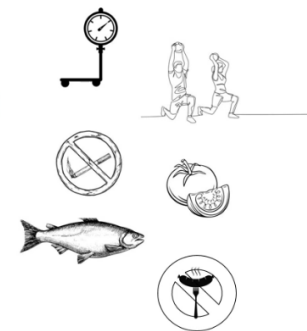
- Previously, Dr. Christopher Haiman and colleagues developed a multi-ancestry genetic test (polygenic risk score; PRS) that can estimate an individual's genetic risk for prostate cancer, as an effort to personalize prostate cancer screening and reduce prostate cancer disparities. This test evaluates for 269 genetic variants found to associate with increased prostate-cancer risk across populations.
- Men with a high PRS have a lifetime risk of prostate cancer that is exceeding 50%, and are also at a higher risk of lethal prostate cancer. Whether lifestyle factors can modify genetic risk for prostate cancer is an important question.
- Dr. Anna Plym discussed early data from a study which examines whether healthy lifestyle behaviors are able to modify genetic risk for prostate cancer.
- The Health Professionals Follow-up Study and the Physicians' Health Study are two large epidemiologic studies which prospectively collected demographic, health and lifestyle data from over 50,000 men for over 20 years.
- Dr. Plym and colleagues applied the 269-genetic variant PRS to 12,441 men from these two cohorts for whom genetic data was available. Within these cohorts, 3,008 developed prostate cancer and 435 developed lethal prostate cancer, during a median follow-up of ~ 20 years.
- In these cohorts, the PRS was validated to stratify men for overall prostate cancer risk as well as risk for lethal prostate cancer. For instance, those with the highest 25% of PRS scores had a 5.7-fold increased risk for prostate cancer and a 4.3-fold increased risk for lethal prostate cancer compared with those with the lowest 25% of PRS scores. This demonstrates that men at highest genetic risk for prostate cancer based on the PRS are also at highest risk for dying from prostate cancer.
- Whether there are modifiable factors that can compensate for high genetic risk for prostate cancer is a critical question.
- The "lifestyle score" is a previously validated assessment tool developed by Dr. Lorelei Mucci and colleagues which is associated with reduced risk for lethal prostate cancer.
- The lifestyle score has six components: healthy weight (BMI < 30), vigorous physical activity (≥ 3 hours/week or ≥ 7 hours/week brisk walking), not smoking (never smoked or quit ≥ 10 years ago), high consumption of tomatoes (≥ 7 servings/week), high consumption of fatty fish (≥ 1 serving/week), and reduced intake of processed meat (<3 servings/week). Based how many of these 6 components are present, men were categorized into unhealthy (0-2), moderate (3) and healthy (4-6) categories.
- To determine whether a healthy lifestyle can reduce prostate cancer in men at high genetic risk, the team examined the incidence of overall and lethal prostate cancer based on joint categories of PRS and lifestyle scores.
- The study found that adhering to a healthy lifestyle was not associated with reduced risk for overall prostate cancer across all genetic risk levels.
- However, among men with highest genetic risk (top 25% of PRS scores), having a healthy lifestyle decreased risk of lethal prostate cancer compared with an unhealthy lifestyle by 45%, and a moderately healthy lifestyle decreased risk of lethal prostate cancer by 39%.

- A healthy lifestyle did not impact risk for lethal prostate cancer in those with lower genetic risk. This may be either because the genes associated with lethal prostate cancer in those with highest genetic risk are most modifiable by a healthy lifestyle, or that prostate cancer deaths in men with lower genetic risk categories are too few in these cohorts to measure an effect by lifestyle modifications.
- In a similar analysis of 2,111 men with a prostate cancer diagnosis, having a healthy lifestyle decreased risk for lethal prostate cancer by 49% compared with an unhealthy lifestyle, and a moderately healthy lifestyle decreased risk of lethal prostate cancer by 40%. Again, having a healthy lifestyle did not impact risk for lethal prostate cancer in lower genetic risk categories.
- The individual contribution of each lifestyle component in modifying risk for lethal prostate cancer was analyzed in men with highest genetic risk. While each healthy lifestyle component trended toward being associated with lower risk for lethal prostate cancer individually, a healthy weight, high physical activity and not smoking were the factors with the largest impact.
- A healthy lifestyle also reduced risk of non-prostate cancer death in all PRS quartiles, by 24-46%.
- Thus, while only men with the highest genetic risk appear to benefit from a healthy lifestyle in terms of reducing risk for prostate cancer mortality, all men benefit from a healthy lifestyle by reducing risk for overall mortality (from any cause).
- Overall, prostate cancer is highly heritable, with over 50% of cases being attributable to inherited factors. The recently developed PRS test can identify men at highest genetic risk for prostate cancer. These studies have validated the PRS test and demonstrate that having a healthy lifestyle can reduce the chance of lethal prostate cancer in men with highest genetic risk by ~45%, suggesting that physical activity, not smoking and a healthy diet are critical keys to prostate cancer interception.
- Additional ongoing studies are evaluating the impact of other lifestyle factors on modifying risk for prostate cancer mortality, validating these findings in additional racial and ethnic populations, and evaluating whether a healthy lifestyle also benefits men with rare genetic prostate cancer risk variants such as in BRCA2 and other DNA repair genes.

The healthy lifestyle score

- Previously developed and validated for lethal prostate cancer
- Includes six components (assigned 1 point each):

- Healthy weight (BMI < 30)
- Vigorous physical activity (≥ 3 h/wk or ≥ 7 h/wk brisk walking)
- Not smoking (never smoked or quit ≥ 10 years ago)
- High consumption of tomatoes (≥ 7 servings/wk)
- High consumption of fatty fish (≥ 1 serving/wk)
- Reduced intake of processed meat (<3 servings/wk)



Kenfield *et al.* JNCI 2016

- Categorized into: unhealthy (0-2), moderate (3) and healthy (4-6)

Session 7: Next Generation Precision Medicine

A Multi-Omic Perspective on mCRPC

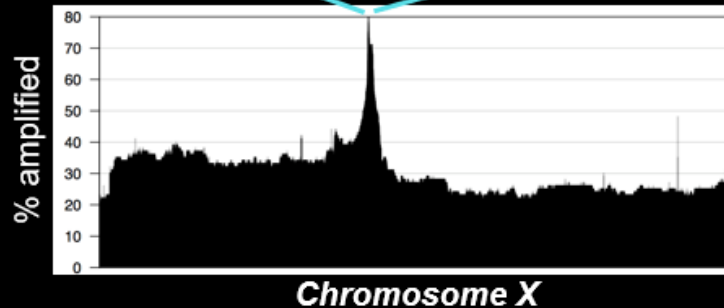
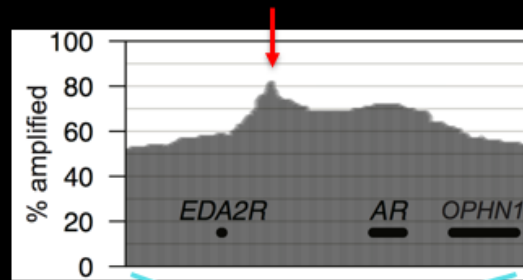
Felix Feng, MD

University of California, San Francisco

- The “PCF West Coast Dream Team” is a multi-institutional team effort of researchers from the U.S. and Canada that were funded by PCF starting in 2012 to sequence the genomes of advanced prostate cancer, reveal novel biological mechanisms and genomic drivers of disease progression and treatment resistance, and determine new precision medicine treatment strategies.
- Since 2012, the team has collected metastatic prostate tumor biopsies and blood samples from over 400 patients with metastatic castration resistant prostate cancer (mCRPC), along with clinical outcomes data.
- The team has performed several types of whole-genome multi-omics studies on these samples, including whole genome sequencing, bisulfite sequencing, transcriptome sequencing, 5hmc sequencing, and ATAC sequencing on tumor biopsies, and circulating tumor DNA analysis and autoantibody analysis using blood samples.
- These studies have led to a large number of important new insights, and the data collected also serves as a resource for additional studies by the prostate cancer research community.
- Dr. Felix Feng discussed some of the most significant recent findings from these studies.
- Deep whole genome sequencing enabled mapping of the landscape of structural variants in mCRPC. These include genomic regions that are frequently altered, including gain or losses of genes and regions where genomic rearrangements have commonly created structural variations.
- The androgen receptor (AR) is the primary driver of prostate cancer and the primary therapeutic target in patients with advanced prostate cancer. It is also one of the most frequently mutated genes in CRPC. These AR-mutations enable the tumors to continue to grow and progress in spite of AR-targeted therapy.
- A common site of gene amplification was found in the genomic region upstream from the AR gene (on chromosome X), that was present in 80% of mCRPC cases. The amplified site was found to be a specific control region for the AR gene, known as an enhancer (**Figure**). Amplification of this enhancer region led to increased levels of AR.
- Whole genome bisulfite sequencing is a method used to determine the location of methylation (5-methyl-Cytosine; 5mC) marks on the genome. DNA methylation is a major mechanism of controlling how tightly or loosely wound the DNA in that region is, and thus controls whether a gene in that region can be expressed or not. Higher levels of methylation cause the DNA to be more tightly wound and inaccessible, while lower levels allow the DNA to loosen and allow in transcription factors that turn on gene expression.
- A whole genome bisulfite sequencing study found aberrantly low levels of methylation on the AR gene and the AR enhancer in mCRPC samples. Additional areas of aberrantly low methylation were found near the AR gene in CRPC samples, which were then confirmed to be additional new AR enhancers.
- While methylation (5mC) marks repressed genes, 5-hydroxy-methyl-cytosine (5hmC) marks activated genes that are poised for expression.

- A genome-wide 5hmC sequencing study was performed to identify the genes that are poised for expression in mCRPC compared with localized prostate cancer. Genes that commonly had high levels of 5hmC marks in mCRPC included AR and most genes turned on by AR.
- Altogether, these studies demonstrate that mutations or epigenetic alterations in the AR gene and its enhancers are the primary mechanism by which prostate cancer develops resistance to AR-targeted therapy and progresses to CRPC.
- To identify genes that regulate the expression of AR, a CRISPRi gene-knockdown screen was performed using prostate cancer cell lines that had been engineered to express a neon-green fluorescent AR. These cells will glow green when AR is present, allowing identification of cells with vs. without AR based on green coloration.
- This study identified several genes that when knocked down, resulted in loss of AR expression. These included *AR* itself, *HOXB13*, *GATA2*, and *GRHL2* which are known regulators of *AR*, and *PTGES3* which was previously not well studied as an AR-regulator.
- *PTGES3* (Prostaglandin E Synthase 3) was confirmed to regulate AR in multiple prostate cancer cell lines. Furthermore, knocking down the expression of *PTGES3* significantly slowed the growth of various AR-dependent prostate tumor models in mice, including enzalutamide-resistant models. The growth of AR-independent prostate tumors was unaffected by knock-down of *PTGES3*.
- Preliminary mechanistic studies found that *PTGES3* binds to DNA at sites adjacent to where AR binds, and likely functions to assist AR in turning on gene expression.
- Together, these studies suggest that *PTGES3* may be a promising new therapeutic target for the treatment of prostate cancer.
- Small molecule drugs that target *PTGES3* are currently under development at UCSF. Several lead compounds that bind to its catalytic site have been developed and have shown preliminary efficacy in prostate cancer cell lines. These compounds are undergoing further preclinical development and may lead to new treatments that can be tested in clinical trials.
- Altogether, these studies have demonstrated the power of genome-wide approaches in mapping out the genomic and epigenomic landscape of mCRPC, and in identifying promising new treatment targets.
- The long-term goal of Dr. Feng and the West Coast Dream Team's studies are to integrate data from clinical samples with functional genomics studies to identify targets and develop new therapies for mCRPC.

An Amplification Peak 624kb Upstream of AR



Quigley, Dang, Zhao,
Cell 2018



Using Genomics and Histopathology to Understand Therapeutic Responses in Prostate Cancer

Joel Greshock
Janssen Oncology

- Classifying prostate cancer into different subgroups based on shared biological features is critical in developing new precision medicines.
- Cancer is a disease of the genome, and currently prostate cancer is often subtyped based on the presence or absence of certain genomic alterations. Classification using other tumor features, such as molecular features or pathology, can improve prostate cancer subtyping.
- Joel Greshock discussed using gene expression patterns and pathology to improve tumor subtyping, which will aid in developing new therapeutic strategies for patients.
- The SPARTAN trial was a randomized Phase 3 trial that evaluated the efficacy of apalutamide in addition to androgen deprivation therapy (ADT) in patients with non-metastatic castration resistant prostate cancer (CRPC). In this trial, the addition of apalutamide to ADT was found to significantly improve metastasis-free survival (MFS), time to symptomatic progression, time to second progression (PFS2), and overall survival (OS), which led to its FDA-approval.
- Whether different prostate cancer molecular subgroups show different benefit from apalutamide + ADT was investigated. A published, retrospective biomarker analysis was

performed using samples from 233 patients enrolled on the SPARTAN trial: 154 who received apalutamide + ADT and 79 who received placebo + ADT.

- Tumors were classified based on the PAM50 gene expression test. PAM50 is a tumor profiling test used in breast cancer that has been adapted for study in prostate cancer, and subsets cancers into one of three subtypes: Luminal A, Luminal B, and Basal.
- Associations between molecular profiles with clinical outcome were evaluated.
- The PAM50 test classified the prostate cancer cases from the SPARTAN trial as mostly Basal (152 cases), some as Luminal B (70 cases), and very few as Luminal A (11 cases).
- Patients from all subtypes benefitted from apalutamide + ADT vs. placebo + ADT. However, among patients who received apalutamide + ADT, those with Luminal subtypes experienced significantly longer metastasis-free survival times than those with Basal subtypes. Similar trends were seen for overall survival and progression-free survival.
- This observation demonstrates that subtyping by transcriptomic features can provide valuable information for precision medicine.
- Digitized pathology data, in which pathologists examine tumor biopsy or surgery samples under a microscope to make a diagnosis and prognosis, can also be used for tumor subtyping. Pathology can be used at various times in routine patient care during disease progression, including initial diagnosis and to evaluate samples from recurrent or metastatic tumor sites.
- Artificial intelligence applied to tumor pathology slides offers a way to perform more precise and rapid evaluations of tumors, including disease biology, molecular features and clinical outcomes.
- Several artificial intelligence algorithms have been developed to diagnose and subtype cancer, and to predict clinical outcomes and the presence of tumor genomic alterations. One AI platform has received FDA approval thus far, for the diagnosis of prostate cancer.
- Greshock and colleagues are developing a new AI platform to classify prostate cancer from pathology slides. An AI algorithm was trained to determine Gleason grade using >1,000 randomly selected whole-slide prostate images from a publicly available, manually curated dataset. The algorithm achieved 90.5% accuracy in predicting Gleason grade as compared with standard pathologist evaluation (**Figure**).
- More sophisticated algorithms are now being developed to identify additional biologically and therapeutically relevant prostate cancer subgroupings.
- Together, these studies demonstrate the potential for gene expression signatures and AI-based pathology platforms to refine prostate cancer subgrouping to better reflect disease biology and predict treatment responses.
- It is important to address the challenges being faced in the development and use of optimal AI platforms. This includes that fact that models are often difficult to interpret, which can lead to mistrust and underuse. Also, a lot of quality data is required to build effective models, which is often hard to aggregate due to scarcity.
- Obtaining regulatory engagement and guidance is important through the model development and deployment process.

Building tissue classifiers using AI

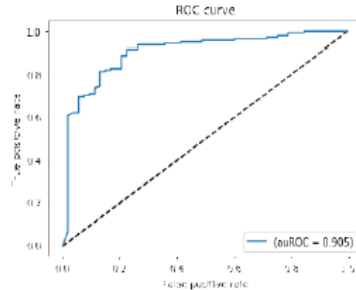
Step #1: Foundation is detecting tumor



>1,000 Whole-Slide Images

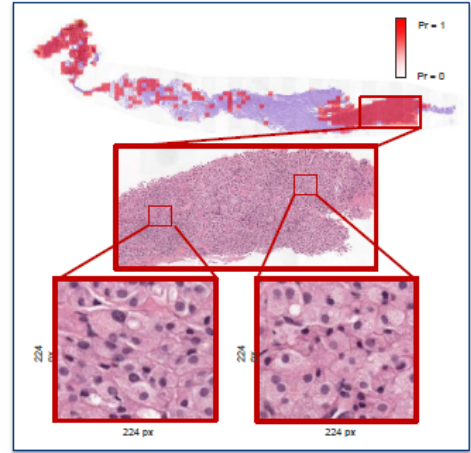
0.905 – Area Under ROC

Interpretable Visualizations



Data: the experiment was conducted on 1000 randomly selected samples from Kaggle PANDA dataset¹

¹ <https://www.kaggle.com/c/prostate-cancer-grade-assessment/data>



Lessons from Esophageal Cancer Genomics

Rebecca Fitzgerald, PhD

University of Cambridge, United Kingdom

- In the U.S., esophageal cancer is newly diagnosed in ~19,300 people per year, and causes ~15,500 deaths per year.
- There are two main types of esophageal cancer: squamous cell carcinoma and adenocarcinoma. Esophageal squamous cell carcinoma occurs in the more proximal (higher) region of the esophagus, affects men and women equally, is more common in Eastern countries, and is associated with smoking and drinking. Esophageal adenocarcinoma tends to occur closer to the junction with the stomach, affects men more than women, is more common in Western countries, and is associated with gastroesophageal reflux disease (GERD) and obesity.
- Early detection of esophageal adenocarcinoma at the pre-cancer stage is possible, as it tends to occur on the background of Barrett's esophagus, a condition which develops in people with chronic reflux. Early detection and early intervention are associated with excellent long-term outcomes and less treatment associated side-effects, while detection when cancer symptoms have developed leads to much poorer outcomes with ~80% of patients eventually dying from the disease by five years.
- Dr. Rebecca Fitzgerald discussed using multi-omics data from esophageal adenocarcinoma to advance new precision diagnosis and treatment strategies, in order to improve survival,

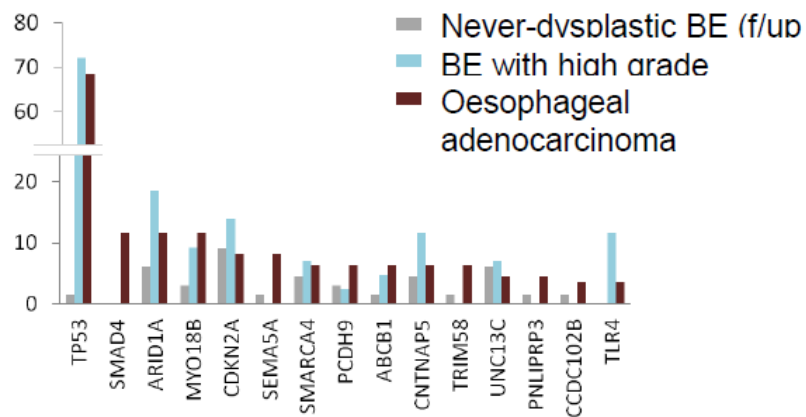
reduce morbidity of treatment, and to improve detection at the pre-cancer stages and prevent development of cancer.

- Oesophageal Cancer Clinical and Molecular Stratification (OCCAMS) is a consortium consisting of research and clinical teams from 20 clinical centers in the U.K., to recruit patients with esophageal cancer to clinical and correlative research studies. The group has recruited over 3,000 patients and performed whole genome sequencing on over 600 esophageal cancer cases thus far. Samples collected from patients undergo genomic, transcriptomic, and epigenomic sequencing, and the consortium has a bioinformatics team for data analysis.
- In 2016, the team published an initial analysis of whole genome sequencing of 129 esophageal adenocarcinomas. This study identified the landscape of genomic alterations driving esophageal cancer. The disease was found to be very heterogeneous, with many different tumor driver mutations identified at low prevalence.
- In 2020, the team published results from whole genome studies on 551 esophageal adenocarcinoma cases. This study, which also included RNA sequencing data and improved bioinformatics methods, confirmed the heterogeneous genomic landscape of esophageal cancer and identified many more tumor driver gene mutations. This study also showed that copy number aberrations and large-scale structural variants account for much of the genomic instability.
- Overall, these studies have identified 76 tumor driver gene mutations in esophageal adenocarcinoma. 69% of these driver mutations are known to drive the development of other cancer types. 86% of these driver mutations were not previously known to occur in esophageal adenocarcinoma.
- The most commonly mutated gene was *TP53*, seen in 70% of esophageal adenocarcinomas. Many passenger mutations were also observed.
- Integration of clinical outcomes data enabled identification certain tumor genomic alterations that may be prognostic. For instance, *GATA4* amplification and/or *SMAD4* mutation or deletion were associated with significantly shorter overall survival times.
- To understand tumor evolution, it is important to compare pre-cancerous with metastatic lesions and to compare multiple tumor regions from the same patient.
- The mutations present in pre-cancerous Barrett's esophagus samples were compared between patients who never progressed to dysplasia, who developed high-grade dysplasia with Barrett's esophagus, and who eventually progressed to esophageal adenocarcinoma (**Figure**). The surprising finding was that even non-dysplastic Barrett's that never progresses to cancer harbors mutations in what are traditionally considered to be cancer driver genes. The mutation that best characterized the boundary between benign (non-dysplastic) and dysplastic Barrett's was *TP53*, suggesting that this is a useful biomarker for individuals at risk requiring early intervention (**Figure**).
- These studies enabled the generation of evolutionary charts of when certain mutations arose during progression from pre-cancerous stages to adenocarcinoma. *TP53* mutations are an early, likely initiating event in the development of esophageal adenocarcinoma.
- A study was done to compare multiple metastatic lesions from different sites and over time in patients with metastatic esophageal adenocarcinoma. The resulting "body maps" suggest that the tumor cells that seed metastatic sites come from multiple other tumor regions in the body, as opposed to a step-wise fashion in which only one metastatic site seeds another.
- Tumor cells release their DNA into the blood as they die. Blood tests that evaluate tumor DNA are being developed to detect tumor presence, study tumor genomics, and estimate levels of tumor burden. At the current time such tests are most relevant to test for residual

cancer in patients who have undergone treatment, although this is not yet implemented in routine clinical practice.

