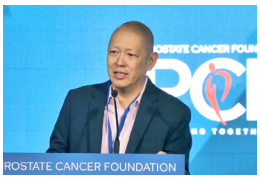
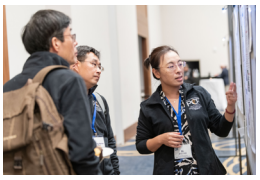
STATE of the SCIENCE REPORT



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Thirty-First Annual
Prostate Cancer Foundation
SCIENTIFIC RETREAT

Highlights from the 31st Annual PCF Scientific Retreat

October 24-26, 2024








Provided compliments of the
Prostate Cancer Foundation

PROSTATE CANCER FOUNDATION
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Introduction

The 31st Annual Prostate Cancer Foundation (PCF) Scientific Retreat was held at the Omni La Costa Resort in Carlsbad, CA on October 24–26, 2024. This annual conference brings together top scientists and clinicians specializing in prostate cancer research, along with experts from related fields who can offer valuable insights to advance the study of the disease. It provides a platform for attendees to showcase their latest findings, share ideas, and discuss emerging trends. The Retreat is attended by researchers from academia, industry, government, and non-profit organizations, as well as patients and advocates.

The Retreat takes place over two and a half days and includes scientific lectures, panel discussions, poster sessions, and other events. As a leading conference in prostate cancer research, the PCF Annual Scientific Retreat has been instrumental in enhancing scientific knowledge and accelerating the development of innovative treatments for prostate cancer.

The 31st Annual PCF Scientific Retreat featured the following:

- 62 Speakers in Plenary Session.
- 158 poster presentations.
- 31 different scientific disciplines related to prostate cancer research presented and discussed.
- 56% of speakers presented at a PCF Scientific Retreat for the first time.
- 639 individuals from 17 countries attended the Retreat, including 262 PhD, ScD, or DSc, 185 MD, MBBS, or DO, 109 MD/PhD, 23 PharmD, 13 MBA, and 18 MS.
- Retreat registrants included 426 academic researchers or health care professionals and 185 biopharmaceutical industry professionals.
- 117 academic institutions, 54 biopharmaceutical companies, and 9 medical research foundations.
- NIH, NCI, Dept. of Defense, and Veterans Affairs research leaders from over 10 organizations.
- Attendance by 210 PCF Young Investigators.
- Attendance by 28 PCF Board of Director members, major donors and special guests.
- The 9th Annual PCF Gender Equity Networking Initiative (GENI) Forum (formerly, PCF Women in Science Forum) was held with over 210 attendees, including 28 high school girls interested in STEM.

The Prostate Cancer Foundation (PCF) is the world's leading philanthropic organization dedicated to funding life-saving prostate cancer research. Founded in 1993 by Mike Milken, PCF has been responsible for raising more than $1 billion in support of cutting-edge research by more than 2,250 research projects at 245 leading

cancer centers, with a global footprint spanning 28 countries. Since PCF's inception, and through its efforts, patients around the world are living longer, suffering fewer complications, and enjoying better quality of life. PCF is committed to the mission of ending death and suffering from the disease. Learn more at pcf.org.

We thank the sponsors of the Retreat for their generous support: Bayer, Janssen Oncology, Daiichi Sankyo, Novartis, Pfizer, Regeneron, Amgen, Bristol-Meyers Squibb, Lantheus, AstraZeneca, Foundation Medicine, Royalty Pharma, Sun Pharma / SPARC, Astellas, Actinium Pharmaceuticals, Exelixis, Lilly, Merck, AdvanCell, Dendreon, Flare Therapeutics, Genentech, Convergent Therapeutics, Chevron, EcoR1 Capital, ESSA Pharmaceuticals, MacroGenics, Telix, BostonGene, Sumitomo Pharma, Abbvie, Belharra Therapeutics, and Oncternal Therapeutics.

The 2024 State of Science Report translates the key scientific insights shared at the Retreat into a format accessible to the general public. By widely sharing this knowledge, we aim to improve understanding of current prostate cancer research, encourage discussions, promote the exchange of ideas, inspire new research initiatives, and strengthen public support for science and research. Any questions about this report can be directed to Dr. Andrea Miyahira at amiyahira@pcf.org.

All of the presentations, panels, and discussions from the 31st Annual PCF Scientific Retreat, the 9th Annual PCF GENI Forum, and the PCF Young Investigator Forum, can be viewed here: https://www.pcf.org/31st-annual-scientific-retreat-video-replays/.

Yours sincerely,

Gina B. Carithers
President & Chief
Executive Officer

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

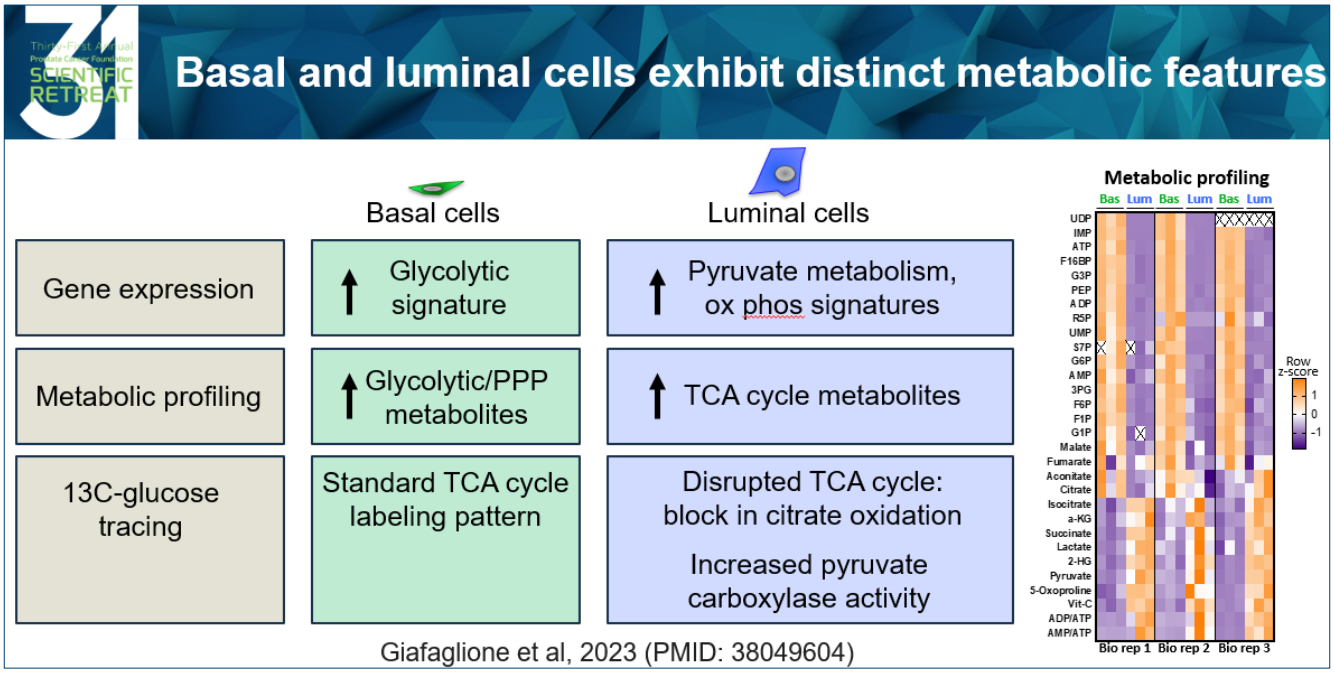
Andrea K. Miyahira, PhD
Senior Director, Global Research
& Scientific Communications

Session 1: Tumor Metabolism

Prostate Lineage-Specific Metabolism Governs Luminal Differentiation and Response to Antiandrogen Treatment

Andrew Goldstein
University of California, Los Angeles

- Dr. Andrew Goldstein discussed how lactate, often considered a metabolic waste product, is actually an important cell signaling molecule that regulates cancer phenotypes and behaviors.
- In the normal prostate, there are two main lineages of prostate cells - basal and luminal, which compose different regions of the prostate organ. In prostate cancer, these lineages are also observed, with luminal prostate cancer representing typical prostate adenocarcinoma which expresses and is driven by the androgen receptor (AR) and is more sensitive to hormone therapy, while basal-like prostate cancer is associated with low/no AR, aggressive phenotypes including neuroendocrine prostate cancer (NEPC), and resistance to hormone therapy.
- Dr. Goldstein's team investigated the role for metabolism in prostate lineage differentiation and prostate cancer response to therapy.
- Metabolic profiling of prostate cells revealed distinct metabolic preferences in these lineages, with basal cells exhibiting a glycolytic signature and standard TCA cycling, and luminal cells exhibiting a pyruvate and oxidative phosphorylation signature, and a disruption in the TCA cycle which blocks citrate oxidation **(Figure).**
- In the normal prostate, basal prostate cells are multipotent and differentiate into luminal cells. During basal to luminal differentiation, increases were observed in TCA cycle metabolites and pyruvate oxidation, with decreases in nucleotide metabolites. Blocking pyruvate oxidation interfered with luminal differentiation. Similar results were observed in prostate cancer cells.
- One byproduct of blocking pyruvate metabolism is the accumulation of lactate. Lactate accumulation can affect histone deacetylase activity and reprogram the chromatin landscape, particularly at lineage-specific genes. Increasing lactate concentrations blocked luminal differentiation. In prostate cancer cells, increasing lactate decreased sensitivity to AR-inhibition.
- These studies demonstrate that lactate accumulation can regulate lineage identity and therapy response in prostate cancer cells by altering histone acetylation and gene expression. Lactate is not just a waste product but a powerful regulator of cell fate. Understanding these complex metabolic systems is important for harnessing them for therapeutic benefit.

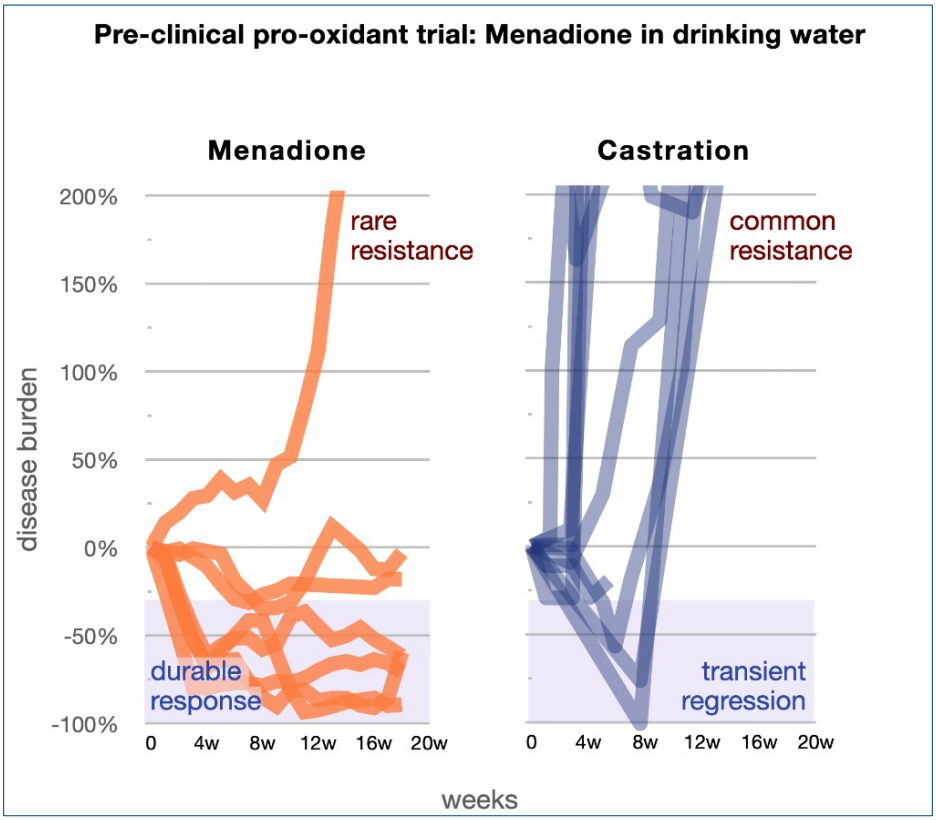


Dietary Target Therapy and Oxidative Death

Lloyd Trotman
Cold Spring Harbor Laboratory

- Dr. Lloyd Trotman discussed the impacts of antioxidants, pro-oxidants and diet on prostate cancer growth and therapy.
- The SELECT (Selenium and Vitamin E Cancer Prevention Trial) trial evaluated whether supplements of the classic antioxidants selenium or vitamin E, could decrease risk of prostate cancer in 35,000 men without prostate cancer. Paradoxically, it was found that these did not decrease the risk of prostate cancer, and that vitamin E supplements instead increased risk for prostate cancer by 17% compared with placebo, even in some men that had stopped taking it.
- These data suggest that antioxidants may increase the risk of prostate cancer, leading to questions about the impact of pro-oxidants.
- Dr. Trotman and team used mouse models genetically engineered to develop prostate cancer, to investigate the effects of a pro-oxidant, menadione (a precursor of vitamin K), in prostate cancer progression.
- Menadione supplementation (added to mouse drinking water) was found to induce a strong and durable anti-tumor response in the mouse model (**Figure**). This is unlike hormone therapy, which leads to a response, but is often followed by relapse with more aggressive disease.
- Further analysis revealed that menadione induces a new form of cell death, called "triaptosis," which is mediated by the oxidation of a specific kinase, VPS34, that is essential for endosome formation and sorting.

- These data suggest that dietary pro-oxidant therapy with menadione could be a viable approach for prostate cancer treatment, and that the VPS34 kinase could be a potential therapeutic target.
- Pre-clinical translational studies are underway to explore the potential of this approach in prostate cancer and fatal infant myopathy, as this approach also delayed fatal infant myopathy in preclinical models.



In Vivo Nutrient Tracing and Targeted Metabolic Vulnerabilities in Rare Cancers

Heather Christofk

University of California, Los Angeles

- Dr. Heather Christofk discussed an approach to identify and target metabolic vulnerabilities in rare cancers driven by mutations in metabolic enzymes.
- Certain metabolic enzymes like fumarate hydratase (FH) and succinate dehydrogenase (SDH) are tumor suppressor genes, and their loss leads to accumulation of oncometabolites like fumarate and succinate that can drive tumorigenesis.

- Dr. Christofk and team investigated whether the accumulation of these metabolites in FH-deficient tumors drives a fixed metabolic dependency that can be therapeutically targeted.
- They studied a genetic cancer condition called Hereditary Leiomyomatosis with Renal Cell Cancer (HLRCC), a lethal and currently untreatable form of kidney cancer, where patients inherit one bad copy of FH and lose the other, leading to fumarate accumulation and tumor formation.

- Hereditary FH gene variants are found in 1.3% of individuals on germline testing, approximately half of which are variants of unknown significance. It is critical to define the impact of FH variants of unknown significance, to properly identify individuals at risk of developing FH mutant-driven cancers. For example, a patient at UCLA with a family history of kidney cancer and a renal mass suspicious of kidney cancer, and was found upon germline testing to have an FH variant of unknown significance.
- Dr. Christofk's lab measured the enzymatic activity of 80 FH missense variants of unknown significance and found that nearly half were completely enzyme-dead (inactive), providing evidence of cancer pathogenicity.
- Metabolomic analysis showed that fumarate accumulation in FH-deficient HLRCC cells drives reversal of a key step in purine biosynthesis, leading to buildup of purine intermediates and a deficiency in purines needed for cell growth. FH-deficient HLRCC cells then become dependent on purine salvage pathways for attaining purines, and upregulate purine salvage pathway genes. This makes them sensitive to the purine salvage pathway inhibitor 6-mercaptopurine (6-MP).
- 6-MP treatment was shown to block the growth of HLRCC tumors in mouse models (**Figure**), suggesting a potential therapeutic approach for these patients.
- The lab is initiating a phase 1 trial to test 6-MP in HLRCC patients and exploring whether 6-MP or a low-purine diet could be a form of cancer prevention in people carrying hereditary FH mutations.

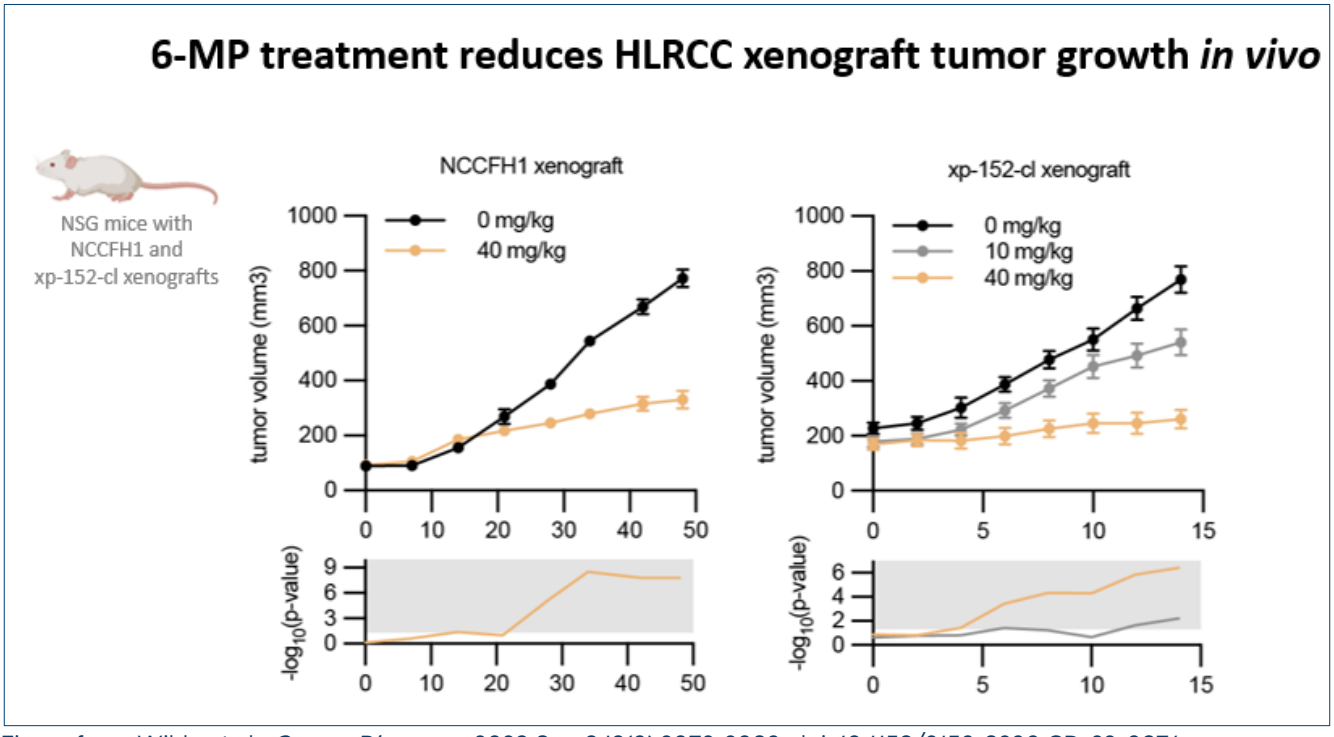


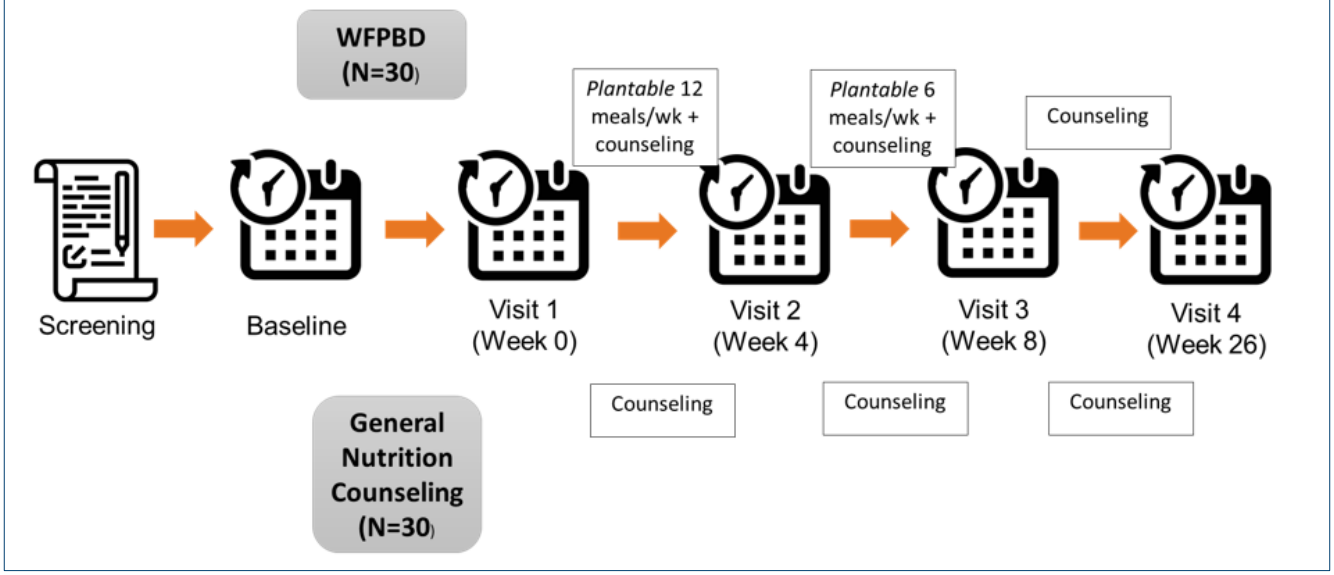
Figure from: Wilde et al., *Cancer Discovery.* 2023 Sep 6;13(9):2072-2089. doi: 10.1158/2159-8290.CD-22-0874.

Whole-Food Plant-Based Diet to Control Weight and Metabo-Inflammation in Overweight/Obese Men with Prostate Cancer Receiving ADT

David Nanus
Weill Cornell Medicine

- Dr. David Nanus discussed a clinical trial testing the potential for a whole-food plant-based diet (WFPBD) to improve weight and metabolic and inflammatory biomarkers in overweight/obese patients with prostate cancer undergoing androgen deprivation therapy (ADT).
- While it is unclear if obesity increases risk for prostate cancer, patients diagnosed with prostate cancer who are obese have increased risks for prostate cancer mortality, advanced disease, PSA recurrence, faster progression to castration resistance, and development of comorbidities.
- Prior trials have evaluated associations between obesity and prostate cancer outcomes. The PLCO screening trial found that higher BMI was associated with prostate cancer mortality, and that every 5 kg/m2 increase in BMI was associated with a ~20% increase in risk of PSA recurrence and prostate cancer mortality. Gaining weight after a prostate cancer diagnosis is associated with increased prostate cancer mortality. Obesity was also associated with mortality from prostate cancer, cardiovascular disease, and all causes among survivors of non-metastatic prostate cancer.
- The mechanisms that link obesity with prostate cancer include production of certain growth hormones by fat cells which drive oncogenic activities in prostate cancer cells.
- Unfortunately, ADT which is the primary prostate cancer systemic therapy, also causes side effects that impact metabolism and obesity. This includes weight gain by ~70% of patients, sarcopenic obesity (the loss of skeletal muscle and accumulation of body fat), and increases in total cholesterol, LDL, and triglycerides. ADT also alters the gastrointestinal microbiota, which can impact metabolism, immunity, and other factors to promote prostate cancer growth. Certain gut microbes can also produce androgens, which may fuel prostate cancer and limit the efficacy of ADT.
- Thus, overweight and obese patients on ADT need practical, sustainable interventions to promote weight loss, lower inflammation, improve cardiovascular health and metabolism, and shift the gut microbiome into a flora associated with healthier outcomes.
- Whole-food plant-based diets (WFPBD) have been associated with many of these desired outcomes including promoting weight loss, reducing metabolic and cardiovascular disorders, and impacting the gut microbiome.
- The CaPSURE study which followed over 2,000 men diagnosed with non-metastatic prostate cancer, found that plant-based diets were associated with lower risks of prostate cancer progression.
- A phase 2 clinical trial is underway, which is randomizing 60 patients with prostate cancer undergoing ADT to general nutritional counseling vs. home-delivered WFPBD meals plus intensive nutritional counseling (**Figure**). The trial is evaluating outcomes including weight loss, biomarkers of inflammation, metabolism, and quality of life, the durability of any effects, and the impact on metabolites and gut microbiota.
- 46 patients have been enrolled at the time of this presentation. In preliminary results, patients on both trial arms were observed to lose weight, with patients on the WFPBD arm experiencing significantly greater weight loss, and greater decreases in BMI and fat mass. Weight loss in most patients persisted at 6 months. Correlative studies, including microbiome analyses, are ongoing.
- These data provide promising indications that a WFPBD may improve health outcomes in patients with prostate cancer undergoing ADT.

Trial Schema

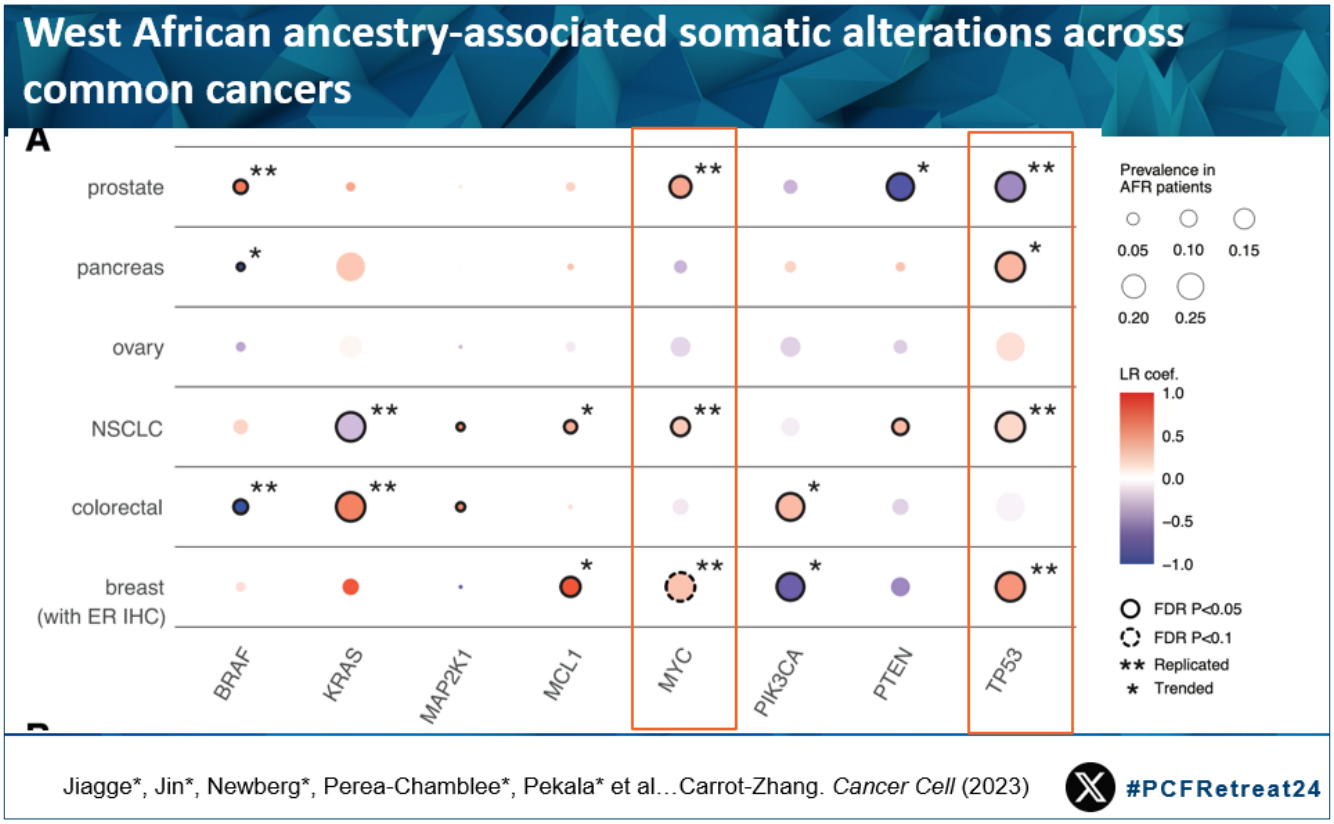


Session 2: Genomics of Prostate Cancer Racial Disparities

African-Ancestry Associated Genomic Differences in Cancer

Jian Carrot-Zhang
Memorial Sloan Kettering Cancer Center

- Dr. Jian Carrot-Zhang discussed the influence of genetic ancestry and germline-environment interactions on mutations that drive cancer, and how this impacts racial disparities in cancer outcomes.
- There is a significant underrepresentation of non-White patients with cancer in research and clinical studies. Black and Hispanic populations in the US are highly admixed, further necessitating better representation in genetic and genomic studies.
- To overcome this knowledge gap, Dr. Carrot-Zhang developed a method to use data from genomic sequencing of tumor samples to accurately identify patient ancestry and inherited cancer risk genes.
- Data from two large real-world tumor genomic sequencing studies from patients with a wide variety of cancers were evaluated to determine relationships between patient ancestry and cancer mutations. For instance, West African ancestry was associated with tumor mutations in the *MYC* oncogene in patients with breast, lung, and prostate cancer.
- Interactions between patients' ancestry, environmental exposures, and tumor mutations were evaluated in these datasets. Smoking was associated with *TP53* gene alterations among patients with West African ancestry, suggesting that in West African individuals, smoking increases risk of developing mutations in *TP53*, a key tumor suppressor gene.
- Among patients with lung cancer, clinically actionable tumor mutations were found to vary by ancestral group. Tumor driver mutations associated with various cancers also differed by ancestral group. For instance, *EGFR* gene mutations were more frequent in tumors from patients with Native American ancestry.
- Studies are being done to identify germline and environmental/socio-demographic modifiers that impact cancer outcomes in different ancestral populations, to understand the contributors to racial cancer disparities. While Black patients tend to have higher social deprivation index and lower insurance rates than White patients, these social factors could not fully explain the higher rates of prostate cancer mortality in Black patients, suggesting that biological or other social factors contribute to prostate cancer racial disparities.
- These studies demonstrate that genetic ancestry can be inferred from tumor genomic sequencing data and allows real-world data to be leveraged to study associations between ancestry, tumor mutations, and environmental/socio-demographic factors to better determine cancer etiologies in different populations and accelerate precision medicine for all.