- The data from these studies are being used to develop models to help predict which treatments will be most effective in a patient based on their tumor mutations.
- Overall, the data and lessons from these studies are being used to improve understanding of esophageal adenocarcinoma biology and to develop new treatment strategies for patients. Sharing knowledge across research fields is critical to more rapid development of new and better treatments for all patients.

Mutation prevalence in Barrett's



Weaver et al Nature Genetics 2014

PCF WOMEN IN SCIENCE AWARD LECTURE: Tumor Suppressors Reimagined: Converting Understanding of RB Action into Translational Potential

Karen Knudsen, MBA, PhD
American Cancer Society

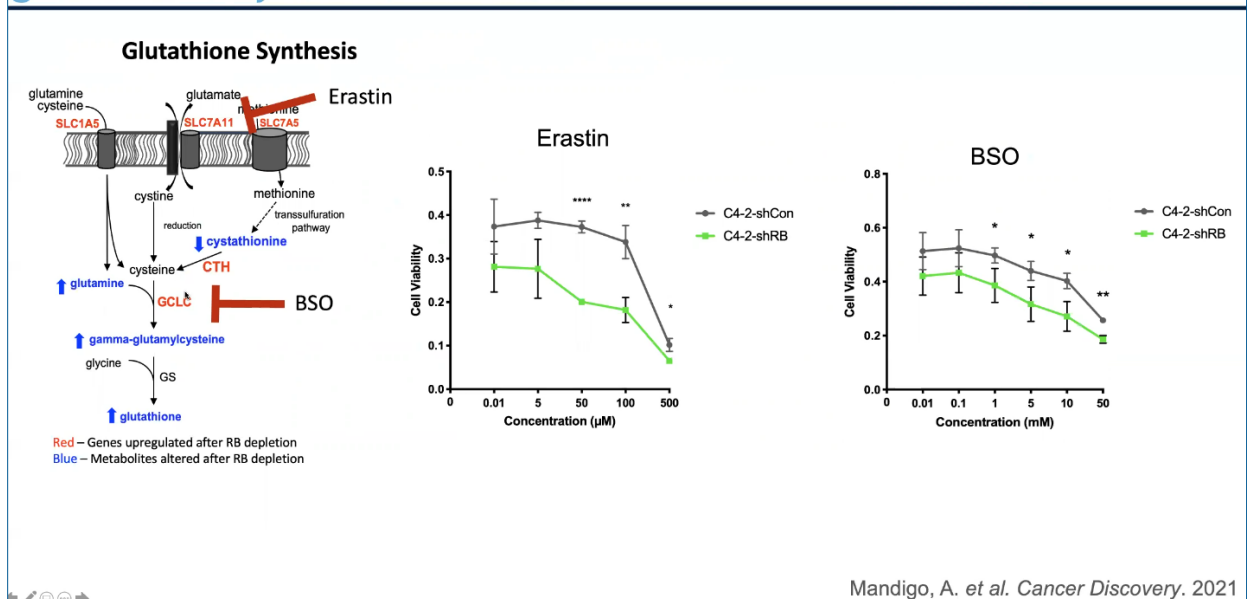
- The 2021 PCF Women in Science Award and Lecture was awarded to Dr. Karen Knudsen.
- Dr. Knudsen is the Chief Executive Officer of the American Cancer Society and the ACS Cancer Action Network.
- Prior to taking on these roles in June 2021, Dr. Knudsen was the Executive Vice President of Oncology Services and Enterprise Director of the Sidney Kimmel Cancer Center at Jefferson Health. In this role, Dr. Knudsen was one of only a very few women Directors of NCI-designated cancer centers. Under her leadership, Sidney Kimmel Cancer Center expanded its care region and elevated its clinical care and institutional standing, including becoming ranked as one of the top cancer centers in the nation by US News & World Report. Further, Dr. Knudsen's research in steroid hormone pharmacology and targeted therapy in oncology is now benefitting patients all over the world.
- During her tenure at Thomas Jefferson University, she significantly increased the number of women faculty and created one of the most diverse leadership teams.
- Dr. Knudsen was also one of the original founders of the PCF Women in Science Forum in 2016, and every year since, has helped to make this Forum very valuable and informative for women who attend the PCF Scientific Retreat.
- Dr. Knudsen exemplifies what it means to break glass ceilings, and has made it her personal and professional mission to challenge and remove the barriers faced by women in cancer research and medicine. She is a strong and effective advocate for advancing the professional growth of women in cancer research and medicine, both within and far beyond her own institutions.
- For her 2021 PCF Women in Science Award and Lecture, Dr. Knudsen discussed the incidence of prostate cancer in the Sidney Kimmel Cancer Center (SKCC) catchment area, and research on the role of a major tumor suppressor gene, RB1, in prostate cancer.
- SKCC is located in Philadelphia, Pennsylvania. 80% of SKCC patients live in a densely populated 7-county area with a total population of nearly 5 Million. There are significant health disparities in this 7-county region, including some of the highest prostate cancer incidence rates in the U.S.
- Overall, the SKCC catchment area has a prostate cancer incidence rate of 130.1 per 100,000 compared to the Philadelphia State average of 103.7 per 100,000 and U.S. average of 104.5 per 100,000, and a prostate cancer mortality rate of 21.9 per 100,000 compared to the Philadelphia State average of 18.6 per 100,000 and U.S. average of 19.0 per 100,000.
- There are significant racial disparities in this region, with higher rates of cancer mortality among African Americans than Whites seen for many cancer types. However, prostate cancer is by far the most disparate of these, with African American men experiencing over 2-fold higher prostate cancer mortality rates compared to White men.
- Dr. Knudsen's research has uncovered the roles of various molecular pathways in prostate cancer, including PARP1, DNA-PKcs, P300/CBP, CRY1, and the RB1 pathway.

- RB1 (Retinoblastoma-1) is a tumor suppressor protein that blocks expression of cell division and growth genes. Its function is commonly lost in prostate and other cancers.
- In prostate cancer, loss of the RB pathway is seen with increasing frequency in more advanced cases. RB-loss is also associated with earlier disease recurrence and shorter overall survival.
- Gene expression signatures have been developed by Knudsen and colleagues that can identify tumors with RB-loss. The most advanced of these is a 186-gene signature developed using samples from 951 cancer cells lines with known RB1 genomic status. This gene signature can optimally differentiate tumors with intact an RB gene vs those that have lost RB. These data will aid in better understanding the role of RB in prostate cancer and the clinical biology of RB-loss tumors.
- RB pathway function can be lost via several mechanisms in cancer. The most common mechanism in prostate cancer is deletion of the *RB1* gene, which occurs in ~30% of metastatic castration resistant prostate cancer (mCRPC) cases. Deletion of other genes (*RBL1*, *RBL2*, *E2F1*, *CDK2*, *CDK4*, *CCND1*, and *CDKN2A*) can give a similar phenotype, however such deletions are rare in prostate cancer.
- Cells have two copies of most genes. Studies by Knudsen and colleagues found that in many prostate cancers that had lost one copy of *RB1* (retaining one normal copy), the RB protein was no longer expressed. Thus, tests that look at RB1 protein levels may better indicate whether RB function is lost compared with genomic sequencing.
- In most newly diagnosed cases of metastatic prostate cancer, the *RB1* gene is still intact. However, it is lost in ~30% of cases during progression to mCRPC. The role of RB-loss in progression to mCRPC was investigated.
- Loss of RB1 was found to be associated with increased levels of the androgen receptor (AR) and the cell cycle regulator E2F1.
- The genome-wide impact of RB1-loss on AR and E2F1 function was investigated. In prostate cancer cells with RB1-loss, E2F1 was found to bind many more sites in the genome, many of which were gene enhancers (whereas normal E2F1 tends to bind gene promoter sites). This led to aberrant expression of these genes, which included AR. The genes that were aberrantly activated by E2F1 in RB-loss cells were used to create a gene expression signature that could be used to identify tumors with RB1-loss.
- These data suggest that aberrant E2F1 activity is a major mechanism of disease progression caused by RB1-loss.
- In ~70% of metastatic prostate cancers, RB1 remains intact during progression to mCRPC. Whether subsequent loss of RB1 would be an advantage in those tumors was investigated.
- When the *RB1* gene was experimentally deleted in CRPC cells, E2F1 was able to aberrantly activate many more genes. However, these genes differed from those seen in tumors that lost RB1 during the transition to CRPC. Instead, many of these genes were found to overlap with genes bound by AR, indicating that if RB1 is lost in the CRPC setting, E2F1 and AR cooperate to activate a new pattern of gene expression.
- One of the E2F1/AR-activated genes was TNF-AIP8, which suppresses cell death during treatment with chemotherapy or the cell death-inducing signal TNF α . Correspondingly, RB1-loss CRPC cells were more resistant to death when treated with chemotherapy or TNF α . These data suggest that RB1-loss in CRPC may increase resistance to chemotherapy by rewiring E2F1/AR gene expression activities.
- The impact of RB1-loss in CRPC on E2F1 function beyond its cooperation with AR was investigated. ~1,600 genes were found to be aberrantly activated by E2F1 when *RB1* was deleted in CRPC cells. A large proportion of these genes were found to play a role in cell

metabolism. Using metabolomics profiling, 7 altered metabolic pathways were identified: 5 involved in amino acid metabolism and 2 involved in lipid metabolism.

- The effect of RB1-loss and E2F1 on glutathione production (an amino acid metabolism pathway) was studied in further detail. RB1-loss resulted in upregulation of glutathione production enzymes and metabolites created during the glutathione production process. An increase in glutathione production enzymes was also observed in other cancer types when *RB1* was deleted, including breast cancer, non-small cell lung cancer, and bladder cancer.
- Another byproduct of the altered glutathione pathway was lower levels of ROS (reactive oxygen species). ROS causes cells to be more sensitive to death signals. The lower ROS levels in RB1-loss CRPC cells increased resistance to treatment with chemotherapy agents.
- The relationship between E2F1 and glutathione production enzymes was then confirmed in clinical CRPC cases with RB1-loss. No relationship between E2F1 and glutathione production enzymes was observed in RB1-intact prostate cancer cases.
- Whether targeting the glutathione production pathway may be an effective treatment strategy for RB1-loss CRPC is now under investigation. In preclinical studies, RB1-loss CRPC cells were more sensitive to treatment with Erastin and BSO (**Figure**). Erastin is an agent that blocks early steps in glutathione production. BSO blocks later steps in glutathione production.
- Together, these data demonstrate the specific roles of RB1-loss and aberrant E2F1 activity in driving progression to CRPC and in protection from chemotherapy in tumors that have already progressed to CRPC. Ongoing studies are evaluating the potential for glutathione production and other pathways as new treatment targets.
- Clinical trials are underway to test new treatment strategies in CRPC based on tumor RB status. The Phase 2 ABICABAZI trial is testing the efficacy of abiraterone alone vs. with cabazitaxel chemotherapy in RB-low CRPC. The Phase 2 RIBOX trial is testing enzalutamide alone vs. with ribociclib, a treatment that can restore RB activity, in CRPC that has retained RB expression. These studies will help to determine whether RB status is an actionable tumor subtype, and may lead to new precision medicine options for patients.

RB depletion increases sensitivity to glutathione synthesis inhibition



SPECIAL LECTURE: Oncology: A Storied Past and Portentous Future

Anna Barker, PhD

Lawrence J. Ellison Institute for Transformative Medicine of the University of Southern California

- Dr. Anna Barker discussed the history, current status, and future of cancer research. Her talk was dedicated to the late Dr. Donald Coffey, a pioneer in the prostate cancer research field whose research and mentorship inspired many.
- Dr. Barker divided the history of cancer research and oncology into several eras.
- The earliest era was defined by the discovery of oncogenes and tumor suppressor genes. This era was initiated by the discovery of the Rous Sarcoma virus by Dr. Peyton Rous in 1909-1911. This led to discovery of the first oncogene, v-SRC in the 1950s. This era heralded in the beginning of retrovirus research (1960s), the discovery of the reverse transcriptase gene (1970s), the discovery of the ability of retroviruses to integrate into the host genome and produce oncogenes (1976), the discovery of p53 (1979) and the later discovery that it is a tumor suppressor gene (1989), and the discovery of the RAS oncogene (1982). This era resulted in the discovery of numerous oncogenes and tumor suppressor genes and advances in cellular and molecular biology.
- In 1971, the National Cancer Act was declared, which created a lot of expectations and the largest enterprise in any disease research field. This initiated the second era of oncology, which had an increased focus on DNA alterations in cancer. During this time, chemotherapy became standard of care treatment for many cancers and hormone therapy was introduced (1970s). Many more cancer genes and their roles were discovered including HER in breast cancer and HPV genes (1980s). Also, targeted therapies as treatments for cancer became a focus, such as Gleevec (FDA-approved in 2002).
- The third era began with the Human Genome Project which aimed to sequence the entire human genome, in 1990. The sequencing project was completed in ~1999, and the first complete human genome sequence was published in 2004.
- The Cancer Genome Atlas (TCGA), a project initiated by the NCI and NHGRI, was co-led by Dr. Barker of NCI and Dr. Francis Collins of NHGRI. TCGA sequenced the genomes of 30 types of cancers, including rare cancer types, and created an open access database of this information as a resource for the cancer research community. This remains one of the richest cancer databases ever developed.
- The first paper published by TCGA in 2008 reported on the glioblastoma multiforme genome. This study made clear that cancers can be classified into different molecular subtypes based on their genomic alterations. Furthermore, this study confirmed the importance of the early-discovered oncogenes and tumor suppressor genes in cancer, with *RAS*, *P53*, and *RB* pathway alterations found in the vast majority of glioblastoma multiforme cases (**Figure**). However, one of the most important discoveries made by this study, was the finding that every cancer case was different, with different genomic alterations present due to the heterogeneity of cancer.
- In the present day of cancer research, there is a tsunami of data that have been generated. It is not unusual to generate a TB of data per patient, and approximately one Exabyte (1-million TB) of genomics data are being generated annually.
- Cancer is a complex adaptive system. Complex adaptive systems are composed of many interacting and self-organizing agents and layers, which exhibit independent properties and behaviors that function together without central control. These systems are dynamic, co-

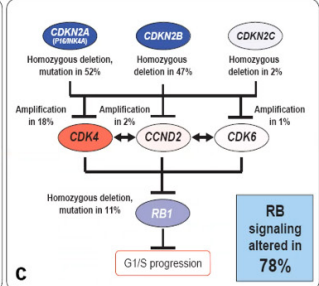
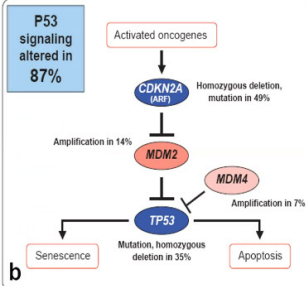
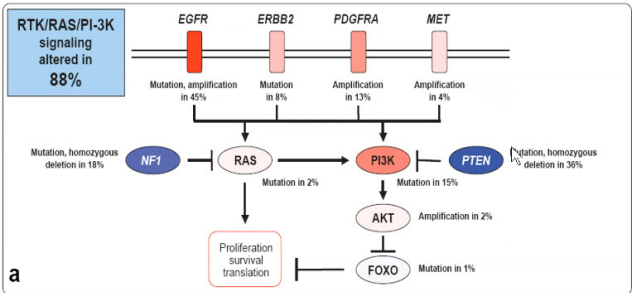
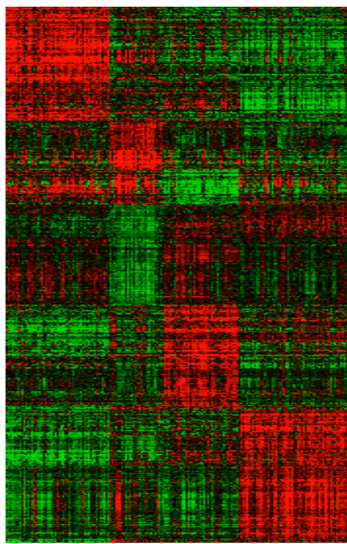
evolve with their environments, produce emergent properties, and cannot be predicted by isolated understanding of the interacting agents. Interventions may lead to unintended consequences.

- Strategies that can integrate multiple types of data are needed to best understand and predict cancer biology. The integration of physics, mathematics, and engineering fields, will be necessary to create the strategies and unifying theories needed for new cancer research solutions.
- “Information Theory,” first developed by Dr. Claude Shannon in the 1940s, is the study of how information is encoded and transmitted, primarily in signals. This theory distinguishes information from entropy, and determines how to use context and information to resolve uncertainty and make predictions with accuracy that are better than chance. Using Shannon Information Theory, cancer can be viewed as a disease of dysregulated communications.
- Applying methods including Shannon Information Theory and artificial intelligence (AI) will enable researchers to use big data to gain new understandings of cancer biology.
- One of the most complex and important interactions that can be better understood using this approach, are cancer-immune system interactions. This will enable the development of new immunotherapy strategies.
- Another important information-rich area that will benefit from AI and Information Theory, is imaging, including patient scans with MRI, CT, etc., and digital pathology, all of which generate information-rich, temporal, and spatial data on patients. This will enable earlier and more accurate diagnosis of disease states and improved patient management.
- Dr. Barker predicts that the next era of cancer research will be information-informed oncology, in which significant improvements will be made in pre-cancer and cancer diagnostics, precision medicine, real-time therapeutic response measurements, and improved survivorship care. For instance, self-monitoring using smart devices will enable real time reporting and may lead to improved predictions of when a patient will experience a recurrence or other event.
- Overall, embracing complexity and applying Information Theory and other new technologies and methodologies will lead to the next revolution in cancer biology and oncology.

TCGA: Glioblastoma Multiforme: Subtypes Molecular Path (Learning Systems)



Proneural Neuronal Classical Mesenchymal



TCGA: Nature 2008

SPECIAL LECTURE:
PCF 3.0: Serving the Science, the Scientist, and the Patient

Charles J. Ryan, MD
President and CEO
Prostate Cancer Foundation

This presentation can be viewed in full here:
<https://www.pcf.org/scientific-retreat/28th-annual/video-replays/>

KEYNOTE ADDRESS:

Michael Milken
Founder and Chairman
Prostate Cancer Foundation

This presentation can be viewed in full here:
<https://www.pcf.org/scientific-retreat/28th-annual/video-replays/>

Session 8: Glucocorticoid Receptor Biology in Castration Resistant Prostate Cancer

Acquired Defects in Glucocorticoid Metabolism in Enzalutamide-Resistant Prostate Cancer

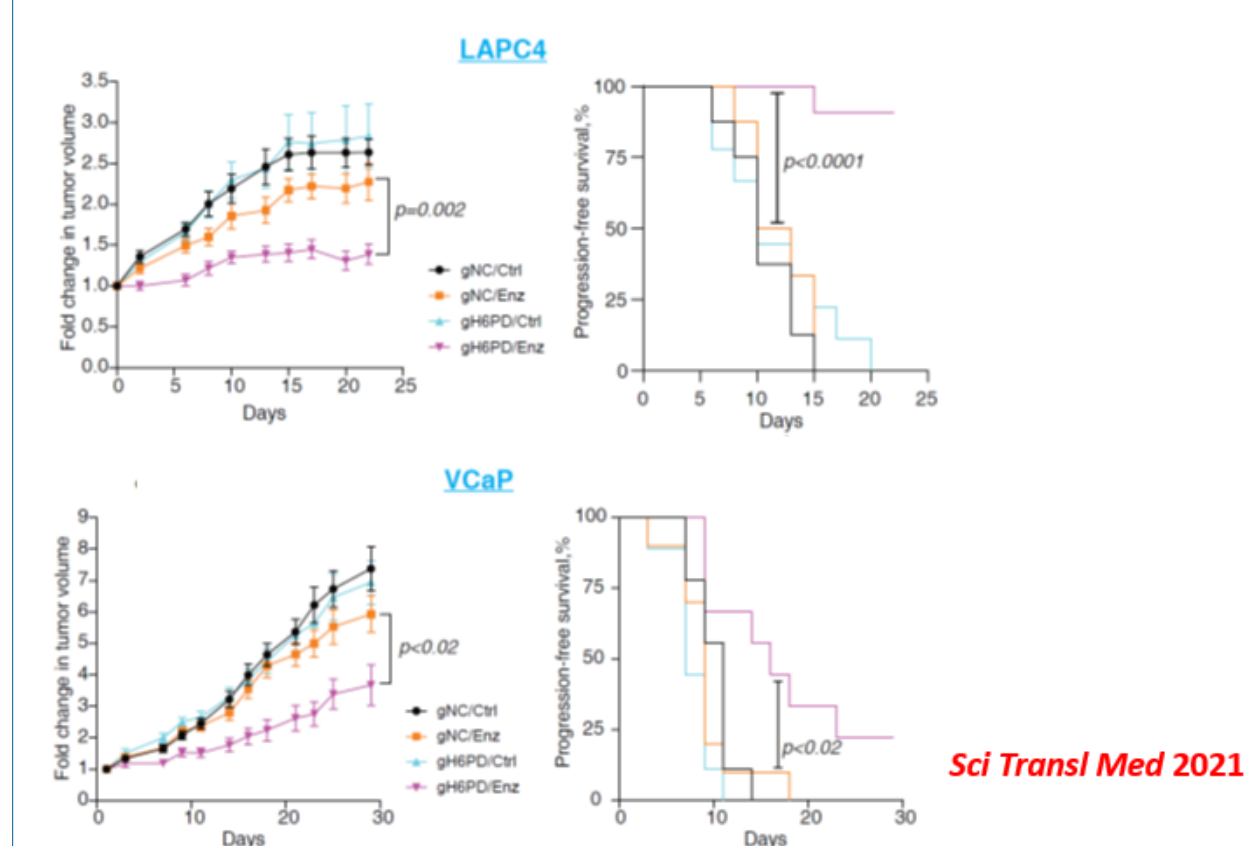
Nima Sharifi, MD
Cleveland Clinic

- The Androgen receptor (AR) is the primary driver of prostate cancer, and is the primary target of treatment for patients with advanced disease. However, in many cases, the cancer eventually develops resistance to AR-targeted therapy and progresses. Understanding the mechanisms of resistance to AR-targeted therapy is critical to developing improved treatment strategies.
- One mechanism of resistance, observed in ~30% of patients with metastatic castration resistant prostate cancer (mCRPC), occurs through upregulation of the glucocorticoid receptor (GR), a protein that is related to AR with a similar sequence and function.
- Dr. Nima Sharifi discussed the mechanisms by which the GR pathway becomes activated and maintains growth of prostate cancer cells during treatment with AR-targeted therapy.
- GR is activated by the metabolite cortisol. To prevent overstimulation of GR, cortisol is normally constantly converted to an inactivate form, cortisone, by the enzyme 11 β -HSD2. This inactive form is unable to bind to GR.
- The constant conversion of cortisol to cortisone also occurs in prostate cancer cells. However, when treated with the AR-targeted therapy enzalutamide, this process was impeded, and higher levels of cortisol were maintained. This was found to happen because enzalutamide treatment greatly reduced levels of 11 β -HSD2.
- Whether reduction of 11 β -HSD2 is a mechanism of resistance to enzalutamide was investigated. When mice with enzalutamide-resistant prostate tumors were treated with enzalutamide, tumor growth was slightly slowed. However, increasing the levels of 11 β -HSD2 in these tumors greatly increased their sensitivity to enzalutamide, resulting in significantly reduced tumor growth and significantly prolonged survival.
- While 11 β -HSD2 functions to convert cortisol to cortisone and reduce GR activity, the enzyme 11 β -HSD1 performs the opposite reaction, converting cortisone to cortisol to increase GR activity. The activity of 11 β -HSD1 requires metabolites produced by another enzyme, H6PD. Targeting H6PD may be a way to inhibit 11 β -HSD1 and thereby increase the activity of 11 β -HSD2.
- In preclinical studies, knocking out expression of H6PD in prostate cancer cells led to reduction of the metabolites necessary for 11 β -HSD1 function. Consequentially, the conversion of cortisol to cortisone was increased.
- Similar to what was seen in mouse prostate tumor models with increased levels of 11 β -HSD2, turning off expression of H6PD in enzalutamide-resistant prostate tumors cells significantly increased their sensitivity to treatment with enzalutamide, resulting in significantly reduced tumor growth and prolonged survival (**Figure**).
- Pharmacologic inhibition of H6PD is under investigation.
- Rucaparib, a PARP-inhibitor, was previously found to have modest H6PD-blocking activity. Rucaparib was found to synergize with enzalutamide in the treatment of enzalutamide-

resistant prostate tumor models in mice, reducing survival and prolonging survival. Olaparib, another PARP-inhibitor that does not have H6PD-blocking activity, did not have synergy with enzalutamide in this model.