The Interplay of Epigenome and Environmental Factors in Prostate Cancer Disparities

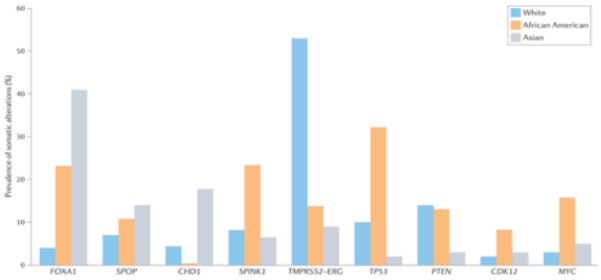
Bernard Kwabi-Addo

Howard University College of Medicine

- Dr. Bernard Kwabi-Addo discussed the interplay of epigenomic and environmental factors in addressing prostate cancer disparities, particularly between Black and White patients.
- Black men have a 1.7-fold higher risk of prostate cancer diagnosis and a 2.4-fold higher risk of prostate cancer mortality compared to White men. It is critical to understand the underlying causes of these disparities, so they can be addressed and overcome.
- Dr. Kwabi-Addo previously published a book "Health Outcomes in a Foreign Land: A Role for Epigenomic and Environmental Interaction," that discussed how various environmental and social determinants such as income, education, employment, and access to health care, may interact with biological variants such as genetics and epigenetics, to drive health disparities.
- Prostate cancer is a very heterogenous disease, with different molecular subtypes driven by different genomic alterations (**Figure**). Distinct genomic subtypes of prostate cancer have been observed across racial groups. For instance, Black men have higher frequencies of *SPOP* mutations, *FOXA1* mutations, *and MYC* amplification, while White men have higher frequencies of *TMPRSS2-ERG* fusions, *TP53* mutations, and *PTEN* deletions. These differences have important implications for developing and selecting optimal therapies for individual patients.

- Epigenetic changes, particularly DNA methylation, also differ between racial/ethnic groups and impact prostate cancer progression. DNA methylation is a gene regulatory mechanism that reduces expression of the methylated gene(s).
- DNA methylation patterns change with age, and DNA methylation biomarkers have been developed to estimate the biological age of individuals. Interestingly, individuals who live to be 100 had a slower rate of biological aging compared to non-centenarian individuals. These studies suggest that DNA methylation has an important role in aging and age-related diseases.
- A study evaluated methylation profiles in matched benign and prostate cancer regions from radical prostatectomy samples from White and Black patients. Increased DNA methylation (which reduces gene expression) of tumor suppressor genes were observed in prostate cancer vs. benign tissues. Higher frequencies of DNA methylation were also observed in prostate and breast cancer samples from Black compared to White patients, and patterns of certain genes correlated with poor outcome. In another study, significant differences were observed in the genomic locations of DNA methylation in prostate cancer from Black vs White patients. This suggests that differences in chromatin structure and differential regulation of gene expression may contribute to prostate cancer disparities.
- Treatment of prostate cancer cells with various sex steroid hormones, including androgens and estrogens, also impacted DNA methylation patterns. This suggests that the steroidal hormones that a growing fetus is exposed to could impact predisposition to diseases later in life including prostate cancer.
- Over 25 candidate differentially methylated genes were identified that significantly correlated with prostate tumor progression, particularly involving glucocorticoid receptor signaling and the tumor microenvironment.
- Together, these studies demonstrate that environmental factors like diet, stress, and sex steroid hormones can influence DNA epigenetic changes and contribute to prostate cancer disparities.
- Ongoing studies are examining the impact of lifestyle factors and geographic location on epigenetic changes and prostate cancer outcomes to better understand and address these persistent health disparities.

Race and prostate cancer subtypes: genomic/epigenomic landscape



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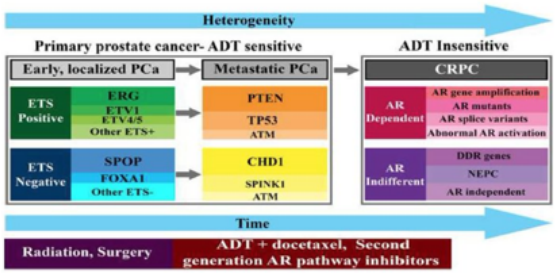

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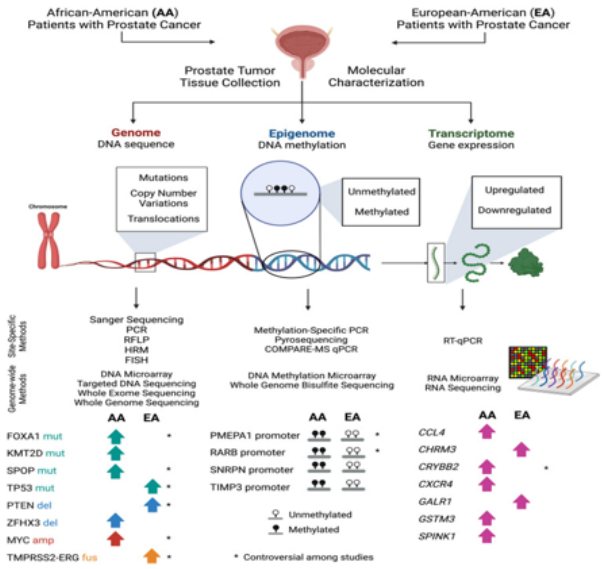

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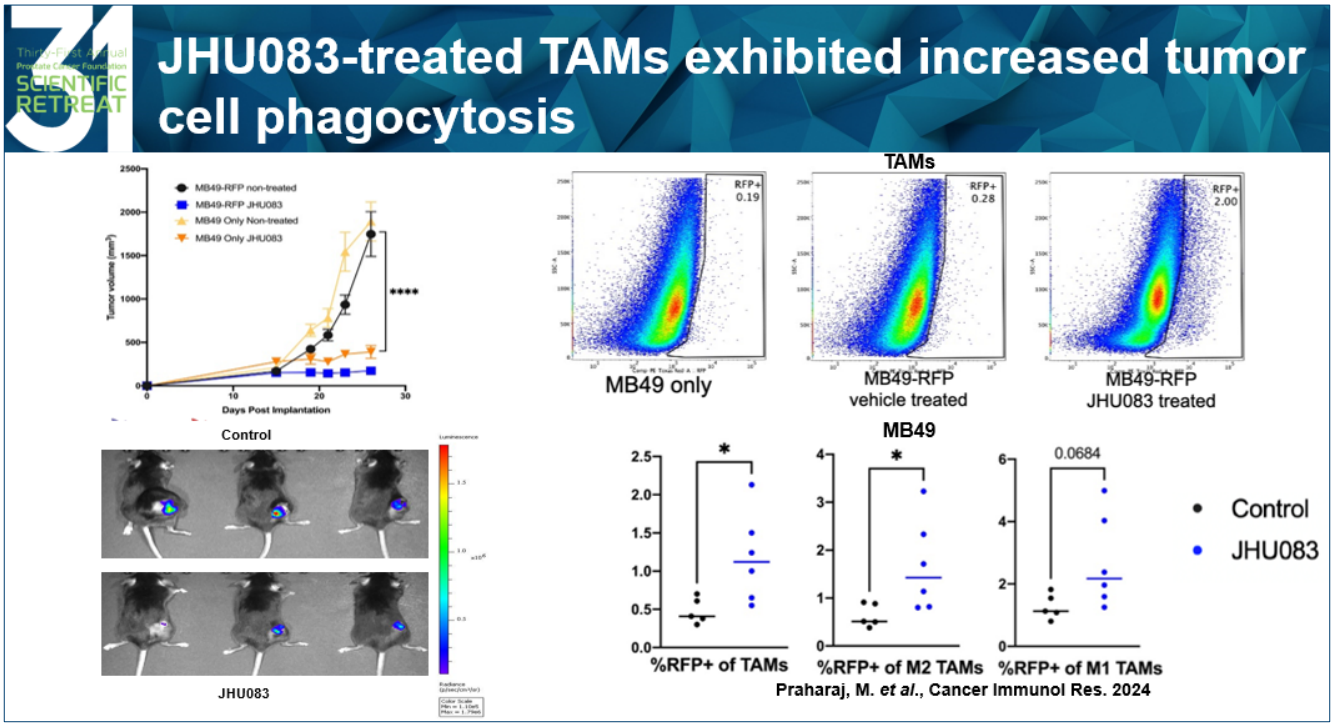
Session 3: The Tumor Immune Microenvironment: Reprogramming Macrophages

Metabolic Reprogramming of Tumor-associated Macrophages using Glutamine Antagonist JHU-083 Drives Tumor Immunity in Myeloid-Rich Prostate and Bladder Cancer Tumors

Jelani Zarif
Johns Hopkins University

- Dr. Jelani Zarif discussed the role of tumor-associated macrophages in prostate cancer and the potential to therapeutically target them by targeting their metabolism.
- Macrophages are a type of immune cell that plays key roles in innate immune responses and various normal physiological and pathological processes.
- Macrophages were thought to exist as two main subtypes: inflammatory/TH1 activated macrophages and wound healing/TH2 activated macrophages. However, at least 15 different subtypes with differing functions have been described.
- Tumor-associated macrophages (TAMs) are often found in increasing numbers in prostate cancer as it progresses, with highest numbers seen in advanced metastatic cases. TAMs are known to produce growth and immunosuppressive factors, aiding tumor growth.
- TAMs are uniquely dependent on the amino acid glutamine for their function and metabolism, suggesting that targeting glutamine may have therapeutic impact in prostate cancer.
- Researchers at Johns Hopkins developed a novel drug, JHU-083, which is a prodrug of the glutamine antagonist DON, which was previously tested in clinical trials and found to be too toxic. JHU-083 can be specifically activated in the tumor microenvironment by a TAM-associated enzyme, reducing its effects on other tissues to minimize toxicity.
- JHU-083 treatment was able to metabolically reprogram TAMs, shifting them from a glutamine-dependent to a more glycolytic phenotype.
- JHU-083 treatment led to reduced tumor growth in various mouse models of prostate and bladder cancer, increased phagocytic ability of TAMs, allowing them to engulf and clear tumor cells, and enhanced antitumor immune responses, including increased TNF-α production, MHC class II expression, and activation of CD8+ T cells and natural killer cells (**Figure**).
- The findings demonstrate that targeting the metabolic dependencies of TAMs can be a promising approach for cancer immunotherapy.
- Much of this data presented was recently published: Praharaj M., et al., *Cancer Immunol Res.* 2024 Jul 2;12(7):854-875.



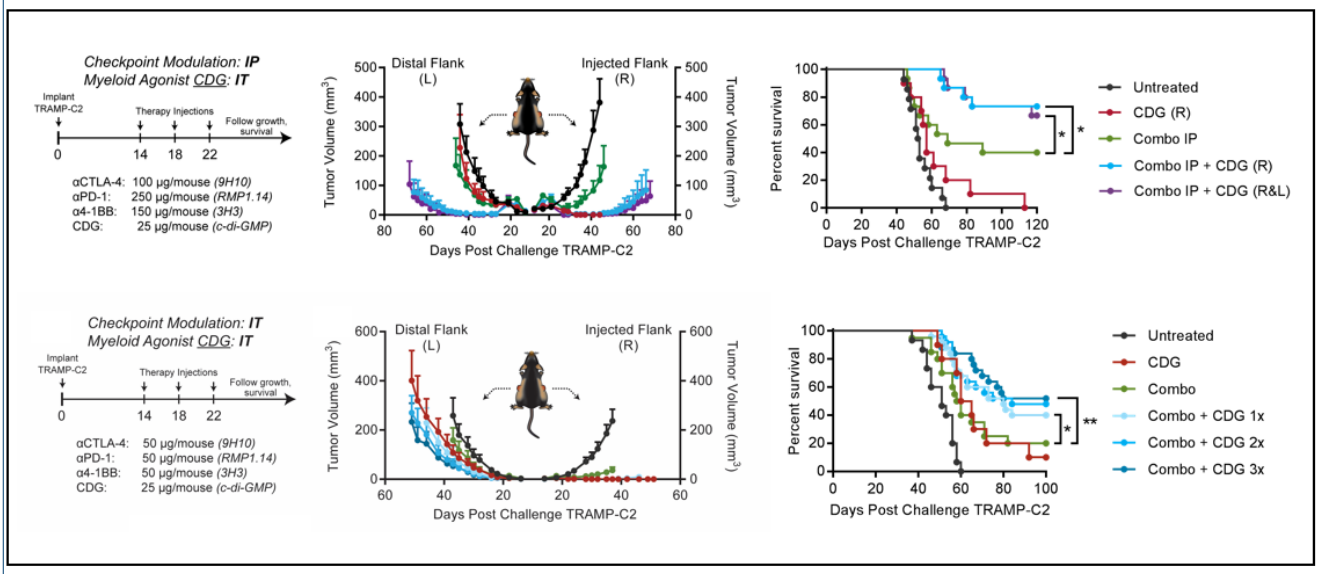
Multimodal Pro-Inflammatory Conversion of Tumor Myeloid Stroma by STING Activation

Michael Curran
University of Texas MD Anderson Cancer Center

- Dr. Michael Curran discussed the role of the STING (Stimulator of Interferon Genes) pathway in the immune response against tumors, particularly in prostate and pancreatic cancer.
- STING is a key sensor of cytosolic DNA, which is a sign of viral infection or cellular stress. When activated, STING triggers a pro-inflammatory immune response, including the production of type I interferons. Type I interferons are a major alert system for immune activation during pathogen infection and can also trigger anti-tumor immune responses.
- In tumors, STING activation can have several advantages. It can increase the presence of active antigen-presenting dendritic cells, which is important for T cell activation, and can reprogram immunosuppressive myeloid cells, such as tumor-associated macrophages and neutrophils, making them less immune-suppressive and more pro-inflammatory.
- This suggests that STING activation may improve anti-tumor immune responses, particularly in tumors such as prostate cancer which have not had optimal responses to standard immunotherapy approaches.
- Therapeutic synergy between STING-activation and checkpoint immunotherapy was demonstrated in preliminary studies of prostate cancer models (**Figure**).
- Dr. Curran and team have developed a potent STING activator (“agonist”), IMGS-203, which was more effective in preclinical studies than previous STING agonists.

- In mouse models of pancreatic cancer, the combination of the STING agonist and checkpoint blockade therapy was able to induce complete tumor regression in some cases, even in very aggressive and refractory models.
- The mechanism of action appeared to involve the STING agonist's ability to downregulate the immunosuppressive functions of myeloid cells, including reducing their proliferation, metabolism, and suppressive capacity.
- To improve the clinical translation of STING agonists, a strategy was developed to deliver the agonist using a tumor-specific antibody, which can replicate the benefits seen with intratumoral injections.
- In a proof-of-concept study the STING agonist was attached to the anti-HER2 antibody Trastuzumab, which is approved for the treatment of breast cancer. This agent had better efficacy in HER2-expressing cancer models compared with STING agonist or Trastuzumab alone.
- In other ongoing work in prostate cancer, phase 1/2 clinical trials have been opened at MD Anderson Cancer Center to test checkpoint immunotherapy in combination with Evofosfamide, which targets tumor hypoxia, and is hypothesized to sensitize tumor cells to checkpoint immunotherapy.
- In preclinical prostate cancer models, the combination of the STING agonist IMGS-203, Evofosfamide, and checkpoint blockade therapy exhibited curative potential.
- Overall, these studies demonstrate promise for STING agonists in combination with checkpoint immunotherapy in the treatment of immunotherapy-refractive cancers such as pancreatic and prostate cancer.

STING activation complements checkpoint blockade to induce abscopal immunity in TRAMP-C2 prostate cancer



Ager CR, Curran MA, *et al* (2017) Cancer Immunology Research

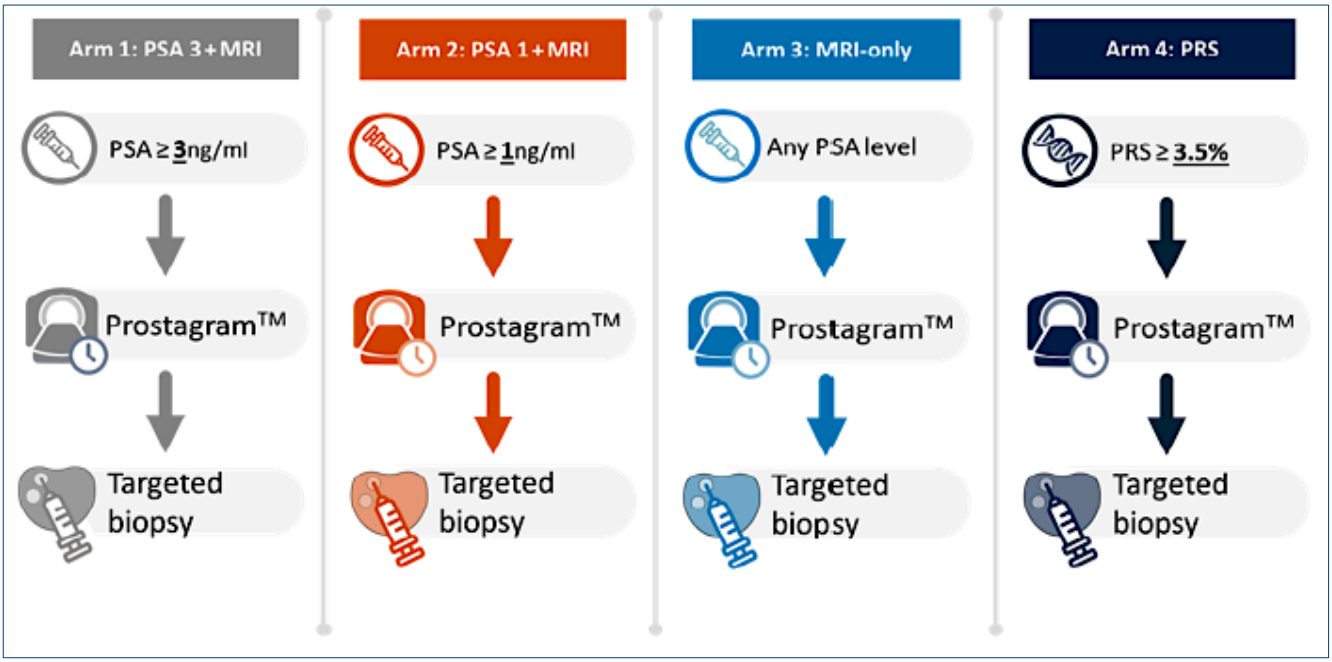
Session 4: High Impact Clinical Trials for Patients with Prostate Cancer

Prostate Cancer UK's TRANSFORM Programme: A Randomised Clinical Trial of Prostate Cancer Screening and a National Prostate Cancer Bio-Digital Twin to Power Biomarker Discovery, Innovation and Validation

Matthew Hobbs
Prostate Cancer UK

Rakesh Heer
Imperial College London, UK

- Prostate Cancer UK is the largest funder of prostate cancer research in the UK, spending about £10-12 million per year on a broad research strategy.
- The current approach for prostate cancer detection using PSA tests followed by TRUS biopsy is important for identifying and managing early prostate cancer, but also can result in harms including unnecessary biopsies and diagnoses of clinically insignificant disease. This limits the adoption of this detection approach as screening policy.
- Real world data has shown that the introduction of MRI into the diagnostic pathway prior to biopsy has reduced unnecessary biopsies and diagnoses of clinically insignificant disease by about 80%. However, there has never been a prospective trial of this diagnostic pathway in a screening population. Upfront fast MRI and polygenic risk score have also shown very encouraging results, but have not been evaluated in a large prospective screening trial.
- The TRANSFORM study is a multi-arm, multi-stage trial that aims to test promising screening pathways using MRI and polygenic risk scores, to find the best approach for detecting clinically significant prostate cancer and ultimately reducing mortality while minimizing harm (**Figure**). In the UK, because there is currently no screening, the trial screening arms will also be compared to a "natural" control arm, of individuals attaining normal care.
- The study will recruit approximately 250,000 men. At least 10% of participants will be Black, to assure representation and minimize health disparities outcomes.
- In parallel, the study will establish a National Prostate Cancer Bio Digital Twin, a powerful next generation modeling platform for rapid biomarker testing and discovery analysis, including a "living biobank" in which tissue will be evaluated and outcomes data obtained in real time. Digital Twin data will include clinical meta-data, scanned digital pathology, molecular imaging (MRI/CT), and genomic sequencing and gene expression data from biobank tissues including blood, urine, fecal microbiome, prostate biopsy and prostatectomy samples, and saliva/mouth swab.
- The Bio Digital Twin will support the TRANSFORM DISCOVERY program by enabling real time biomarker testing, natural history experiments, trial simulations, and health technology assessments across the prostate cancer pathway, including health economic analysis.

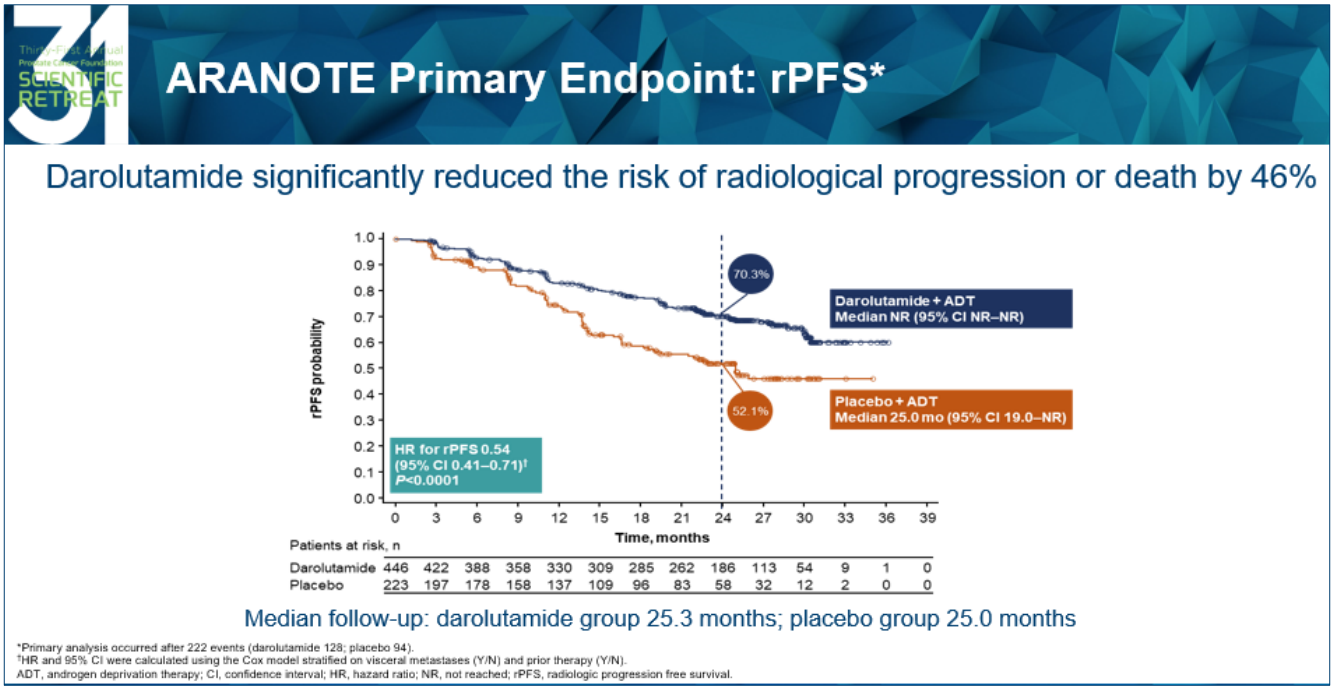


Efficacy and Safety of Darolutamide Plus Androgen-Deprivation Therapy (ADT) in Patients with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) from the Phase 3 ARANOTE Trial

Rana McKay
University of California, San Diego

- Dr. Rana McKay discussed results from ARANOTE, a global randomized phase 3 trial to evaluate the use of darolutamide plus androgen deprivation therapy (ADT) versus placebo plus ADT in patients with metastatic hormone-sensitive prostate cancer (mHSPC).
- The treatment landscape for advanced prostate cancer has rapidly evolved over the last decade with the introduction of new therapies like androgen receptor (AR) pathway inhibitors, chemotherapy, and targeted therapies.
- There are multiple current standard of care options for patients with mHSPC. Recently, the ARASENS trial established the triplet combination of ADT + darolutamide + docetaxel as one of these options, with favorable efficacy and safety compared with ADT + docetaxel.
- ARANOTE was designed to evaluate darolutamide + ADT versus ADT, without docetaxel, to provide a new treatment option for mHSPC. The trial enrolled 669 patients with an ECOG of 0-2, who were randomized 2:1 to receive darolutamide + ADT versus placebo + ADT. The primary endpoint was radiographic progression free survival (rPFS), which is the time from randomization to disease progression on scans or death (whichever comes first).
- Overall, darolutamide + ADT significantly reduced the risk of radiographic progression or death by 46% compared to placebo + ADT (**Figure**).
- In subgroup analyses, darolutamide + ADT demonstrated a consistent benefit across all subgroups compared with ADT alone, including significant benefit for patients with both low and high-volume disease.

- Darolutamide + ADT demonstrated benefits across secondary endpoints, including delayed time to metastatic castration-resistant prostate cancer (mCRPC), time to PSA progression, time to initiation of subsequent therapy, and time to pain progression. Overall survival data remains immature, but a trend toward an overall survival benefit is also indicated.
- The safety profile of darolutamide + ADT was similar to that of ADT alone, with similar rates of treatment-related adverse events, and a lower rate of treatment-related adverse events that led to discontinuation of study drug (6.1% vs. 9.0%). Adverse events with an incidence ≥10% in the darolutamide group were anemia, arthralgia, and urinary tract infection.
- Altogether, this trial demonstrated darolutamide + ADT without docetaxel should be considered an additional standard of care option for patients with mHSPC.



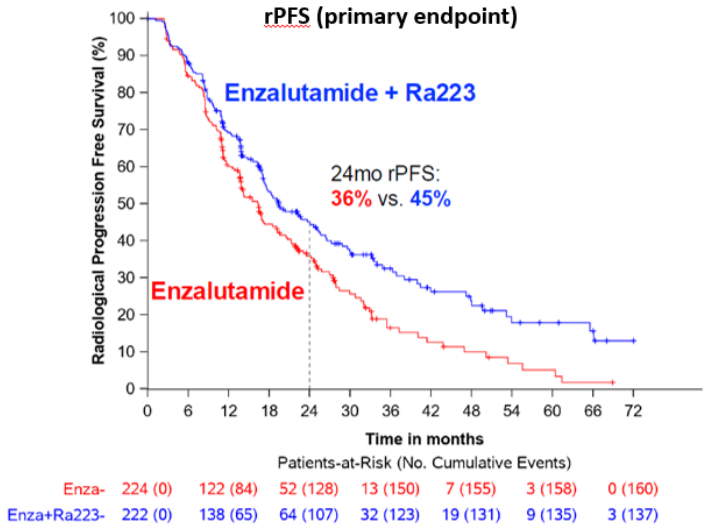
A Randomized Multicenter Open-Label Phase III Trial Comparing Enzalutamide vs a Combination of Radium 223 and Enzalutamide in Asymptomatic or Mildly Symptomatic Patients with Bone Metastatic mCRPC

Andrey Soares
Hospital Albert Einstein, Sao Paulo, Brazil and Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Brazil

- Dr. Andrey Soares discussed the PEACE3 trial, a randomized, multicenter, open-label Phase 3 trial that compared the combination of enzalutamide + radium-223 vs. enzalutamide alone in patients with asymptomatic or mildly symptomatic bone-metastatic prostate cancer.