- Together, these data demonstrate that activation of GR is a mechanism of resistance to enzalutamide. GR activity is turned on by enzalutamide via reducing levels of 11 β -HSD1 and upregulating levels of H6PD, resulting in higher levels of the GR-activating metabolite cortisol. Blocking H6PD is a promising strategy to increase 11 β -HSD2 function and reduce GR activity, and thereby restore sensitivity to enzalutamide.
- Abiraterone is another AR-targeted therapy that has a different mechanism of action than enzalutamide. A study of tumor samples from patients who developed resistance to abiraterone found that GR was increased in ~30% of cases. These GR-high tumors also had high levels of cortisol. These data suggest that increased cortisol levels and GR activity may also drive resistance to abiraterone.
- Future studies are needed to better understand the biology and role of the GR metabolism pathway in AR-therapy resistance, and to investigate pharmacologic strategies to target H6PD including the potential for rucaparib.

H6PD knockout restores enzalutamide responsiveness



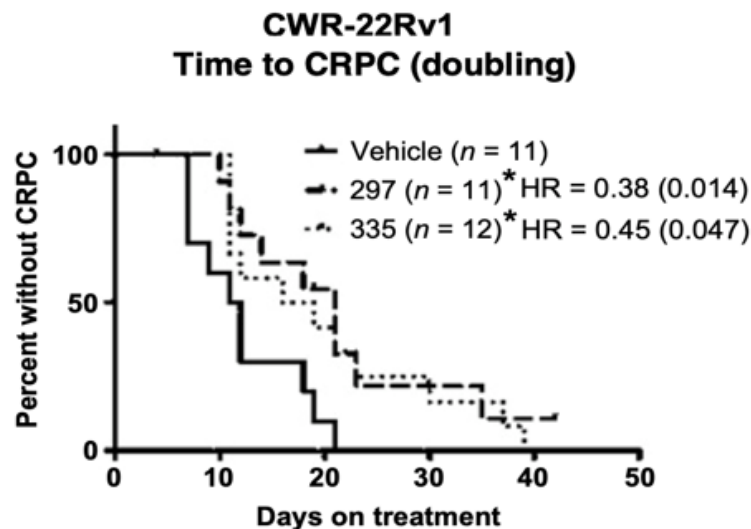
Targeting the Glucocorticoid Receptor Pathway in CRPC

Suzanne D. Conzen, MD
UT Southwestern Medical Center

- Nuclear receptors are a family of evolutionarily related proteins that have related and overlapping but distinct functions. These include the estrogen receptor (ER), mineralocorticoid receptor (MR), glucocorticoid receptor (GR), progesterone receptor (PR), and androgen receptor (AR). These receptors are activated by the respective hormones for which they are named, and function to turn on and off the expression of specific gene programs.
- AR, which is activated by androgens, is the primary driver of prostate cancer and also the primary target for systemic therapy. Unfortunately, most metastatic prostate cancer patients eventually develop resistance to AR-targeted therapy and progress to castration-resistant prostate cancer (CRPC).
- Dr. Suzanne Conzen discussed the role of increased GR expression and activity as a driver of prostate cancer resistance to AR-targeted therapy.
- Studies have demonstrated that AR represses the expression of GR, while AR-inhibition can increase the expression of GR. In prostate cancer models and patient samples, levels of GR are moderate in benign prostate tissues (where AR activity is moderate), decreased in primary early-stage prostate cancer (where AR activity is high), and increase after treatment with androgen deprivation therapy (ADT) or enzalutamide, which suppresses AR activity. For instance, in primary prostate cancers, pre-operative treatment with ADT increases detectable GR expression from 38% in pre-ADT cases to 78% in post-ADT cases. Furthermore, high levels of GR are associated with enzalutamide-resistance in CRPC.
- In prostate cancer cells, AR and GR activate the expression of both unique and overlapping gene sets. These data suggest that GR may substitute for some AR functions when AR is suppressed, and thus may enable resistance to AR-targeted therapy. Targeting GR is under investigation as a strategy to treat or prevent CRPC.
- Dr. Conzen and colleagues are examining selective GR modulators (SGRMs) as a novel treatment for prostate cancer, which can block GR activity in prostate cancer cells without causing broad toxicity. For example, CORT-(108)297 and CORT-(118)335 are non-steroidal SGRMs developed that have potent activity against GR without blocking PR.
- Treatment of both AR-dependent and AR-independent prostate cancer cell lines with CORT-297 and CORT-335 significantly reduced GR activity, as measured by reduced expression of GR-dependent genes, including both GR-unique genes and GR/AR-shared genes. CORT-297 and CORT-335 did not repress the ability of AR to activate gene expression.
- Pathology of xenografted human prostate cancers found clusters of GR-expressing tumor cells appeared after castration. These patches appear clonal, meaning they likely evolved from a shared ancestor cell that developed increased GR expression.
- Treatment of prostate cancer mouse models with CORT-297 or CORT-335 delayed tumor growth after castration (**Figure**). This suggests that increased GR signaling contributes to castration-resistance, and that GR-inhibitors can delay progression of CRPC. Treatment of mouse prostate cancer models with CORT-297 or CORT-335 also resulted in repression of GR-targeted genes, including cell proliferation genes.
- Based on these data, clinical trials have been initiated to test the combination of SGRMs with AR-targeted therapy in patients with CRPC.
- One trial tested the SGRM CORT-125134 (relacorilant) + enzalutamide in patients with enzalutamide-resistant CRPC. The Phase 1 portion of the trial has been completed, which evaluated safety and identified an optimal dose for the combination. The expansion Phase, which is evaluating GR activity in patient biopsies, is ongoing.

- A second ongoing trial is testing CORT-125281 (exacorilant) + enzalutamide in cohorts of patients with CRPC resistant to abiraterone or AR-antagonists.
- Other GR modulators are of interest. Mifepristone is a steroidal GR-inhibitor that is limited by cross-reactivity against other nuclear receptors. ORIC-101 is a derivative of mifepristone has similar activity against GR with reduced activity against AR and nuclear receptors compared to mifepristone.
- A clinical trial testing mifepristone + enzalutamide in patients with enzalutamide-resistant CRPC has been completed and will be reported soon.
- A trial testing ORIC-101 in combination with enzalutamide in patients with CRPC resistant to AR-antagonists is underway.
- Questions that require further study include whether GR-specific gene expression patterns may be a tumor biomarker for specific patients that may benefit from SGRM treatment.
- Better understanding of the biology of GR in both early and late-stage prostate cancer is needed.
- For example, whether treatment with GR-inhibitors may be more effective earlier in prostate cancer disease history remains to be investigated. A trial testing AR-inhibition (ADT + enzalutamide) alone vs. AR-inhibition plus a SGRM in patients with newly-diagnosed high-risk prostate cancer (i.e. neoadjuvant therapy) is being planned.

In vivo tumor doubling time following castration is delayed by selective GR antagonism



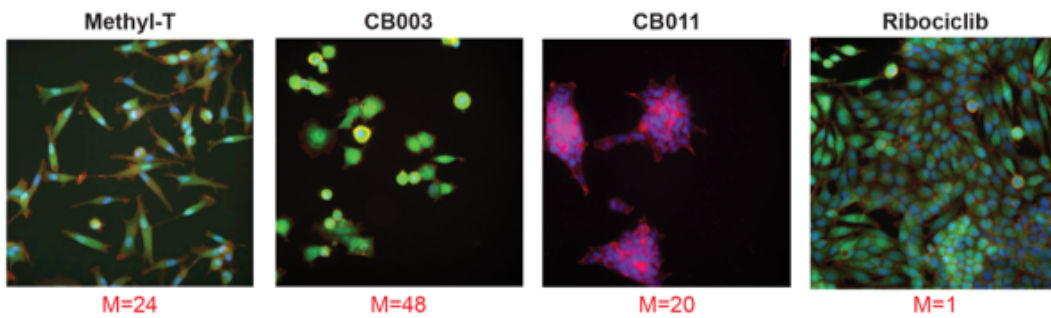
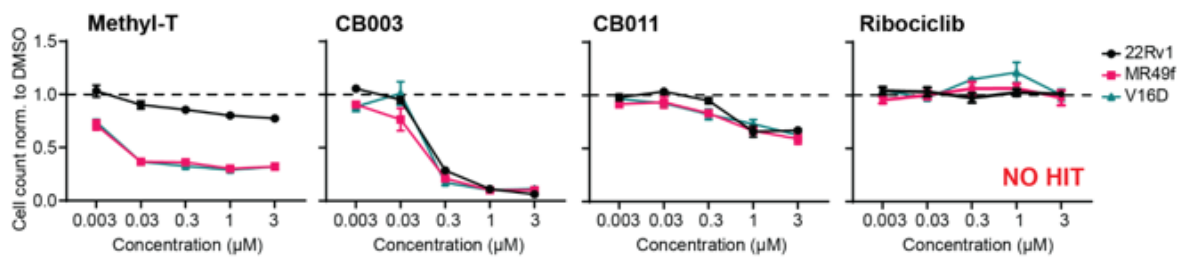
Kach et al, 2017

Diverse Roles of the Androgen Receptor in Breast and Prostate Cancer

Wayne Tilley, PhD
University of Adelaide, Australia

- Prostate cancer and breast cancer are sex hormone-driven cancer types. Prostate cancer is driven by androgens and the androgen receptor (AR), while about 80% of breast cancer is driven by estrogens and estrogen receptor- α (ER).
- AR and ER are related transcription factors in the nuclear receptor family. They have some overlapping functions. Recently, it has been shown that they can affect the activity of the other in various ways.
- Dr. Wayne Tilley discussed studies on the role of AR in breast cancer and how these lessons can be applied in prostate cancer.
- Interestingly, although AR is expressed in nearly all breast cancers and it is an independent prognostic factor, its role and potential as a therapeutic target has been controversial.
- Previous preclinical studies using cell line models have suggested that both AR-inhibiting and AR-activating therapies may have an effect against breast cancer, and indeed clinical trials have been conducted to test both strategies in ER+ breast cancer.
- Dr. Tilley and colleagues performed studies aiming to resolve the controversy over whether inhibiting or activating AR would be a better therapeutic strategy in breast cancer.
- Growth of patient-derived ER+ AR+ human breast tumors in either explant culture or as xenograft tumors in mice was nearly completely suppressed when treated with DHT (a potent natural androgen) or Enobosarm (a selective AR modulator).
- The growth in mice of several ER+ breast cancer models resistant to ER-targeted therapy and from a range of disease states, was also significantly inhibited by treatment with DHT or Enobosarm, while the AR antagonist enzalutamide was ineffective.
- Studies were done to understand why AR activation inhibits the growth of ER+ breast cancer. Collectively, these studies found that AR displaces ER from DNA on ER-activated tumor growth genes and sequesters ER's coactivators to instead drive expression of AR-regulated tumor suppressor genes. This results in suppression of ER-driven breast cancer growth.
- Whether AR can be reprogrammed in prostate cancer to act as a tumor suppressor instead of an oncogene is under study. A library of ~3,200 nuclear receptor ligands was screened for the ability to inhibit the growth and at the same time change the morphology of 4 prostate cancer cell lines that represent a variety of disease states. Compounds that inhibited growth while at the same time inducing morphological changes associated with differentiation were selected. 10 compounds were identified that are being further studied for how they affect AR activity.
- The most promising lead compound identified, CB003, potently inhibited growth of 3 of the prostate cancer cell lines and significantly altered their morphology (**Figure**).
- Methyl-T, a chemically altered form of testosterone that activates AR, was found to potently inhibit the growth of the AR-dependent prostate cancer cell lines (**Figure**), but did not affect AR-independent prostate cancer cell lines.
- Methyl-T was found to significantly increase the ability of AR to bind DNA and more potently activate gene expression, compared with DHT.
- Together, these data suggest that activation of AR with a SARM is a promising treatment strategy for ER+ breast cancer, including therapy-resistant ER-mutant breast cancers (i.e., lethal breast cancers).
- AR activation with SARMS or other AR-modulating agents may also be an effective treatment strategy in patients with androgen-sensitive or castration-resistant prostate cancer. Further studies to better understand the biology and clinical potential of these AR modulators are warranted.

Candidate SARMs/AR reprogramming compounds



Session 9: Real World Evidence and Synthetic/Virtual Control Arms

Opportunities and Pitfalls of Conducting Prostate Cancer Research using Big Data in the VA

Julie Lynch, PhD, RN, MBA

VINCI Precision Medicine, Salt Lake City VA & University of Utah

- The Veterans Administration (VA) Healthcare System is the largest healthcare system in the U.S., including 153 medical centers and 990 outpatient clinics, with over 8.76 million Veterans enrolled and over 6 million treated each year.
- VINCI (VA Informatics and Computing Infrastructure) is a gateway to the national electronic medical records database for the VA. This massive database represents opportunities for big data medical research. However, pitfalls must first be overcome, including understanding the quality of the data, standardizing the data, and developing machine learning-based methods to process, harmonize, and study the data.
- Since 2000, over 22.6 million patients have been seen at the VA, with collectively over 7.2 billion lab tests, 4.3 billion orders, 3.0 billion procedures, 2.8 billion clinical notes, 2.1 billion medication fills, 2.2 billion outpatient visits, and 14.7 million inpatient visits.
- The VA Computerized Patient Record System (CPRS) tracks patient visits, labs, medications, and notes from visits and procedures. These data are recorded in both structured and unstructured data fields (**Figure**).
- VINCI has standardized the VA electronic health records data, and stored it in a standardized format. VINCI has contributed data to several multinational efforts and patient outcomes registries.
- Several groups have published their findings from the VA datasets and VA cancer registry data. However, the data is messy and the variables can be discordant or incomplete, thus it can be hard to identify the errors and know which variables are the best to use. The quality of the data is reflective of the quality of data entry at that VA. Understanding the pitfalls is essential to appropriately using this data.
- Several studies have been published without acknowledgment of incomplete or inaccurate data, and how these caveats may impact the data and study conclusions. For instance, some studies on “prostate cancer” cohorts included patients who underwent biopsies but were not diagnosed with prostate cancer.
- Dr. Lynch and colleagues have developed a machine-learning based algorithm to identify prostate cancer patients in VINCI and create a prostate cancer data core. This algorithm uses diagnosis codes to identify cases and then applies natural language processing to assess clinical notes for mentions of Gleason score or indicators of metastatic prostate cancer. This second step removes patients who had premalignant lesions or atypical prostate features but were not diagnosed with prostate cancer.
- Altogether, 685,847 Veterans with prostate cancer were identified.
- Natural language processing is necessary for identifying actual cases, for instance of metastatic prostate cancer, because simple keyword searches will identify many false positives due to notes containing documentation of references or rule-out/negation phrases.
- Additional natural language processing tools are being developed for the prostate cancer data core. These include tools to identify and classify biorepository samples, to identify the

highest Gleason score from notes or pathology reports, to identify castration status, to identify HRR genetic testing, and to extract additional data elements from pathology reports including TNM stage, number of cores positive, and other characteristics.

- Over 20,000 Veterans have now undergone genomic sequencing of their tumors. In a collaboration with the National Oncology Office, Dr. Lynch and team are structuring and curating genetic test results.
- The LEAP (Leveraging Electronic Health Information to Advance Precision Medicine) study is investigating the use of real-world VA data for mimicking clinic trials. For this project, a national cohort of Veterans was created with glycemic status (normal, pre-diabetes, diabetes) at various time points, in order to mimic a clinical trial of metformin. Such methods are complex and require well curated data on clinical characteristics and treatment of patients.
- Overall, the efforts to develop a curated and standardized VA Prostate Cancer Data Core has resulted in a valuable resource for research of real-world evidence and to mimic clinical trials.

Unstructured data from clinic and procedure notes, pathology reports, admissions, discharges, consults, etc

JCO Clin Cancer Inform. 2021 Sep;5:1005-1014. doi: 10.1200/JCO.21.00030.

Ascertainment of Veterans With Metastatic Prostate Cancer in Electronic Health Records: Demonstrating the Case for Natural Language Processing

Patrick R Alba^{1,2}, Anthony Gao^{1,2}, Kyung Min Lee^{1,2}, Tori Anglin-Feete^{1,2}, Brian Robison^{1,2}, Evangelia Katsoulakis³, Brent S Rose^{4,5}, Olga Efimova^{1,2}, Jeffrey P Ferraro^{1,2}, Olga V Patterson^{1,2}, Jeremy B Shelton^{6,7}, Scott L Duvall^{1,2}, Julie A Lynch^{1,2,8}

TABLE 2. Performance Comparison of the NLP Model and Alternative Structured Metastatic Definitions, n = 327

mPcA Classification Method	Specificity	Sensitivity	PPV	NPV
NLP	0.979	0.919	0.969	0.944
Prescription alone ^a	0.995	0.596	0.988	0.776
Secondary ICD alone	0.953	0.809	0.924	0.875
Prescription or ICD	0.921	0.897	0.891	0.926

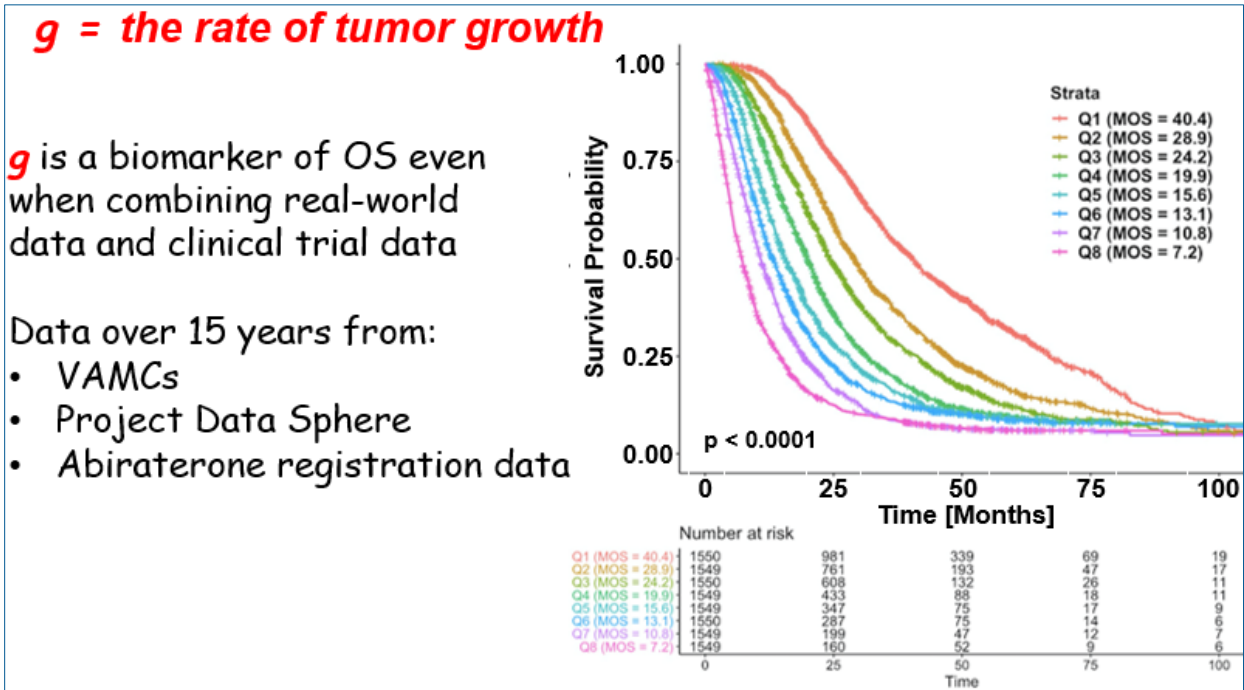
Analysis of the VA Prostate Cancer Data: A Valuable Resource that can now be Leveraged by Everyone

Tito Fojo, MD, PhD

Columbia University and the James J. Peters VAMC

- Reliable and validated criteria for measuring prostate cancer growth vs. regression is critical for clinical trial determinations of how effective a treatment is, and in the clinic to guide treatment selections and determinations about when a treatment is working vs. when a patient should change to a different treatment.
- RECIST criteria is a standard used in clinical trials for measuring disease response versus progression, based on changes in tumor diameter on scans. This criterion, expressed as radiographic progression free survival (rPFS), is accepted by the FDA to make determinations about treatment efficacy in some settings, where it has been validated to correlate with overall survival.
- PSA responses are also commonly evaluated as outcome measurements in prostate cancer trials but are not considered valid for FDA determinations on the efficacy of new treatments, as they do not always correlate with overall survival.
- Overall survival and rPFS can take a long time to measure in clinical trials. Clinical trial endpoints that act as valid surrogates for overall survival and indicate treatment efficacy earlier or with fewer patients would help to speed clinical trials and bring new treatments to patients faster.
- Dr. Tito Fojo discussed a new method to measure tumor growth rates that correlates with overall survival and thus can be used to determine treatment efficacy in trials, as well as to guide treatment decisions the clinic.
- An equation was developed that calculates the rate of tumor growth (termed “*g*”) using PSA levels acquired over time. The basic equation is based on population kinetics, and calculates the separate rates and fractions of tumor that are growing vs. regressing, to determine the total change in tumor burden over time.
- *g* was validated to be strongly predictive of overall survival using clinical trial and real-world settings using data from over 12,000 patients with castration-resistant prostate cancer (**Figure**).
- Dr. Fojo and team performed a study to evaluate *g* in >5,000 Veterans with castration resistant prostate cancer (CRPC) undergoing treatment with abiraterone or enzalutamide, and upon switching from one to the other (typically at the time of PSA progression). *g* was similar between patients receiving abiraterone and enzalutamide as first-line therapies, and across different VA hospitals. However, when patients on abiraterone were switched to enzalutamide, *g* slowed in ~33%, but accelerated in ~66% of patients. Thus, *g* may help to identify which patients should remain on a therapy vs. switch to another, and the optimal timing to switch therapies.
- Using *g*, a patient can serve as their own control to determine if a new treatment is working, by comparing tumor growth rates before vs. after starting the new treatment. As an example, Dr. Fojo and team used *g* to calculate “tumor doubling time,” and used this to determine benefit of using the PARP-inhibitor olaparib. They compared tumor doubling times on olaparib vs. the doubling times on the therapy prior to olaparib (when patients were on abiraterone, enzalutamide, docetaxel or cabazitaxel) for each patient. From this, patients could be grouped into those who benefited from olaparib (tumor doubling time slowed) vs. patients that were doing better on the treatment prior to olaparib.

- The correlation between g and overall survival was validated by the FDA in a study on lung cancer patients. Dr. Fojo and team also validated g as strongly correlated with overall survival in colorectal cancer clinical trials. In these studies, data from scans were used instead of PSA levels.
- Using data from the colorectal cancer trial, Dr. Fojo and colleagues estimated that using g , the number of patients that would have been needed in the treatment arm to determine its overall survival efficacy, was only 23 (compared with >1,000 that were on the actual trial).
- Using existing data, g can also be used to reduce the size of or even eliminate control arms.
- g could also be used to inform go/no-go decisions about new treatments under development by helping make decisions with small numbers of patients including those with rare cancers or that harbor rare mutations.
- The FDA has requested prospective studies to validate g as a surrogate endpoint for overall survival, for use in clinical trials.
- Overall, “ g ” is a new method developed to calculate the rates at which tumors grow, and strongly correlates with overall survival. g may be used to make treatment decisions and is being investigated as a surrogate biomarker for overall survival that can be used in clinical trials. g using real-world and clinical trial data may also be used to create virtual control arms for clinical trials, reducing the numbers of patients needed in trials and speeding trials and the development of new treatments.



Using Real World Evidence to Drive Stakeholder Decisions in Oncology

Michael Spencer, MSc
Janssen Oncology

- Real world evidence is data on the use of medical treatments and patient outcomes in real world clinical situations. These are data collected outside of clinical trials, and thus vary in what data is collected, time points, and other variables. However, this data is critical for understanding the impact of diseases and treatments.
- Various healthcare system stakeholders use real world evidence in various ways, including policy makers, regulators, health technology assessment agencies and payers, and patients.
- It is a common complaint that policy makers should be more informed on decisions than they are, and often rhetoric is not supported by the data. For instance, a study on the proportion of total disease deaths vs. total healthcare spend found that despite oncology being thought of as highly expensive, healthcare spending per capita, was lower than other diseases such as cardiovascular disease and diabetes (**Figure**). Researchers have the opportunity to ensure relevant data is available and communicated to policy makers to improve decision making and accountability to the populations they serve
- Regulators such as the FDA have traditionally used real world evidence to inform regulatory strategies and for post-approval surveillance of safety and efficacy. More recently, a shift is being seen in the use of such data to inform approval and pre-approval decisions.
- Health technology assessment agencies and payers use real world evidence to evaluate the relative efficacy and value of a new treatment when making decisions about reimbursement. These needs include determining the description and size of the population that will be impacted, the unmet need, and comparing the new treatment with standard of care options.
- For example, studies on the prevalence and outcomes for patients with defects in DNA repair genes in patients with metastatic castration resistant prostate cancer (mCRPC) may inform payer decisions about PARP inhibitors which were FDA-approved in 2020 for use in certain such patients.
- Regulators have been increasingly accepting single-arm trials to inform decisions about new treatments. As a result, health technology assessment agencies and payers are relying more on real world evidence as external standard of care controls for decisions. For example, the efficacy of CD19-CAR T cells was shown to be highly effective compared with external controls. Lack of acceptance of single arm data by U.S. health technology assessment agencies and payers has caused delays in the availability to the treatment to other countries.
- Many health technology assessment agencies and payers apply approaches such as cost or quality-adjusted-life-year metrics to model the economic impact of a treatment, based on the trial data and external evidence. These models rely on curve-fitting assumptions that can have high uncertainty; careful use of real-world evidence can help to improve the certainty of these models.
- There is also a large role for real world evidence in validating the relevance of endpoints measured in clinical trials by relating them to longer-term outcomes that have greater impacts on patients.

- Multi-stakeholder pre-competitive consortia present an opportunity to bring together regulators, health technology assessment agencies and payers, and patient groups to create evidence frameworks and reference models for assessing new treatments and technologies, assessing unmet needs, and creating alignment for how to collect, analyze, interpret and used real world evidence in healthcare decision making.
- PIONEER was an example of such a consortium, and addressed new prostate cancer technologies used in early-line settings, emerging prognostic/predictive endpoints and tools, adoption of technologies that are accompanied by co-diagnostics, and agreement on value-flexibility for new technologies.
- The successful use of real-world evidence depends on the data source, data completeness and quality, the population, and the methods used to collect and analyze the data. Consistency is necessary for the successful use of real-world evidence.
- The COVID-19 pandemic has represented an inflection point that has rapidly driven a greater need for, and understanding of, real world evidence to drive policies and research. Stakeholders have been pushed outside their 'comfort zone' to leverage of existing real-world data to assess the impact of the disease and vaccines. This may lead to a new paradigm of real-world evidence supporting critical real-time decisions across the globe.

Stakeholders' data needs vary by their roles

Policy Makers

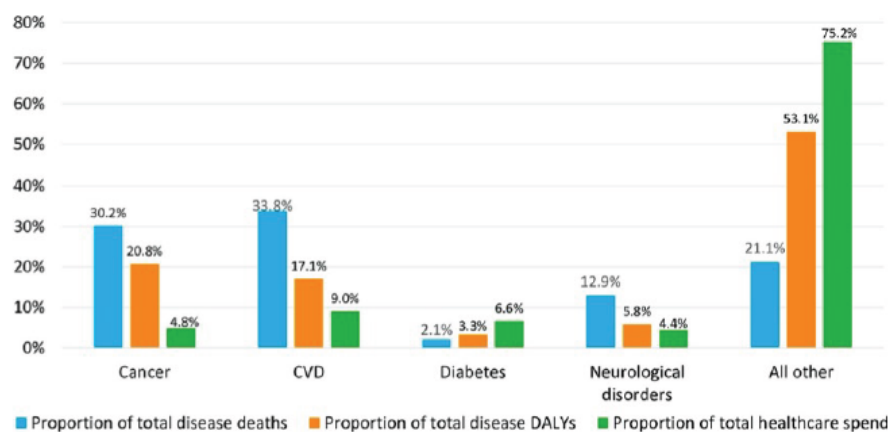


Fig 3. Average proportion of mortality, DALYs and healthcare expenditure, by disease (2015).

<https://doi.org/10.1371/journal.pone.0241354.g003>

PLOS ONE | <https://doi.org/10.1371/journal.pone.0241354> November 11, 2020

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SPECIAL LECTURE: Tumor Metabolism as a Driver and Treatment Target in Prostate Cancer

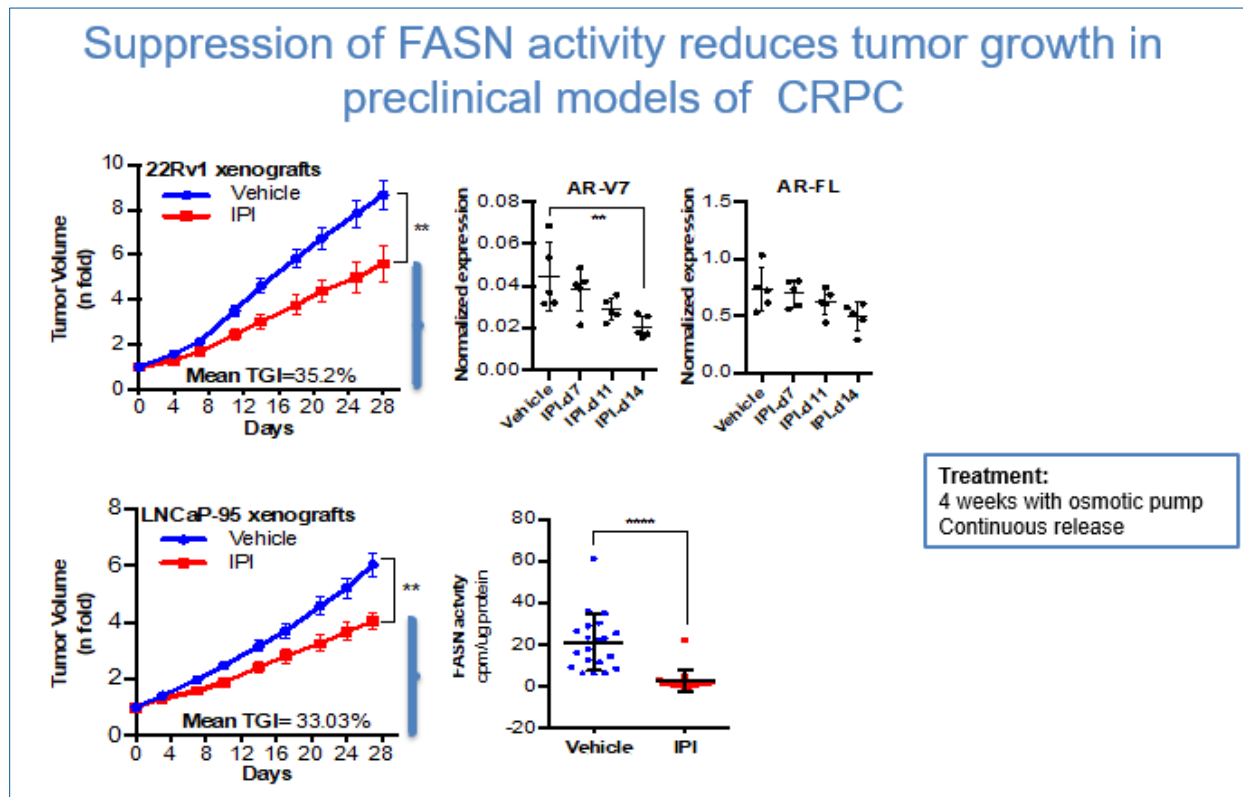
Massimo Loda, MD
Weill Cornell Medicine

- In order to maintain their rapid growth, tumors have altered metabolism. Some metabolic alterations may offer opportunities as novel treatment targets.
- Dr. Massimo Loda discussed tumor metabolism as a driver and treatment target in prostate cancer.
- Primary prostate cancers do not usually display increased utilization of glucose, and thus FDG-PET scans (which identify tumors with high glucose uptake) are not reliable methods for detecting sites of disease. This indicates that prostate cancer cells rely on other energy sources.
- Instead, prostate cancer cells produce most of their own fatty acids via lipogenesis metabolism, despite adequate nutritional supply in the environment.
- Citrate is a precursor for lipogenesis (fatty acid metabolism) and the Krebs cycle. Prostate cancer cells have a peculiar metabolism that results in an abundance of citrate. While normal prostate cells excrete citrate, prostate cancer cells retain citrate and use it for either the Krebs cycle or fatty acid synthesis. Citrate levels in prostate cells decrease with Gleason grade due to utilization in lipogenesis.
- The rate-limiting enzyme in fatty acid metabolism is FASN, which is expressed at high levels in prostate cancer cells but low levels in normal tissues except for the liver and lactating mammary glands.
- Dr. Loda and colleagues have completed multiple studies that validate the fatty acid synthesis enzyme FASN as a promising therapeutic target for prostate cancer.
- *FASN* was demonstrated to be highly expressed in metastatic castration-resistant prostate cancer (mCRPC), and its expression is regulated by the androgen receptor (AR). Germline variations in the *FASN* gene were found to be associated with risk of lethal prostate cancer in patients with metabolic syndrome. Studies in preclinical models have shown that overexpression of *FASN* in prostate cells increases their growth and promotes transformation into precancerous lesions. Deletion of *FASN* blocks the ability of prostate tumor cells to invade in mouse models. In addition, endogenous fatty acid synthesis is needed for prostate cancer cells to complete cellular division.
- Based on these data, Dr. Loda hypothesizes that exogenous supplies of nutrients and metabolites fuel early stages of prostate cancer initiation. However, established cancer cells produce their own fatty acids to continue to grow and progress, and at these stages, endogenous synthesis of lipids by tumor cells may be therapeutically targeted.
- One role of cancer oncogenes is to alter tumor cell metabolism to enable rapid and continual growth. A study which compared the impact of the MYC and AKT oncogenes in prostate cancer models and human tumor samples, found that MYC-driven tumors used lipogenesis to fuel their growth, while AKT-driven tumors used glycolysis (glucose as an energy source) to fuel their growth.
- Dr. Loda's study in MYC-driven prostate cancer mouse models found that high-fat diets accelerated prostate cancer progression by altering tumor metabolism and amplifying the MYC oncogenic program. The altered metabolism from the high-fat diet resulted in decreased metabolism of methyl groups needed for epigenetic regulation of the genome.

This resulted in de-methylation of MYC-driven genes, causing them to be “open,” and highly expressed.

- To investigate whether high fat diets promote prostate cancer progression in patients, a study was performed using data from the Physicians’ Health Study and Health Professionals Study, two registries with collectively over 80,000 male health professionals that followed health outcomes and collected demographic and lifestyle information for over 25 years. This study found that prostate cancer patients with increased saturated fat intake were more likely to die of their disease.
- A small molecule FASN-inhibitor (IPI-9119) was co-developed with Infinity Pharmaceuticals and tested against several prostate cancer cell lines. The FASN-inhibitor inhibited prostate cancer cell growth and blocked the activity of FASN including incorporation of glucose into lipids. However, there was a rebound of FASN expression after treatment, suggesting the cells were attempting to compensate for FASN-inhibition.
- A metabolomics study found that FASN-inhibition in prostate cancer cells resulted in a large increase in expression of lipogenic enzymes, but production of lipogenesis metabolites was blocked and metabolic precursors accumulated. In response, the cells attempted to compensate by increasing uptake of poly-unsaturated fatty acids (PUFAs) from the environment. Ultimately, the block on lipogenesis plus accumulation of PUFAs caused by FASN-inhibition resulted in increased cell stress and cell death.
- In preclinical laboratory and mouse models, an additive effect on prostate cancer cell death was observed when FASN-inhibition was combined with poly-unsaturated fatty acid supplementation (DHA omega-3 fatty acids).
- Importantly, in these models, FASN-inhibition downregulated the levels and activities of AR and AR-V7, a highly active AR variant.
- The FASN-inhibitor had synergy with AR-inhibitors (enzalutamide or darolutamide) in blocking prostate cancer growth in models. Expression of AR and AR-V7 was found to correlate with FASN expression in human prostate cancer samples, providing further rationale in support of this treatment combination.
- In mouse models, treatment with the FASN-inhibitor slowed prostate tumor growth but did not completely block it (**Figure**). Additional strategies to improve efficacy of this treatment are needed.
- Men of African ancestry experience disparately higher rates of prostate cancer incidence and death compared with men of European ancestry. Determining the factors that contribute to these disparities is a critical area of research.
- Another study has found that prostate cancers from African Americans have higher levels of AR binding on lipid metabolism genes compared with prostate cancers from European Americans. This was found to drive higher levels of lipid metabolism gene expression in African American prostate cancer. FASN was one of the genes most highly upregulated genes in African American prostate cancer.
- These data suggest that targeting FASN may be of particular therapeutic value in African American patients with prostate cancer.
- Several FASN inhibitors are in preclinical development for the treatment of prostate and other cancers.
- TVB-2640 is a FASN-inhibitor that has been tested in a Phase 1 clinical trial for astrocytomas, breast cancer, and colon cancer.
- A randomized clinical trial is being planned to test the FASN-inhibitor TVB-2640 in combination with enzalutamide in patients with mCRPC. This trial will evaluate safety, identify an optimal dose for the combination, and include correlative research studies to evaluate the impact of FASN inhibition on biology and metabolism.

- Overall, these studies demonstrate that FASN is a highly promising therapeutic target in mCRPC. Dietary intervention with PUFAs may potentiate the anti-tumor effects of FASN-inhibitors. Clinical trials testing FASN-inhibitors and the effects of diet and/or AR-antagonists in combination, are of great interest.



Session 10: Widening the Aperture; New Approaches for Immunotherapy in Prostate Cancer

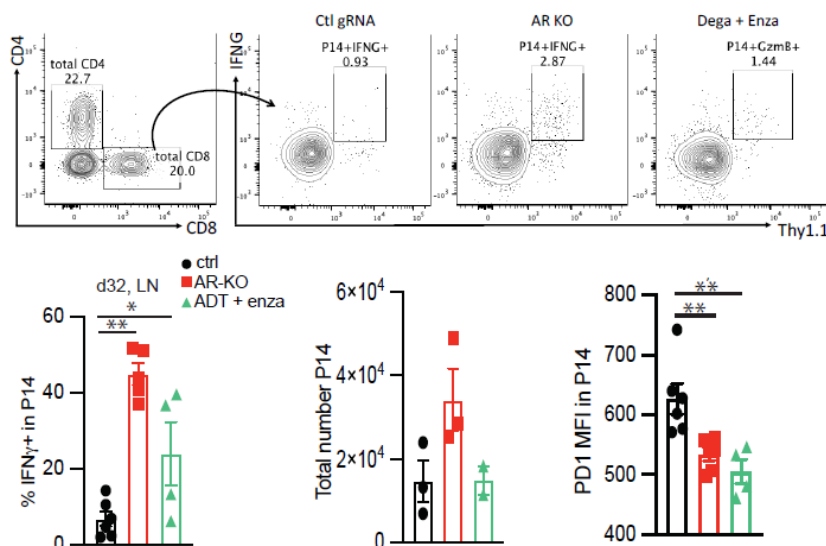
A T Cell Intrinsic Role for Androgen Receptor Signaling and Immunotherapy Resistance

Amy Moran, PhD
Oregon Health & Science University

- Sex hormones (androgens and estrogens) and chromosomes (X vs. Y) are known to impact the biology of our immune system.
- Epidemiological studies have found that male gender is protective against autoimmunity, with significantly lower rates of autoimmune diseases seen in males compared with females.
- The goal of cancer immunotherapy, is to generate an autoimmune-like response against one's own tumor.
- Dr. Amy Moran discussed the biology of androgens on T cells, and how they may impact anti-tumor immunity in patients with prostate cancer.
- T cells are a major type of immune effector cell, which can recognize small pieces of a protein associated with infections or cancer, and kill target cells that express the antigen.
- Testosterone has been shown to suppress T cell functions, including the types of responses needed for T cells to kill targeted cells.
- Dr. Moran and colleagues found that T cells found in normal healthy tissues and prostate cancer express the androgen receptor (AR).
- Activation of T cells greatly increased their expression levels of AR. This suggests that upon activation of T cells, the increase in AR may limit the T cell's activity.
- To investigate whether targeting AR in T cells will enhance the efficacy of cancer immunotherapy, samples were studied from patients enrolled in a clinical trial testing the combination of the AR-targeted therapy enzalutamide plus the immunotherapy pembrolizumab.
- Biopsy samples were subjected to single cell gene expression analyses to evaluate the immune cell types present in tumors. A comparison of 5 patients who did not respond vs. 3 patients who did respond to the combination, found that responders had a greater number of CD8+ T cells, and that CD8+ T cells from responders vs. non-responders had distinct gene expression programs.
- In depth evaluation of the of T cell gene expression data revealed that T cells from responders had reduced AR activity and increased functional signatures compared with T cells from non-responders.
- An analysis of additional patients on the trial confirmed that lower activity of AR in T cells was associated with a better response to enzalutamide + pembrolizumab.
- To better understand the role of AR in T cells, CRISPR was used to delete the *AR* gene from T cells. *AR*-deleted T cells exhibited a stronger interferon-gamma response. Interferon-gamma is a key immune activation protein produced by activated T cells. Using data from this experiment, an *AR*-deficient T cell gene expression signature was developed. This signature was stronger in T cells from responders vs. non-responders on the enzalutamide + pembrolizumab clinical trial.