- Abiraterone and enzalutamide are standard of care options for first-line treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who are progressing on androgen deprivation therapy (ADT).
- Radium-223 is a radioligand therapy that mimics calcium and thereby selectively targets bone metastases, where it kills cancer cells by emitting alpha particle radiation that damages DNA.
- Radium-223 was demonstrated in the ALSYMPCA trial to increase overall survival in patients with mCRPC and became a standard of care option. However, this trial was done in an era before the introduction of abiraterone and enzalutamide, warranting trials to test such combinations.
- The ERA-223 trial tested abiraterone + radium-223 versus abiraterone + placebo. No benefits were observed for this combination in symptomatic skeletal event-free survival or overall survival and was in fact associated with an increase in bone fractures.
- The PEACE3 trial tested enzalutamide + radium-223 (6 cycles) vs. enzalutamide alone (with ongoing ADT in both arms) in 446 patients with asymptomatic or mildly symptomatic bone-metastatic prostate cancer. The primary endpoint was radiographic progression-free survival (rPFS), and key secondary endpoints included overall survival, time to next treatment, time to pain progression, and time to first symptomatic skeletal event.
- Because the ERA-223 trial showed an increase in bone fractures, the use of bone-protective agents (BPAs) was made mandatory in the PEACE3 trial after the inclusion of 119 patients.
- The PEACE3 trial met its primary endpoint, demonstrating a statistically significant improvement in rPFS with enzalutamide + radium-223 vs. enzalutamide (median rPFS of 19.4 months vs. 16.4 months) (**Figure**).
- The combination arm also demonstrated a statistically significant improvement in overall survival, with a median overall survival of 42.3 months with enzalutamide + radium-223 compared to 35 months with enzalutamide alone.
- The time to next systemic treatment was longer in the combination arm, with 30% of patients receiving a next treatment at 24 months compared to 51% in the enzalutamide alone arm.
- Time to pain progression and time to first symptomatic skeletal event were similar between both arms.
- The combination was generally well-tolerated, with higher rates of drug-related adverse events and grade 3-5 adverse events with enzalutamide + radium-223 compared to enzalutamide alone, but no treatment-related deaths. The most common grade 3-5 treatment emergent adverse event was hypertension in both arms, in around 33% of patients. Fatigue, fracture, anemia and neutropenia were higher in combination arm compared with enzalutamide alone, but still a low number of patients (4.6-5.5% vs. 0-2.2%) were affected.
- The results support the combination of enzalutamide and 6 cycles of radium-223 plus a bone-protecting agent as a potential new first-line treatment option for patients with bone-metastatic prostate cancer who have not received an androgen receptor pathway inhibitor previously.

Primary endpoint: rPFS



	Enza+Ra-223	Enza
n/N	139/222	160/224
Median (months)	**19.4** (17.1-25.3)	**16.4** (13.8-19.2)
HR (95% CI)	**0.69** (0.54-0.87)	
Logrank *P*-value	**0.0009 (threshold *P*<0.025)**	
Assumption of proportional hazard achieved		

Enza, enzalutamide; **Ra-223**, radium-223; **rPFS**, radiological progression-free survival.

Presented by: Andrey Soares
@SoaresAndrey

Gillessen S, ESMO 2024

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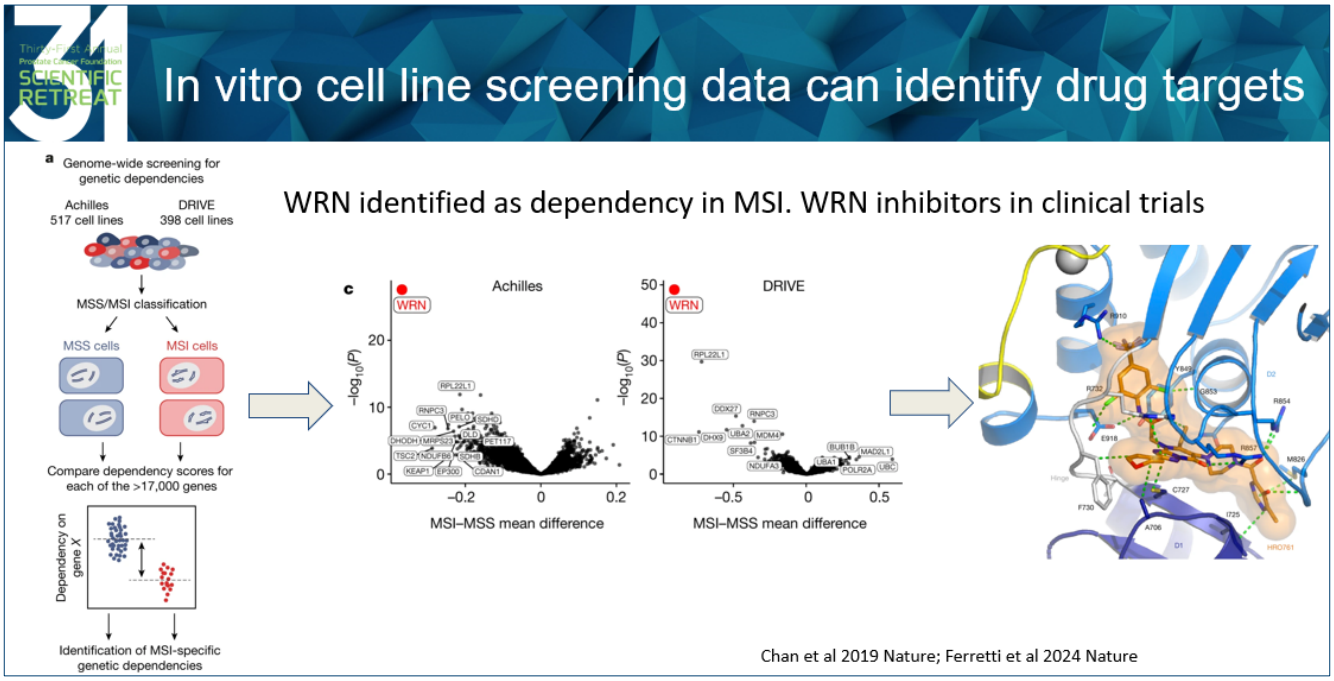
Session 5: Can AI Drive Innovation in Cancer Research and Cancer Care?

Using AI to Predict Patient Drug Responses and Outcomes from Preclinical Data

Katie Campbell
Broad and MIT

- Dr. Katie Campbell discussed using machine learning models to understand cancer cell vulnerabilities from genome-scale CRISPR screens integrated with data from multi-omic genomic and gene expression studies.
- Genome-scale CRISPR screens, which systematically delete genes in cell lines to test their functions, can be used to classify how essential or non-essential a gene is for cell viability and indicate its role in tumor biology.
- By applying machine learning models to genome-scale CRISPR screens combined with multi-omic data such as genomic sequencing and gene expression, one can connect gene dependencies to genomic features, and identify cancer subtypes, genotypes, molecular features, and cell states that predict and explain cancer cell responses to different perturbations. The goal is to identify biomarkers for specific dependencies that can be targeted in a precision medicine approach.
- It is important to select the appropriate machine learning model to apply, based on the data used and the questions being asked. It is also important to account for known biological relationships to interpret the biological connections in the results.
- "Random forests" are interpretable modeling approaches highly suited for this approach. Individual decision tree models can be built for each data type, and then integrated into a random forest model to define a model with the best predictive performance. Deep learning models are more complex and not necessary for data of this structure and size.
- This approach has led to the identification of the *WRN* gene as a dependency in cancers with microsatellite-instability (MSI). WRN-inhibitors are now in clinical trials in patients with MSI cancers. (**Figure**)
- Efforts are ongoing to improve the models by adding new features, such as aggregated cancer driver annotations, gene signatures, and exploring new data types like proteomics and long-read RNA-seq.



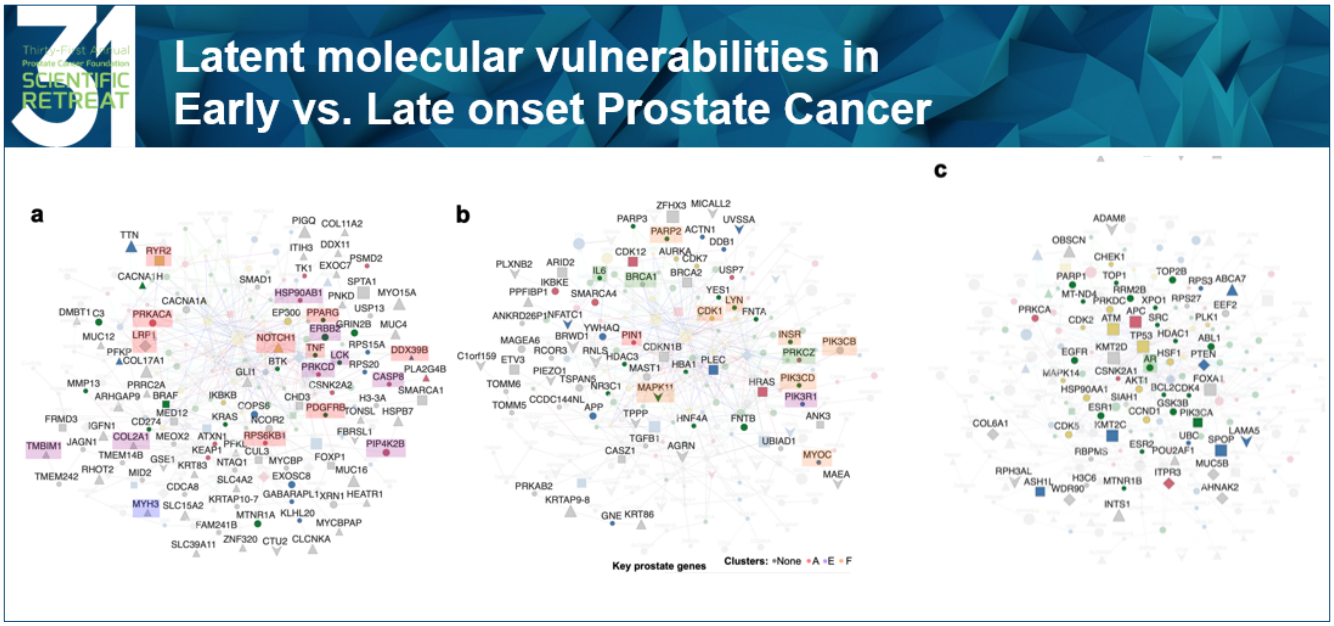
Digital Twins for Drug Development to Individualized Therapy

Bissan Al-Lazikani

The University of Texas MD Anderson Cancer Center

- Dr. Bissan Al-Lazikani discussed the concept of digital twins, which are virtual computational representations of physical objects, processes, or systems that can simulate their real-world behavior using real-time data.
- For instance, digital twins of patients could be used to simulate a specific individual throughout diagnosis, treatment, relapse and remission. A digital twin of a cohort could simulate virtual clinical trials, while a digital twin of systems could be used in drug discovery and development.
- Drug discovery and development process could benefit greatly from a digital twin approach, as it would allow for rapid learning, adaptation, and simulation of different paths to identify where failures are likely to occur and where successes can be achieved.
- Key hurdles in the drug discovery and development process include: integrating and making sense of complex patient data to identify optimal therapeutic targets; validating targets clinically in a meaningful and timely manner; designing drugs that can effectively target specific sites on proteins; and selecting the right drug for the right patient at the right time.
- Some of the solutions and tools developed by Dr. Al-Lazikani's team to address these hurdles include an AI-powered model that can enhance the signal-to-noise ratio in various types of patient molecular or other data to create a molecular map of protein communications and identify key disease vulnerabilities.

- This approach was applied to develop molecular maps of early versus late onset prostate cancer. Significantly different genes, pathways, and tumor microenvironmental components were identified as having a key role in these different disease settings (**Figure**).
- Dr. Al-Lazikani and colleagues developed canSAR, a free online resource that maps druggable sites on proteins and annotates them with mutation hotspot data and functional information such as sites of post-translational modifications and ligand and protein interactions. This tool has been applied to identify druggable sites on the androgen receptor (AR).
- In typical small molecule drug discovery approaches, ~10,000 molecules are typically physically tested for activity, which is time consuming and wasteful. To overcome this, an AI-driven drug discovery virtual screening approach was developed to match small molecule and protein target sites virtually, and significantly reduce the number of compounds that need to be physically tested.
- Finally, to enable identification of the right drug for the right patient at the right time, a dynamic model was developed that can predict the most likely single-agent and combination therapies for individual patients based on ex-vivo studies. For example, proteomics data from lung cancer patient pleural effusion samples were used to predict the most likely single agent and combination of drugs that could work for each individual patient, with 79% accuracy.
- These AI models are being integrated into a platform called "Adaptive AI Augmented Drug Discovery and Development" (A_3D_3a) to enable a rapid, data-driven, and patient-centric drug discovery and development process, with the aim of reducing the time to discover a new drug and bring it to the clinic, to just 5 years.



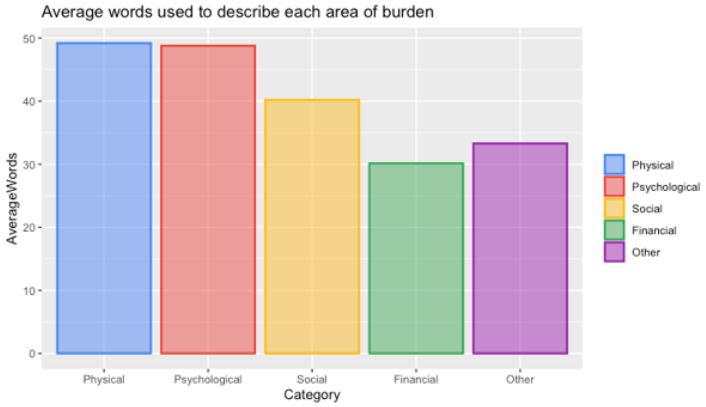
Using Large Language Models to Improve Representation of Patients' Experience with Cancer and its Treatment – Insights from the Lancet Commission on Cancer and Health Systems

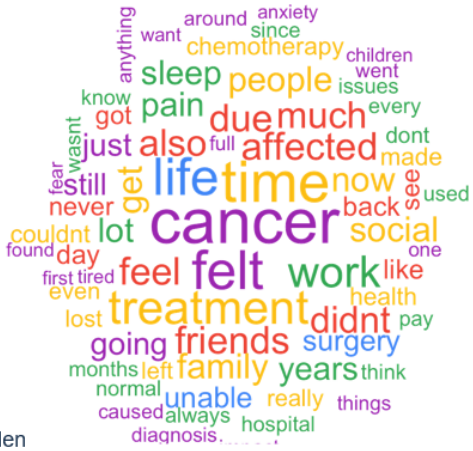
André Pfob
Heidelberg University Hospital; Breast Center Heidelberg, Hospital St. Elisabeth

- Dr. André Pfob discussed the use of large language models (LLMs) to improve the representation of patients' experiences with cancer and its treatment.
- LLMs are probabilistic models of text, that generate coherent text by predicting which word is most likely to come next, considering the context of words, phrases, and sentences.
- While early LLM chatbots were unable to generate coherent text and would ramble on continually, modern LLMs such as ChatGPT are based on a transformer architecture, which consists of several of thousands of neural networks that each pay attention to adjectives, nouns, words, and their position across a text.
- However, while these new LLMs can generate coherent text, they are computationally expensive and lack domain-specific knowledge, which is crucial for clinical research.
- A newer concept is retrieval-augmented generation (RAG), which combines LLMs with a collection of private or domain-specific texts to provide more accurate and informative responses.
- Studies done to evaluate the global cancer burden can only be interpreted on a health-systems or population level. For instance, a 2019 global cancer burden study reported 240 million disability adjusted life years, 10 million deaths, 241 million years of life lost, and 8 million years lived with disability. However, what this means to an individual patient and their experience is unclear.
- Dr. Pfob is part of the *Lancet* Commission on Cancer and Health Systems, which aims to raise the bar and close the gap for cancer control globally. As part of this project, the Redefining Cancer Burden Measurement Working Group has launched the RESPECT initiative to collect patient experiences and create a scalable technique for assessing the subjective burden of cancer.
- The RESPECT initiative is collecting open-text responses from thousands of patients worldwide about their experiences with cancer burden (**Figure**), as well as quantitative health-related quality of life data on physical well-being, psychological, financial, social and other quality of life areas. The team is developing a dashboard that allows patients, clinicians, and policymakers to interact with the collected experiences through a chatbot using RAG technology. For instance, users can evaluate cancer burden experiences by country or other demographic factors, or ask questions, such as what it feels like to undergo chemotherapy.
- Key needs of a cancer experience chatbot include ensuring the alignment between the quantitative analysis and the chatbot responses, as well as the need to provide grounded and contextual responses without hallucinating or altering the original patient quotes.
- These studies demonstrate the potential of LLMs and RAG to provide actionable insights, enhance patient feedback systems, enable real-time monitoring and policy adjustment, promote patient-centered health policy development and provide open access to shared experiences. Human expert supervision and eventually regulatory approval are also needed for the development and use of clinical chatbots.
- The full results of the RESPECT study will be published alongside the *Lancet* Commission Report in mid-2025.

RESPECT pilot

- Collection of open text responses related to cancer burden





Over 400,000 words describing cancer burden

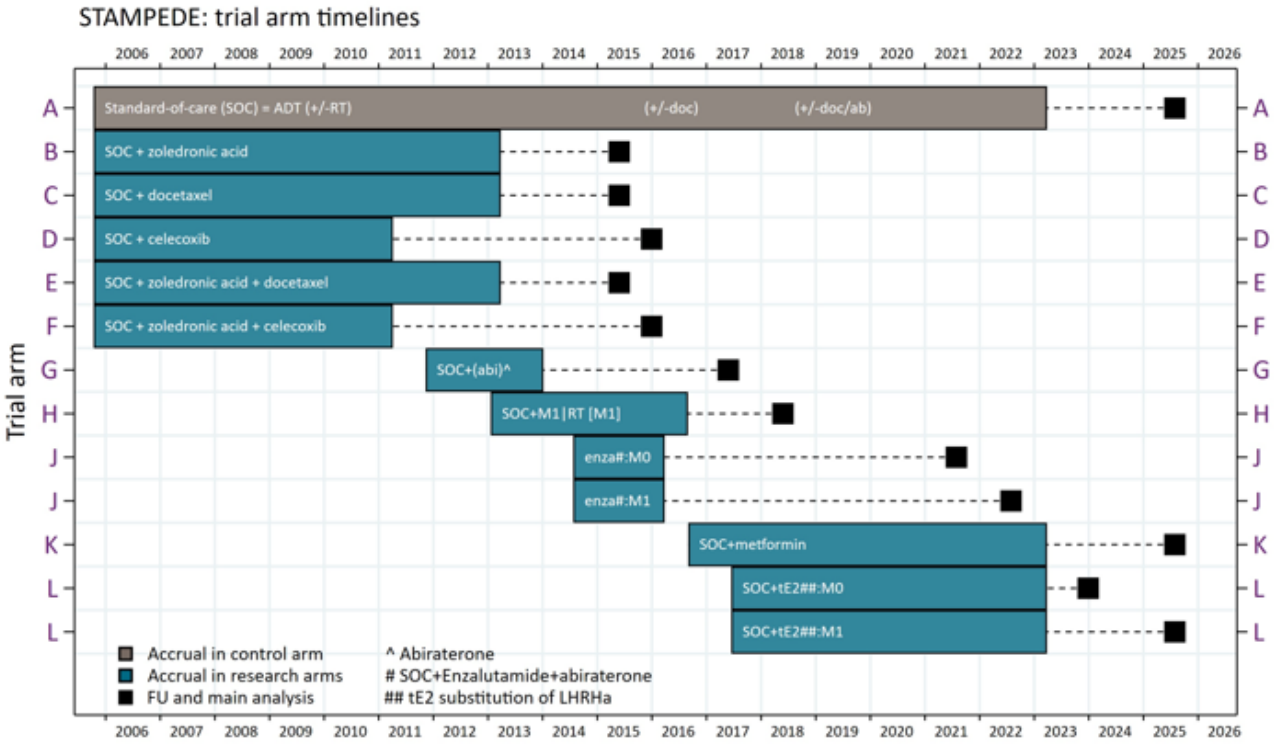
SPECIAL LECTURE: Lessons From 20 Years of STAMPEDE

Nicholas James

The Institute of Cancer Research, UK

- Dr. Nicholas James discussed the lessons learned from running the STAMPEDE trial, a large multi-arm, multi-stage phase 3 clinical trial for patients with high-risk or hormone-sensitive metastatic prostate cancer that has been ongoing for over 20 years.
- In conventional clinical trials, a treatment arm is compared to a standard of care control arm, to determine if the treatment is superior or not, based on overall survival, quality of life, or other measures that serve as surrogates for survival. However, these trials are costly and take many patients to complete, with each new trial requiring a new control arm.
- The STAMPEDE trial used a novel design, with a single ongoing standard of care control arm, and multiple treatment arms which could be added to the trial over time, as new therapies of interest became available. To date, there have been 12 treatment arms, 9 of which have been completed.
- As the standards of care for high-risk and hormone-sensitive metastatic prostate cancer have shifted over time, newer treatment arms would be compared to patients from the control arm treated contemporaneously.
- Key lessons from the STAMPEDE trial design include being flexible and open to opportunities rather than rigidly sticking to the original plan. This allowed the trial to adapt and incorporate new treatments as they emerged.
- Engaging with a wide range of stakeholders, including urologists and health authorities, enabled building support and facilitating implementation of the trial's findings.
- Incorporating translational research and career development opportunities into the trial structure has led to numerous scientific publications and advances.
- Prioritizing patient-reported outcomes and health economic analyses also supported adoption of the trial's findings.
- The trial's innovative multi-arm, multi-stage design has since served as a model for many other platform trials, including those for COVID-19.
- By implementing a long-term stable platform to also collect patient samples for molecular and genomics profiling and other data, the trial has enabled the performance of significant translational research, with over 100 scientists and clinicians working on translational projects internationally.
- Overall, over 12,000 patients were enrolled on the trial across 120 hospitals. Patients enrolled on the trial benefited significantly, with each positive trial arm extending life by ~1.5 years, resulting in a collective ~7,000 life-years gained.
- The trial has had a substantial clinical impact, leading to five new standard of care treatments for prostate cancer extending patient survival by at least 1.5 years, and generating an estimated 700,000 life-years gained for patients globally.

STAMPEDE trial – the final version



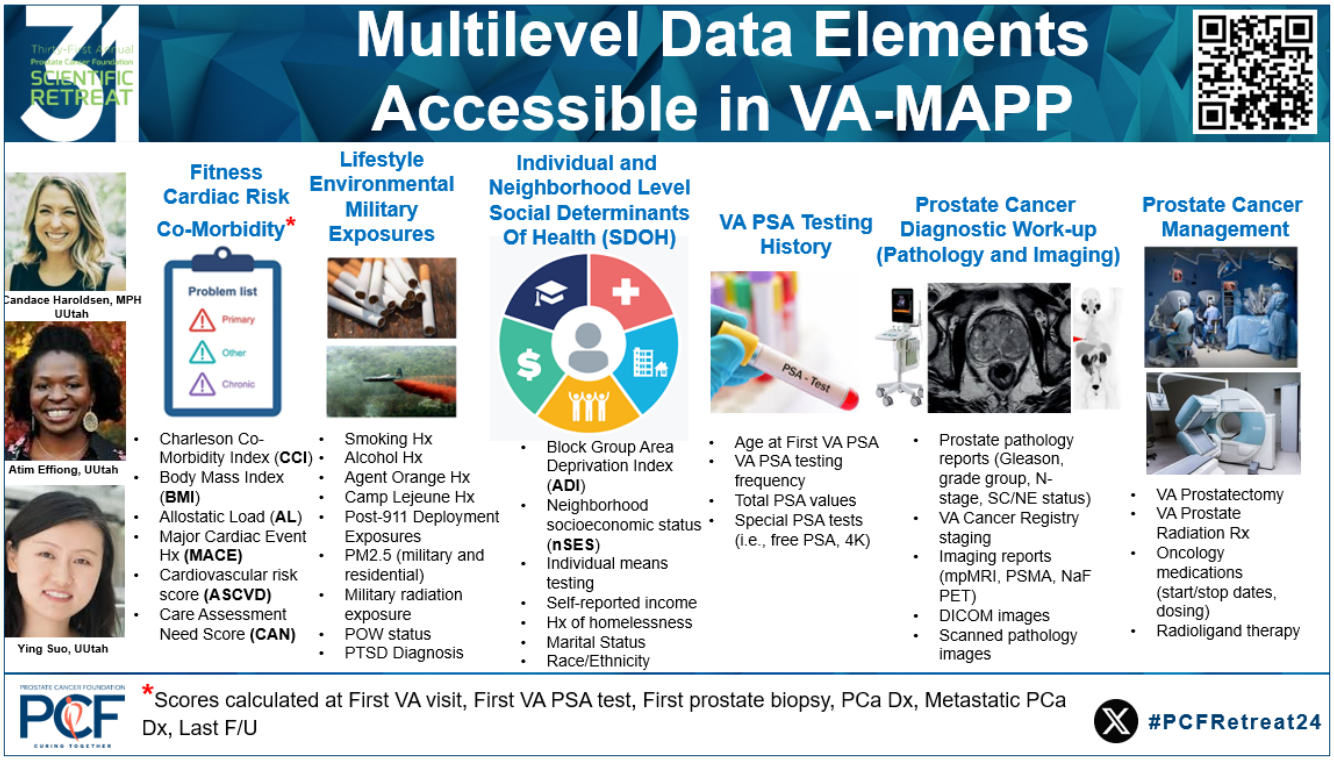
Session 6: The PCF-VA Partnership: Bringing Precision Medicine to Veterans

VA MAPP: Multilevel Data and Biospecimen Repository for Unprecedented Discovery and Validation

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

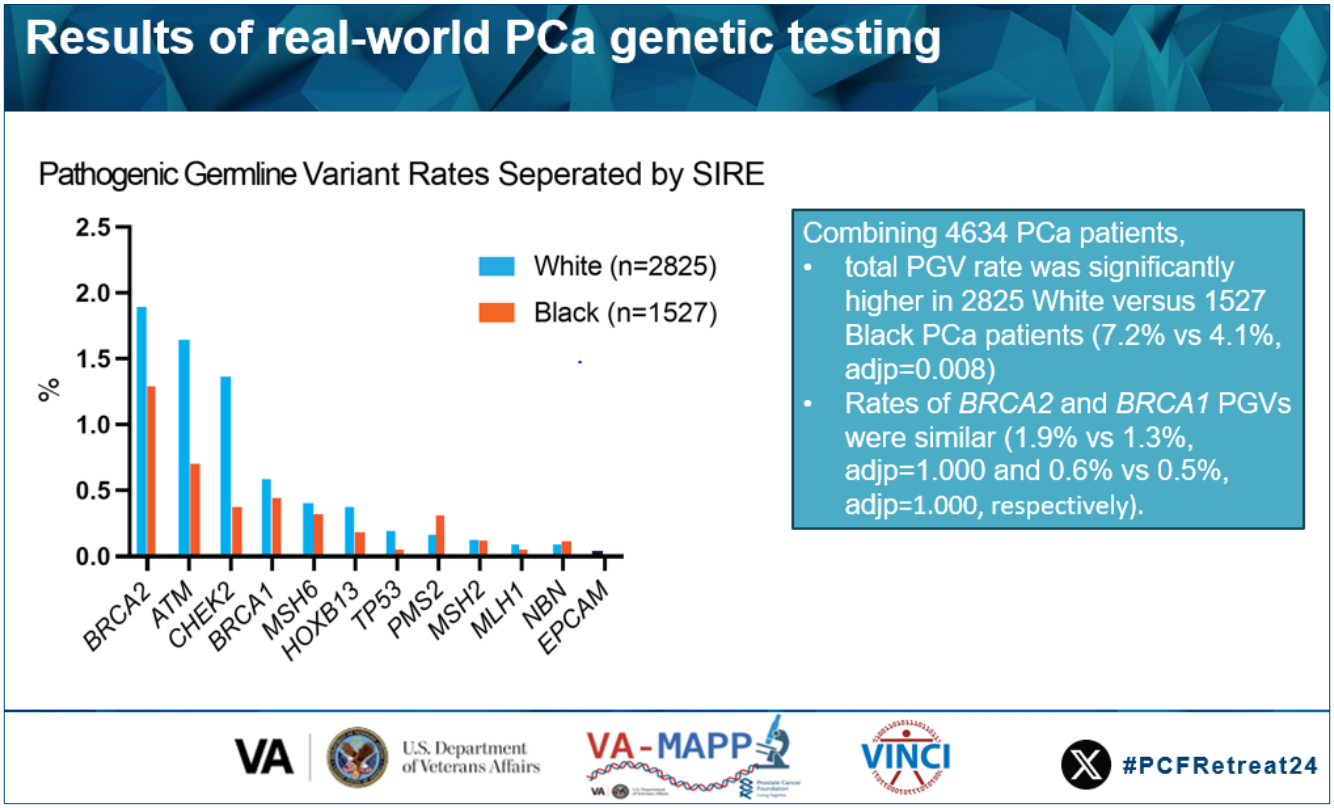
Kara Maxwell
University of Pennsylvania; Corporal Michael J. Crescenz VA Medical Center

- The PCF partnered with the Department of Veterans Affairs (VA) in 2016 to establish the Precision Oncology Program for Prostate Cancer (POPCaP), a $50 million initiative.
- Dr. Isla Garraway introduced the PCF-VA partnership and discussed the goals and progress of POPCaP.
- The goals of POPCaP were to ensure that precision oncology and prostate cancer clinical trials could be accessed by Veterans for testing, treatment, and trials.
- As of 2024, there are 12 POPCaP Centers of Excellence across the U.S., led by clinician-scientists affiliated with academic institutions near VA sites.
- The POPCaP initiative has delivered impressive results. Over 11,000 somatic tumor tests have been completed, allowing over 900 patients to receive precision oncology medications in the VA. Nearly 30 precision clinical trials have been opened at VA sites, enabling Veterans across the country to access these trials.
- To leverage the VA's extensive data, the VA Multi-omics Analysis Platform for Prostate Cancer (VA-MAPP) was developed, a VA-approved and compliant biorepository.
- VA-MAPP has two components. One is retrospective collection of data and samples from 11 million Veterans at risk of prostate cancer, including over 1 million diagnosed cases and 83,000 with metastatic disease. The second component is prospective collection of samples and data from patients undergoing prostate cancer diagnosis and treatment through an informed consent process.
- Thus far, nearly 400 patients have been prospectively enrolled and archival tissues have been retrospectively collected from 2,200 patients. These patients reflect the diversity of the VA population, with ~36% having African American ancestry and ~10% of other, non-White races.
- VA-MAPP aims to contribute to biomarker discovery and validation, as well as the development of new biological models like organoids, xenografts, and cell lines, such that Veterans' data is ultimately used to help advance and improve their care.
- The VA's extensive electronic health records is the oldest in the U.S., spanning 25 years, and provides rich data on Veterans' cardiovascular risk, social determinants of health, lifestyle, environmental and military exposures, and clinical history (**Figure**).
- Researchers interested in leveraging the VA-MAPP resource are encouraged to collaborate with VA investigators, and can obtain access to the data through an applications and approval process. Bladder cancer and kidney cancer MAPPs are also being developed.