- Previous studies have demonstrated that the interferon-gamma gene is epigenetically silenced in exhausted T cells (activated T cells that have been chronically exposed to their antigen, until the point where they can no longer function).
- Evaluation of gene control regions (“enhancers”) for the interferon-gamma gene and granzyme-B gene (a protein that T cells use to kill target cells), identified binding sites for AR. AR could be prevented from binding to the enhancers by treating T cells with enzalutamide. This suggests that AR may bind to these regions to suppress expression of interferon-gamma and granzyme-B.
- This hypothesis was investigated using a mouse model of chronic virus infection (LCMV), in which anti-viral T cells become exhausted. The impact of AR on T cell function in this model was tested by either deleting *AR* in T cells, or by treating mice with androgen deprivation therapy (ADT) + enzalutamide. In early stages of viral infection (before T cells become exhausted), neither *AR*-deletion nor ADT + enzalutamide treatment affected the function of T cells. However, at later times when T cells normally become exhausted in this model, T cells with *AR*-deletion had maintained their functional capacity including high levels of interferon-gamma. Treatment with ADT + enzalutamide also maintained T cell function, though to a lesser degree than *AR*-deletion. These results demonstrate that AR enables T cell exhaustion, while *AR*-deletion maintains the functional capacity of chronically stimulated T cells.
- In tumors from patients with metastatic castration-resistant prostate cancer (mCRPC) or metastatic melanoma, high AR activity was associated with low CD8 activity and interferon-gamma activity signatures.
- Collectively, these data suggest that AR in T cells acts to limit their activity, and that targeting AR may improve responses to immunotherapy in prostate cancer patients. Further studies are needed to determine how this knowledge may be translated into the clinic to improve outcomes for patients.

T cell intrinsic *Ar* deletion maintains the functional capacity of chronically stimulated T cells

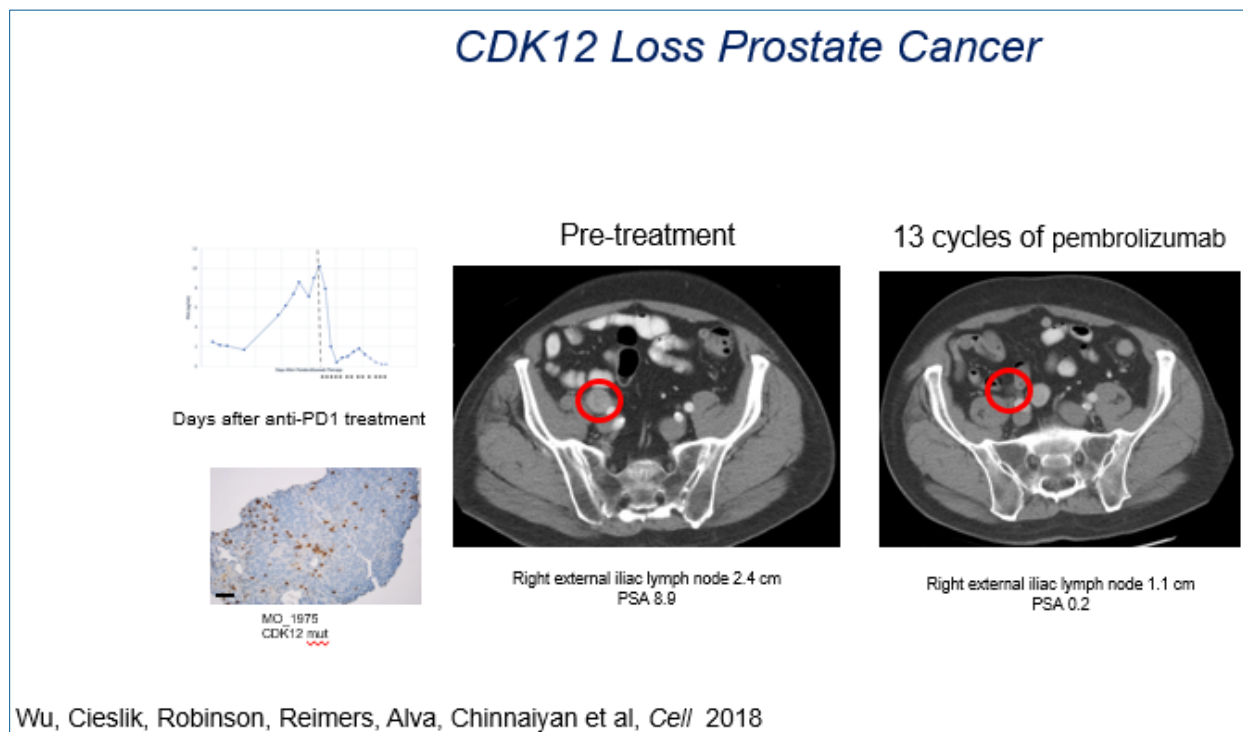


Checkpoint Immunotherapy in mCRPC with CDK12-Loss

Ajjai Alva, MD
University of Michigan

- Prostate cancer can be classified into different molecular subtypes based on the genomic alterations present, which may cause distinct biology and be used to select specific treatment options.
- Prostate cancers that have lost the *CDK12* gene comprise a distinct molecular subtype. Loss of *CDK12* is observed in ~7% of patients with metastatic prostate cancer. *CDK12*-loss does not appear to overlap with other key prostate cancer driver gene alterations such as *SPOP*-mutations, *ETS* gene fusions, and mismatch repair gene defects.
- Loss of *CDK12* causes genomic instability, characterized by focal tandem duplications and greatly increased gene fusions.
- The gene fusions result in increased numbers of “neoantigens” – mutated proteins that can be recognized and targeted by the immune system. Accordingly, increased numbers of T cells and expansion of T cell clones are seen infiltrating *CDK12*-loss prostate cancers. These data suggest that *CDK12*-loss prostate cancers may be more susceptible to treatment with immunotherapy.
- Dr. Ajjai Alva discussed investigations into the potential for immunotherapy for the treatment of *CDK12*-loss prostate cancer.
- A post-hoc analysis of prostate cancer patients at the University of Michigan identified anecdotal cases of patients with *CDK12*-loss who had received immunotherapy. A case report for one exceptional responder was presented, in which a patient with *CDK12*-loss experienced profound PSA and radiographic responses after treatment with pembrolizumab, and remained on pembrolizumab for several years (**Figure**).
- A case series report on different prostate cancer molecular subtypes found that patients with *CDK12*-loss mCRPC tended to have more aggressive disease, faster time to metastasis, less benefit from hormone therapy, and shorter time to castration-resistance than patients with *BRCA1/2*-mutant or *ATM*-mutant mCRPC.
- Based on these data, Dr. Alva and colleagues initiated a clinical trial to test the immunotherapies ipilimumab and nivolumab in patients with *CDK12*-loss tumors. Cohort A is testing ipilimumab + nivolumab in patients with *CDK12*-loss metastatic castration resistant prostate cancer (mCRPC). Cohort B is testing ipilimumab + nivolumab in patients with *CDK12*-loss solid tumors. Cohort C is testing nivolumab alone in patients with *CDK12*-loss mCRPC. *CDK12*-loss was determined by genomic sequencing of tumor or blood samples, and could be mono-allelic (loss of one gene copy) or bi-allelic (loss of both gene copies) for enrollment onto the trial.
- For Cohort A, the primary endpoint was overall response rate (ORR) as measured by PSA 50% decline from baseline. Secondary endpoints included toxicities, radiographic progression-free survival, duration of response, duration of therapy, time to progression, overall survival, PSA progression-free survival, and quality of life measures. Correlative studies were also performed to evaluate tumor genomics and immune biology.
- Overall, 33 mCRPC patients were enrolled into Cohort A across eight cancer centers.
- In preliminary results, 4 of 23 (17.4%) evaluable patients in Cohort A experienced PSA $\geq 50\%$ responses to the treatment. Several patients experienced hyper-progression, in which PSA levels increased over 10-fold after treatment.

- Grades 3-5 serious adverse events were observed in 9 of 25 evaluable patients (36%). Treatment emergent adverse events of any grade (possible, probable, or definite attribution to either/both study drugs) were observed in 19 of 33 evaluable patients and were consistent with known side effects from these treatments.
- This study, which is the first precision genomic selection study for immunotherapy in mCRPC, is ongoing. Future questions include determining whether loss of both copies of the *CDK12* gene may confer better sensitivity to immunotherapy, and whether immunotherapy may work better if given earlier in the disease course.



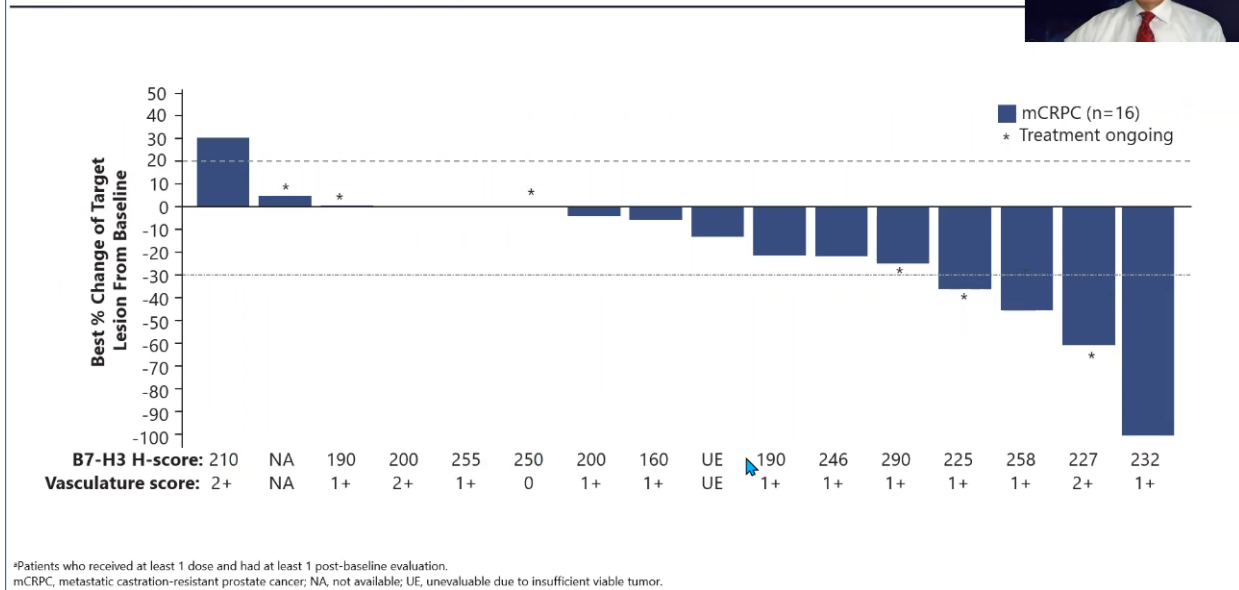
MGC018, an Anti-B7-H3 Antibody-Drug Conjugate (ADC), in Patients With mCRPC: Preliminary Results of Phase 1 Cohort Expansion

Chet Bohac, PharmD, MD, MSc
MacroGenics, Inc.

- B7-H3 is an immunosuppressive protein that is highly expressed on multiple solid tumor types, including prostate cancer, but has limited expression on normal tissues. B7-H3 is present on tumor cells, as well as tumor-associated blood vessels and tumor stroma (non-tumor cells that support tumor growth). Because of these features, B7-H3 is under investigation as a target for cancer treatments.

- Dr. Chet Bohac discussed the development of MGC018, an antibody-drug conjugate that targets B7-H3, and delivers the chemotherapy agent duocarmycin.
- Upon binding to target cells that express B7-H3, duocarmycin is cleaved off by cell enzymes and released to kill targeted and nearby cells. On average, each MGC018 molecule can carry 2.7 molecules of duocarmycin.
- In preclinical studies, MGC018 was able to kill tumor cells including multidrug-resistant tumor cell lines, in a way that activates immune responses against tumor cells.
- MGC018 exhibited potent anti-tumor activity in preclinical animal models of B7-H3-expressing prostate, breast, ovarian, lung, head and neck, and melanoma tumors.
- Preclinical toxicology studies found MGC018 has an acceptable safety profile. Side effects observed in cynomolgus monkeys after several doses included transient low blood cell counts, dry skin, and hyperpigmentation.
- A Phase 1/2 clinical trial was completed in patients with certain advanced solid tumors, which tested escalating doses to determine toxicities and establish the optimal dose of MGC018. Two dose limiting toxicities were observed: one Grade 4 neutropenia and one Grade 3 fatigue.
- Nine patients with metastatic castration resistant prostate cancer (mCRPC) were included in the dose-escalation portion of this trial, of whom 5 (55.5%) experienced $\geq 50\%$ PSA reductions. Responses were also observed in some melanoma patients.
- A Phase 1 cohort expansion was then performed, which evaluated additional patients treated with the determined optimal dose of MGC018, given intravenously every 21 days. As of August 2021, 88 patients had been enrolled onto the expansion cohort, including 40 patients with mCRPC.
- Histology was performed on tumor samples from enrolled patients to evaluate the levels of B7-H3 expression. 93% of the mCRPC patients had high B7-H3 levels.
- 83 of the 88 patients enrolled (96.5%) experienced a treatment-emergent adverse event (TEAE), 48 of whom (55.8%) had a Grade 3 or higher TEAE, and 29 (33.7%) patients had at least 1 serious TEAE. There were two on-study deaths, one due to COVID-19, and one who discontinued MGC018 after a second dose due to Grade 4 thrombocytopenia and died 42 days later of unknown cause. Four mCRPC patients discontinued MGC018 due to toxicities.
- The most common TEAEs (any Grade) included fatigue (37%), neutropenia (34%), hand-foot syndrome (31%), pleural effusion (23%), nausea (22%), and asthenia (20%).
- Grade ≥ 3 TEAEs that occurred in $>5\%$ of patients were neutropenia (22%), thrombocytopenia (7%), and anemia (5.8%).
- At the time of this presentation, 32 patients had undergone scans after 9 weeks and were evaluable, including 16 patients with mCRPC.
- Four of 16 (25%) of patients with mCRPC experienced $\geq 30\%$ tumor shrinkage on scans, and 10 had reductions in target lesion sums from baseline (**Figure**).
- 39 of the mCRPC patients were evaluable for PSA responses. 21 of 39 (53.8%) had a PSA reduction $\geq 50\%$ from baseline. 24 of the 39 (61.5%) patients remained on treatment at the time of this presentation.
- Overall, these data demonstrate that MGC018 appears safe and has promising efficacy in multiple solid tumor types including mCRPC, non-small cell lung cancer and melanoma. Future studies will evaluate alternative starting doses and identify the optimal total number of doses and overall treatment duration.

Best Percent Change of Target Lesions in mCRPC Cohort (Tumor Response-Evaluable Population)^a



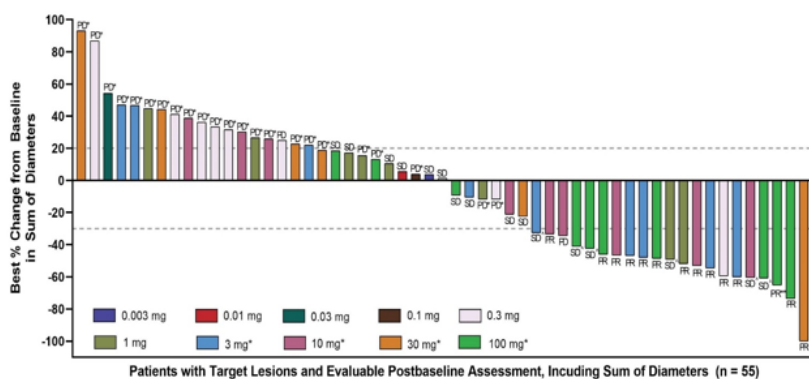
Targeting DLL3 with a Bi-Specific T Cell Engager: Tarlatamab (AMG 757) in De Novo and Treatment-Emergent Small Cell Neuroendocrine Prostate Cancer

Rahul Aggarwal, MD
University of California, San Francisco

- Neuroendocrine prostate cancer (NEPC) is an advanced subtype of highly aggressive prostate cancer, that may arise *de novo* (1%), or as a form of castration-resistant prostate cancer (CRPC) (15-25%) as a mechanism of resistance to prolonged use of androgen-targeted therapy.
- NEPC has distinct pathological and genomic features compared with other types of CRPC, including common combined loss of the tumor suppressor genes RB1 and TP53.
- NEPC is highly aggressive, rapidly lethal, and responds poorly to standard prostate cancer treatments. Currently, there are limited treatment options for NEPC beyond platinum chemotherapy. New treatment strategies are urgently needed.
- Dr. Rahul Aggarwal discussed the development of AMG 757 (tarlatamab), a novel immunotherapy that targets the NEPC-associated protein DLL3.
- DLL3 is a protein that is commonly present at a range of expression levels on the cell surface of NEPC, small cell lung cancer, and other cancers with neuroendocrine features.
- A study of 723 patients with prostate cancer found that 77% of NEPC tumors expressed DLL3, on 64% of their tumor cells on average.

- In another study, patients with DLL3-expressing prostate cancer had significantly shorter overall survival than patients with DLL3-negative prostate cancer. DLL3-expressing NEPC also tended to have low levels of the prostate cancer proteins PSMA and STEAP1, which are the targets of other treatments being developed.
- AMG 757 is a bispecific antibody (BiTE®) immunotherapy treatment that simultaneously binds CD3 on T cells and DLL3 on target cells. This treatment works by bringing T cells into contact with DLL3-expressing tumor cells, causing the T cells to become activated and kill the tumor cells.
- Treatment of preclinical DLL3-expressing NEPC models with AMG 757 led to durable tumor regressions of NEPC tumors and prolonged survival.
- In a NEPC model in which DLL3 expression levels were heterogeneous (different in different tumor cells), some tumors eventually relapsed after treatment with AMG 757; some of these late relapsed tumors expressed lower levels of DLL3 suggesting a mechanism of treatment escape.
- AMG 757 is currently being tested in a Phase 1 trial in patients with small cell lung cancer previously treated with platinum chemotherapy to evaluate safety and identify an optimal dose. Preliminary results suggest the treatment is safe and may have efficacy. Overall, tumor shrinkage was observed across a range of AMG 757 doses, with an observed disease control rate of 47% and objective response rate of 20% (Figure).
- A Phase 1b trial testing AMG 757 in patients with NEPC has recently opened to accrual. This trial is testing several doses of AMG 757 to identify an optimal dose and determine safety, and will be followed by testing the optimal dose in an expanded cohort of patients.
- The NEPC trial will identify patients based on tumor biopsy or circulating tumor DNA profile harboring the pathologic and genomic hallmarks of neuroendocrine differentiation.

Tarlatamab Demonstrates Anti-Tumor Activity in Patients with SCLC



PD* indicates PD in post baseline scan and came off study without further confirmation scan. PR** indicates the PR is unconfirmed. SD[†] indicates patients who had an initial PR, but did not have confirmation of PR on the subsequent scan. *Step dosing. †Includes patients who received ≥ 1 dose of tarlatamab and had at least 8 weeks follow-up. PD, progressive disease; PR, partial response; SD, stable disease.

Modified RECIST 1.1 Response, n (%)	Patients [†] (N = 64)
PR, confirmed	13 (20)
0.3 mg target dose	1/12 (8)
1 mg target dose	1/8 (13)
3 mg target dose	4/11 (36)
10 mg target dose	3/10 (30)
30 mg target dose	1/8 (13)
100 mg target dose	3/11 (27)
PR, unconfirmed	1 (2)
100 mg target dose	1/11 (9)
SD	17 (27)
Disease control rate, %	30 (47)

Tumor shrinkage is observed across a range of tarlatamab doses

1. Owonikoko TK, et al. Abstract 8510. Presented at: ASCO Annual Meeting, June 4–8, 2021; Virtual.

Advancing the Frontiers of T Cell Redirecting Agents in Prostate Cancer

Oliver Sartor, MD
Tulane University

- Dr. Oliver Sartor discussed the development of several T cell redirecting agents for the treatment of prostate cancer. T cell redirecting agents are a class of immunotherapies that work by simultaneously binding to tumor cells and T cells. This activates the T cell to kill the tumor cell.
- Prostate cancer-associated proteins that are promising targets for T cell redirecting agents and other types of targeted therapies include PSMA, STEAP1, KLK2 and TMEFF2.
- Bi-specific T cell engagers (BiTE®) are T cell redirecting agents that simultaneously bind a tumor cell target (a tumor-associated protein) and a T cell target (typically CD3).
- Blinatumomab is a BiTE® that targets CD19 expressed on acute lymphoblastic leukemia (ALL) cells and CD3 on T cells (CD19xCD3) and is FDA-approved for the treatment of patients with certain types of ALL. FDA approval was based on a Phase 3 trial which demonstrated that Blinatumomab significantly improved overall survival in patients with ALL.
- BiTEs for the treatment of prostate cancer and other solid tumor types are under development.
- AMG 212 is a BiTE that targets PSMA on prostate cancer cells and CD3 on T cells (PSMAxCD3). In preclinical studies, AMG 212 administration significantly blocked the growth of prostate tumors in mice models.
- A Phase 1 study was performed to evaluate safety and identify the optimal dose of AMG 212 in patients with metastatic castration resistant prostate cancer (mCRPC). This treatment has a short half-life in human serum and requires administration by continual IV infusion.
- In this study, 16 mCRPC patients were treated with AMG 212 at one of 5 dose levels. The maximum tolerated dose was not reached and promising clinical activity was observed. Two patients had long-term PSA responses (>14 & 19 months) and three patients had stable disease. Cytokine release syndrome (CRS), a side effect often seen with immunotherapies, was reported in 3/16 patients (19%; 2 Grade 2, 1 Grade 3).
- Because of the need for continual IV administration of AMG 212 and subsequent development of an improved BiTE product with an extended serum half-life (AMG 160), further clinical development of AMG 212 has been ceased.
- AMG 160 is a PSMAxCD3 targeting BiTE with an extended serum half-life that can be administered bi-weekly.
- A Phase 1 study was initiated to evaluate safety and identify the optimal dose of AMG 160. 35 patients with mCRPC were treated in this study at one of 6 doses. PSA reductions were observed in 68.6% (24/35) of patients and PSA \geq 50% responses occurred in 34.3% of patients (**Figure**). 3 of 15 patients with measurable disease on scans experienced partial tumor shrinkage (**Figure**).
- CRS was observed in 90% of patients (60.5% Grade 1-2; 25.6% Grade 3; no Grade 4 or 5 events). CRS events tended to be reversible, manageable, were most severe in cycle 1, and were associated with fever, hypotension, transient transaminitis, nausea/vomiting and diarrhea. Four (9.3%) patients experienced reversible atrial fibrillation (irregular, often rapid heart rate) in the setting of CRS and/or tachycardia.
- A prophylactic mitigation strategy consisting of using a lower run-in dose before starting the maintenance target dose, dexamethasone premedication, and prophylactic IV hydration, was tested in a cohort of 5 patients. This strategy eliminated grade 3 CRS events, and will

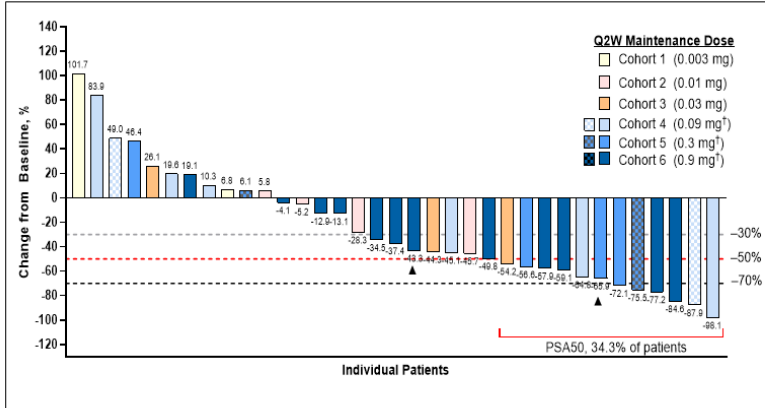
be used during treatment with AMG 160 going forward. In comparison, Grade 3 CRS events were experienced by 2 of 4 patients who received the same dose without prophylactic mitigation.

- In ongoing clinical trials, AMG 160 is being tested in combination with pembrolizumab, and with enzalutamide, abiraterone, or AMG 404, an anti-PD1 antibody.
- Tri-specific T cell redirecting agents are also under development. These are similar in concept to bi-specific T cell redirecting agents, and simultaneously bind tumor cells and T cells.
- HPN424 is a tri-specific T cell redirecting agent that targets PSMA on prostate cancer cells, CD3 on T cells, and albumin, which extends its half-life in human serum.
- In preclinical studies, HPN424 demonstrated efficient solid tumor penetration, a long half-life, and excellent stability. In addition, it is designed to activate the T cell only when simultaneously bound to the tumor cell target, preventing T cell killing of non-tumor targets and minimizing off-target toxicities.
- A Phase 1 study was performed to test safety and determine the optimal dose of HPN424 in 89 patients with mCRPC. In the dose ranges tested, no maximum tolerated dose was identified, and no Grade 4 CRS events or Grade 5 events occurred.
- HPN424 showed promising activity, including 20% (15/74) with PSA reductions and 4/74 patients with PSA \geq 50% responses. 19 of 34 patients with measurable disease on scans showed stable disease and 1 had a partial response. 56% (36/64) of patients with evaluable circulating tumor cells (CTC) at baseline had a reduction in CTC counts, including 14 who had no detectable CTCs after treatment.
- A third T cell redirecting technology discussed employs next-generation tumor target discovery strategies and multi-specific antibodies based on humanized rats (rats engineered to express human antibody genes). This novel approach also uses antibodies that bind less tightly to CD3 on T cells, which results in efficient tumor cell lysis but with lower immune-related side effects, reduced T cell exhaustion, and reduced activation of negative regulatory T cells.
- TNB-585 is a CD3xPSMA bi-specific antibody using this technology. In preclinical studies in prostate cancer models, TNB-585 activated T cells to kill tumor cells, but release lower amounts of CRS-related immune-activating cytokines. Reduced activation of negative regulatory T cells also occurred.
- A Phase 1 trial testing TNB-585 in patients with mCRPC has been initiated.
- AMG 509 is a bispecific antibody under development that has two regions that bind the prostate cancer protein STEAP1, and one region that binds CD3 on T cells. A clinical trial testing AMG 509 in patients with mCRPC is underway.
- There are at least 5 additional prostate cancer-targeted T cell redirecting agents that are in clinical trials, as well as many more in preclinical development. The prostate cancer-associated protein targets of these agents include PSMA, KLK2, and TMEFF2.
- The emergence of anti-drug antibodies has been observed in patients treated with these agents, and are a concerning resistance mechanism to this new treatment class. Strategies to prevent this are needed.
- Overall, T cell redirecting agents are a promising new class of treatments for prostate cancer, with efficacy seen in clinical trials for several PSMA-targeted T cell redirectors. Future studies will test new agents and address mechanisms of resistance.

PSMAxCD3 AMG 160 Demonstrated Early Evidence for Efficacy in mCRPC Patients

Interim data from first-in-human study NCT03792841 (ESMO 2019)

PSA response in 68.6% of patients (24/35)

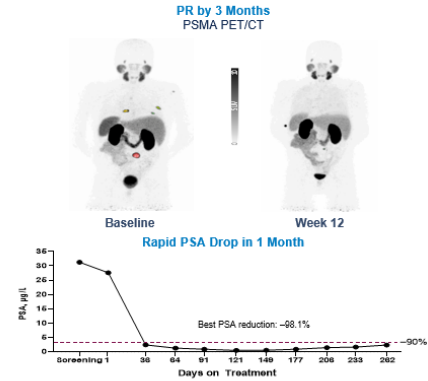


20 July 2020 data cutoff. PSA = prostate-specific antigen; PSA50 = PSA decrease of 50%; Q2W = every 2 weeks
 * Best PSA reductions at any time point in evaluable patients included those who had received ≥ 1 dose of AMG 160 and had measurable baseline PSA
[†] Checkered bars indicate cohorts with optimized cycle 1 priming strategies
 ▲ Indicates patient who had failed prior LuPSMA treatment

Tran B, et al. *Annals of Oncology*, Volume 31, Supplement 4, 2020, Page S507

Deep antitumor responses observed:
 3 PR (1 unconfirmed) out of 15 patients with measurable disease

Patient 10112001002
Prior Rx Surgery, radiotherapy, docetaxel, enzalutamide, bicalutamide, and talazoparib
Cohort 4 (0.09 mg with cycle 1 priming)



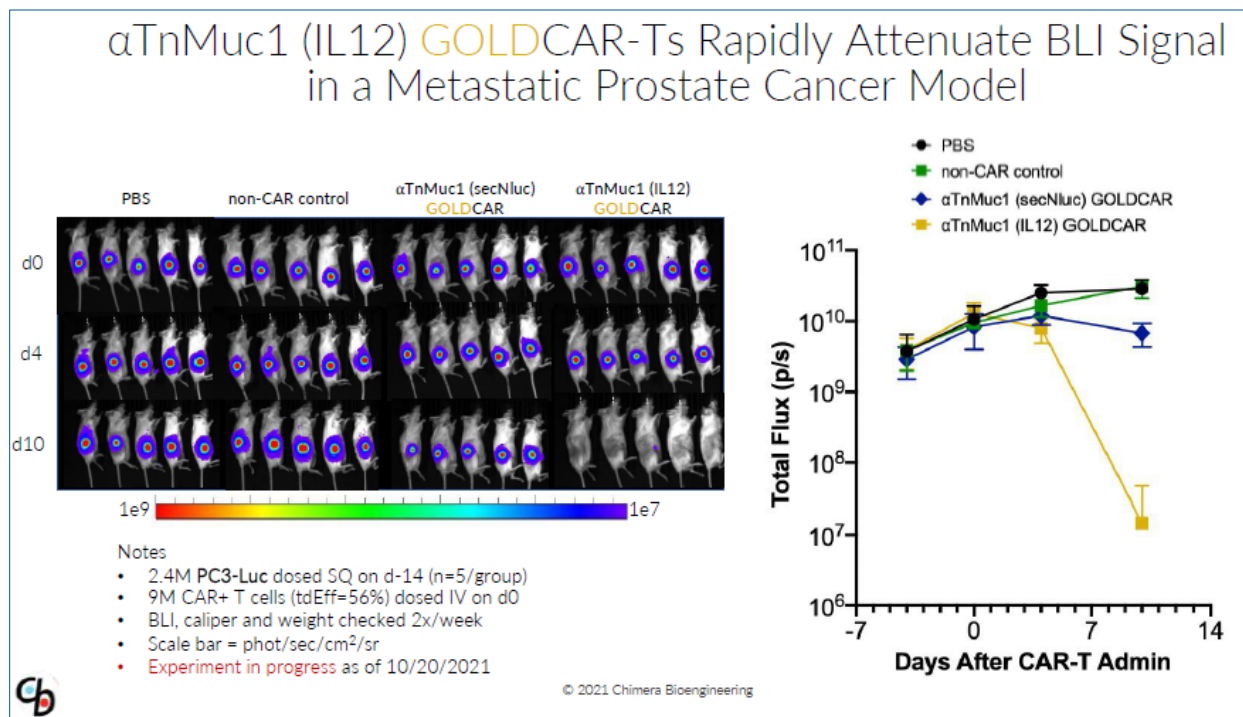
Session 11: Novel Technologies to Overcome the Suppressive Tumor Microenvironment

Improving CAR Responses against Solid Tumors with Conditional Payload Delivery

Gus Zeiner, PhD
Chimera Bioengineering

- Chimeric antigen receptor (CAR) T cells are a type of personalized immunotherapy in which a patient's own T cells are genetically engineered to target and eliminate their tumor(s). CAR-Ts have been successfully developed against several B cell malignancies, and are under development for solid tumor types including prostate cancer.
- While CAR-T cells have the potential to be highly potent, their efficacy against solid tumors is often limited by an immune-suppressive tumor microenvironment (TME), which suppresses CAR-T potency.
- One approach to make CAR-Ts more effective is to target the TME through "arming" the CAR-Ts with additional transgenes that encode immune-modulators. While this approach does enhance CAR-T potency, armed CAR-Ts are often too toxic for clinical use due to systemic exposure to immune-modulators produced by the armed CAR-Ts.
- Dr. Zeiner discussed "GOLD", a novel technology that aims to overcome the efficacy and toxicity limitations of standard and armed CAR T cells. GOLDCAR-T cells are armed CAR-T cells that are engineered to only deliver payloads that counteract the suppressive tumor microenvironment upon tumor cell interaction. This approach increases CAR-T potency and reduces toxic side effects.
- Proof-of-concept in vivo studies using a preclinical lymphoma model demonstrated that GOLDCAR-T cells only expressed their payload upon interaction with the tumor.
- GOLDCAR-T cells which target the leukemia/lymphoma tumor antigen CD19 and carry the immune activation cytokine IL-12 as its GOLD payload were highly effective against lymphoma tumors in mice, and did not release detectable IL-12 into the mouse bloodstream. In contrast, unarmed CD19-targeted CAR-Ts were ineffective against these tumors. CD19-targeted armed CAR-Ts that were engineered to constantly express IL-12 were effective against lymphoma tumors but also released IL-12 into the mouse bloodstream. As systemic IL-12 exposure can be highly toxic, these findings demonstrate the promising safety and efficacy of the GOLDCAR approach.
- DLL3 is a protein that is located inside of healthy cells, but is abnormally present on the surface of cancers with neuroendocrine features, including small cell lung cancer, neuroblastoma, IDH-mutant gliomas, and neuroendocrine prostate cancer (NEPC). DLL3 is being explored as a GOLDCAR-T target in these cancer types.
- DLL3-targeting GOLDCAR-Ts that deliver IL-12 as the GOLD payload were developed and found to have efficacy in an aggressive neuroendocrine tumor mouse model.
- TnMuc1 is a tumor-specific glycoform of the Muc1 protein that is expressed in a number of adenocarcinomas, including the five highest-mortality indications (lung, colon, pancreas, breast, and prostate cancers). TnMuc1 is being explored as a promising GOLDCAR-T target in these cancer types.

- A TnMuc1-targeting GOLDCAR-T that delivers IL-12 as the GOLD payload is rapidly advancing through development. TnMuc1 (IL-12) GOLDCAR-Ts were more effective at killing tumors in pancreatic adenocarcinoma and metastatic prostate cancer (**Figure**) mouse models than unarmed TnMuc1-CAR-Ts.
- Together, these studies demonstrate promising preclinical efficacy and safety for GOLDCAR-T cells. Further preclinical studies are underway to ready GOLDCAR T cells for clinical trials.



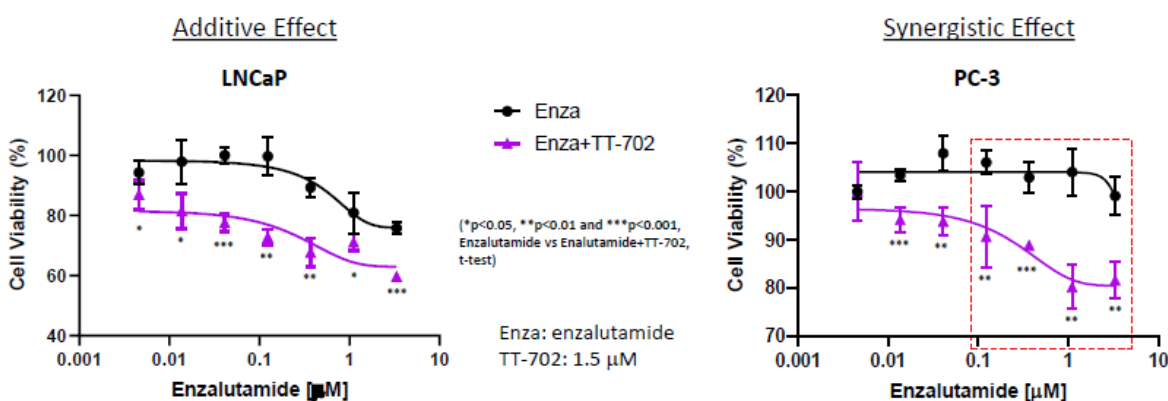
Combining Adenosine Pathway Inhibitors with Immunotherapy Agents in Prostate Cancer

Peter Fan, PhD
Teon Therapeutics

- Adenosine is one of the four nucleotides used to make DNA and RNA. However, adenosine can also act as a signal to relay certain environmental stresses to cells, and high levels promote immune suppression, cancer cell proliferation, and blood vessel growth.
- Adenosine levels are often highly increased in the tumor microenvironment, where they activate signals that support tumor growth and promote immune suppression. Blocking these adenosine-mediated activities may be beneficial in patients with cancer.

- Adenosine levels are sensed by adenosine receptors on the cell surface, including A_{2B}R.
- Dr. Peter Fan discussed the development of A_{2B}R-targeting agents as a new therapeutic approach to improve anti-tumor immunity and reduce tumor progression.
- TT-702 is an inhibitor of A_{2B}R that is being studied as a potential new cancer therapy.
- Dendritic cells are a type of immune cells that act as sentinels for detecting danger signals and activating T cells. In preclinical studies, TT-702 blocked inhibitory signals from adenosine analogs in dendritic cells, and promoted their maturation and activation.
- Preladenant is a previously studied inhibitor of a different adenosine receptor, A_{2A}R. Preladenant was compared with TT-702 in these assays, and was ineffective at rescuing dendritic cell responses from being blocked by high adenosine levels.
- Treatment with TT-702 caused prostate cancer cell death in laboratory assays, while preladenant had no effect. TT-702 also synergized with enzalutamide in causing prostate cancer cell death (**Figure**).
- In preclinical animal studies, TT-702 slowed the growth of colon cancer and melanoma in mice and strongly synergized with anti-PD1 immunotherapy.
- Evaluation of tumors from these mice showed that TT-702 treatment significantly increased the number of T cells and dendritic cells infiltrating tumors, but reduced the numbers of immune-suppressive cell types (myeloid derived suppressor cells and regulatory T cells) in tumors.
- TT-702 treatment also reduced the growth of new blood vessels within these tumors, an effect which would prevent tumors from receiving enough oxygen and nutrients needed for their continued growth.
- Together, these data provide preclinical evidence that the adenosine receptor-inhibitor TT-702 is able to prevent growth of multiple tumor types by improving anti-tumor immunity, reducing cancer cell growth, and reducing tumor blood vessel formation. TT-702 may have promise as a new cancer treatment alone or in combination with immunotherapy or other treatments.
- A Phase 1 clinical trial testing the safety and efficacy of TT-702 in multiple cancer types, alone and in combination with anti-PD1 immunotherapy or hormonal therapy, is being initiated in the United Kingdom, led by Dr. Johann de Bono.

TT-702 Enhances the Effect of Enzalutamide to Inhibit Human Prostate Cancer Cell Growth



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Mobilizing the Immune System with Bispecific Antibodies and Optimized Cytokines

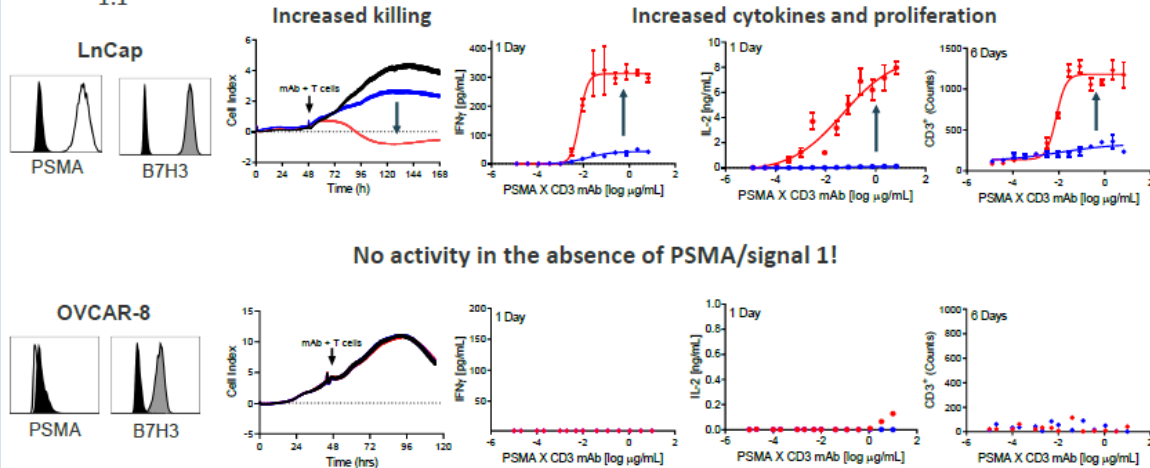
John Desjarlais, PhD
Xencor

- T cells are a type of immune cell with the powerful ability to recognize and kill tumor cells. T cell-based cancer immunotherapies can be highly effective and even curative, but have yet to be optimized in prostate cancer.
- T cell activation requires three signals: antigen recognition (signal 1), a co-stimulatory signal (signal 2), and signals from cytokines, which are secreted immune communication proteins (signal 3). On the other hand, T cell activation can be inhibited by immune-suppressive signals, such as PD1 or CTLA4.
- Bispecific antibodies are a treatment approach in which single antibody molecules are engineered to recognize two targets simultaneously. These could be a T cell + tumor target to bring T cells to tumor cells, or two T cell targets to optimally activate T cells.
- XmAb717 (vudalimab) is an experimental bispecific antibody treatment that activates T cells by blocking the suppressive signals PD1 and CTLA4. In a Phase 1 clinical trial, vudalimab had activity against multiple cancer types including prostate cancer; in this trial, 4 of 9 patients with castration-resistant prostate cancer (CRPC) experienced PSA reductions or partial tumor regression on scans. Based on these promising data, a Phase 2 trial in metastatic CRPC was initiated.