- Dr. Kara Maxwell discussed how VA-MAPP sub-studies and curated data elements have potential to support studies related germline genetic risk in prostate cancer.
- Prostate cancer is one of the most hereditary forms of cancer, with ~50% of cases having a genetic etiology component. Hereditary alterations in the *BRCA1* or *BRCA2* genes that increase risk for prostate cancer and other types of cancer including breast and ovarian cancers, are carried by 1 in 200 people, with variations by ancestry. It is important to know the frequency of cancer risk gene variants in each population so genetic resources can be properly deployed and patient care expectations can be properly set.
- Dr. Maxwell and colleagues performed a study to examine the frequency of rare germline prostate cancer risk gene variants in a real-world setting, in patients diagnosed with prostate cancer in VA clinics (>3,600 patients) and Penn Medicine oncology clinics (>1,000 patients). The study analyzed two cohorts: a clinical cohort of patients who underwent genetic testing based on NCCN guidelines, and a validation cohort using data populated from VA-MAPP and the VA National Precision Oncology Program (NPOP) databases. NPOP provides NCCN guideline based genetic testing at VA medical centers.
- The presence of germline pathogenic variants were evaluated for 12 prostate cancer risk genes: *ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PMS2*, and *TP53*. Clinical, pathological, and family history data were abstracted from patient medical records at Penn Medicine and the Philadelphia VA.
- Overall, 7% of the clinical cohort and 5.8% of the VA cohort had pathogenic germline variants in the 12 genes studied.
- This study also included one of the largest analysis of genetic variants in self-identified Black individuals, with just over 1500 patients. The overall pathogenic mutation rate was lower in self-identified Black vs. White participants (4.1% versus 7.2%), primarily due to higher rates of *ATM* and *CHK2* variants in the White population (**Figure**). *BRCA2*, *BRCA1*, and Lynch gene (*MLH1, MSH2, MSH6, PMS2*) mutation rates were similar between self-identified Black and White men (**Figure**).
- Pathogenic variants were associated with earlier age of diagnosis, and *BRCA2* variants were associated with higher Gleason scores.

- A comparison of the mutation rates in this prostate cancer patient cohort to cancer free males demonstrated that mutations in *BRCA2*, *ATM*, *BRCA1*, *CHEK2*, and the Lynch genes were significantly associated with prostate cancer in self-identified White men.
- This study highlights the importance of understanding the frequency and clinical impact of germline genetic variants in diverse patient populations to improve prostate cancer screening and treatment.

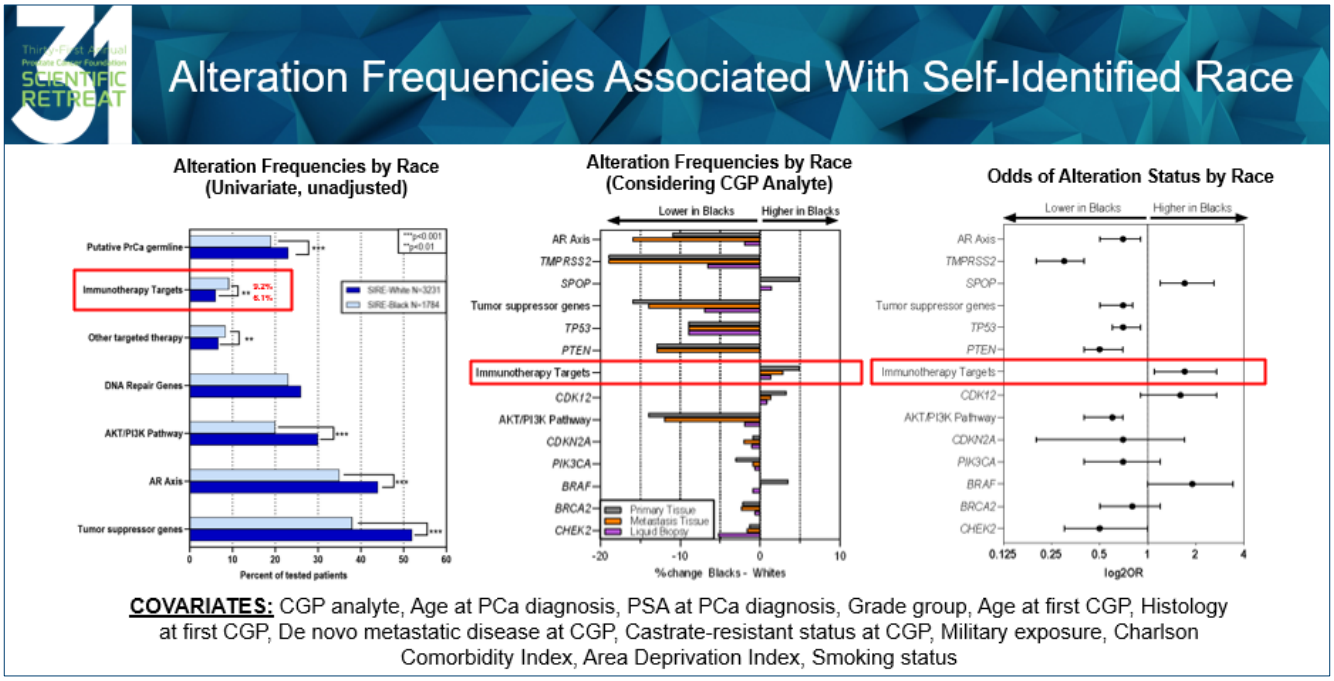


VA Studies Led by Young Investigators: Landscape of Somatic Prostate Cancer Alterations in the VA population

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

- Dr. Luca Valle discussed the landscape of somatic prostate cancer mutations in the VA population, with a focus on racial and ethnic disparities. Somatic mutations are those which occur specifically in tumor cells to drive cancer development and progression, and are not inherited.
- Men who self-identify as Black experience significantly higher rates of prostate cancer diagnosis and mortality compared to other racial/ethnic groups. Patients of African ancestry are also underrepresented in next-generation sequencing and precision oncology cohorts, exacerbating prostate cancer racial disparities. More research is needed to define the landscape of somatic tumor mutations that drive prostate cancer in Black patients.

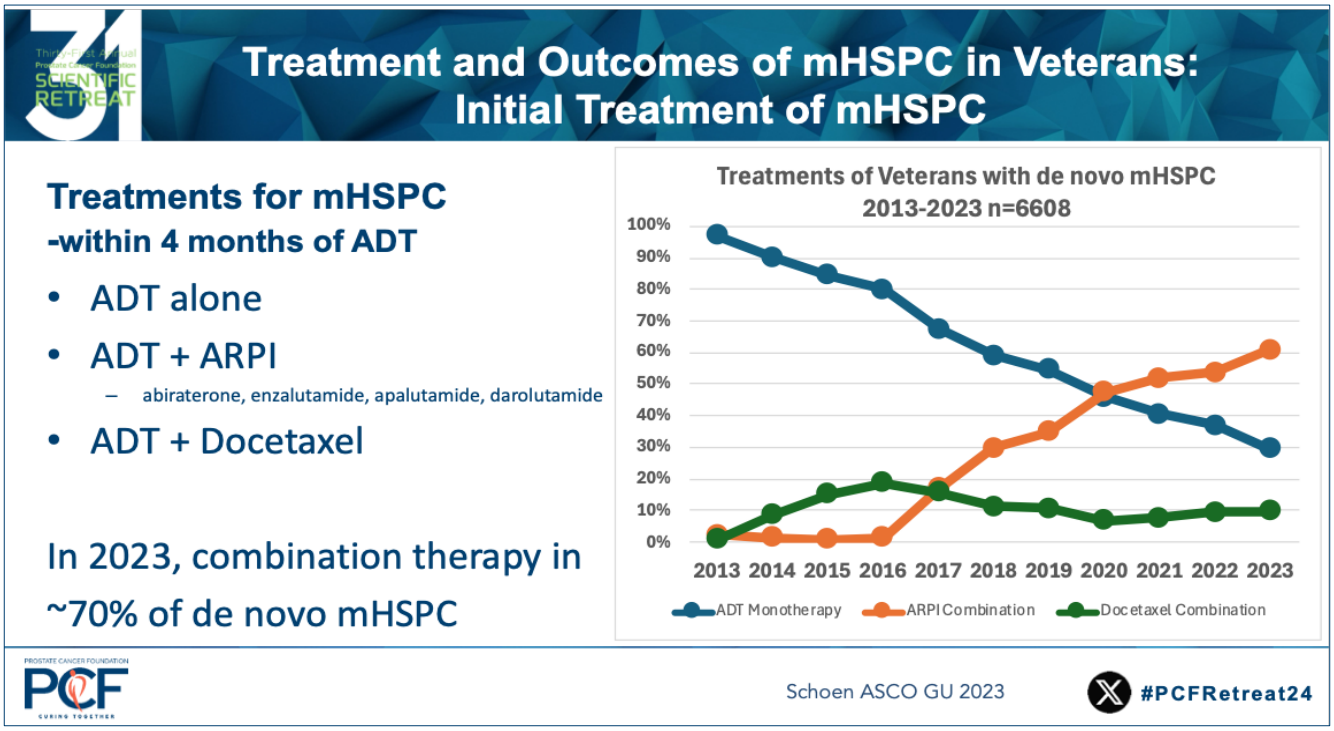
- Dr. Valle sought to define the spectrum and frequency of hallmark and potentially actionable somatic prostate cancer alterations in racially and ethnically diverse populations, to identify equitable precision oncology applications.
- The study analyzed a cohort of 5,015 U.S. Veterans diagnosed with prostate cancer and who received tumor genomic sequencing in the VA National Precision Oncology Program (NPOP), with 36% identifying as non-Hispanic Black.
- Compared to non-Hispanic White Veterans, non-Hispanic Black Veterans were younger at diagnosis, had higher PSA levels, and were more likely to reside in areas with higher deprivation.
- The 10 most frequent tumor alterations were similar between the two groups, but the proportions varied. *TP53* was the most commonly altered gene in tumors from non-Hispanic Black Veterans while *TMPRSS2* gene fusions were the most common in non-Hispanic White Veterans.
- Immunotherapy targets (genes in which alterations are associated with improved responses to immunotherapy) were more frequently altered in non-Hispanic Black patients, while alterations in the AKT/PI3K pathway, the AR axis, and tumor suppressor genes were more common in non-Hispanic White patients (**Figure**). These differences persisted after adjusting for potential confounders, including castrate-resistant status, PSA, and comorbidities.
- Survival analysis showed that in the near universal access VA health care system, with equal access to precision oncology, most tumor alterations did not have a clear impact on survival, except for those in *TP53*, which was associated with worse survival in both racial/ethnic groups.
- Overall, these findings highlight the importance of comprehensive genomic profiling for all patients with high-risk and metastatic prostate cancer, regardless of race or ethnicity, to identify actionable alterations and improve outcomes.



VA Studies Led by Young Investigators: Treatment and Outcomes of mHSPC in Veterans: Initial use of Tumor Suppressor Genes for Prognosis

Martin Schoen
Saint Louis University; St. Louis Veterans Affairs Medical Center

- Dr. Martin Schoen discussed the use of VA-MAPP data to understand the real-world treatment and outcomes of patients with metastatic hormone-sensitive prostate cancer.
- The survival of patients with metastatic hormone-sensitive prostate cancer treated in the VA was compared to the nationwide SEER database. In both datasets, overall survival increased over time, reflecting an improvement in patient treatment and management strategies. This comparison also demonstrated that VA-MAPP data is generalizable and the survival outcomes for patients seen in the VA are as good or better than the national average.
- Evaluation of trends in treatment approaches for metastatic hormone-sensitive prostate cancer within the VA showed a decrease over time with androgen deprivation therapy (ADT) alone and a corresponding increase in the use of combination therapies (ADT plus docetaxel or androgen receptor pathway inhibitors (ARPI; abiraterone, enzalutamide, apalutamide, darolutamide)), with over 70% of Veterans receiving combination therapy as of 2023 (**Figure**).
- Combination therapies were found to be associated with improved survival compared to ADT monotherapy, though the patient populations receiving the different treatments had different characteristics such as average age that need to be accounted for.
- Patient outcomes were also evaluated in association with specific tumor mutations. The presence of alterations in the tumor suppressor genes *TP53, RB1,* and *PTEN* were associated with decreased overall survival, and having more than one tumor suppressor gene alteration was associated with even worse survival. Patients with tumor suppressor gene alterations also did better with combination therapies compared to ADT alone.
- Overall, these studies demonstrate the power and generalizability of the VA-MAPP data, as well as its potential to provide insights into precision and personalized medicine as more genetic and genomic information is incorporated.



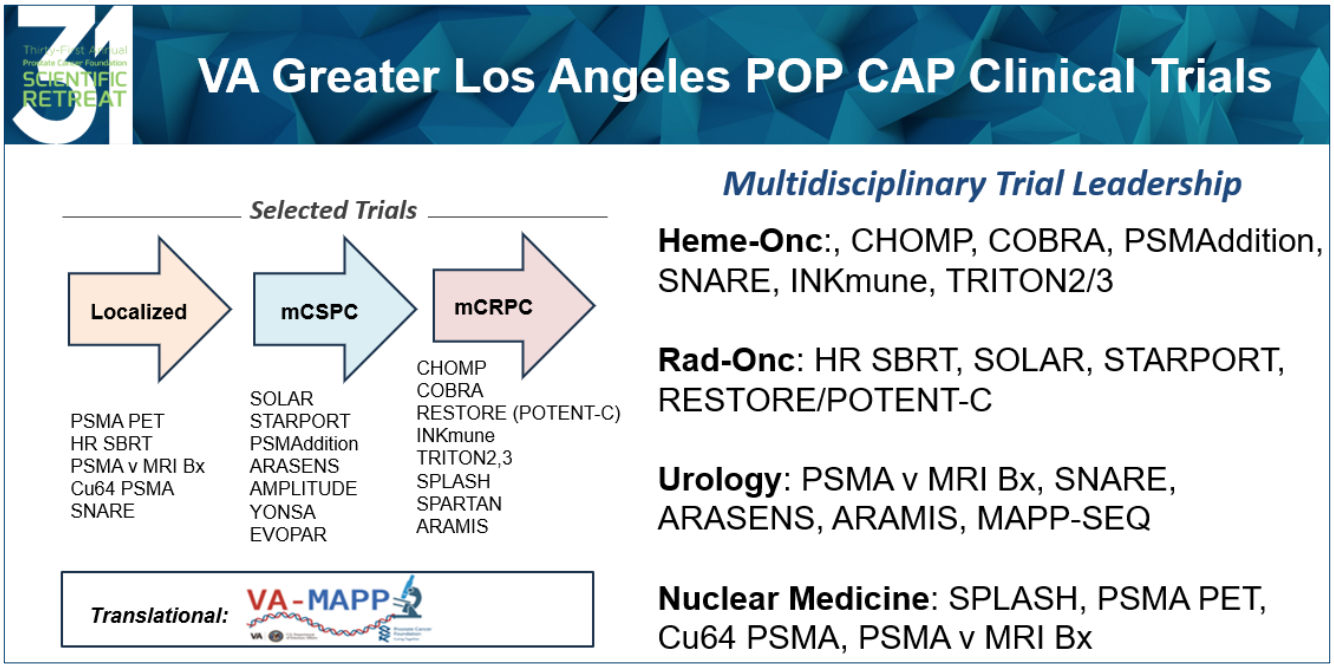
Full Spectrum VA Clinical Studies from SOLAR to AI

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

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

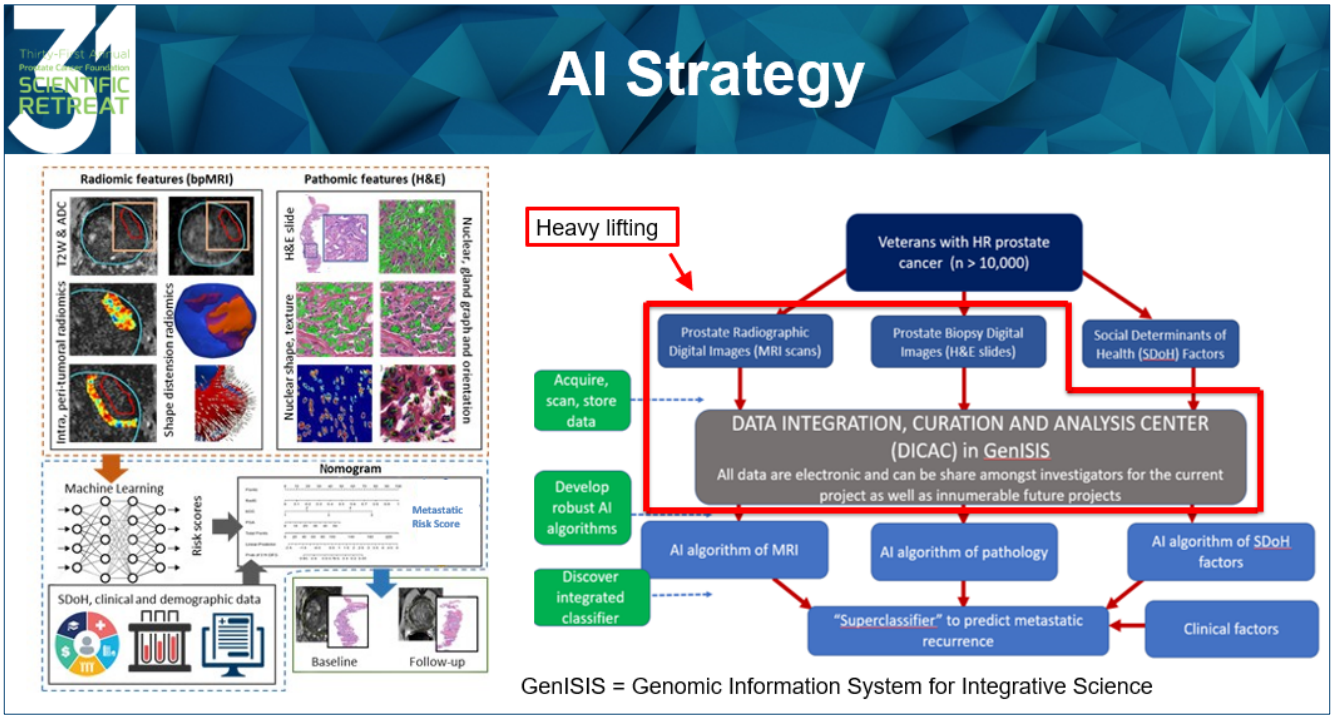
- Dr. Nicholas Nickols discussed PCF-VA Precision Oncology Program for Prostate Cancer (POPCaP) clinical trials at the VA Greater Los Angeles (GLA) for prostate cancer patients.
- Nearly 1,000 veterans with prostate cancer have been enrolled onto POPCaP clinical trials at GLA since 2018, with approximately 40% being African-American or Black veterans.
- GLA has a multidisciplinary trial leadership team, including hematology, oncology, urology, radiation oncology, and nuclear medicine.
- POPCaP trials cover the full spectrum of prostate cancer from initial staging to treatment of advanced disease (**Figure**). GLA prioritizes investigator-initiated precision oncology trials that improve both efficacy and quality of life outcomes.
- GLA has a robust pipeline to ensure veterans with metastatic prostate cancer have appropriate molecular sequencing, and was the first VA to offer PSMA PET imaging and PSMA-targeted radiopharmaceutical therapy.

- In the phase 2 "Systemic and Tumor Directed Therapy for Oligometastatic Prostate Cancer" (SOLAR) trial, newly diagnosed patients with oligometastatic (1 to 5 metastases) prostate cancer received a combination of treatment of the primary prostate tumor with radical prostatectomy and lymph node dissection or radiation therapy, 6 months of systemic therapy (Leuprolide + abiraterone/prednisone + apalutamide), and metastasis-directed radiation therapy.
- The primary endpoint of the SOLAR trial was remaining with undetectable PSA at 6 months after treatment. The trial showed promising results, with 83% (20 of 24) of patients meeting the primary endpoint. After longer follow-up, 83% of patients maintained an undetectable PSA after two years. The treatment was generally well tolerated, with no unexpected toxicities. Quality of life declined while on active therapy, and then recovered after the treatment regimen ended.
- Patients enrolled on SOLAR were also co-enrolled on the VA-MAPP study, to enable collection of patient tissues for molecular characterization and other studies.
- Results from this trial were comparable to similar trials performed including the "Total Eradication Therapy; TET" trial at Johns Hopkins, the "EXTEND" trial at MD Anderson, and the "SATURN" trial at UCLA, and the “METACURE” trial at Memorial Sloan Kettering Cancer Center, all of which have shown good progression-free survival outcomes.
- The VA is now engaged in a large phase 2/3 "STARPORT" trial in oligometastatic prostate cancer. Patients on this trial will receive ADT alone vs. enhanced systemic therapy, followed by randomization to standard systemic therapy alone or in combination with metastasis directed radiation therapy. The primary endpoint is CRPC-free survival (time to development of castration-resistance).
- Another ongoing randomized phase 2 trial in patients with metastatic castration resistant prostate cancer (mCRPC) with up to 10 metastases, is testing PSMA-targeted radioligand therapy (Pluvicto) plus metastasis-directed therapy with or without continued palliative Pluvicto, all in the absence of continued ADT.



- Dr. Matthew Rettig discussed the development of a predictive AI model for metastatic recurrence in high-risk localized prostate cancer using data from the VA (Veterans Affairs) system.

- High-risk prostate cancer is a heterogeneous disease, with wide-ranging biochemical recurrence rates (14-60%) and ten-year distant metastasis rates (8.1 – 25.4%). Ultimately, most of these patients will die from something other than prostate cancer.
- Existing models to predict metastatic recurrence, such as NCCN, CAPRA, and genomic classifiers like Decipher, even when combined, have suboptimal predictive accuracy and are expensive, tissue-destructive, time-consuming, and have largely been developed in White patients.
- Dr. Rettig and colleagues hypothesized that a “super classifier” machine learning and deep learning-based model integrating multi-dimensional data (pathology, radiology, social determinants of health, and standard clinical-pathologic features) can improve outcome predictions for high-risk prostate cancer patients.
- A pipeline (**Figure**) was established in the VA to acquire and process the necessary data, including: 1) identifying patients with high-risk prostate cancer from the VA-MAPP repository where they have undergone quality control, segmentation, annotation, and deidentification, 2) retrieving and scanning prostate needle biopsies and MRI images, and 3) transferring the data to the VA's Genomic Information System for Integrative Science (GenISIS) for storage and algorithm development.
- AI algorithms are being developed for each data type (prostate needle biopsies, MRI, social determinants of health, and clinical-pathologic factors). These AI models will be integrated into a "super classifier" to predict metastatic recurrence.
- The team has identified over 16,000 cases of non-metastatic disease (defined as no evidence of metastases within five years of initial treatment for high risk localized prostate cancer) and over 1,900 patients who developed metastases between 3 months and 5 years after initial therapy.
- To date, pathology slides have been scanned from 2,100 non-metastatic and 320 metastatic cases. Over 10,000 patients have eligible prostate MRI images, with 2,300 cases having matching biopsies. These will be used for super classifier development and validation.
- The project is currently in the second year of a four-year grant, and the team expects to complete patient accrual within the next one to two years and initiate development of the AI models.



SPECIAL ANNOUNCEMENT: The PCF Gender Equity Networking Initiative

Claire Fletcher

Imperial College London, UK

- Dr. Claire Fletcher discussed the PCF Gender Equity Networking Initiative (GENI), previously known as the PCF Women in Science Forum, and the forward look on this initiative and efforts to increase allyship and inclusivity.
- The GENI Forum was established in 2016 to raise awareness of inequalities and inequities faced by women and others in research, provide a supportive forum for researchers, and promote allyship within the community.
- The Forum is held in-person annually in conjunction with the PCF Annual Scientific Retreat, and has also established a virtual component to organize events throughout the year. The GENI Forums include keynote speeches, panel discussions, and networking opportunities, that address issues related to gender equity in science, inspire women to pursue and continue upward careers in research and medicine, and create a vibrant network and pipeline of women in the field.
- Data shows that while the proportion of women is higher than men at the undergraduate student level and approximately equal at the PhD student level, the percentage of women in more advanced positions declines continually thereafter, with women in only ~20% of full professor positions, and even lower proportions at leadership levels. This highlights the "leaky academic pipeline."
- The reasons for this leaky pipeline are seen across many important metrics, including start-up funds being on average over $500,000 lower for female than male researchers starting independent labs. Women also submit fewer grants and have fewer renewals or simultaneous grants compared to men, a disparity which has been exacerbated by the pandemic. Women are also less likely to get excellent letters of recommendation, awards, and have their lab's manuscripts accepted by all-male panels of reviewers.
- Research indicates that diverse and inclusive environments lead to better outputs and outcomes, underscoring the importance of the Gender Equity Networking Initiative. For instance, gender-diverse companies are 15% more likely to outperform industry medians, and ethnically-diverse companies are 35% more likely to outperform industry medians. There are also direct correlations between ethnic diversity, gender diversity, and age diversity in research teams with their citation counts.
- In the coming years, the GENI Forum organizers are seeking to expand the focus of the Forums to address inequities beyond gender, such as those related to race, sexuality, and social deprivation, to meet the needs of the research community and increase the value and impact of these Forums.