- XmAb808 is a bispecific antibody that targets CD28 (a co-stimulatory signal for T cells) and B7-H3, a target which is highly expressed on multiple tumor types including most prostate cancers. This treatment is designed to enhance the ability of T cells to recognize tumor cells and kill them.
- In preclinical experiments studying the ability of T cells to kill prostate cancer cells, addition of a bispecific antibody that targets the prostate cancer antigen PSMA and the T cell activation protein CD3 (PSMA x CD3), enabled moderate T cell activation and prostate cancer cell killing (**Figure**). Then, when XmAb808 (B7-H3 x CD28) combined with PSMA x CD3, T cell activation and prostate cancer cell killing were significantly increased (**Figure**). In contrast, T cells under these conditions were unable to kill cells that did not express PSMA, demonstrating tumor-specific killing and suggesting safety of this treatment approach (**Figure**).
- In mouse tumor models, similar results were seen: treatment with a bispecific antibody targeting CD3 + a tumor associated antigen (TAA x CD3) had little effect alone, but T cell activation and anti-tumor activity were significantly increased with the addition of XmAb808.
- These results suggest that XmAb808 should be explored in clinical trials for the treatment of prostate cancer and other malignancies.
- Treatments that provide cytokine signaling (signal 3) to activate T cells are also under development.
- XmAb306 is an engineered protein that provides the T cell activating cytokine IL-15, a highly potent molecule that induces high toxicities when dosed in its natural form. XmAb306 is ~100-fold less potent than normal IL-15, which potentially increases its safety and stability, and actually induces more prolonged activation of T cells and natural killer (NK) cells, another immune cell type that can kill tumor cells. A Phase 1 trial testing the safety of XmAb306 alone and in combination with atezolizumab immunotherapy is underway.
- IL-12 is another important immune cell activating cytokine. XmAb662 is an engineered version of IL-12 that is ~100-fold less potent than normal IL-12. XmAb662 was highly active in humanized mouse tumor models alone, and had synergistic activity in combination with anti-PD1 immunotherapy. XmAb662 also demonstrated promising safety and pharmacokinetic properties in preclinical non-human primate models, suggesting that XmAb662 should be explored in clinical trials.
- Altogether, multiple promising cancer immunotherapy approaches are under development, which may have improved efficacy with reduced toxicity. Studies like these are particularly important for patients with prostate cancer, as immunotherapy remains to be optimized for them.

B7H3 x CD28 enhances PSMA x CD3 activity

Effector : Target 1:1 ● PBS ◆ PSMA x CD3 ● 1 $\mu\text{g/mL}$ B7H3 x CD28 + PSMA x CD3

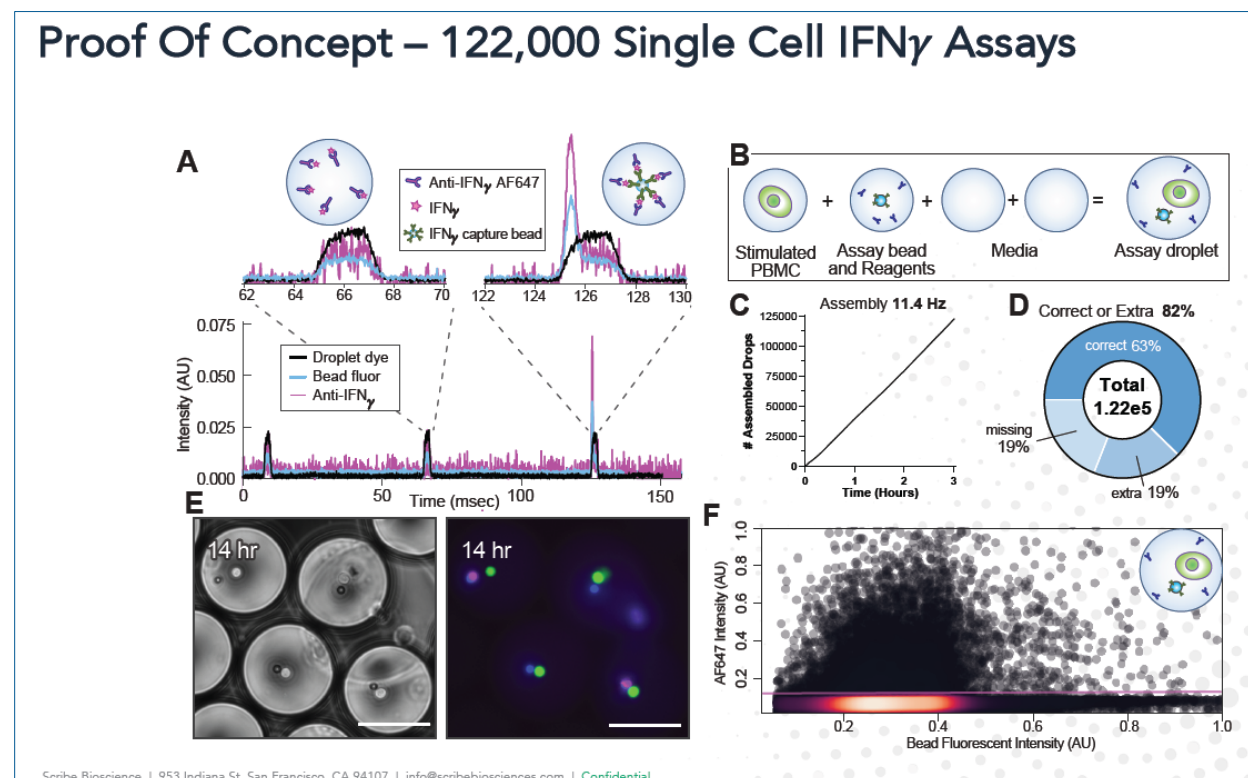


Microenvironment on Demand (MOD) - A Flexible Droplet-Microfluidic Platform to Accelerate Cell/Antibody Therapy Discoveries

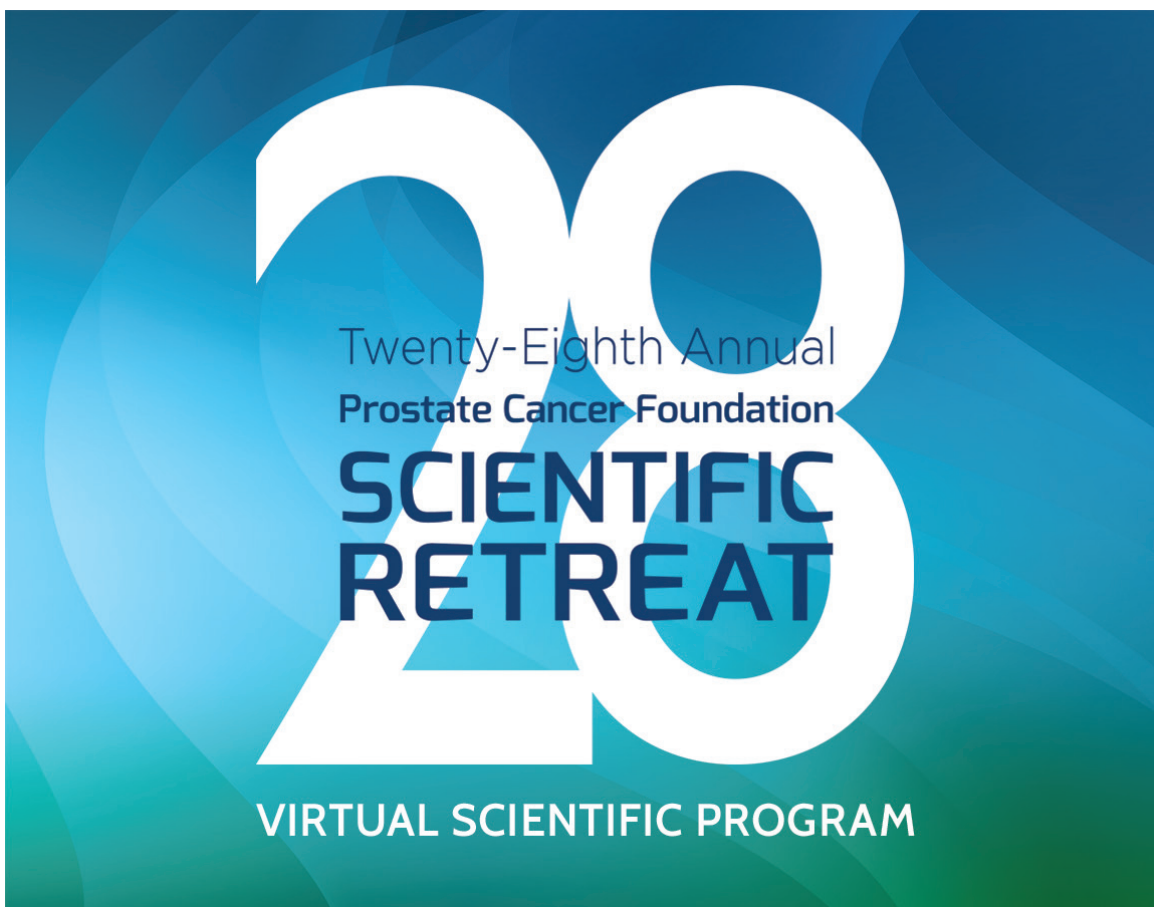
Maithreyan Srinivasan, PhD
Scribe Biosciences

- Immune cells, particularly T cells, have the capacity to recognize, target and kill pathogen-infected cells and tumor cells. Better understandings of the molecular interactions between immune cells and tumor cells would accelerate the development of improved tumor immunotherapies.
- New immunotherapy strategies are especially important for prostate cancer, for which such treatments have yet to be optimized.
- Dr. Maithreyan Srinivasan discussed the development of a new technology, “Microenvironment on Demand” (MOD) that enables rapid and single-cell studies of tumor cells, anti-tumor T cells, and other cell types found in patient tumors. Such studies typically take 2-3 months using standard methods to be completed, but with this technology can be completed in about 5 days.
- The MOD instrument uses an intricate combination of microfluidics channels, lasers, and electrodes to sort single cells into individual droplets that can be studied alone or combined with droplets of other individual cell types to study cell-cell interactions, such as the interactions between a tumor cell and a T cell. Assay reagents can be added in droplets to the cell-containing droplets. Various assays, such as the evaluation of gene expression, can then be performed on the cell droplets.

- In a proof-of-concept study, the MOD instrument was able to measure levels of IFN γ produced by ~122,000 individual T cells (**Figure**). IFN γ is an immune communication protein produced by activated immune cells that functions to activate other immune cells.
- In another proof-of-concept study, the instrument combined single lymphoma-targeted CAR T cells and lymphoma cells into droplets, and then evaluated IFN γ production in CAR T cells. In this study, 55% of sorted droplets contained the proper combination of cells, while only 3% of the “waste” contained IFN γ -producing CAR T cells. This indicates that the vast majority of desired droplets are being captured properly by the instrument.
- The ability to perform single-cell RNA sequencing in the workflow is currently being added to the instrument.
- This will enable researchers to perform many types of studies, such as sequencing T cell receptor (TCR) genes from individual tumor-targeting T cells. Each T cell has a unique TCR gene that gives it the ability to detect its target antigen. Knowing the sequence of tumor-targeting TCR genes could enable identification of tumor antigens and contribute to the development of novel immunotherapy approaches.
- Altogether MOD is a flexible platform that combines several different technologies into a single instrument to rapidly perform single-cell level studies of cell biology and gene expression, and study interactions between two or more types of different individual cells. This platform has the potential to greatly enhance research on tumor-immune cell interactions.



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APPENDIX I:

28th ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT



Prostate Cancer Foundation
Women in Science Forum

OCTOBER 21, 2021

PROGRAM AGENDA

Times subject to small changes based on the final event production



PCF Women in Science Forum

Thursday, October 21, 2021

***All times in U.S. PDT**

Organizers: **Himisha Beltran, MD** (Harvard: Dana-Farber Cancer Institute), **Lorelei Mucci, ScD** (Harvard T.H. Chan School of Public Health), **Karen Knudsen, MBA, PhD** (American Cancer Society), **Amina Zoubeidi, PhD** (Vancouver Prostate Centre), **Ayesha Shafi, PhD** (Center for Prostate Disease Research (CPDR); USU Walter Reed Surgery), **Sarah Amend, PhD** (Johns Hopkins University), **Susan Halabi, PhD** (Duke University), **Claire Fletcher, PhD** (Imperial College London), **Salma Kaochar, PhD** (Baylor College of Medicine), **Andrea Miyahira, PhD** (Prostate Cancer Foundation), **Howard Soule, PhD** (Prostate Cancer Foundation).

Overview: This is a half-day networking event in support of women in science in conjunction with the 28th Annual PCF Scientific Retreat. This sixth annual event is open to all individuals attending the PCF Scientific Retreat, both junior and senior and regardless of gender across all disciplines of science and people interested in this topic. The goals are to build teams and solve scientific problems through dialogue and social events. This will ensure a strong pipeline of women prostate cancer researchers, and will identify opportunities for further training, mentoring and synergy of a stellar network of women in science.

Welcome, Introductions and Vision

7:00 AM – 7:05 AM

Sarah Amend, PhD
Johns Hopkins University
Salma Kaochar, PhD
Baylor College of Medicine

Session 1: Keynote: Personal Perspectives on Women in Research & Academic Leadership

7:05 AM – 8:05 AM

Introduction by Karen Knudsen, MBA, PhD (American Cancer Society)

Vivian Pinn, MD
Senior Scientist Emerita, Fogarty International Center, NIH
Former Director (Retired), Office of Research on Women's Health, NIH

Live Question and Answer
Moderated by Karen Knudsen, MBA, PhD

8:05 AM – 8:20 AM ***BREAK, Please Return to the Virtual Lobby to Join the Next Session***

Times subject to small changes based on the final event production



Session 2: Panel: Celebration of Achievements of Women in Prostate Cancer Oncology and Research

8:20 AM – 10:00 AM

Moderators: Karen Knudsen, MBA, PhD

American Cancer Society

Dana Rathkopf, MD

Memorial Sloan Kettering Cancer Center

Panelists: Remi Adelaiye-Ogala, PhD

University at Buffalo

Elena Castro, MD

Spanish National Cancer Research Centre (CNIO)

Tanya Dorff, MD

City of Hope

Isla Garraway, MD, PhD

University of California, Los Angeles; VA Greater Los Angeles Healthcare System

Beatrice Knudsen, MD, PhD

University of Utah

Natasha Kyprianou, PhD, MBBS

Icahn School of Medicine at Mount Sinai Hospital

Ayesha Shafi, PhD

Center for Prostate Disease Research (CPDR); USU Walter Reed Surgery

Panel Discussion followed by Live Question and Answer

10:00 AM – 10:15 AM **BREAK, Please Return to the Virtual Lobby to Join the Next Session**

Session 3: Panel: High School Students in Research and Mentoring

10:15 AM - 11:00 AM

Moderator: Elisabeth Heath, MD

Karmanos Cancer Institute, Wayne State University

Panelists: Lorelei Mucci, ScD

Harvard T.H. Chan School of Public Health

Amina Zubeidi, PhD

Vancouver Prostate Centre

Precious Amuwha

FocuSStem NextGen Program at the Karmanos Cancer Institute

Tiffany Dang

Boston Latin High School; Dana-Farber/Harvard Cancer Center CURE Program

Ishana Lodhia

Microbiology & Immunology, University of British Columbia

Panel Discussion followed by Live Question and Answer

Times subject to small changes based on the final event production



11:00 AM – 11:15 AM ***BREAK, Please Return to the Virtual Lobby to Join the Next Session***

Session 4: Panel: Honest Discussion: Challenges That We don't Talk About

11:15 AM – 12:10 PM

Moderators: Susan Halabi, PhD

Duke University

Eileen Parkes, MD, PhD

University of Oxford

Panelists: Claire Fletcher, PhD

Imperial College London

Janielle Maynard, PhD

The Johns Hopkins University School of Medicine

Kimiko Krieger, PhD

Baylor College of Medicine

Susan Slovin, MD, PhD

Memorial Sloan Kettering Cancer Center

Panel Discussion followed by Live Question and Answer

Session 5: Closing Remarks and Introduction to Breakout Networking Session

12:10 PM – 12:15 PM

Himisha Beltran, MD

Harvard: Dana-Farber Cancer Institute

Andrea Miyahira, PhD

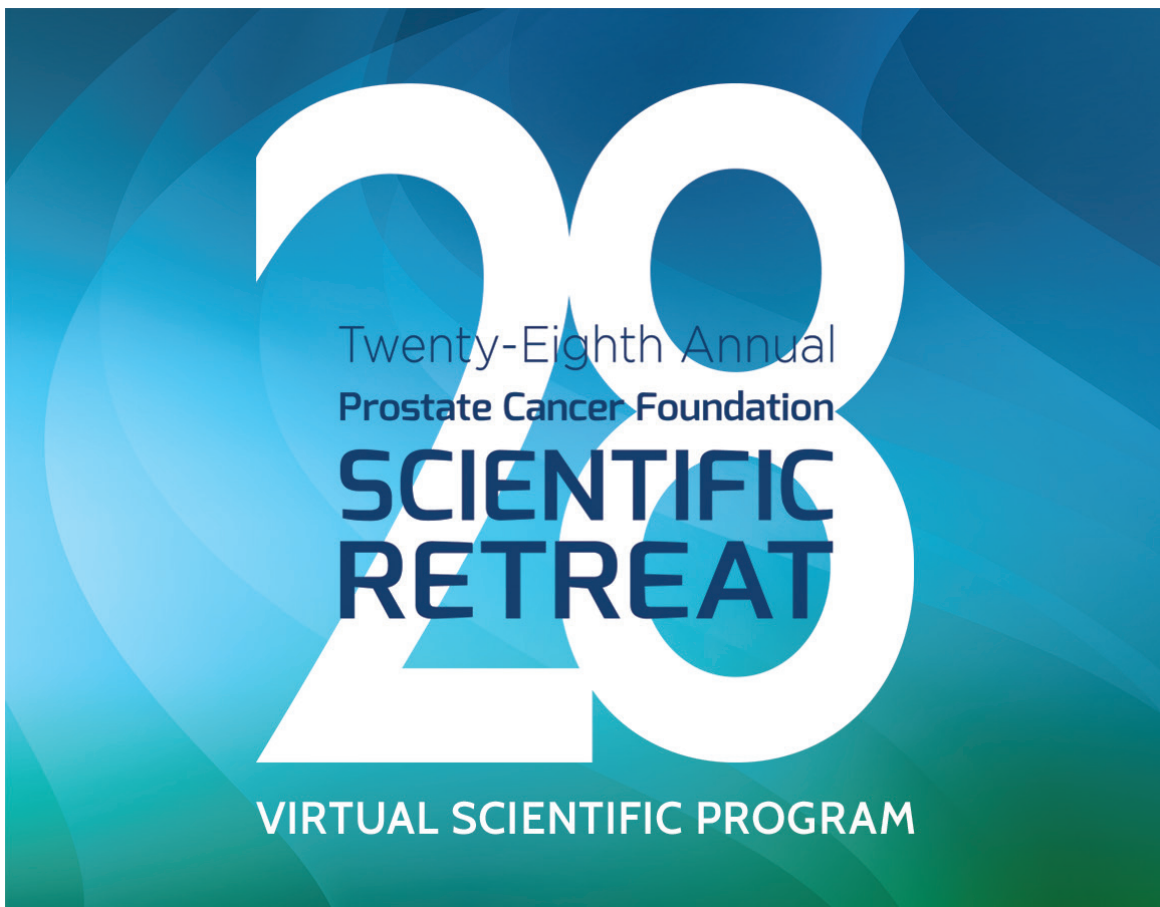
Prostate Cancer Foundation

12:15 PM – 12:30 PM ***BREAK, Please Return to the Virtual Lobby to Enter Breakout Networking Rooms***

Session 6: Breakout Networking Session: Conversations on Opportunities and Challenges for Women in Science

12:30 PM – 2:00 PM

**** Meeting Adjourned ****



APPENDIX II:

28th ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT



Prostate Cancer Foundation
Young Investigator Forum

OCTOBER 22, 2021

PROGRAM AGENDA



AGENDA

YOUNG INVESTIGATOR FORUM

Friday, October 22, 2021

*All times in U.S. PDT

Session 1: Welcome & Introduction

7:00 AM - 7:15 AM

Howard Soule, PhD

Prostate Cancer Foundation

Andrea Miyahira, PhD

Prostate Cancer Foundation

Session 2: Things I Learned During My Scientific Journey

7:15 AM - 8:00 AM

Amina Zubeidi, PhD

Vancouver Prostate Centre

Introduced by Howard Soule, PhD

Prostate Cancer Foundation

Live Question & Answer

Moderators: *Howard Soule, PhD & Andrea Miyahira, PhD*

8:00 AM - 8:15 AM ***BREAK, Please Return to the Virtual Lobby to Join the Next Session***

Session 3: Panel: Science Careers in the Age of the Pandemic and Zoom

8:15 AM - 9:30 AM

Moderators: Howard Soule, PhD

Prostate Cancer Foundation

Andrea Miyahira, PhD

Prostate Cancer Foundation



Panelists: **Leigh Ellis, PhD**
Cedars-Sinai Medical Center
Jessica Hawley, MD
University of Washington; Fred Hutchinson Cancer Research Center
Vasanthi Viswanathan, PhD
Kojin Therapeutics
Vivek Arora, MD
Bristol Myers Squibb
David Takeda, MD, PhD
National Cancer Institute, NIH

Live Question & Answer

9:30 AM - 9:45 AM ***BREAK, Please Return to the Virtual Lobby to Join the Next Session***

Session 4: Panel: Where Do Clinical Trials Come From?

9:45 AM - 10:45 AM

Moderator: **Atish Choudhury, MD, PhD**
Dana Farber Cancer Institute

Panelists: **Maha Hussain, MD**
Northwestern University
S. Percy Ivy, MD
Cancer Therapy Evaluation Program (CTEP), National Cancer Institute
Bin Liu, PhD
University of California, San Francisco
Alexander Wyatt, PhD
Vancouver Prostate Centre
Margaret K. Yu, MD
Janssen R & D. LLC.