Highlights from Previous GENI Forums

Keynote speeches from inspirational female leaders

Inspiring the next generation

Panel discussions

Celebrating achievement

Building networks

The power of coaching

Dr. Felix Feng Special Lecture: Science and Friendship

Himisha Beltran

Dana-Farber Cancer Institute

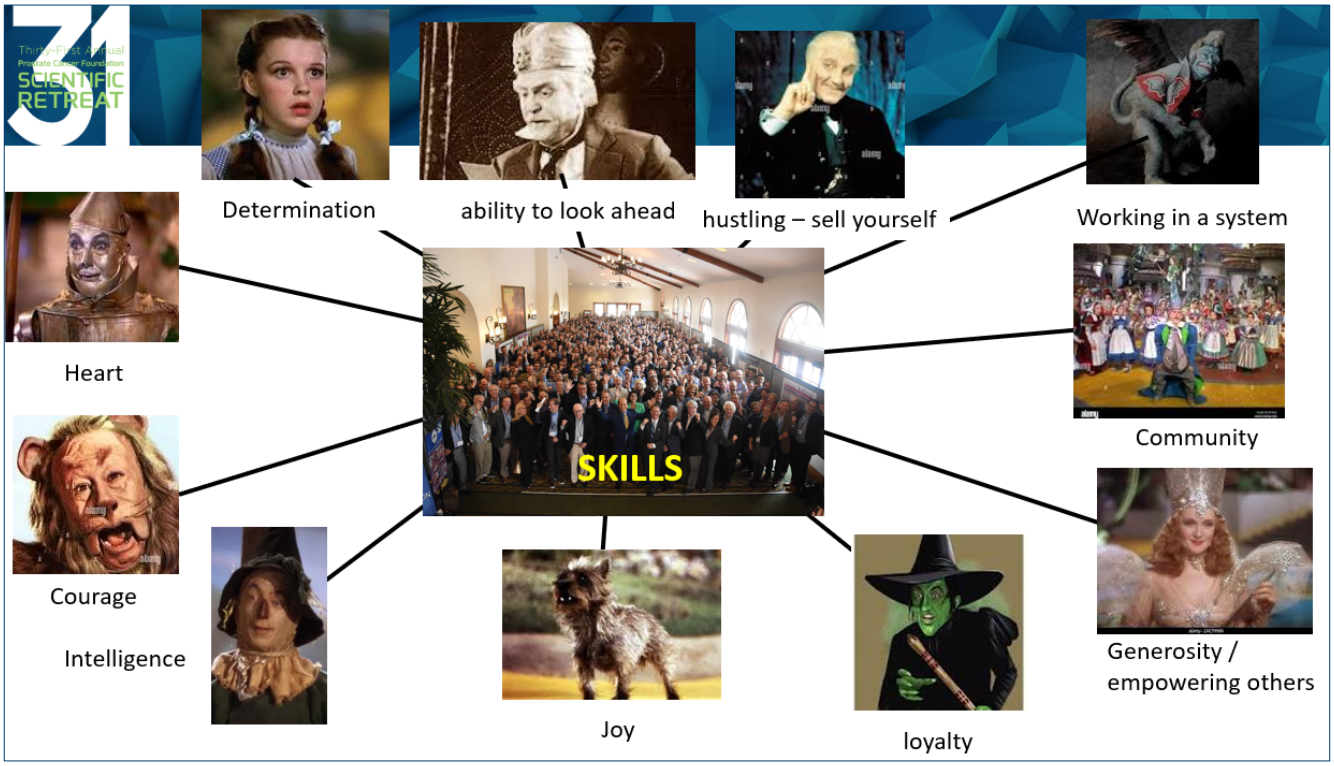
- Dr. Himisha Beltran gave a Special Lecture on Science and Friendship, to honor Dr. Felix Feng, a visionary translational research innovator who bridged lab discoveries with clinical applications, artificial intelligence guru, entrepreneur, and clinical trial expert in the field of prostate cancer research, an extraordinary radiation oncologist beloved by his patients, and a dear friend, teammate, and mentor to all who knew him.
- Dr. Feng has made significant contributions in several areas of prostate cancer research and patient care:
  - Extensive molecular profiling of metastatic castration-resistant prostate cancer, providing important datasets and changing the understanding of the disease landscape.
  - Characterizing the genomic, epigenomic, and transcriptional features of prostate cancer, including identifying novel subtypes and therapeutic targets.
  - Pioneering the use of cell-free DNA and AI-based approaches to improve diagnosis and prognosis.
  - Developing genomic classifiers and leveraging AI to advance precision medicine and predictive/prognostic tools, which led to his founding a startup, Artera, that uses multimodal AI to improve prognosis estimation.
  - As a leader in NROG oncology, he designed and executed numerous impactful clinical trials that could benefit over 1 million patients per year.
- Dr. Feng's exceptional leadership, collaboration, and mentorship skills were instrumental in advancing the field and launching the careers of many young investigators.
- Dr. Feng also exemplified the importance of friendship and community in scientific endeavors, and forged a strong bond with many in the prostate cancer research community. Numerous multi-institutional and global collaborative research teams have been built and maintained through his efforts, and his approach to team science has inspired a deeply rooted culture of collaboration and community throughout the prostate cancer research field.
- In his closing remarks, Dr. Feng expressed gratitude for the support and camaraderie of the Prostate Cancer Foundation (PCF) community, and acknowledged the challenges he faced as a cancer patient and the importance of the patient perspective in research.
- Dr. Feng passed away on Dec.10, 2024, at the age of 48, after a valiant battle with cancer. His memory and legacy will live on in the hearts, minds, and work of the entire prostate cancer research community. He is dearly missed by everyone who knew him.


Science and Friendship

SPECIAL LECTURE: "We're Not in Kansas Anymore" — Cancer Lessons from the Wizard of Oz

Kenneth Pienta
Johns Hopkins University

- Dr. Ken Pienta discussed how to create change in life, business, and medicine, emphasizing the need for skills, resources, a disruptive event, the right place, a vision, and an action plan.
- He drew parallels between the characters in The Wizard of Oz and the skills required for researchers and clinicians working in the field of cancer research and patient care. These include determination, heart, courage, intelligence, joy, generosity and empowerment of others, community and loyalty to it, working in a system, the ability to look ahead, and the ability to sell yourself and your ideas (**Figure**).
- A final necessary component for change is to build a team with diverse expertise, including physicists, computational scientists, cancer biologists, mathematical oncologists, social scientists, evolutionary biologists, and philosophers, to tackle the challenge of cancer.
- There is a high attrition rate in health sciences, with ~40% leaving academia within 5 years and 50% within ten years; and this rate is even worse for women.
- The PCF Young Investigator Awards program has been successful in retaining researchers in academia by finding the right people with the right skills and providing them with resources and support.
- Dr. Pienta presented the disruptive event and case for change as the continually increasing number of cancer deaths worldwide. For instance, the number of deaths from prostate cancer worldwide is expected to increase from ~366,000 in 2000 to ~700,000 in 2040. The number of total cancer deaths worldwide is expected to increase from ~6 million in 2000 to ~15 million in 2040. Researchers all must find and follow their own "yellow brick road" to reject this status quo and define a path towards curing cancer.
- Dr. Pienta's "yellow brick road" is integrating the concept of cancer ecology, which applies evolutionary ecology principles, into the study of lethal cancer. Cancer can be considered analogous to a new species that emerges from a single cell in a multi-cellular organism. However, the traits of therapy resistance and metastasis are observed in all lethal cancers, as a result of convergent evolution due to environmental pressures, adaptation, and selection. Therapy resistance and metastasis can be driven by tumor cell heterogeneity, evolutionary triage, dormancy, and epigenetic plasticity.
- Examples of how eco-evolutionary strategies have be applied to prostate cancer treatment to increase radiographic progression free survival include SBRT (radiation targeted to individual metastatic sites) in patients with oligo-metastases (≤5 metastases) and adaptive therapy (starting and stopping systemic anti-androgen therapy based on PSA levels) in patients with metastatic castration-resistant prostate cancer.



KEYNOTE ADDRESS

Michael Milken
Founder and Chairman
Prostate Cancer Foundation

Introduced by Stuart Holden
Prostate Cancer Foundation, University of California, Los Angeles

This talk can be viewed in full at:
https://www.pcf.org/31st-annual-scientific-retreat-video-replays/

SPECIAL LECTURE: Germline DNA Damage Repair Variants and Prognosis of Patients with High-Risk or Metastatic Prostate Cancer

Konrad Stopsack

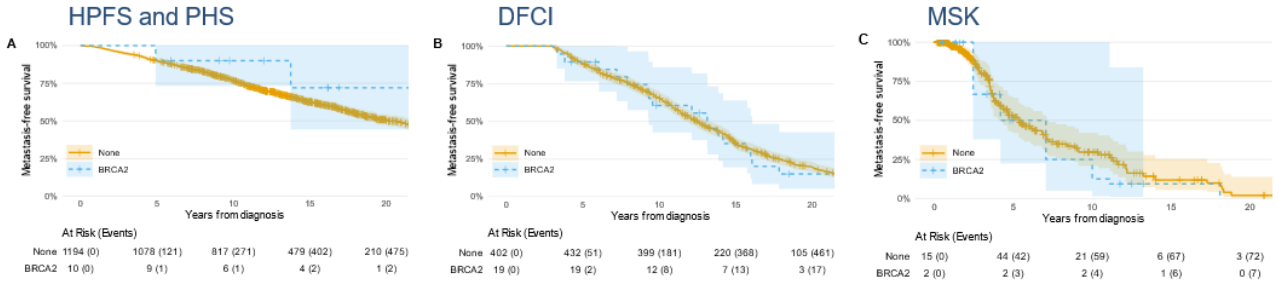
Massachusetts General Hospital; Harvard T.H. Chan School of Public Health

- Dr. Konrad Stopsack discussed the relationship between germline DNA damage repair variants and prognosis in patients with high-risk or metastatic prostate cancer.
- Predictive biomarkers indicate outcome under a specific treatment, while prognostic biomarkers indicate outcome independent of treatment.
- Germline (inherited) variants in genes that function to repair damaged DNA, particularly *BRCA2*, are strong risk factors for the diagnosis of prostate cancer and for death from prostate cancer in the general population. These cancers also have more aggressive features at the time of diagnosis, like a higher Gleason score or stage.
- It has been previously shown that carriers of pathogenic *BRCA2* variants have higher risk for diagnosis of prostate cancer, more aggressive disease when diagnosed, and death from prostate cancer, compared to the general population.
- Whether having a pathogenic *BRCA2* variant is associated with worse outcomes among patients already diagnosed with prostate cancer was unclear.
- Dr. Stopsack and colleagues investigated this question in cohorts of patients diagnosed with high-risk localized prostate cancer, metastatic castration-sensitive prostate cancer (mCSPC), and metastatic castration-resistant prostate cancer (mCRPC).
- They found that among patients diagnosed with the same prostate cancer disease state, the presence of pathogenic *BRCA2* variants was not associated with a substantially worse prognosis in terms of metastasis-free survival (**Figure**)or overall survival.
- This absence of a worse prognosis was not explained by factors like age, race, Ashkenazi Jewish founder variants, Gleason score, PSA, primary treatment (radiation therapy vs. prostatectomy), or use of PARP inhibitors or platinum chemotherapy.
- When looking at a broader set of 26 DNA repair genes, the prevalence of pathogenic variants was 10%, but the prognostic impact of these variants could not be clearly determined.
- These data suggest that while *BRCA2* variants are a strong risk factor for the development of aggressive prostate cancer, and while they are *predictive* of response to PARP-inhibitors, they are not strongly *prognostic* once the cancer is already present and defined by other clinical features.
- Similar results have been seen for breast and ovarian cancer in which carriers of *BRCA1* and *BRCA2* variants have a substantially higher risk of getting one of those cancers, of those cancers being more aggressive, and of dying from them, while *BRCA* variants aren't generally considered to be prognostic or used for risk stratification after diagnosis.

BRCA2 variants, disease state, and prognosis

89 patients had pathogenic/likely pathogenic germline variants in *BRCA2.*
Prevalence 0.8% (95% CI 0.4, 1.4) in HPFS/PHS
3.6% (95% CI 2.9, 4.4) at DFCI, MSK

Metastasis-free survival in high-risk localized disease

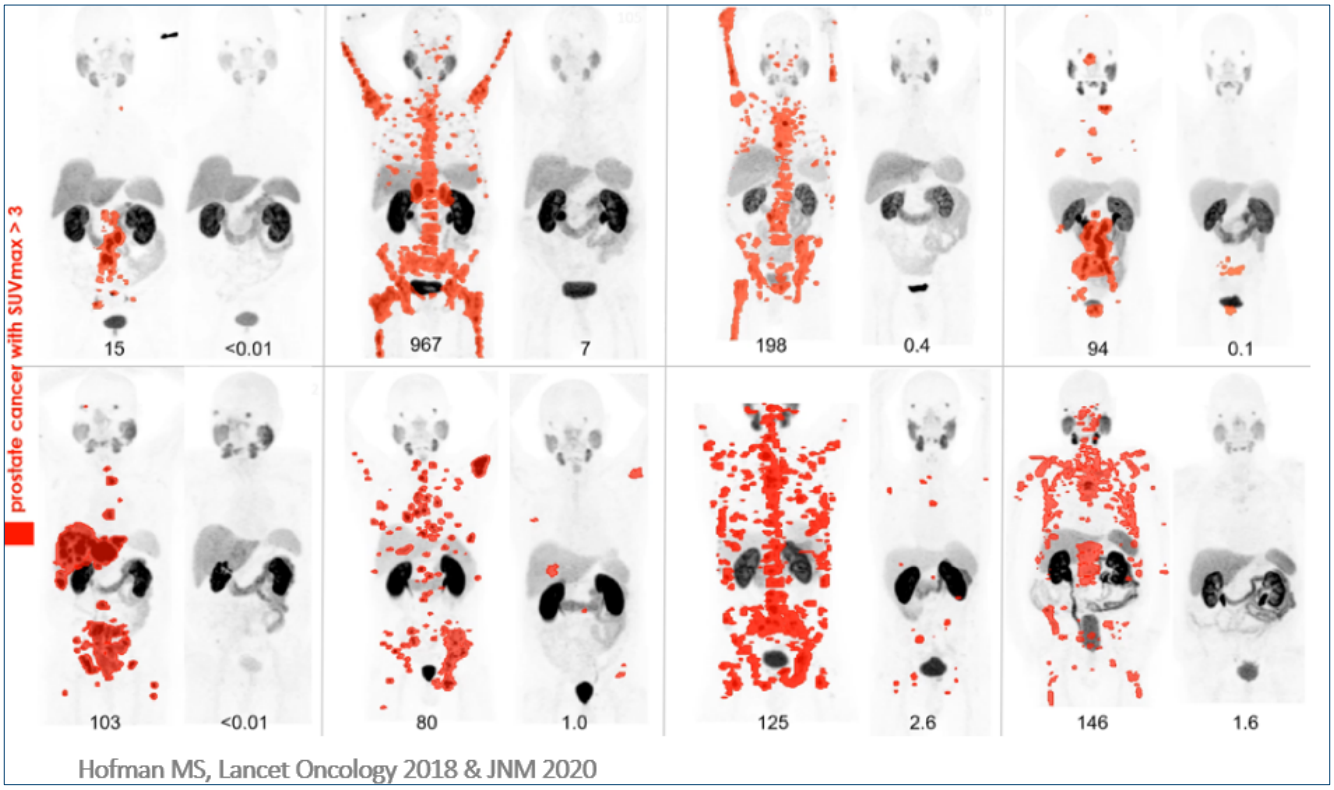


Session 7: Next Generation Theranostics

Introduction

Michael Hofman
Peter MacCallum Cancer Centre, Australia

- Dr. Michael Hofman gave an overview on advancements in theranostics, which is the combination of diagnostic and therapeutic technologies, over the past decade.
- Over two and half decades, molecular imaging has evolved from a research tool to a new standard of care, with over 100 PET/CT scanners available in Australia, a relatively small country, and this trend has been replicated globally. Radiopharmaceutical therapy has also become a new standard of care with rapid growth globally since FDA approval of Lutetium-177-DOTATATE (Lutathera®) in 2018.
- Lutetium-177-PSMA-617 (Pluvicto®), is a new theranostic treatment that shown incredible responses in clinical trials and was FDA-approved for the treatment of PSMA PET-positive metastatic castration-resistant prostate cancer (mCRPC) in 2022.
- In the past 18 months, there have been over $5 billion in mergers and acquisitions in the theranostics space, indicating the significant potential for further development.
- The Peter MacCallum Cancer Centre in Australia established the Prostate Cancer Theranostic & Imaging Center of Excellence (ProsTIC) focused on theranostics imaging and therapy, enabling the expansion of clinical trials, discovery research, and educational initiatives. The first phase 2 study and subsequent randomized trial testing ^{177}Lu-PSMA-617 was conducted at this Centre (**Figure**).
- There have been 5 randomized trials at the Peter MacCallum Cancer Centre testing ^{177}Lu-PSMA-617 in various combinations or different clinical situations. Results from the most recent three of these trials were published in 2024.
- Lutetium-177-PSMA-617 can cause significant tumor regression in patients with mCRPC but is ultimately not curative. It remains important to find new radioactive atoms and tumors targets to drive the next generation of theranostics development, which was the topic of this session and discussed by the other speakers.
- Radioactive iodine (I-131) which has been used to treat metastatic thyroid cancer for over 80 years, is a benchmark for the potential of theranostics to achieve curative outcomes. Uptake by tumors of I-131 is far greater than Lutetium-177-PSMA-617, suggesting that tumor uptake is a significant indicator of efficacy and can be used to drive decisions in future theranostic drug development.
- Other challenges in theranostics include ensuring equitable access to theranostic treatments, as highlighted in a recent *Lancet Oncology* commission on the topic.

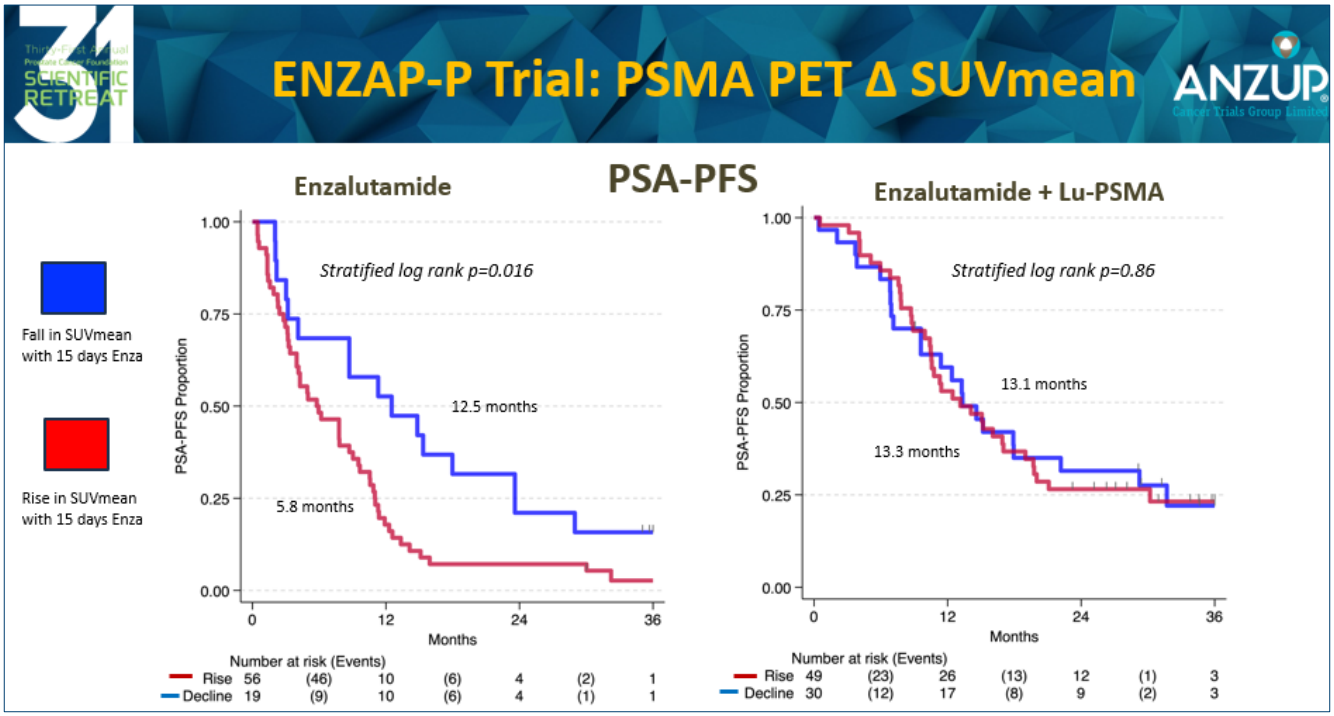


PSMA: What's New in 2024?

Louise Emmett
The University of New South Wales, Australia

- Dr Louise Emmett discussed advances in PSMA theranostics in prostate cancer, including biomarkers for moving PSMA theranostics earlier in prostate cancer and new PSMA-targeted peptide technology.
- TheraP was a randomized phase 2 trial that compared Lutetium-177-PSMA-617 (Pluvicto®; up to 6 doses) vs. standard-of-care cabazitaxel chemotherapy (up to 10 doses) in patients with PSMA PET-positive metastatic castration-resistant prostate cancer (mCRPC). Overall survival was observed to be similar for these treatments, suggesting Lutetium-177-PSMA-617 is a treatment option in this patient population.
- Using samples from the TheraP trial, circulating tumor DNA (ctDNA), which can be obtained from a simple blood draw, was shown to be a predictive biomarker for Lutetium-177-PSMA-617, with higher response rates in patients with lower ctDNA levels. ctDNA levels were not predictive for responses to cabazitaxel, with similar response rates seen across different ctDNA levels.

- EnzaP was a randomized phase 2 trial that compared enzalutamide alone vs. enzalutamide + Lutetium-177-PSMA-617 (2-4 doses beginning after 15 days of just enzalutamide) in patients with PSMA PET-positive mCRPC. This trial was designed based on the hypothesis that treatment with enzalutamide will increase PSMA expression and thereby increase efficacy of Lutetium-177-PSMA-617. This trial included serial blood collection, PSMA PET, and FDG PET imaging, to assess how enzalutamide changes PSMA levels and perform other correlative studies.
- After 15 days of enzalutamide treatment, ~70% of patients had increased PSMA PET levels, while ~30% of patients instead had a decrease.
- In patients treated with enzalutamide alone, those who had an early decrease in PSMA levels experienced significantly better PSA progression free survival than those who had an early increase in PSMA levels (median of 12.5 vs. 5.7 months), suggesting that PSMA PET can be used to predict efficacy of enzalutamide alone after only 15 days of treatment (**Figure**).
- However, in patients that were treated with the combination, similar PSA progression free survival was seen between patients with early increased and decreased PSMA levels (median of 13.3 vs. 13.1 months), suggesting that treatment with Lutetium-177-PSMA-617 overcomes a poor response to enzalutamide alone (**Figure**). This also suggests that the patients who benefit the most with the addition of Lutetium-177-PSMA-617 therapy are those ~70% who don't respond in the first 15 days to enzalutamide.
- Overall survival results from the Enza-P trial will be reported soon.
- In 2024 results from two similar phase 3 trials were reported, PSMAFORE and SPLASH, both of which tested a PSMA-targeted radionuclide vs. a switch in androgen receptor pathway inhibitor. While the PSMA-targeted radionuclide tested in these trials differed slightly, the major difference in the trial designs was the dose level and treatment schedule.
- PSMAFORE tested 6 doses of 7.4Gb Lutetium-177-PSMA-617 given every 6 weeks and was a positive trial. SPLASH tested 4 doses of 6.8Gb Lutetium-177-PSMA-I&T given every 8 weeks (fewer, lower, and more spaced-out doses) and was a negative trial. This demonstrates that optimizing dosing and dosing intervals for Lutetium-PSMA therapy is needed to improve patient outcomes.
- Upfront PSMA was a phase 2 trial testing docetaxel alone vs. docetaxel + Lutetium-177-PSMA-617 (2-4 doses beginning after 15 days of just enzalutamide) in patients with PSMA PET-positive metastatic hormone sensitive prostate cancer (mHSPC). Significantly improved rates of undetectable PSA at 12 months were observed with the combination vs. docetaxel alone (41% vs 16%). Radiographic progression free survival was also significantly better in the combination arm. These results demonstrate promise for Lutetium-PSMA therapy earlier in the disease course.
- New high-affinity PSMA-targeted peptides, such as Copper-64 Sarbis PSMA, appear promising in early trials for improving diagnostic sensitivity for early biochemical recurrence and staging compared to current PSMA-targeted imaging agents.



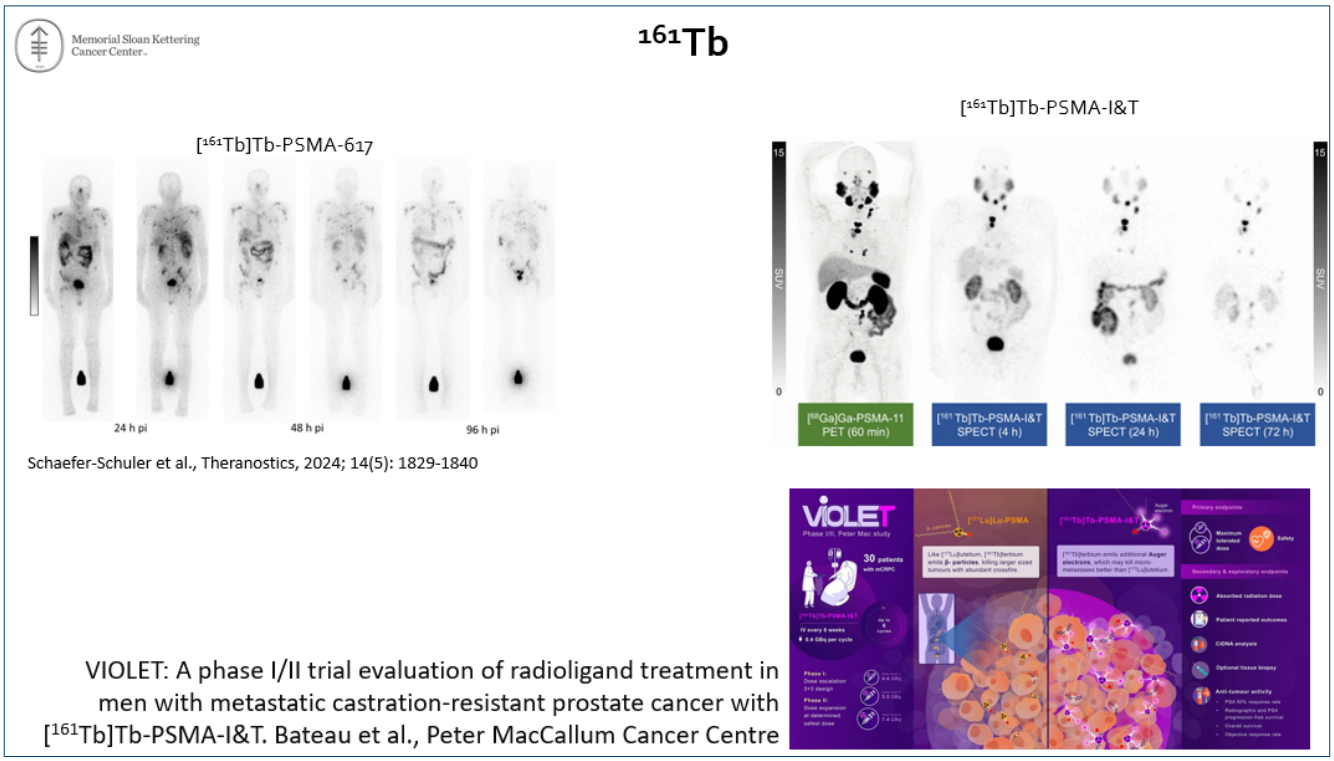
New Atoms

Jason Lewis

Memorial Sloan Kettering Cancer Center

- Dr. Jason Lewis discussed the need for new atoms and isotopes in radiopharmaceuticals for cancer imaging and therapy, known as theranostics.
- Radiopharmaceutical agents consist of a cancer-targeting component (small molecule, antibody, peptide, nanoparticle, etc.) attached to a radioactive isotope. Molecular imaging isotopes emit positrons (PET imaging) or photons (SPECT imaging), while therapeutic isotopes emit high energy particles (alpha or beta particles, auger electrons) that damage DNA and kill cancer cells.
- In theranostics, a molecular imaging agent and therapeutic agent that bind the same cancer target are used together. This enables clinicians to use molecular imaging to determine if a patient's tumor expresses the target, before prescribing the therapy. For example, PSMA PET is used to determine which patients with metastatic castration-resistant prostate cancer (mCRPC) are eligible for treatment with PSMA-targeted radioligand therapy (Pluvicto®). Theranostics targeting other prostate cancer proteins are under development.
- Dr. Lewis and colleagues are developing DLL3-targeted theranostics for the treatment of neuroendocrine prostate cancer.
- A recent *Lancet Oncology* commission on Radiotherapy and Theranostics has published several papers highlighting challenges the field faces to improve these therapies and increase global capacity.

- Current therapeutic radiopharmaceuticals use a limited set of isotopes, such as the beta particle emitter Lutetium-177 and the alpha particle emitter Actinium-225.
- The field faces isotope supply challenges, as the rising demand for theranostics has outpaced the capabilities of the aging population of nuclear reactors that supply these isotopes. New isotopes that don't rely on reactors can overcome supply issues and are being studied.
- It is important to match the isotope's half-life and emission properties to the biological behavior of the targeting molecule (e.g., small molecules, antibodies, peptides) for optimal imaging and therapy.
- Examples of new isotopes with potential for Theranostics include:
  - Lead-212, which can be produced using a generator and has both SPECT imaging and alpha-particle therapy capabilities. The phase 1/2 TherapB trial is testing Lead-212-PSMA SPECT and radioligand therapy in patients with mCRPC.
  - Copper-64 for PET imaging and Copper-67 for beta-particle therapy, using the same targeting molecule. The phase 1/2 SECuRE trial is testing Copper-64 / Copper-67 SAR-bisPSMA for identification and treatment of PSMA-expressing mCRPC.
  - Terbium isotopes, which can emit a variety of therapeutic particles (beta particles, Auger electrons) and may be useful for targeting DNA. The phase 1/2 VIOLET trial is testing Terbium-161-PSMA-I&T radioligand treatment in patients with mCRPC (**Figure**).
  - There remains a need to explore a wider range of isotopes to overcome challenges such as supply limitations and to provide more personalized and effective theranostic approaches for cancer patients.



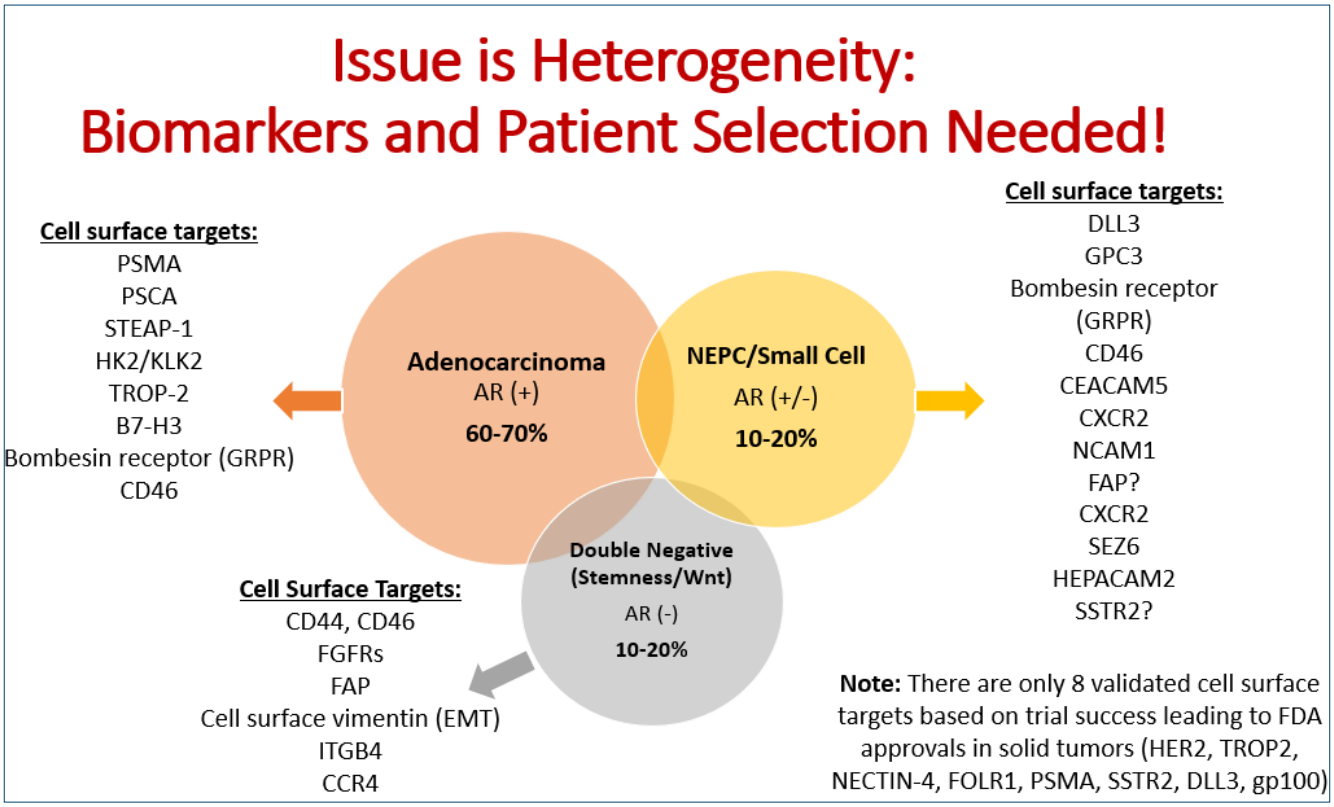
Schaefer-Schuler et al., Theranostics, 2024; 14(5): 1829-1840

VIOLET: A phase I/II trial evaluation of radioligand treatment in men with metastatic castration-resistant prostate cancer with [161Tb]Tb-PSMA-I&T. Bateau et al., Peter MacCallum Cancer Centre

New Theranostic Targets

Andrew Armstrong
Duke University

- Dr. Andrew Armstrong discussed the heterogeneity of prostate cancer and the need for targeting multiple cell surface targets to overcome treatment resistance.
- PSMA-radioligand therapy is a relatively new treatment for patients with advanced prostate cancer that has high PSMA levels on PET scans. However, nearly all patients eventually develop resistance within 1-2 years. Additionally, 10-20% of prostate cancer patients have discordant or low PSMA uptake on PET scans so are not eligible for PSMA-radioligand therapy and also have poor survival with conventional therapies. New treatments and treatment targets remain an urgent need.
- Prostate cancer can be categorized into different subtypes based on androgen receptor (AR) dependence, neuroendocrine features, and "double negative" or stem-like characteristics.
- Each subtype has distinct cell surface targets that can be targeted with therapies like bispecific T-cell engagers, antibody-drug conjugates, and radioligand therapies.
- Potential new cell surface targets for various prostate cancer subtypes include AR dependent pathways (HK2, STEAP1, PSMA, PSCA, TROP2, EpCAM), neuroendocrine prostate cancer targets (GPC3, Bombesin, CEACAM5, EpCAM, Somatostatin, DLL3, CD46, ISM1, CXCR2), stemness and other pathways (WNT, FGFR, CD44, TROP2), and tumor microenvironment targets (FAP, B7H3) (**Figure**).
- Prostate cancer theranostics targeting STEAP1, HK2, DLL3, GPC3, B7H3, CD46, FAP, and others are under development; some of these have entered clinical trials with promising early results.
- Companion diagnostics and biomarkers are needed to assess for these targets and their heterogeneity, to guide patient selection and therapy. Cell surface targets enable development of PET imaging as a companion diagnostic/biomarker, like how PSMA PET imaging is used to determine patient eligibility for PSMA radioligand therapy.
- Challenges include addressing lineage plasticity, spatial and temporal heterogeneity, and determining the optimal use of these targeted therapies (sequential, combination, or evolutionary steering).



Trials in Action: What's Hot?

James Buteau
Peter MacCallum Cancer Centre, Australia

- Dr. James Buteau discussed several ongoing clinical trials and research related to improving outcomes and theranostics for patients with prostate cancer:
- The PRIMARY2 trial is investigating the value of adding PSMA PET scans prior to prostate biopsy in patients with a normal or equivocal MRI (PI-RADS 2 with other high-risk features or PI-RADS 3), with the goal of improving accuracy in detecting clinically relevant cancer, guiding biopsies and avoiding unnecessary biopsies.
- PSMA PET scans have been shown to be promising biomarkers to predict response to PSMA-radioligand therapy. Higher PSMA uptake is associated with better overall survival, while those with low PSMA uptake may benefit from combination treatments rather than receiving PSMA-radioligand therapy alone.
- FDG PET is a highly available molecular imaging technology that has also been demonstrated to be prognostic of poorer outcomes with various therapies, including cabazitaxel and PSMA-radioligand therapy.

- Several Lutetium-177-PSMA-617 (LuPSMA; Pluvicto®) combination therapy trials in patients with metastatic castration-resistant prostate cancer (mCRPC) were discussed:
  - LuCAB is a phase 1/2 trial combining cabazitaxel with LuPSMA, aiming to leverage the radio-sensitizing properties of cabazitaxel and treat PSMA-negative metastases.
  - LuPARP is a dose escalation trial combining olaparib (a PARP inhibitor) with LuPSMA, to potentially increase DNA damage and cell death. Among patients who received doses at or just below the dose selected for further testing, PSA50% response rates were 75% and PSA90% response rates were 58% (**Figure**).
  - EVOLUTION is a randomized trial comparing LuPSMA alone to LuPSMA in combination with ipilimumab and nivolumab immunotherapy.
- Dr. Buteau also discussed trials investigating novel radioligand therapies in patients with mCRPC.
  - VIOLET is a phase 1/2 trial testing Terbium-161-PSMA-I&T. Compared to beta-emitting LuPSMA, Terbium-161 emits additional Auger electrons, and thus may be able to better target micro-metastases and improve the duration of response.
  - AcTION is a phase 1 trial testing Actinium-225-PSMA-617, to determine the appropriate dosing for this alpha-emitting radioisotope.
  - AlphaBet is a phase 1/2 trial combining Radium-223 and LuPSMA, aiming to leverage the complementary mechanisms of action of these two radiopharmaceuticals, both of which are already approved for use in patients with mCRPC separately.
- Overall, there are several promising approaches to improve outcomes for patients with advanced prostate cancer, including novel imaging techniques, combination therapies, and emerging radioisotopes.

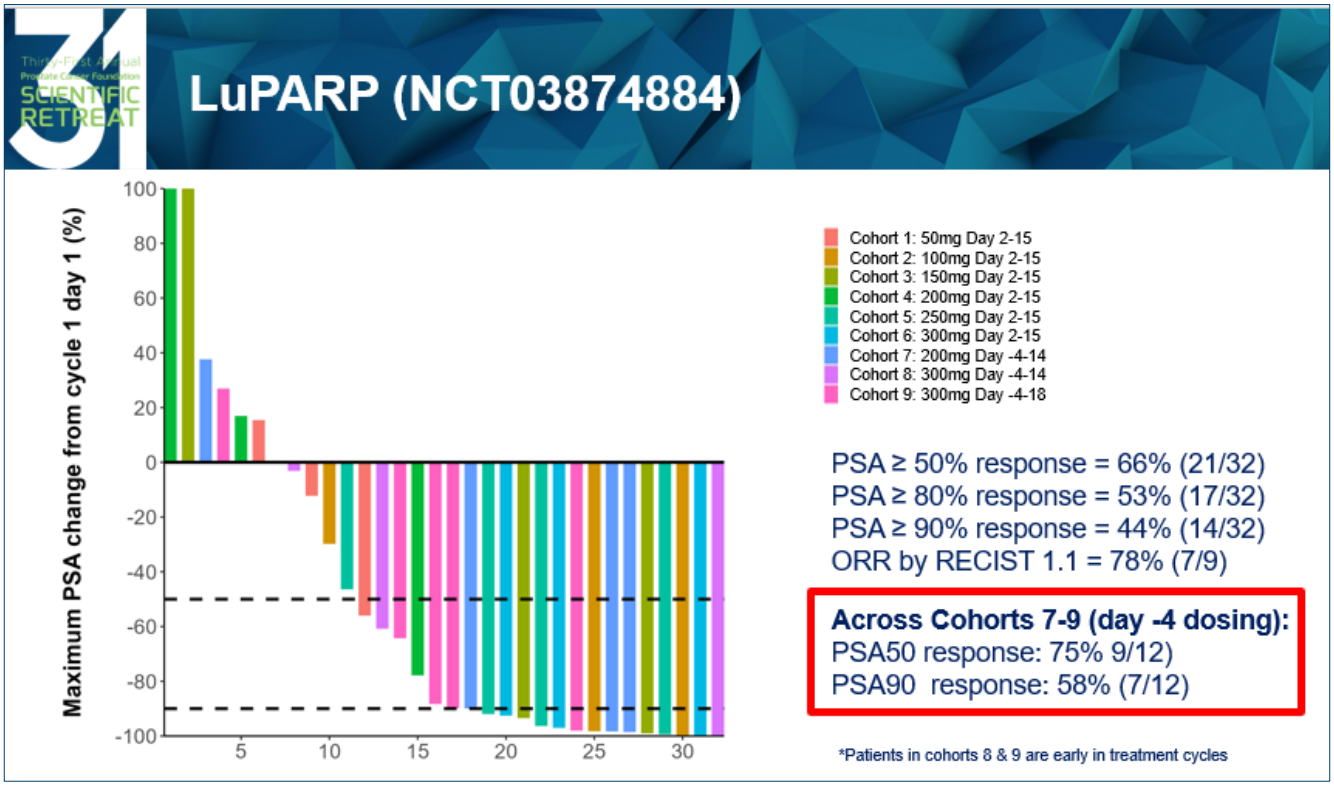


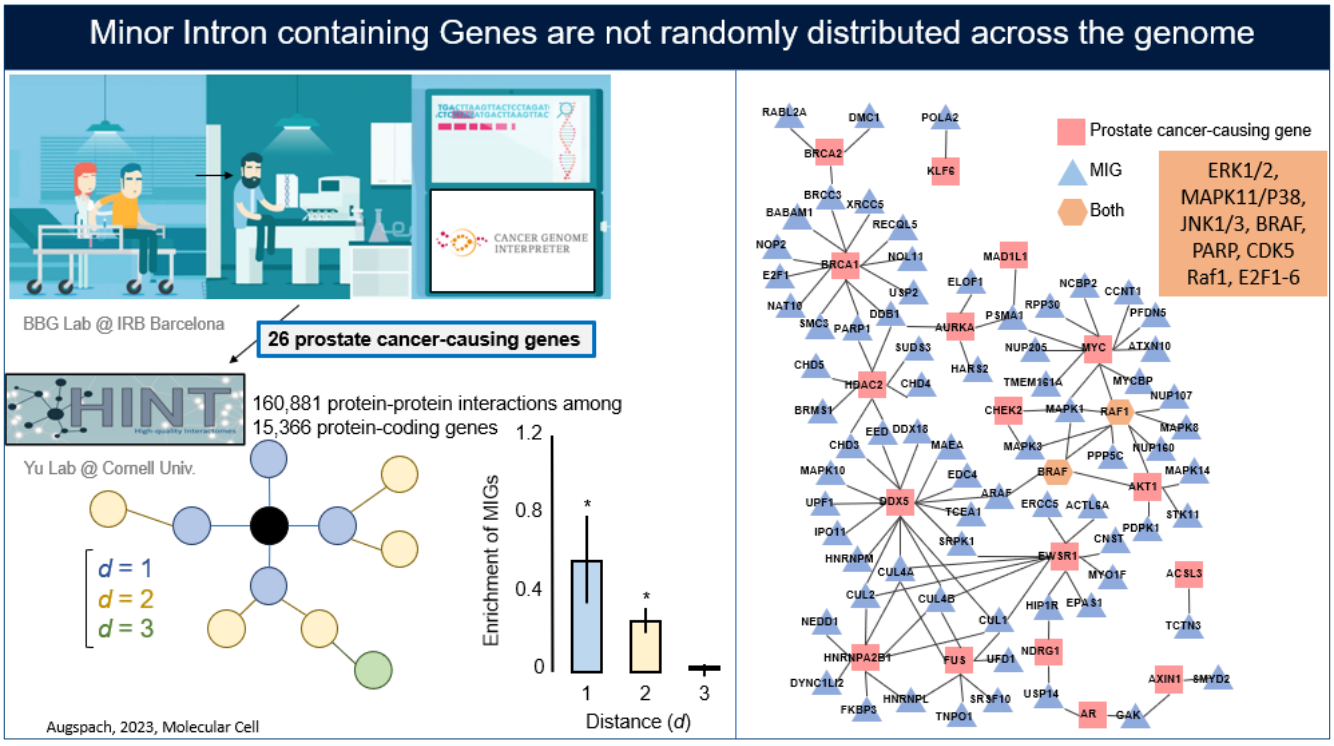
Figure courtesy of Dr. Shahneen Sandhu.

Session 9: Advanced Molecular Biology of Lethal Prostate Cancer

Minor Intron Splicing in the Pathogenesis of Lethal Prostate Cancer

Mark A. Rubin[1], Anke K. Augespach[1], Rahul N. Kanadia[2]
[1]University of Bern and Inselspital, Switzerland
[2]University of Connecticut, Connecticut, USA

- Dr. Mark Rubin discussed the role of minor intron splicing in prostate cancer development.
- Minor introns are a small subset (around 0.5%) of introns not recognized by the major spliceosome but instead require a specialized minor spliceosome for their removal. This translates to about 750 genes in the human genome. These genes are important in development and are hijacked in cancer.
- Dr. Rubin and colleagues identified ~26 genes containing minor introns known to be cancer-driver genes in prostate cancer. This was not a random distribution but a tight link between minor intron-containing genes and prostate cancer (**Figure**).
- The expression and activity of minor spliceosome genes, including the minor spliceosome component U6atac, increased with prostate cancer progression. In contrast, major spliceosome activity did not correlate with prostate cancer progression.
- The androgen receptor (AR) stabilized U6atac and maintained minor intron splicing in AR-sensitive models, while MAPK signaling regulated minor splicing in other contexts.
- Knockdown of U6atac lead to decreased viability in castration-resistant prostate cancer (CRPC), neuroendocrine prostate cancer (NEPC) models, and patient-derived organoids, but not in benign prostate cells. The effects of minor splicing knockdown appear mediated through cell cycle and E2F transcription factor pathways.
- The team developed a reporter for minor and major intron splicing that was used to identify small molecules that preferentially inhibit the minor spliceosome without significantly inhibiting it.
- These data suggest that targeting minor intron splicing is a promising therapeutic approach for prostate cancer.
- Dr. Rubin, Dr. Augspach, and Dr. Kanadia have founded a BioTech company called VerIntas Therapeutics to translate these seminal findings to treat lethal prostate cancer.

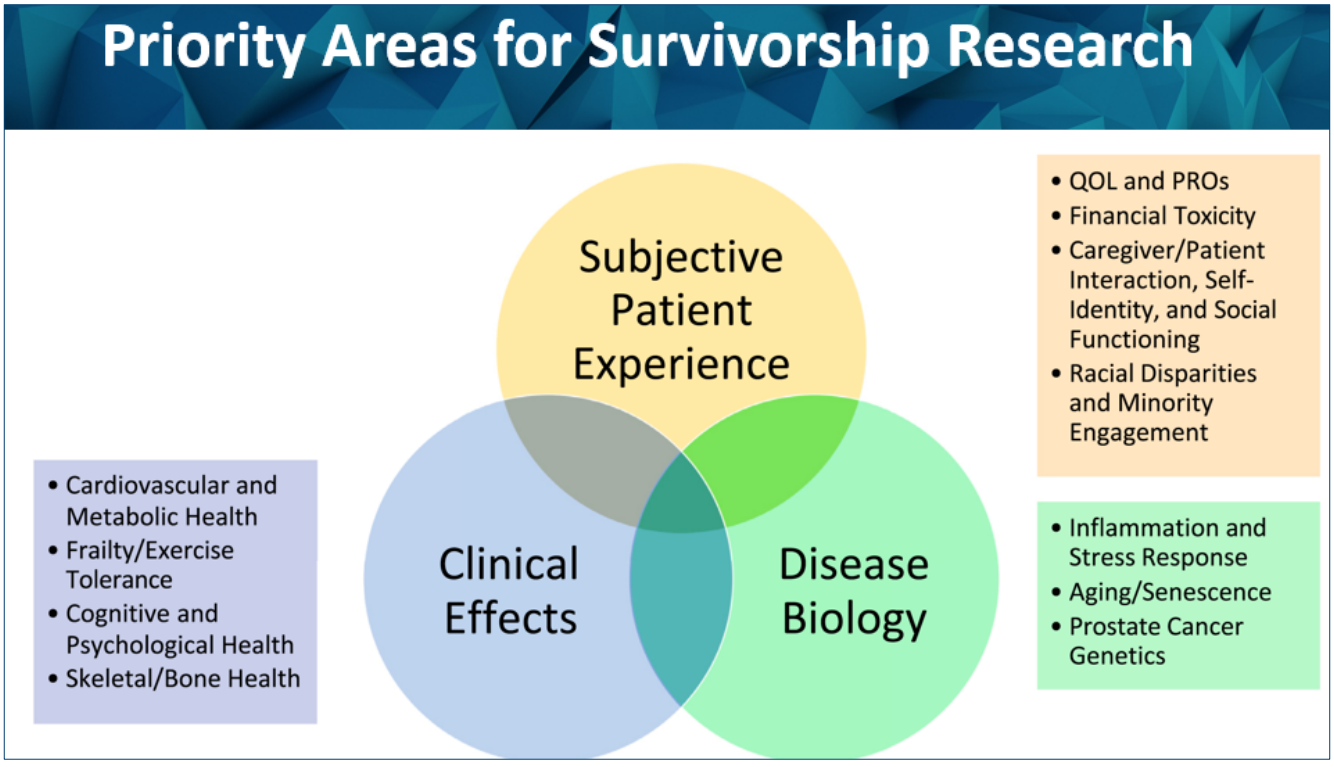

Minor Intron containing Genes are not randomly distributed across the genome
CANCER GENOME INTERPRETER
BBG Lab @ IRB Barcelona
26 prostate cancer-causing genes
HINT
160,881 protein-protein interactions among 15,366 protein-coding genes
Yu Lab @ Cornell Univ.
d = 1
d = 2
d = 3
Enrichment of MIGs
1.2
0.8
0.4
0
1
2
3
Distance (d)
Augspach, 2023, Molecular Cell
Prostate cancer-causing gene
MIG
Both
ERK1/2, MAPK11/P38, JNK1/3, BRAF, PARP, CDK5 Raf1, E2F1-6

Session 10: Clinical Survivorship 2.0: Metabolic Effects in Survivorship Biology

Introduction

Alicia Morgans
Dana-Farber Cancer Institute

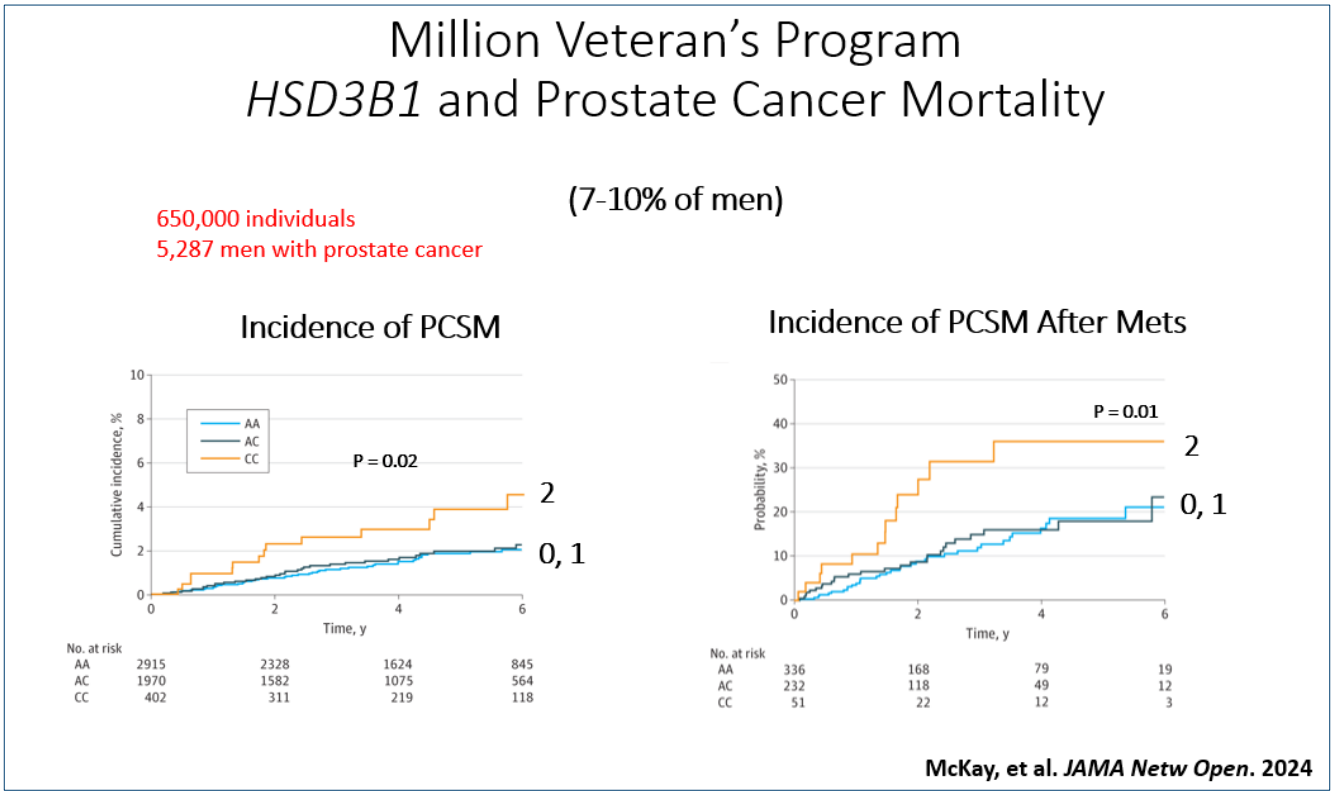
- Dr. Alicia Morgans gave an overview on survivorship, which encompasses the period from cancer diagnosis to end-of-life or initiation of palliative/supportive care.
- Survivorship involves the intersection of the subjective patient experience, the biology of the disease, and the clinical effects of therapies, all of which contribute to the unique experience of each individual.
- Precision survivorship recognizes the heterogeneity of individuals and how it can affect long-term treatment complications, patient-reported outcomes, quality of life, and adverse events.
- Survivorship science encompasses various aspects, including quality of life assessments, behavioral studies, metabolic investigations, genetic evaluations, and exercise science, all of which have the potential to improve both patient experience and disease control outcomes (**Figure**).
- Conducting research in the survivorship space can be challenging, as such studies may not involve testing new drugs, and thus can be more difficult to recruit patients to. Collaborations between clinical teams, basic scientists, behavioral health investigators, and young investigators are crucial to address these important issues and improve the lives of people with prostate cancer.



Metabolism Effects in Response, Resistance, and Complications of Treatment

Nima Sharifi
University of Miami

- Dr. Nima Sharifi discussed the importance of steroid metabolism in prostate cancer and how it can impact treatment outcomes, adverse effects and survivorship.
- Prostate cancer is driven by the androgen receptor (AR), and thus this pathway has been the main target of therapeutic development for decades. There are now several treatments available that target the AR pathway, with recent studies focused on using these treatments earlier in the disease course and in combinations for more intense AR pathway-inhibition.
- However, these treatments remain prescribed based on a patient's disease state and not on their inherited metabolic states or induced changes in their metabolic states.
- The levels of androgens and other hormones in circulation are dependent on several factors including the metabolism of inactive into active forms. This is particularly relevant for hormones that need to be converted to active forms in the target tissue, such as the prostate.
- 3β-hydroxysteroid dehydrogenase 1 (3βHSD1, encoded by the gene *HSD3B1*) is an enzyme that plays a key role in converting adrenal androgen precursors into potent androgens like testosterone and dihydrotestosterone (DHT). There are two genetic variants of *HSD3B1*- a "fast" form that leads to higher testosterone and DHT levels, and a "slow" form that results in lower testosterone and DHT levels.
- Multiple studies have shown that patients with prostate cancer who inherit two copies of the "fast" form of *HSD3B1* have worse clinical outcomes after androgen deprivation therapy (ADT) and higher prostate cancer-specific mortality rates compared to patients with one or two copies of the "slow" form of *HSD3B1* (**Figure**). Patients with one copy of each did similarly to those with two copies of the slow form.
- Further studies found that while inheritance of two copies of the "fast" *HSD3B1* variant did not increase risk for development of prostate cancer or more aggressive disease features at the time of diagnosis, but was highly associated with increased mortality after starting AR-targeted therapy.
- Preliminary data suggests that patients with two copies of the "fast" *HSD3B1* variant may benefit from earlier, more intensive hormonal therapy to prevent the increased mortality risk.
- The *HSD3B1* genotype may also impact the adverse effect profile of hormonal therapies, potentially influencing side effects like gynecomastia, due to 3βHSD1 having a role in estrogen metabolism.
- Overall, *HSD3B1* represents the most common single gene linked to prostate cancer mortality, and is potentially actionable. Further research is needed to fully understand its implications for treatment and management of prostate cancer.