Live Question & Answer

10:45 AM - 11:00 AM ***BREAK, Please Return to the Virtual Lobby to Join the Next Session***



Session 5: Update on the PCF-ONE Virtual Mentoring Initiative

11:00 AM - 11:15 AM

Ayesha Shafi, PhD

Center for Prostate Disease Research (CPDR); USU Walter Reed Surgery

Sarah Amend, PhD

Johns Hopkins University

Introduced by Andrea Miyahira, PhD

Prostate Cancer Foundation

Live Question and Answer

Moderators: *Howard Soule, PhD & Andrea Miyahira, PhD*

Session 6: Closing Remarks and Introduction to Speed Networking Session

11:15 AM – 11:30 AM

Howard Soule, PhD

Prostate Cancer Foundation

Andrea Miyahira, PhD

Prostate Cancer Foundation

11:30 AM - 11:45 AM ***BREAK, Please Return to the Virtual Lobby to Enter Speed Networking Room***

Session 7: PCF Young Investigator Virtual Speed Networking

11:45 AM - 1:00 PM

This session is open to 2015-2021 PCF Young Investigators and special guests. RSVP is required.

The purpose of the 'speed networking session' is to foster a sense of community between young investigators. This a great opportunity for you to get to know your fellow researchers in a relaxed and informal setting. We hope that your discussions will spark some exciting ideas and collaborations!

11:45 AM – 12:10 PM **Speed Networking Session # 1**

12:10 PM - 12:35 PM **Speed Networking Session # 2**

12:35 PM - 1:00 PM **Speed Networking Session # 3**

**** Meeting Adjourned ****



Program Committee:

Program Committee Co-Chair: Howard Soule, PhD (Prostate Cancer Foundation)

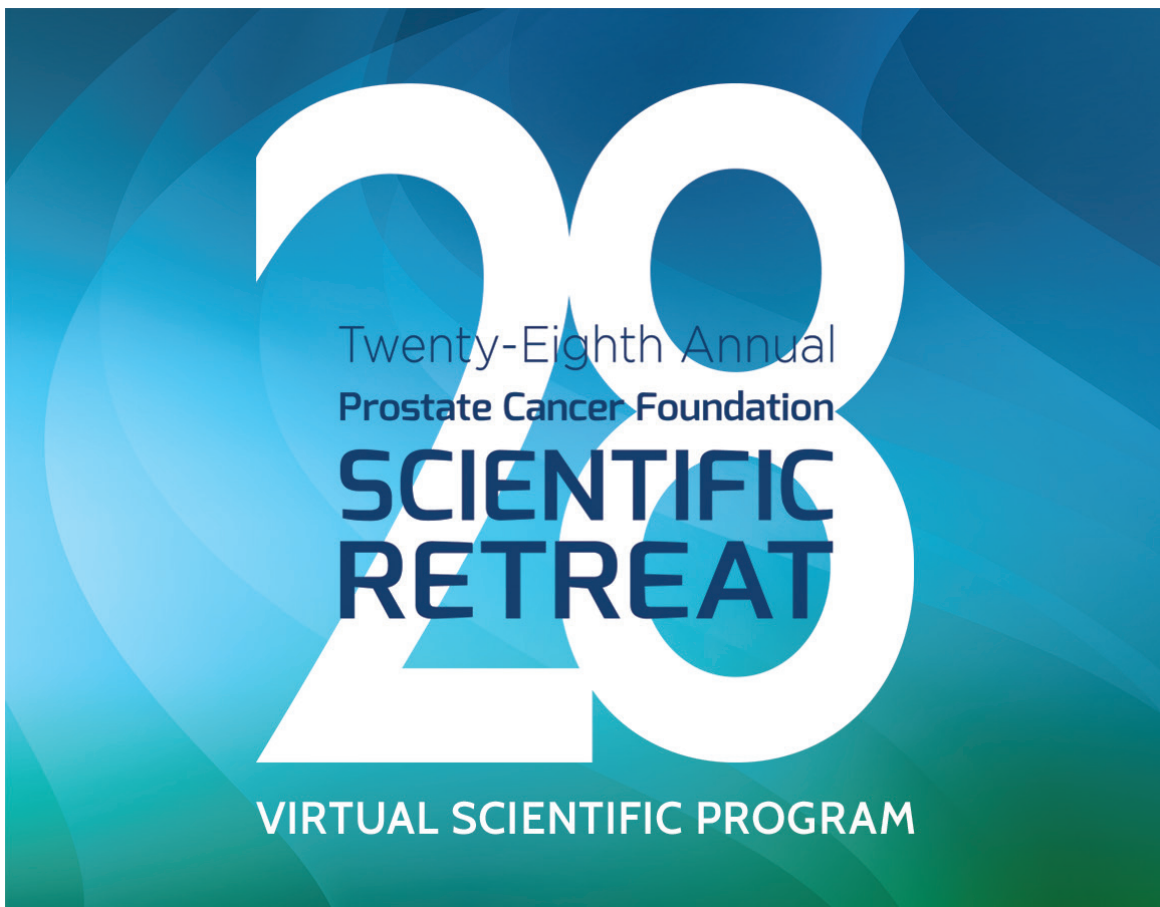
Program Committee Co-Chair: Andrea Miyahira, PhD (Prostate Cancer Foundation)

Atish Choudhury, MD, PhD (Dana Farber Cancer Institute)

Sarah Amend, PhD (Johns Hopkins University)

Ayesha Shafi, PhD (Center for Prostate Disease Research (CPDR); USU Walter Reed Surgery)

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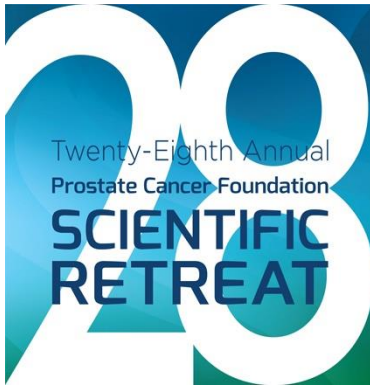
APPENDIX III:

28th ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT

OCTOBER 28-29, 2021

NOVEMBER 4-5, 2021

PROGRAM AGENDA



AGENDA

Thursday, October 28, 2021
***All times in U.S. PDT**

VIRTUAL POSTER SESSION

Starting on Thursday October 28, 2021, 12:01 AM U.S. PDT

GENERAL SESSIONS

Welcome & Opening Remarks

7:00 AM - 7:04 AM

Howard Soule, PhD
Prostate Cancer Foundation

Session 1: Dr. Andrew Hruszkewycz Memorial Session on Measuring and Targeting Lineage Plasticity to Prevent Lethal Prostate Cancer

7:04 AM - 8:30 AM

Moderator: Andrew Armstrong, MD, ScM
Duke University

A Tale of Two Evasions: Lineage Plasticity and Tumor Heterogeneity

Ping Mu, PhD
UT Southwestern Medical Center at Dallas

Measuring CRPC Cellular Heterogeneity at the Single Cell Level to Inform Treatment Strategies

Eliezer Van Allen, MD, PhD
Harvard: Dana-Farber Cancer Institute

Measuring Lineage Plasticity and Heterogeneity in mCRPC with Liquid Biopsies to Inform Treatment

Andrew Armstrong, MD, ScM
Duke University

Thursday, October 28, 2021

Targeting Transformed Neuroendocrine Cells to Overcome Treatment Resistance

Amina Zoubeidi, PhD

Vancouver Prostate Centre, Canada

Followed by Live Session Discussion

8:30 AM - 8:45 AM ***BREAK, Please Return to the Virtual Lobby to Join the Next Session***

Session 2: Therapeutic Degradors as a New Class of Prostate Cancer Treatments

8:45 AM - 9:25 AM

Moderator: Howard Soule, PhD

Prostate Cancer Foundation

Targeting Enhancer Addiction in Prostate Cancer by Impeding Chromatin Accessibility

Arul M. Chinnaiyan, MD, PhD

University of Michigan, Michigan Center for Translational Pathology

Clinical Development of ARV-110, a Novel AR Degradar, in Prostate Cancer

Debbie Chirnomas, MD, MPH

Arvinas, Inc.

Followed by Live Session Discussion

9:25 AM - 9:40 AM ***BREAK, Please Return to the Virtual Lobby to Join the Next Session***

Session 3: PSMA Theranostics: The New Age of Prostate Cancer Imaging and Treatment

9:40 AM - 12:00 PM

Moderator: Michael Hofman, MBBS

Peter MacCallum Cancer Centre; Prostate Cancer Theranostics and Imaging Centre of Excellence (ProSTIC), Australia

LuPSMA: The Newest Treatment Class for Advanced Prostate Cancer

Michael Hofman, MBBS

Peter MacCallum Cancer Centre; Prostate Cancer Theranostics and Imaging Centre of Excellence (ProSTIC), Australia

Thursday, October 28, 2021

Results from the PRINCE Trial: Testing the Combination of LuPSMA with Pembrolizumab in mCRPC

Shahneen Sandhu, MBBS

Peter MacCallum Cancer Centre, Australia

Targeting Micro-Metastatic Disease with Auger or Alpha Emitters

Ana Kiess, MD, PhD

Johns Hopkins University

The Four Sisters of Terbium: PET & SPECT Imaging and Targeted Alpha- & Beta-Therapy

Cristina Müller, PhD, PD

Paul Scherrer Institute, Switzerland

aPROMISE: An Artificial Intelligence Platform to Assist in Standardizing the Detection, Localization and Quantification of Prostate Cancer in PYLARIFY PSMA Scans

Aseem Anand, PhD

Imaging-Oncology Biomarker, EXINI Diagnostics AB. Sweden (a wholly owned subsidiary of Lantheus Holdings)

Targeting Fibroblast Activation Protein-alpha (FAP) in Prostate Cancer: Is FAP the Next Theranostic Target after PSMA in Prostate Cancer?

Andy Simmons, PhD

Clovis Oncology

Insights & Future Predictions from 25 Years of PSMA Research

Neil Bander, MD

Weill Cornell Medical College

Followed by Live Session Discussion

12:00 PM - 12:15 PM *BREAK, Please Return to the Virtual Lobby to Join the Live Poster Discussion Session*

VIRTUAL POSTER SESSION 1

12:15 PM - 1:45 PM

**Come to the Poster Hall for Live Discussions
with Virtual Poster Session 1 Presenters**

PCF DOCTOR-PATIENT SUMMIT: Live from the Scientific Retreat

1:00 PM - 3:00 PM

END DAY

Friday, October 29, 2021

Session 4: Prostate Cancer Disparities

7:00 AM - 8:40 AM

Moderator: Kosj Yamoah, MD, PhD

Moffitt Cancer Center

***Overview on Prostate Cancer Disparities in African Americans:
Lessons from the VA Health System and VANDAAM Study***

Kosj Yamoah, MD, PhD

Moffitt Cancer Center

Isla Garraway, MD, PhD

University of California, Los Angeles; VA Greater Los Angeles Healthcare System

Epidemiologic Aspects of Prostate Cancer in Black Men and Men of African Ancestry

Lorelei Mucci, ScD

Harvard T.H. Chan School of Public Health

Disparities in Metastatic Prostate Cancer and Opportunities to Exploit Biology to Improve Outcomes

Franklin Huang MD, PhD

University of California, San Francisco

Evidence and Solutions in Access with Equitable Health Care as a Contributor to Prostate Cancer Disparities

Brandon Mahal, MD

University of Miami

The Importance of Clinical Trial Diversity & Lessons from the COVID-19 Vaccine Trial

Sandra Amaro, MBA

Pfizer

Followed by Live Session Discussion

8:40 AM - 8:55 AM

BREAK, Please Return to the Virtual Lobby to Join the Next Session

Friday, October 29, 2021

Session 5: Prostate Cancer Survivorship

8:55 AM - 10:45 AM

Moderator: Alicia Morgans, MD, MPH

Harvard: Dana-Farber Cancer Institute

Prostate Cancer Survivorship: New Programs and Strategies

Alicia Morgans, MD, MPH

Harvard: Dana-Farber Cancer Institute

Updates and Preliminary Results from the PCF-SURECaP Survivorship Working Group Initiatives: COGCaP and ARACOG

Charles J. Ryan, MD

University of Minnesota; Prostate Cancer Foundation

Sleep Dysfunction and Prostate Cancer

Stacy Loeb, MD, MSc, PhD (Hon)

New York University; Manhattan Veterans Affairs Hospital

Utilization of an "Exercise is Medicine" Approach to Optimize Treatment and Health Outcomes among Prostate Cancer Survivors

Christina Dieli-Conwright, PhD, MPH

Harvard: Dana-Farber Cancer Institute

Prostate Cancer Survivorship at the VA: Leveraging Existing Veterans' Data to Improve Cardiovascular and Bone Health

Ravi Parikh, MD, MPP

University of Pennsylvania; The Corporal Michael J. Crescenz VA Medical Center

Patient Perspective - ADT, Exercise and QoL

Joël Pointon, MPH

Patient and Advocate

Followed by Live Session Discussion

Special Lecture: ADT and CV Risk: Why Relugolix?

10:45 AM - 11:05 AM

Neal Shore, MD

Carolina Urologic Research Center

GenesisCare, US

Introduced and Moderated by Howard Soule, PhD

Prostate Cancer Foundation

Followed by Live Discussion

Friday, October 29, 2021

11:05 AM - 11:20 AM ***BREAK, Please Return to the Virtual Lobby to Join the Next Session***

Session 6: Predicting Risk of Prostate Cancer with Polygenic Scores

11:20 AM - 12:20 PM

Moderator: Tyler Seibert, MD, PhD
University of California, San Diego

Genetic Risk Prediction for Prostate Cancer

Christopher Haiman, ScD
University of Southern California

Genetic Risk Stratification for Prostate Cancer: Genomics, Ancestry, and Disparities

Tyler Seibert, MD, PhD
University of California, San Diego

A Healthy Lifestyle in Men with a High Prostate Cancer Polygenic Risk Score

Anna Plym, PhD
Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health

Followed by Live Session Discussion

12:20 PM - 12:30 PM ***BREAK, Please Return to the Virtual Lobby to Join the Live Poster Discussion Session***

VIRTUAL POSTER SESSION 2

12:30 PM - 2:00 PM

**Come to the Poster Hall for Live Discussions
with Virtual Poster Session 2 Presenters**

END DAY

Thursday, November 4, 2021

Session 7: Next Generation Precision Medicine

7:00 AM - 8:10 AM

Moderator: Felix Feng, MD
University of California, San Francisco

A Multi-Omic Perspective on mCRPC

Felix Feng, MD
University of California, San Francisco

Using Genomics and Histopathology to Understand Therapeutic Responses in Prostate Cancer

Joel Greshock
Janssen Oncology

Lessons from Esophageal Cancer Genomics

Rebecca Fitzgerald, PhD
University of Cambridge, United Kingdom

Followed by Live Session Discussion

8:10 AM - 8:25 AM ***BREAK, Please Return to the Virtual Lobby to Join the Next Session***

PCF WOMEN IN SCIENCE AWARD LECTURE: Tumor Suppressors Reimagined: Converting Understanding of RB Action into Translational Potential

8:25 AM - 9:10 AM

Karen Knudsen, MBA, PhD
American Cancer Society

*Introduced and moderated by Andrea Miyahira, PhD and Howard Soule, PhD
Prostate Cancer Foundation*

Followed by Live Discussion

Thursday, November 4, 2021

KEYNOTE ADDRESS

9:10 AM - 10:10 AM

Michael Milken

Founder and Chairman
Prostate Cancer Foundation

*Introduced by Stuart Holden, MD
Prostate Cancer Foundation*

10:10 AM - 10:25 AM ***BREAK, Please Return to the Virtual Lobby to Join the Next Session***

SPECIAL LECTURE: Oncology: A Storied Past and Portentous Future

10:25 AM - 11:00 AM

Anna Barker, PhD

Lawrence J. Ellison Institute for Transformative Medicine of the University of
Southern California

*Introduced and moderated by Howard Soule, PhD
Prostate Cancer Foundation*

Followed by Live Discussion

SPECIAL LECTURE

11:00 AM - 11:40 AM

PCF 3.0: Serving the Science, the Scientist and the Patient

Charles J. Ryan, MD

Prostate Cancer Foundation

*Introduced and moderated by Howard Soule, PhD
Prostate Cancer Foundation*

Followed by Live Discussion

Thursday, November 4, 2021

Session 8: Glucocorticoid Receptor Biology in Castration Resistant Prostate Cancer

11:40 AM -12:40 PM

Moderator: Nima Sharifi, MD
Cleveland Clinic

Acquired Defects in Glucocorticoid Metabolism in Enzalutamide-Resistant Prostate Cancer

Nima Sharifi, MD
Cleveland Clinic

Targeting the Glucocorticoid Receptor Pathway in CRPC

Suzanne D. Conzen, MD
UT Southwestern Medical Center

Diverse Roles of the Androgen Receptor in Breast and Prostate Cancer

Wayne Tilley, PhD
University of Adelaide, Australia

Followed by Live Session Discussion

12:40 PM - 1:00 PM ***BREAK, Please Return to the Virtual Lobby to Join the Live Poster Discussion Session***

VIRTUAL POSTER SESSION 3

1:00 PM - 2:30 PM

**Come to the Poster Hall for Live Discussions
with Virtual Poster Session 3 Presenters**

END DAY

Friday, November 5, 2021

Session 9: Real World Evidence and Synthetic/Virtual Control Arms

7:00 AM - 8:00 AM

Moderator: Julie Lynch, PhD, RN, MBA

VINCI Precision Medicine, Salt Lake City VA & University of Utah

Opportunities and Pitfalls of Conducting Prostate Cancer Research using Big Data in the VA

Julie Lynch, PhD, RN, MBA

VINCI Precision Medicine, Salt Lake City VA & University of Utah

Analysis of the VA Prostate Cancer Data: A Valuable Resource that can now be Leveraged by Everyone

Tito Fojo, MD, PhD

Columbia University and the James J. Peters VAMC

Using Real World Evidence to Drive Stakeholder Decisions in Oncology

Michael Spencer, MSc

Janssen Oncology

Followed by Live Session Discussion

Special Lecture: Tumor Metabolism as a Driver and Treatment Target in Prostate Cancer

8:00 AM - 8:35 AM

Massimo Loda, MD

Weill Cornell Medicine

Introduced and moderated by Howard Soule, PhD

Prostate Cancer Foundation

Followed by Live Discussion

8:35 AM - 8:50 AM ***BREAK, Please Return to the Virtual Lobby to Join the Next Session***

Session 10: Widening the Aperture; New Approaches for Immunotherapy in Prostate Cancer

8:50 AM - 10:35 AM

Moderator: Amy Moran, PhD

Oregon Health & Science University

Friday, November 5, 2021

A T Cell Intrinsic Role for Androgen Receptor Signaling and Immunotherapy Resistance

Amy Moran, PhD

Oregon Health & Science University

Checkpoint Immunotherapy in mCRPC with CDK12-Loss

Ajjai Alva, MD

University of Michigan

MGC018, an Anti-B7-H3 Antibody-Drug Conjugate (ADC), in Patients With mCRPC: Preliminary Results of Phase 1 Cohort Expansion

Chet Bohac, PharmD, MD, MSc

MacroGenics, Inc.

Targeting DLL3 with a Bi-Specific T Cell Engager: AMG 757 in De Novo and Treatment-Emergent Small Cell Neuroendocrine Prostate Cancer

Rahul Aggarwal, MD

University of California, San Francisco

Advancing the Frontiers of T-Cell Redirecting Agents in Prostate Cancer

Oliver Sartor, MD

Tulane University

Followed by Live Session Discussion

10:35 AM - 10:50 AM ***BREAK, Please Return to the Virtual Lobby to Join the Next Session***

Session 11: Novel Technologies to Overcome the Suppressive Tumor Microenvironment

10:50 AM - 12:15 PM

Moderator: Marco Gottardis, PhD

Janssen Research & Development, LLC

Introduction

Marco Gottardis, PhD

Janssen Research & Development, LLC

Improving CAR Responses against Solid Tumors with Conditional Payload Delivery

Gus Zeiner, PhD

Chimera Bioengineering

Friday, November 5, 2021

Combining Adenosine Pathway Inhibitors with Immunotherapy Agents in Prostate Cancer

Peter Fan, PhD

Teon Therapeutics

Mobilizing the Immune System with Bispecific Antibodies and Optimized Cytokines

John Desjarlais, PhD

Xencor

Microenvironment on Demand (MOD) – A Flexible Droplet-Microfluidic Platform to Accelerate Cell/Antibody Therapy Discoveries

Maithreyan Srinivasan, PhD

Scribe Biosciences

Followed by Live Session Discussion

Closing Remarks

12:15 PM - 12:20 PM

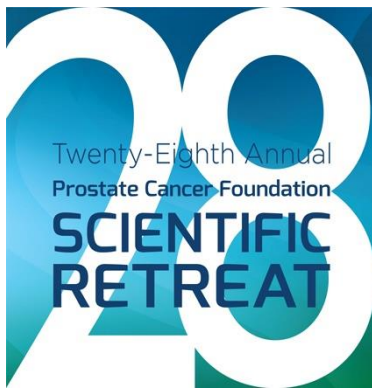
Howard Soule, PhD

Prostate Cancer Foundation

Andrea Miyahira, PhD

Prostate Cancer Foundation

Meeting Adjourned



Program Committee:

Program Committee Co-Chair: Howard Soule, PhD (Prostate Cancer Foundation)

Program Committee Co-Chair: Andrea Miyahira, PhD (Prostate Cancer Foundation)

Andrew Armstrong, MD, ScM (Duke University)

Paul Boutros, PhD (University of California, Los Angeles)

Marco Gottardis, PhD (Janssen Research & Development, LLC)

Michael Hofman, MBBS (Peter MacCallum Cancer Centre; Prostate Cancer Theranostics and Imaging Centre of Excellence (ProSTIC), Australia)

Alicia Morgans, MD, MPH (Harvard: Dana-Farber Cancer Institute)

Nima Sharifi, MD (Cleveland Clinic)

Kosj Yamoah, MD, PhD (Moffitt Cancer Center)

Times subject to small changes based on the final event production. All times in U.S. PDT.

We deeply thank our Retreat supporters for providing funding for this educational initiative.





Prostate Cancer
Foundation
Curing Together.

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