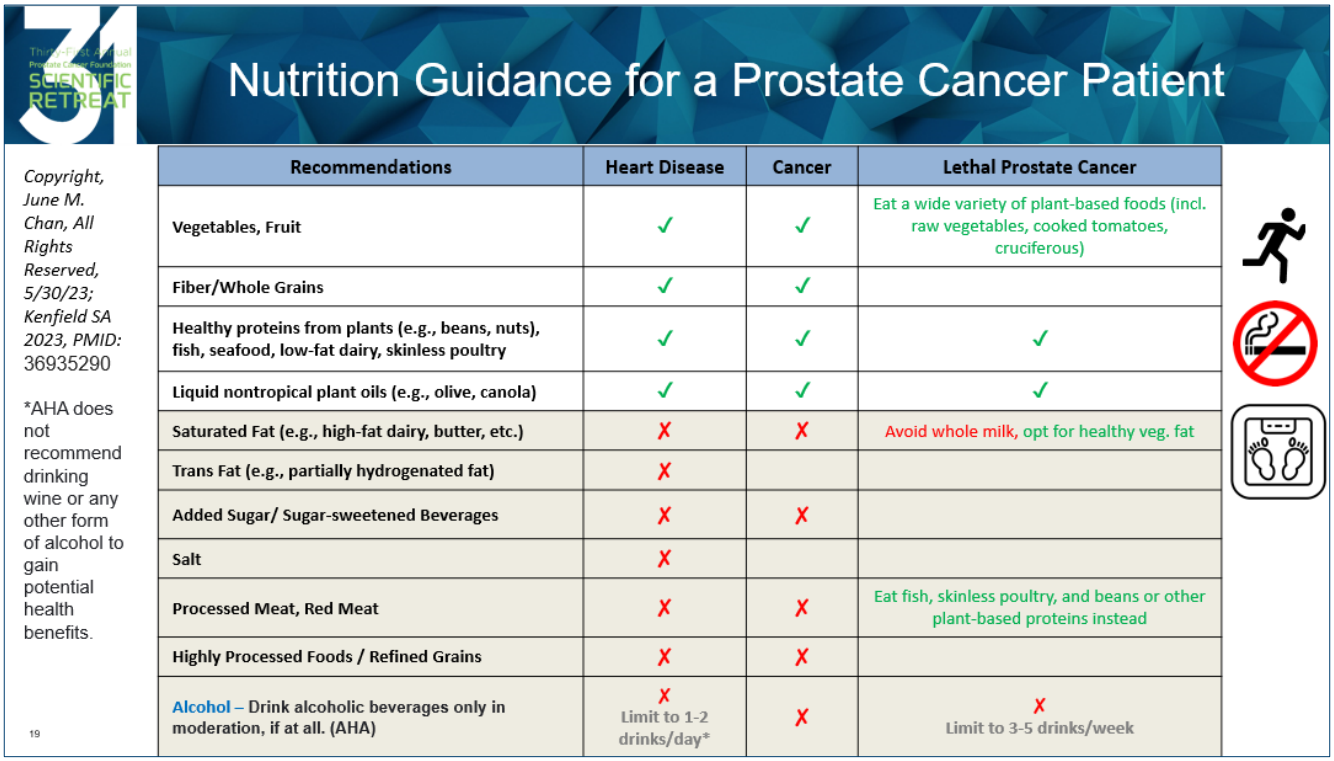


Exercise and Dietary Impacts on Prostate Cancer Outcomes

Stacey Kenfield
University of California, San Francisco

- Dr. Stacey Kenfield discussed the relationship between aerobic physical activity and clinical outcomes, including all-cause mortality, in patients with prostate cancer.
- The first study in men diagnosed with prostate cancer demonstrated that moderate levels of total physical activity (≥9 MET hours/week; about 30 minutes of walking most days per week) were associated with reduced overall mortality, while higher levels of vigorous physical activity ((≥48 MET hours/week; about ≥1 hour a day of jogging) were associated with reduced prostate cancer-specific mortality. No association of non-vigorous activity was observed with reductions in prostate cancer-specific mortality.
- Additional studies include cohorts from the US, Sweden, and Canada, and people across the disease spectrum of stage and grade. Benefits in these studies were also seen at more modest levels of activity. For example, walking and biking at levels of 20 min/day or more were associated with a lower risk of overall mortality and prostate cancer-specific mortality.

- These study findings taken together consistently show a beneficial association of exercise after diagnosis with prostate cancer outcomes and have led to an update to the Physical Activity Guidelines for Americans in 2018, which now states that prostate cancer survivors have a lower risk of dying of prostate cancer with regular physical activity. The guidelines recommend at least 150 minutes a week of moderate intensity aerobic physical activity or at least 75 minutes of vigorous intensity aerobic physical activity, or an equivalent combination. These guidelines also recommend muscle-strengthening activities of moderate or greater intensity and that involve all major muscle groups on 2 or more days a week, and balance training as separate component.
- Studies have also found that fitness and muscle mass are associated with improved outcomes in men with prostate cancer.
- INTERVAL-GAP4 is an ongoing randomized study coordinated at USCF and Edith Cowan University, which aims to determine if supervised exercise (vs. self-directed exercise) improves overall survival in patients with metastatic prostate cancer. Results from this study will be available in 1-2 years.
- Dietary patterns and scores have also been associated with prostate cancer outcomes.
- The Western dietary pattern has been associated with increased prostate cancer-specific mortality and overall mortality, while the Prudent and Mediterranean dietary patterns were associated with lower overall mortality. The Prudent pattern is characterized by higher intake of legumes, vegetables, fruits, whole grains, garlic, soy products, fish, and oil and vinegar dressing. The Mediterranean dietary pattern is characterized by high intakes of vegetables, fruits and nuts, legumes, cereals, fish and seafood, high ratio of polyunsaturated to saturated fat, 10-50 g/day of alcohol, and low intake of red and processed meats and dairy products.
- A plant-based diet (eating more plant-based foods versus animal foods) was associated with lower risk of prostate cancer progression.
- The Healthy Plant-Based Diet index, which gives negative points to foods including fruit juices, sugar-sweetened beverages, refined grains, potatoes, and sweets and desserts, has been associated with lower risk of prostate cancer progression among patients with Gleason Grade ≥7 prostate cancer.
- Prostate-8-II is an ongoing study which aims to determine the effect of a digital health behavioral intervention on clinical, patient-reported, and biological outcomes in patients with prostate cancer who had surgery.
- Overall, recommendations of modifiable health habits to improve prostate cancer outcomes and quality of life, include regular physical activity, smoking cessation, and maintaining a healthy body weight.
- While evidence is less consistent on the impact of diet and specific foods, the data suggest avoiding Western pattern foods and eating more plant-based and Mediterranean diets for overall health, and following nutrition guidelines for heart disease and cancer prevention with some modifications specific for patients with prostate cancer (**Figure**).



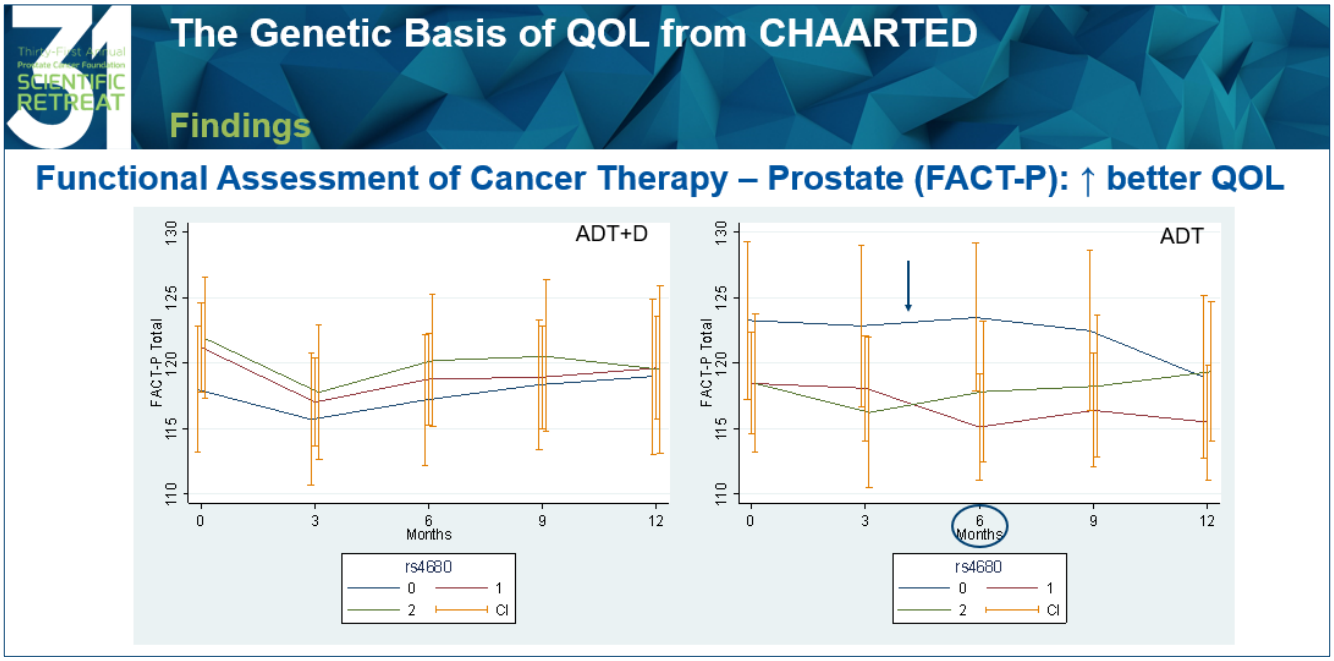
The Genetic Basis of QOL from CHAARTED

Daniel Sentana

Dana-Farber Cancer Institute

- Dr. Daniel Sentana discussed the role of genetic polymorphisms in influencing the quality of life (QOL) and treatment tolerance of prostate cancer patients receiving androgen deprivation therapy (ADT) with or without docetaxel chemotherapy.
- Genetic variants (polymorphisms) of genes involved in neurotransmitter metabolism have been linked with symptoms in non-cancer populations and adverse events in cancer patients.
- The *COMT*(Catechol-O-Methyltransferase) gene plays a role in the metabolism of neurotransmitters like dopamine, and a specific polymorphism (rs4680) which reduces dopamine clearance from the brain, has been linked to improved mood and decreased symptoms in various clinical contexts. The *COMT* rs4680 polymorphism is very common, present in about half of Caucasian populations and about a quarter of African populations.
- Dr. Sentana and colleagues investigated whether the *COMT* rs4680 polymorphism could predict quality of life outcomes in patients with metastatic hormone sensitive prostate cancer (mHSPC) in the CHAARTED clinical trial who received ADT with or without docetaxel.
- Patients with the *COMT* rs4680 polymorphism who received ADT alone had better overall quality of life (**Figure**), less pain, and lower interference of pain with daily activities, compared to those without the polymorphism.

- However, no significant differences in quality of life measures were observed in the docetaxel-treated group (**Figure**), suggesting that the COMT polymorphism cannot overcome the effects of docetaxel on quality of life.
- These findings suggest that the *COMT* rs4680 polymorphism could be a promising genetic biomarker for predicting quality of life outcomes in prostate cancer patients receiving ADT, potentially allowing for better counseling and optimization of supportive care interventions.
- Further validation in other prostate cancer cohorts, including those receiving other treatments like abiraterone, is warranted to confirm these findings and explore the broader implications of genetic factors on patient-reported outcomes. The role of other gene polymorphisms in patient quality of life is also under study. For instance, *VAC14*, which is critical in neural functions, has a polymorphism previously associated with a higher incidence of neuropathy in patients treated with docetaxel.

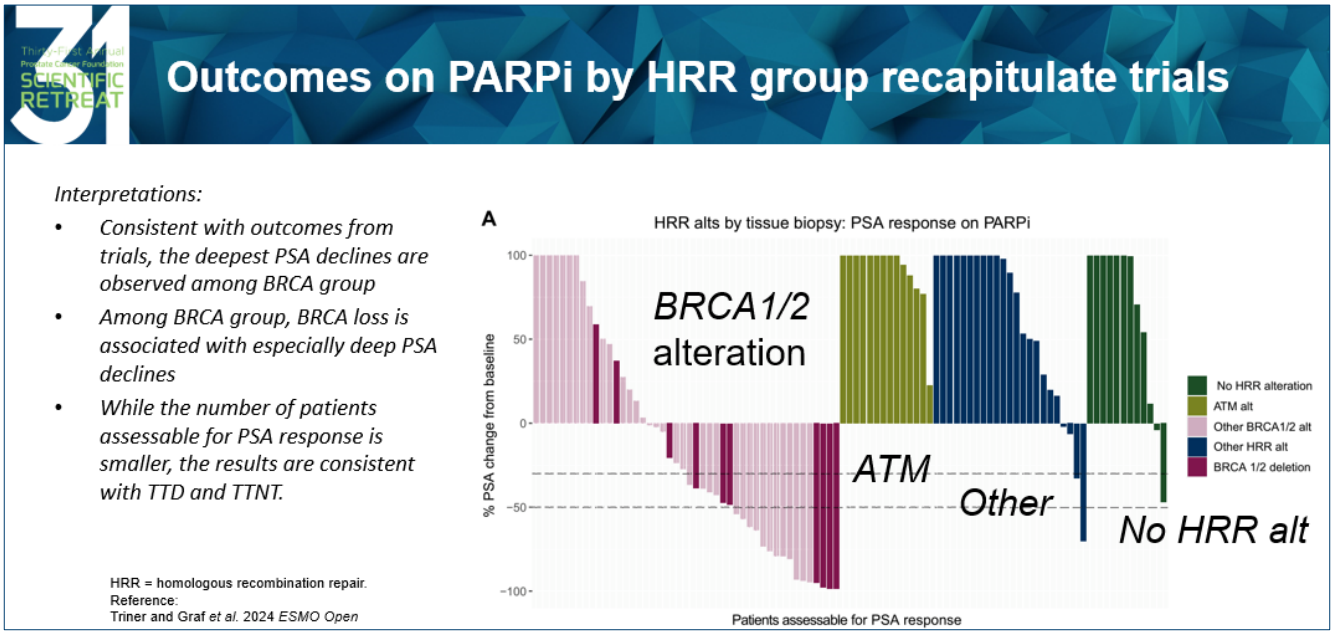


Session 12: New Biotechnologies in Genomic Medicine

Looking Back to Look Forward: Using Genomics and Electronic Health Records to Optimize Current & Future Clinical Decisions

Ryon Graf
Foundation Medicine

- Dr. Ryon Graf discussed the use of real world genomic and clinical data to generate insights that can aid in improving precision medicine decisions for patients.
- Foundation Medicine and Flatiron Health have clinical and genomic real-world datasets that collectively represent over 125,000 patients. This rich dataset can be studied to provide new information that may help clinical decision-making, when there is otherwise incomplete information or insufficient evidence.
- PARP-inhibitors are a class of precision medicine treatments that are approved for patients with prostate cancers that have mutations in certain genes involved in repairing damaged DNA, including *BRCA1, BRCA2, ATM*, and others. However, it remains unclear which specific mutations are the best biomarkers for benefit from treatment with PARP-inhibitors.
- A study examining the use of PARP inhibitors in routine clinical practice in 445 patients with advanced prostate cancer, focused on three key areas: validating the associations between certain genomic alterations (e.g., *BRCA1/2* mutations) and patient outcomes observed in clinical trials, evaluating the impact of homozygous loss of *BRCA1/2* on PARP inhibitor response and survival outcomes, and assessing the optimal methods for detecting these genomic alterations, including the use of archival tissue versus metastatic biopsies or liquid biopsies.
- Patients with homozygous loss of *BRCA1* or *BRCA2* had better PSA responses and significantly longer time to next treatment and overall survival compared to those with other types of *BRCA* alterations or other DNA repair gene alterations (**Figure**). These real-world results recapitulated results observed in clinical trials.
- Homozygous loss of *BRCA1* or *BRCA2* was found to occur in ~3% of patients in this cohort using either primary or metastatic tissue samples. However, when using liquid biopsies, detection of the alterations could be missed if the tumor fraction was below 20%. This suggests that tissue samples are best for performing tumor genomic precision medicine tests on. However, if tissue samples are not available, than liquid biopsy collection should be timed to periods of tumor progression to improve the likelihood of detecting this important genomic marker.
- These data demonstrate the potential for real-world data from large, diverse, mostly community routine practice cohorts for preliminary discovery studies and as well as validation of clinical trial data.
- Much of this data has been recently published: Triner et al., *ESMO Open*. 2024 Sep;9(9):103684. doi: 10.1016/j.esmoop.2024.103684.
- Foundation Medicine and Prostate Cancer Foundation announced a collaboration to new request applications to allow researchers to access this clinical-genomic database and explore additional insights that could be immediately valuable for clinical practice.



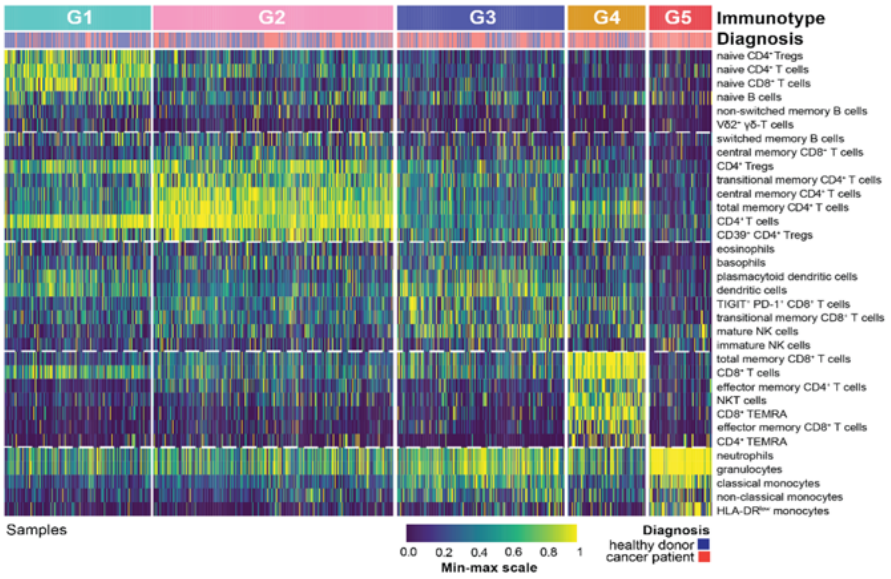
Immune System Profiling - Extracting Dynamic Response Data from the Peripheral Blood

Michael F. Goldberg
BostonGene

- Dr. Michael Goldberg discussed a novel platform to profile the immune system and identify immunity-based response correlatives, to enable patient stratification for immune-based therapies and other treatments that act in part by fundamentally changing a patient's immune system.
- This platform consists of laboratory and computational and AI-based components for performing comprehensive multiomic molecular and cellular profiling of the immune system from the peripheral blood
- A study to characterize peripheral immune cells in a cohort of ~400 healthy donors and 600 patients with various solid tumors, identified five different peripheral immune types: “naïve,” “primed,” “progressive,” “chronic”, and “suppressive”. The “chronic” and “suppressive” types were primarily found in cancer patients and exhibited markers of immune exhaustion and suppression (**Figure**).
- In a cohort of head and neck cancer patients treated with nivolumab, patients with the "primed" immune type had a higher overall response rate, and those who maintained this type throughout treatment had the best overall survival.
- Associations were also found between immune types and response to neoadjuvant chemotherapy in breast cancer and overall survival in pancreatic ductal adenocarcinoma.

- In prostate cancer patients, the distribution of immune types varied with disease severity, with androgen-sensitive patients having more of the "primed" type and castration-resistant patients having less.
- These studies demonstrate that analysis of biomarkers within and outside the tumor can have significant prognostic and predictive value, and the ability to sample immune cells from the peripheral blood can be an effective tool for biomarker discovery and understanding patient cohorts.

Five peripheral immunotypes identified



G1 Naive
Naive T and B cells

G2 Primed
Central and transitional memory CD4+ T cells

G3 Progressive
NK cells, transitional memory CD8+ T cells

G4 Chronic
NKT cells, TEMRA, TEM

G5 Suppressive
Monocytes, granulocytes, MDSC

Dylkanov A, et al. Cancer Cell 2024

Session 13: Advances in "In Vivo" Cell Therapy Platforms and Novel Small Molecule Cancer Therapies

A Novel NK Cell Activator Phase 1 Trial in Prostate Cancer shows Distinct NK Cell Activity

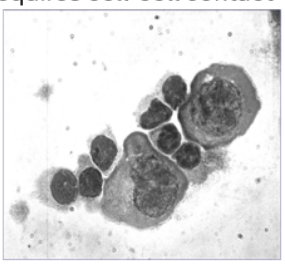
Julie Graff
VA Portland Health Care System; Oregon Health & Science University

- Dr. Julie Graff discussed a phase 1-2 clinical trial investigating a natural killer (NK) cell activator for the treatment of prostate cancer.
- NK cells are a type of immune cell that are central to the natural immune response to viruses and tumor cells.
- Prior studies have found that high grade prostate cancers (Gleason 8-9) are significantly infiltrated by resting NK cells, suggesting activation of this resting NK population as a possible therapeutic strategy. Additionally, a higher abundance of NK cells in prostate cancer has been associated with improved overall survival. Thus, the ability to harness NK cells as an immunotherapy could be a powerful tool for patients.
- INKmune is an “off-the-shelf,” outpatient therapy, composed of a replication-incompetent pediatric leukemia cell (INB16) that upon infusion into patients, contacts resting NK cells and converts them into memory-like NK cells capable of killing tumor cells (**Figure**). After infusion, INB16 cells should be cleared from the body within 48 hours, while the activated NK response can persist for several weeks.
- This strategy has several advantages over the standard cellular immunotherapy approach of infusing patients with activated NK cells, including improved safety and persistence, thus avoiding the need for continual infusion and in-patient treatment.
- Prostate cancer is considered a good target for this approach because it tends to have fewer infiltrating T cells but more resting NK cells that could potentially be activated by the therapy.
- A phase 1-2 trial is examining INKmune in patients with metastatic castration-resistant prostate cancer (mCRPC). The trial is evaluating both immunological endpoints (NK cell activation and persistence) as well as tumor-related endpoints like PSA and circulating tumor DNA.
- The trial is being conducted at 8 sites including two VA medical centers, highlighting the involvement of the VA in supporting this research.
- The trial is ongoing. No significant safety issues have been reported so far. Early data suggests the therapy may be having an anti-tumor effect in at least one patient.

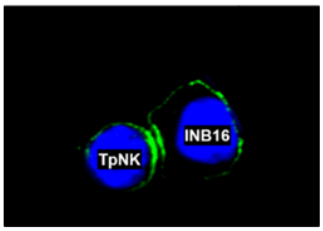
What is INKmune?

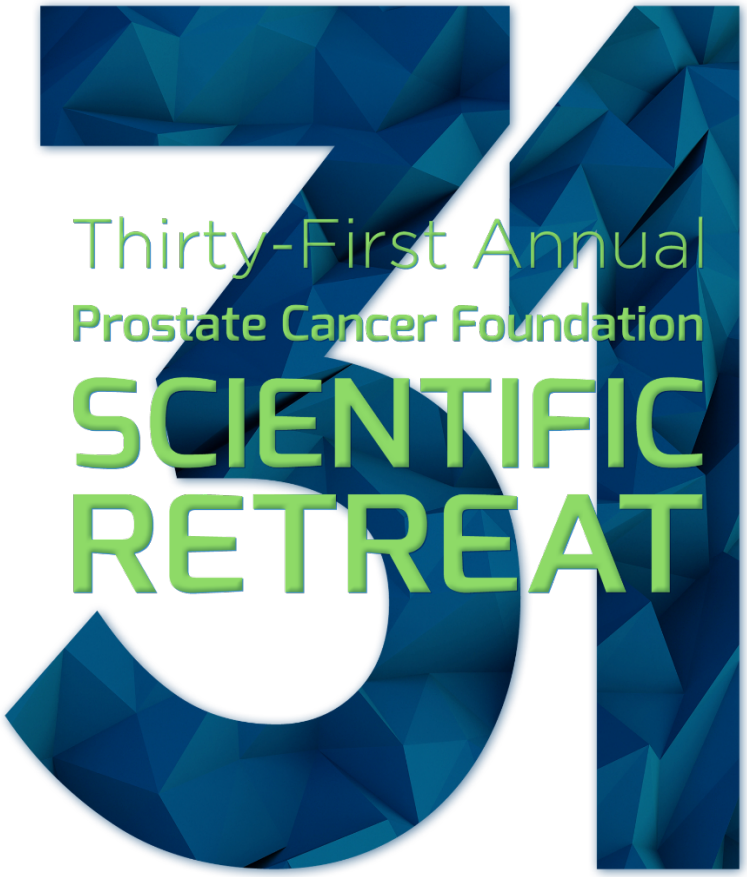
- INKmune is a replication incompetent pediatric leukemia cell (INB16)
- INKmune converts rNK to tumor killing mlNK cells by direct cell-cell contact
- INKmune is cleared by 48h
- INKmune effects “persist” for many weeks
- INKmune expands NK response by serial activation
- Off-the-Shelf product stored can be ordered and delivered like any biologic therapy

NK cells killing tumor cells requires cell-cell contact



Trogocytosis: INKmune “donates” a piece of its membrane to rNK cell to convert it to mlNK





APPENDIX I:

31st ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT

Prostate Cancer Foundation
Young Investigator Forum

OCTOBER 23, 2024

PROGRAM AGENDA

Prostate Cancer Foundation
Young Investigator Forum

AGENDA

YOUNG INVESTIGATOR FORUM

Wednesday, October 23, 2024
***All times in U.S. PDT**

6:30 AM **Registration**

Location: Costa De La Luna Foyer

6:45 AM - 7:45 AM ***Breakfast***

Location: Costa De La Luna Lawn

7:45 AM - 8:00 AM **Move to Session 1**

Location: Costa De La Luna 4

Welcome & Introduction
8:00 AM - 8:10 AM

Howard Soule
Prostate Cancer Foundation
Andrea Miyahira
Prostate Cancer Foundation

Session 1: Panel Discussion: Handbook for Starting a Lab
8:10 AM - 9:10 AM

8:10 AM - 8:50 AM **Moderator: Goutam Chakraborty**
Icahn School of Medicine at Mount Sinai

Panelists:
Rohit Bose (University of California, San Francisco)
Asmaa Elkenawi (Indiana University)
Claire Fletcher (Imperial College London, UK)
Andrew Goldstein (University of California, Los Angeles)
Adam Sowalsky (National Cancer Institute)

8:50 AM - 9:10 AM Discussion

Session 2: Exploring Career Paths in Pharma
9:10 AM - 9:55 AM

9:10 AM - 9:40 AM **Matthew Cotter**
Pfizer

Introduced by Howard Soule

9:40 AM - 9:55 AM Discussion

Session 3: Science Communication to the Public: How to Promote Science in an Increasingly Anti-Science World
9:55 AM - 10:50 AM

9:55 AM - 10:25 AM **Anne Doerr**
American Cancer Society

Introduced by Andrea Miyahira

10:25 AM - 10:50 AM Discussion

Session 4: Introduction to High Achieving PCF Young Investigators
10:50 AM - 11:50 AM

Moderator: Howard Soule
Prostate Cancer Foundation

10:50 AM - 11:00 AM ***Rational ADC Designs and Combination Therapies for mCRPC***
Galina Semenova
Fred Hutchinson Cancer Center

11:00 AM - 11:05 AM Discussion

11:05 AM - 11:15 AM ***Androgen Receptor Drives Polyamine Synthesis Creating a Vulnerability for Prostate Cancer***
Laura Sena
Johns Hopkins University

11:15 AM - 11:20 AM Discussion

11:20 AM - 11:30 AM ***Deciphering and Manipulating Gene Regulation in Advanced Prostate Cancer***
Sarah Hsu
University of California, San Francisco

11:30 AM - 11:35 AM Discussion

11:35 AM - 11:45 AM ***Insights into PSMA Heterogeneity and LuPSMA Resistance from a Rapid-Autopsy Cohort Profiled with Single-Cell Multi-Omics***
Anna Trigos
Peter MacCallum Cancer Centre, Australia
11:45 AM - 11:50 AM Discussion

Group Photo
11:50 AM - 12:00 PM

Lunch
12:00 PM - 1:00 PM

Lunch Location: *Costa De La Luna Lawn*

1:00 PM - 1:15 PM **Move to Session 5**

Location: Costa De La Luna 4

Session 5: The Zen of Grant Writing
1:15 PM - 2:15 PM

1:15 PM - 1:55 PM **Joshua Lang**
University of Wisconsin

Introduced by Andrea Miyahira

1:55 PM - 2:15 PM Discussion

Session 6: An Academic Career Path from a Physician-Scientist Perspective
2:15 PM - 3:00 PM

2:15 PM - 2:45 PM **Himisha Beltran**
Dana-Farber Cancer Institute

Introduced by Andrea Miyahira

2:45 PM - 3:00 PM Discussion

3:00 PM - 3:15 PM **Move to Session 7**

Location: Costa De La Luna 1-3

Session 7: PCF Young Investigator Speed Networking 11.0
3:15 PM - 5:30 PM

Location: Costa De La Luna 1-3

Moderators: **Lisa Chesner** (University of California, San Francisco)
Galina Semenova (Fred Hutchinson Cancer Center)
Adam Weiner (University of California, Los Angeles; Cedars-Sinai Medical Center)

The purpose of the 'speed networking session' is to foster a sense of community between young investigators. This is 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!

3:15 PM - 3:35 PM **Introduction**

3:35 PM - 4:00 PM **Speed Networking Group 1**

4:00 PM - 4:25 PM **Speed Networking Group 2**

4:25 PM - 4:50 PM **Speed Networking Group 3**

4:50 PM - 5:15 PM **Speed Networking Group 4**

5:15 PM - 5:30 PM **Conclusion**

Wednesday, October 23, 2024

Young Investigator Reception
5:30 PM - 6:30 PM

Reception Location: Costa De La Luna Lawn

Young Investigator Dinner
6:30 PM - 8:00 PM

Dinner Location: Costa De La Luna Lawn

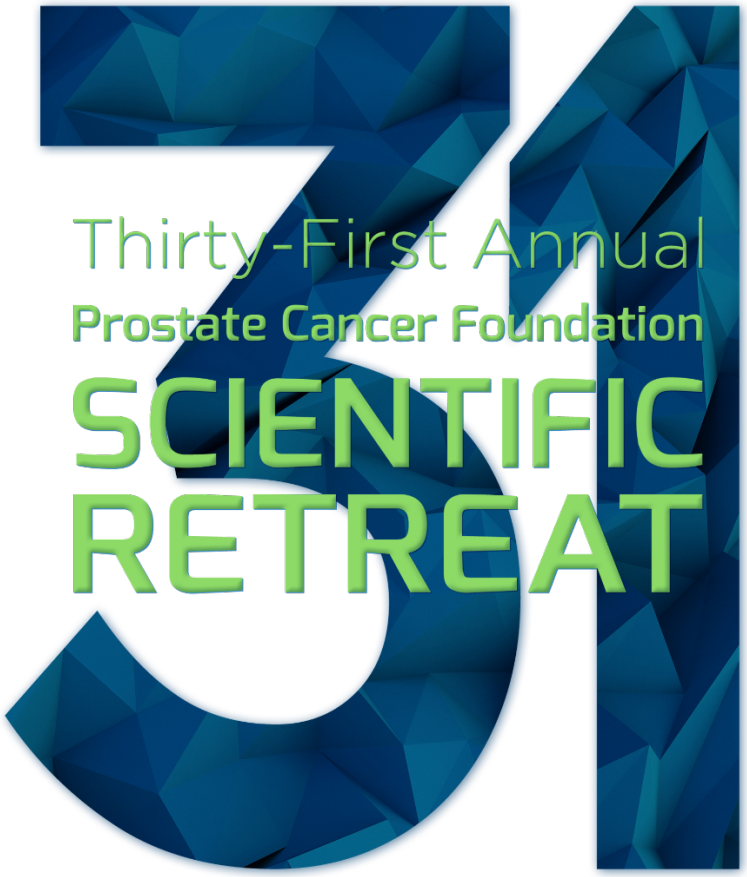
***** Meeting Adjourned *****

Prostate Cancer Foundation
Young Investigator Forum

Program Committee:

Program Committee Co-Chair: Howard Soule (Prostate Cancer Foundation)
Program Committee Co-Chair: Andrea Miyahira (Prostate Cancer Foundation)

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



APPENDIX II:

31st ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT

Prostate Cancer Foundation
Gender Equity Networking Initiative

OCTOBER 24, 2024

PROGRAM AGENDA

Prostate Cancer Foundation
Gender Equity Networking Initiative

The 9th Annual PCF Gender Equity Networking Initiative (GENI) Forum

Thursday, October 24, 2024
***All times in U.S. PDT**

Omni La Costa Resort
Carlsbad, California

Location: Costa De La Luna 4

This is a half-day networking event held in conjunction with the PCF Annual Scientific Retreat, open to all interested individuals of any gender, career level, and discipline, attending the PCF Scientific Retreat. The goals of this event are to create a network of PCF women and allies with the shared goal of achieving gender equity in science and medicine, promote allyship, team build through discussion and social events, ensure a strong pipeline of female prostate cancer researchers and clinicians, and identify opportunities for further training, mentoring and synergy of a stellar network of female prostate cancer researchers and clinicians.

6:30 AM	**Registration**	Costa De La Luna Foyer
7:00 AM – 8:00 AM	**Breakfast, Coffee and Networking**	Costa De La Luna Lawn

Welcome, Introductions and Vision
8:00 AM – 8:05 AM

Fatima Karzai (National Cancer Institute)

Session 1: Keynote
8:05 AM – 8:55 AM

8:05 AM - 8:35 AM **Padmanee Sharma**
Professor, Dept. of Genitourinary Medical Oncology, Division of Cancer Medicine; Professor, Dept. of Immunology, Division of Cancer Medicine; VP Immunobiology, Dept. of Immunology, Division of Cancer Medicine; Director of Scientific Programs, Dept. of James P. Allison Institute, Division of James P. Allison Institute
The University of Texas MD Anderson Cancer Center

Introduced by Sarah Amend

8:35 AM - 8:55 AM Questions

Session 2: Keynote: Trials and Errors: Addressing Conflict and Gender Equity through Restorative Practices
8:55 AM - 10:05 AM

8:55 AM - 9:35 AM **Ada Gregory**
Associate Director, Kenan Institute for Ethics
Duke University

Introduced by Susan Halabi

9:35 AM - 10:05 AM Questions

Session 3: Introduction to Students
10:05 AM – 10:15 AM

Kathryn O'Connor (MedTech Academy, San Diego)
Andrea Miyahira (Prostate Cancer Foundation)

Session 4: Panel Discussion: How to Encourage Women to be Leaders: Nurturing the Pipeline of Women in Science
10:15 AM – 11:30 AM

Introduction by Ayesha Shafi

Moderator: Amina Zoubeidi (Vancouver Prostate Centre)

Panelists:
Leah M. Cook (National Cancer Institute)
Louise Emmett (The University of New South Wales, Australia)
Susan Halabi (Duke University)
Amrita Sawhney (Novartis)
Mary-Ellen Taplin (Dana-Farber Cancer Institute)

Session 5: Closing Remarks
11:30 AM – 11:35 AM

Christina Jamieson (University California, San Diego)
Andrea Miyahira (Prostate Cancer Foundation)

Group Picture
11:35 AM – 11:45 AM

Lunch/Networking Costa De La Luna Lawn
11:45 AM – 12:30 PM

***** Meeting Adjourned *****

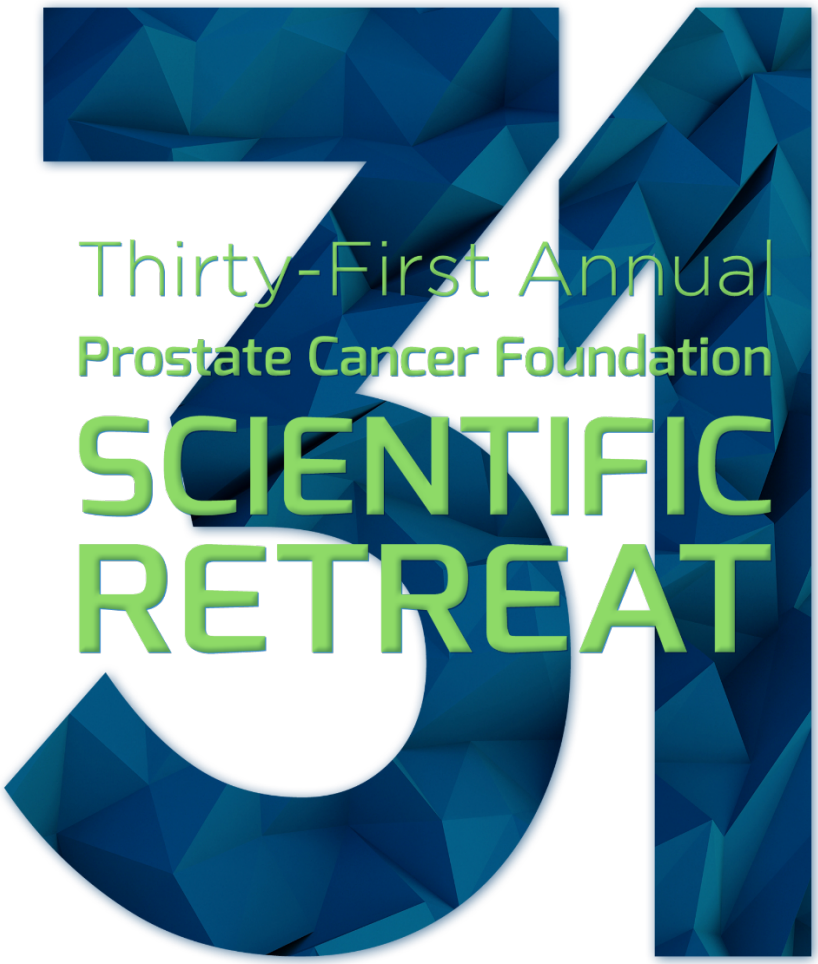
The 31st Annual Prostate Cancer Foundation Scientific Retreat begins promptly at 1:00 PM in the Costa Del Sol Ballroom

Prostate Cancer Foundation
Gender Equity Networking Initiative

Organizing Committee:

Sarah Amend (Johns Hopkins University)
Claire Fletcher (Imperial College London)
Veda N. Giri (Yale University and Yale Cancer Center)
Susan Halabi (Duke University)
Christina Jamieson (University California, San Diego)
Salma Kaochar (Baylor College of Medicine)
Fatima Karzai (National Cancer Institute)
Andrea Miyahira (Prostate Cancer Foundation)
Ayesha Shafi (Center for Prostate Disease Research (CPDR); USU Walter Reed Surgery)
Amina Zoubeidi (Vancouver Prostate Centre)

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



APPENDIX III:

30th ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT

OCTOBER 24-26, 2024

PROGRAM AGENDA

AGENDA

Thursday, October 24, 2024

GENERAL SESSIONS

Location: Costa Del Sol Ballroom

8:00 AM **Registration** **Costa Del Sol Foyer**

Welcome & Opening Remarks
1:00 PM - 1:05 PM

Howard Soule
Prostate Cancer Foundation
Andrea Miyahira
Prostate Cancer Foundation

Session 1: Tumor Metabolism
1:05 PM - 2:25 PM

Moderator: Andrew Goldstein
University of California, Los Angeles

1:05 PM - 1:20 PM ***Prostate Lineage-Specific Metabolism Governs Luminal Differentiation and Response to Antiandrogen Treatment***
Andrew Goldstein
University of California, Los Angeles

1:20 PM - 1:25 PM **Discussion**

1:25 PM - 1:40 PM ***Dietary Target Therapy and Oxidative Death***
Lloyd Trotman
Cold Spring Harbor Laboratory

1:40 PM - 1:45 PM **Discussion**

1:45 PM - 2:00 PM ***In Vivo Nutrient Tracing and Targeted Metabolic Vulnerabilities in Rare Cancers***
Heather Christofk
University of California, Los Angeles

2:00 PM - 2:05 PM **Discussion**

2:05 PM - 2:20 PM ***Whole-Food Plant-Based Diet to Control Weight and Metabo-Inflammation in Overweight/Obese Men With Prostate Cancer Receiving ADT***
David Nanus
Weill Cornell Medicine
2:20 PM - 2:25 PM **Discussion**

Session 2: Genomics of Prostate Cancer Racial Disparities
2:25 PM - 3:45 PM
Moderator: Vanessa M. Hayes
The University of Sydney, Australia

2:25 PM - 2:40 PM ***African-Ancestry Associated Genomic Differences in Cancer***
Jian Carrot-Zhang
Memorial Sloan Kettering Cancer Center
2:40 PM - 2:45 PM **Discussion**

2:45 PM - 3:00 PM ***The Interplay of Epigenome and Environmental Factors in Prostate Cancer Disparities***
Bernard Kwabi-Addo
Howard University College of Medicine
3:00 PM - 3:05 PM **Discussion**

3:05 PM - 3:20 PM ***Utilizing a Pan-African Approach to Reduce Prostate Cancer Disparities***
Clayton Yates
John Hopkins School of Medicine
3:20 PM - 3:25 PM **Discussion**

3:25 PM - 3:40 PM ***Prostate Cancer Genomic Disparities Across the African Diaspora***
Vanessa M. Hayes
The University of Sydney, Australia
3:40 PM - 3:45 PM **Discussion**

Session 3: The Tumor Immune Microenvironment: Reprogramming Macrophages
3:45 PM - 4:45 PM
Moderator: Jelani Zarif
Johns Hopkins University

3:45 PM - 4:00 PM ***Metabolic Reprogramming of Tumor-associated Macrophages using Glutamine Antagonist JHU083 Drives Tumor Immunity in Myeloid-Rich Prostate and Bladder Cancer Tumors***
Jelani Zarif
Johns Hopkins University
4:00 PM - 4:05 PM **Discussion**

4:05 PM - 4:20 PM ***Investigations in the Tumor Microenvironment Pave the Way for New Cell Therapy Approaches***
Rosie Kaplan
National Cancer Institute
4:20 PM - 4:25 PM **Discussion**

4:25 PM - 4:40 PM ***Multimodal Pro-Inflammatory Conversion of Tumor Myeloid Stroma by STING Activation***
Michael Curran
University of Texas MD Anderson Cancer Center
4:40 PM - 4:45 PM **Discussion**

Session 4: High Impact Clinical Trials for Patients with Prostate Cancer
4:45 PM - 5:45 PM
Moderator: Howard Soule
Prostate Cancer Foundation

4:45 PM - 4:55 PM ***Prostate Cancer UK's TRANSFORM Programme: A Randomised Clinical Trial of Prostate Cancer Screening and a National Prostate Cancer Bio-Digital Twin to Power Biomarker Discovery, Innovation and Validation***
Matthew Hobbs
Prostate Cancer UK
Rakesh Heer
Imperial College London, UK
4:55 PM - 5:00 PM **Discussion**

5:00 PM - 5:10 PM ***Abiraterone Decanoate (PRL-02/ASP5541): A Precision Approach to Androgen Biosynthesis Inhibition***
William Moore
Astellas
5:10 PM - 5:15 PM **Discussion**

5:15 PM - 5:25 PM ***Metacure: Multi-Arm Multimodality Therapy for Very High Risk Localized and Low Volume Metastatic Prostatic Adenocarcinoma***
Howard Scher
Memorial Sloan Kettering Cancer Center
5:25 PM - 5:30 PM **Discussion**

5:30 PM - 5:40 PM ***BMS-986365 (CC-94676), a Dual Androgen Receptor Ligand-Directed Degrader and Antagonist, for the Treatment of Advanced Prostate Cancer***
Vivek Arora
Bristol Myers Squibb
5:40 PM - 5:45 PM **Discussion**

Thursday, October 24, 2024

5:45 PM - 5:55 PM ***Efficacy and Safety of Darolutamide Plus Androgen-Deprivation Therapy (ADT) in Patients with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) from the Phase 3 ARANOTE Trial***
Rana McKay
University of California, San Diego

5:55 PM - 6:00 PM **Discussion**

6:00 PM - 6:10 PM ***A Randomized Multicenter Open-Label Phase III Trial Comparing Enzalutamide vs a Combination of Radium 223 and Enzalutamide in Asymptomatic or Mildly Symptomatic Patients with Bone Metastatic mCRPC***
Andrey Soares
Hospital Albert Einstein, Sao Paulo, Brazil and Latin American Cooperative Oncology Group - LACOG, Porto Alegre, Brazil

6:10 PM - 6:15 PM **Discussion**

Dinner
6:30 PM - 7:30 PM

Dinner Location: Costa Del Sol Patio

Poster Session and Dessert
7:30 PM - 10:30 PM

Poster Session and Dessert Location: Costa De La Luna Ballroom

Friday, October 25, 2024

6:00 AM - 6:45 AM ***Breakfast***
Location: Costa Del Sol Patio

6:45 AM - 7:00 AM **Move to Session**

GENERAL SESSIONS
Location: Costa Del Sol Ballroom

Session 5: Can AI Drive Innovation in Cancer Research and Cancer Care?
7:00 AM - 8:00 AM

Moderator: Bissan Al-Lazikani
The University of Texas MD Anderson Cancer Center

7:00 AM - 7:15 AM ***Using AI to Predict Patient Drug Responses and Outcomes from Preclinical Data***
Katie Campbell
Broad and MIT

7:15 AM - 7:20 AM **Discussion**

7:20 AM - 7:35 AM ***Digital Twins for Drug Development to Individualized Therapy***
Bissan Al-Lazikani
The University of Texas MD Anderson Cancer Center

7:35 AM - 7:40 AM **Discussion**

7:40 AM - 7:55 AM ***Using Large Language Models to Improve Representation of Patients' Experience with Cancer and its Treatment – Insights from the Lancet Commission on Cancer and Health Systems***
André Pfob
Heidelberg University Hospital

7:55 AM - 8:00 AM **Discussion**

SPECIAL LECTURE
8:00 AM - 8:20 AM

Lessons From 20 Years of STAMPEDE

Nicholas James
The Institute of Cancer Research, UK

Introduced by Gerhardt Attard
University College London Cancer Institute, UK

8:20 AM - 8:25 AM
Discussion

Session 6: The PCF-VA Partnership: Bringing Precision Medicine to Veterans
8:25 AM - 9:20 AM

Moderator: Isla Garraway
University of California, Los Angeles; Greater Los Angeles VA Healthcare System

8:25 AM - 8:40 AM ***VA MAPP: Multilevel Data and Biospecimen Repository for Unprecedented Discovery and Validation***
Isla Garraway
University of California, Los Angeles; Greater Los Angeles VA Healthcare System
Kara Maxwell
University of Pennsylvania; Corporal Michael J. Crescenz VA Medical Center

8:40 AM - 8:55 AM ***VA Studies Led by Young Investigators: Landscape of Somatic Prostate Cancer Alterations in the VA population***
Luca Valle
University of California, Los Angeles; Greater Los Angeles VA Healthcare System

VA Studies Led by Young Investigators: Treatment and Outcomes of mHSPC in Veterans: Initial use of Tumor Suppressor Genes for Prognosis
Martin Schoen
Saint Louis University; St. Louis Veterans Affairs Medical Center

8:55 AM - 9:10 AM ***Full Spectrum VA Clinical Studies from SOLAR to AI***
Nicholas Nickols
University of California, Los Angeles; Greater Los Angeles VA Healthcare System
Matthew Rettig
University of California, Los Angeles; Greater Los Angeles VA Healthcare System

9:10 AM - 9:20 AM **Session Discussion**

SPECIAL ANNOUNCEMENT
9:20 AM -9:25 AM

The PCF Gender Equity Networking Initiative

Claire Fletcher
Imperial College London, UK

Introduced by Andrea Miyahira
Prostate Cancer Foundation

9:25 AM - 9:30 AM
Discussion

Dr. Felix Feng Special Lecture
9:30 AM - 9:55 AM

Science and Friendship

Himisha Beltran
Dana-Farber Cancer Institute

Introduction by Amina Zoubeidi
University of British Columbia

9:55 AM - 10:00 AM
Discussion

SPECIAL LECTURE
10:00 AM - 10:30 AM

The JnJ Prostate Cancer Portfolio

John Reed
Johnson & Johnson Innovative Medicine

Introduced by Charles Drake
Johnson & Johnson Innovative Medicine

10:30 AM - 10:35 AM
Discussion

SPECIAL LECTURE
10:35 AM - 10:55 AM

"We're Not in Kansas Anymore" - Cancer Lessons from the Wizard of Oz

Kenneth Pienta
Johns Hopkins University

Introduced by Howard Soule
Prostate Cancer Foundation

10:55 AM - 11:00 AM
Discussion

Friday, October 25, 2024

KEYNOTE ADDRESS
11:00 AM - 12:00 PM

Michael Milken
Founder and Chairman
Prostate Cancer Foundation

Introduced by Stuart Holden
Prostate Cancer Foundation; University of California, Los Angeles

Group Photo
12:00 PM - 12:10 PM

Location: Costa Del Sol Foyer

Lunch
12:10 PM - 1:00 PM

Location: Costa Del Sol Patio

1:00 PM - 1:15 PM **Move to Session**

Location: Costa Del Sol Ballroom

SPECIAL LECTURE
1:15 PM - 1:30 PM

Germline DNA Damage Repair Variants and Prognosis of Patients with High-Risk or Metastatic Prostate Cancer

Konrad Stopsack
Massachusetts General Hospital; Harvard T.H. Chan School of Public Health

Introduced by Philip Kantoff
Convergent Therapeutics; Memorial Sloan Kettering Cancer Center; Harvard Medical School; Dana-Farber Cancer Center

1:30 PM - 1:35 PM
Discussion

Session 7: Next Generation Theranostics
1:35 PM - 3:00 PM

Moderator: Michael Hofman
Peter MacCallum Cancer Centre, Australia

1:35 PM - 1:40 PM ***Introduction***
Michael Hofman
Peter MacCallum Cancer Centre, Australia

1:40 PM - 1:55 PM ***PSMA: What's New in 2024?***
Louise Emmett
The University of New South Wales, Australia

1:55 PM - 2:00 PM **Discussion**

2:00 PM - 2:15 PM ***New Atoms***
Jason Lewis
Memorial Sloan Kettering Cancer Center

2:15 PM - 2:20 PM **Discussion**

2:20 PM - 2:35 PM ***New Theranostic Targets***
Andrew Armstrong
Duke University

2:35 PM - 2:40 PM **Discussion**

2:40 PM -2:55 PM ***Trials in Action: What's Hot?***
James Buteau
Peter MacCallum Cancer Centre, Australia
2:55 PM - 3:00 PM **Discussion**

Session 8: Next Generation Cancer Immunotherapies
3:00 PM - 4:20 PM
Moderator: Saul Priceman
University of Southern California

3:00 PM - 3:15 PM ***Novel CAR T Cells for Prostate Cancer***
Saul Priceman
University of Southern California
3:15 PM - 3:20 PM **Discussion**

3:20 PM - 3:35 PM ***Novel Incorporation of Transgenic Cytokines into Immunotherapeutic Strategies***
Rosa Nguyen
National Cancer Institute
3:35 PM - 3:40 PM **Discussion**

3:40 PM - 3:55 PM ***Cancer Immunotherapy Using Multiplex Non-Viral Genome Engineered Immune Effector Cells***
Branden Moriarity
University of Minnesota
3:55 PM - 4:00 PM **Discussion**

4:00 PM - 4:15 PM ***Next Generation CAR T cells for Patients with Cancer***
Marcela Maus
Massachusetts General Hospital
4:15 PM - 4:20 PM **Discussion**

Session 9: Advanced Molecular Biology of Lethal Prostate Cancer
4:20 PM - 5:00 PM
Moderator: Adam Sharp
Institute of Cancer Research, UK

4:20 PM - 4:35 PM ***AR-V7 Expression in AR Mutated and Non-Mutated mCRPC***
Alec Paschalis
Institute of Cancer Research, UK
4:35 PM - 4:40 PM **Discussion**

4:40 PM - 4:55 PM ***Minor Intron Splicing in the Pathogenesis of Lethal Prostate Cancer***
Mark A. Rubin
University of Bern and Inselspital, Switzerland
4:55 PM - 5:00 PM **Discussion**

5:00 PM - 7:00 PM *Break*

Dinner, Awards Ceremony, and Special Lecture
7:00 PM - 10:00 PM

Location: Costa Del Sol Ballroom

PCF Awards Ceremony
7:45 PM - 9:00 PM

2024 PCF Young Investigator Awards

2024 PCF Challenge Awards

2023 PCF Challenge Awards

2024 PCF-Pfizer Visiting Professorship Awards

2024 HBCU-PCF Recognition Award

Saturday, October 26, 2024

6:00 AM - 6:45 AM ***Breakfast***

Location: Costa Del Sol Patio

6:45 AM - 7:00 AM **Move to Session**

GENERAL SESSIONS
Location: Costa Del Sol Ballroom

Session 10: Clinical Survivorship 2.0: Metabolic Effects in Survivorship Biology
7:00 AM - 8:05 AM

Moderator: Alicia Morgans
Dana-Farber Cancer Institute

7:00 AM - 7:05 AM ***Introduction***
Alicia Morgans
Dana-Farber Cancer Institute

7:05 AM - 7:20 AM ***Metabolism Effects in Response, Resistance, and Complications of Treatment***
Nima Sharifi
University of Miami

7:20 AM - 7:25 AM **Discussion**

7:25 AM - 7:40 AM ***Exercise and Dietary Impacts on Prostate Cancer Outcomes***
Stacey Kenfield
University of California, San Francisco

7:40 AM - 7:45 AM **Discussion**

7:45 AM - 8:00 AM ***The Genetic Basis of QOL from CHAARTED***
Daniel Sentana
Dana-Farber Cancer Institute

8:00 AM - 8:05 AM **Discussion**

SPECIAL LECTURE
8:05 AM - 8:20 AM

Lessons on the Mechanisms of Plasticity from Small Cell Lung Cancer

Triparna Sen
Icahn School of Medicine at Mount Sinai

Introduced by Andrea Miyahira
Prostate Cancer Foundation

8:20 AM - 8:25 AM
Discussion

Session 11: Targeting Post-Transcriptional Gene Regulation in Prostate Cancer
8:25 AM - 9:45 AM

Moderator: Duygu Kuzuoglu Ozturk
University of California, San Francisco

8:25 AM - 8:40 AM ***Small Molecule RNA Therapeutics to Target Prostate Cancer***
Duygu Kuzuoglu Ozturk
University of California, San Francisco

8:40 AM - 8:45 AM **Discussion**

8:45 AM - 9:00 AM ***The RNA Components of the Translational Machinery in Prostate Cancer Pathogenesis***
Andrew Hsieh
Fred Hutchison Cancer Center

9:00 AM - 9:05 AM **Discussion**

9:05 AM - 9:20 AM ***An RNA-Dependent Positive Feedback Loop Drives Malignant Ribosome Biogenesis***
Faraz Mardakheh
University of Oxford, UK

9:20 AM - 9:25 AM **Discussion**

9:25 AM - 9:40 AM ***Regulation of Ribosome Biogenesis by Noncoding RNAs in Senescence and Cancer***
Josh Mendell
UT Southwestern
9:40 AM - 9:45 AM **Discussion**

Session 12: New Biotechnologies in Genomic Medicine
9:45 AM - 10:25 AM
Moderator: Howard Soule
Prostate Cancer Foundation

9:45 AM - 10:00 AM ***Looking Back to Look Forward: Using Genomics and Electronic Health Records to Optimize Current & Future Clinical Decisions***
Ryon Graf
Foundation Medicine
10:00 AM - 10:05 AM **Discussion**

10:05 AM - 10:20 AM ***Immune System Profiling - Extracting Dynamic Response Data from the Peripheral Blood***
Michael F. Goldberg
BostonGene
10:20 AM - 10:25 AM **Discussion**

Session 13: Advances in "In Vivo" Cell Therapy Platforms and Novel Small Molecule Cancer Therapies
10:25 AM - 12:05 PM
Moderator: Marco Gottardis
Gottardisbiotech LLC

10:25 AM - 10:30 AM ***Introduction***
Marco Gottardis
Gottardisbiotech LLC

10:30 AM - 10:45 AM ***Novel Cell Therapy Platforms without Lymphodepletion for Solid Tumors***
David Fontana
Umoja Biopharma
10:45 AM - 10:50 AM **Discussion**

10:50 AM - 11:05 AM ***In Vivo Cell Engineering with Targeted Lipid Nanoparticles***
Priya Karmali
Capstan Therapeutics
11:05 AM - 11:10 AM **Discussion**

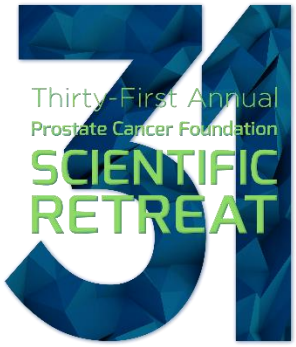
11:10 AM - 11:25 AM ***Small Molecule Sequence-Selective Translation Inhibitors Inhibit the Growth of MYC-Driven Tumors by Target Deprivation***
Lawrence Hamann
Interdict Bio
11:25 AM - 11:30 AM **Discussion**

11:30 AM - 11:45 AM ***Synthetic Lethality in a Plastic Genome - Novel ecDNA Targeted Therapy Platform***
Christian Hassig
Boundless Bio
11:45 AM - 11:50 AM **Discussion**

11:50 AM - 12:00 PM ***A Novel NK Cell Activator Phase 1 Trial in Prostate Cancer shows Distinct NK Cell Activity***
Julie Graff
VA Portland Health Care System; Oregon Health & Science University
12:00 PM - 12:05 PM **Discussion**

Closing Remarks
12:05 PM - 12:10 PM **Howard Soule**
Prostate Cancer Foundation
Andrea Miyahira
Prostate Cancer Foundation

Meeting Adjourned



Program Committee:

Program Committee Co-Chair: Howard Soule (Prostate Cancer Foundation)
Program Committee Co-Chair: Andrea Miyahira (Prostate Cancer Foundation)

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

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