STATE *of the* SCIENCE REPORT









Thirty-Second Annual
Prostate Cancer Foundation
SCIENTIFIC RETREAT
32

Highlights from the 32nd Annual PCF Scientific Retreat

October 23-25, 2025









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Introduction

The 32nd Annual Prostate Cancer Foundation (PCF) Scientific Retreat was held at the Omni La Costa Resort in Carlsbad, CA on October 23–25, 2025. This annual conference brings together leading scientists and clinicians focused on prostate cancer research, along with experts from related disciplines who contribute valuable perspectives to advance understanding of the disease. It offers a forum for participants to present their latest findings, exchange ideas, and explore emerging trends in the field. Attendees include researchers from academia, industry, government, and nonprofit organizations, as well as patients and advocates.

Held over two and a half days, the Retreat features scientific lectures, panel discussions, poster sessions, and other collaborative events. As one of the premier conferences in prostate cancer research, the PCF Annual Scientific Retreat has played a significant role in expanding scientific knowledge and accelerating the development of innovative treatments for prostate cancer.

The 32nd Annual PCF Scientific Retreat featured the following:

- 624 attendees from 17 countries attended the Retreat, representing 176 institutions, 17 countries and 5 continents
- 61 Speakers in Plenary Session.
- 155 poster presentations.
- 30 different scientific disciplines related to prostate cancer research were presented and discussed.
- Retreat registrants included 409 academic researchers or health care professionals and 188 biopharmaceutical industry professionals.
- 114 academic institutions, 50 biopharmaceutical companies, and 8 medical research foundations.
- NIH, NCI, Dept. of Defense, and Veterans Affairs research leaders from over 10 organizations.
- Attendance by 217 PCF Young Investigators, plus 4 former PCF Young Investigators who now work in BioPharma.
- Attendance by 27 PCF Board of Director members, major donors and special guests.
- The 10th Annual PCF Gender Equity Networking Initiative (GENI) Forum (formerly, PCF Women in Science Forum) was held with over 200 attendees, including 19 high school girls interested in STEM.
- The PCF Young Investigator Forum had over 149 attendees including 117 PCF Young Investigators, and included 7 sessions, including the 12th Annual Speed Networking session.

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 raised more than $1 billion to fund cutting-edge research through more than 2,615 research projects at 312 leading cancer centers, with a global

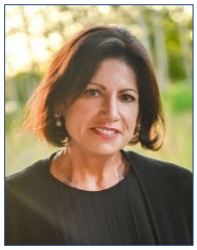
footprint spanning 29 countries. Since PCF's inception, and through its efforts, patients around the world are living longer, suffering fewer complications, and enjoying better quality of life. PCF is committed to the mission of ending death and suffering from this disease. Learn more at pcf.org.

We thank the sponsors of the Retreat for their generous support: Janssen, Bayer, Regeneron, Pfizer, Novartis, Daiichi Sankyo, Amgen, AstraZeneca, Sun Pharma / SPARC, Foundation Medicine, Astellas, Lilly, Lantheus, Bristol-Meyers Squibb, Actinium Pharmaceuticals, Merck, Veracyte, GSK, Flare Therapeutics, AdvanCell, Convergent Therapeutics, Abbvie, Telix, EcoR1 Capital, Candel Therapeutics, Nuclidium Pharma, Myriad Genetics, ArsenalBio, Sumitomo, Pathos, MacroGenics, Genentech, Exelixis, and Clarity Pharma.

The 2025 State of Science Report presents the key scientific insights from the Retreat in a format designed for a general audience. By sharing this knowledge broadly, we seek to enhance understanding of current prostate cancer research, spark meaningful discussions, encourage the exchange of ideas, inspire new research efforts, and build stronger public support for science and research.

The presentations, panels, and discussions from the 32nd Annual PCF Scientific Retreat can be viewed here: https://www.pcf.org/category/scientific-retreat-replays/scientific-retreat-replays-2025/.

Yours sincerely,



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Session 1: Theranostics: New Targets, New Atoms

Prostate Cancer Theranostics: What's Hot in 2025?

Michael Hofman
Peter MacCallum Cancer Centre

What is the scientific background for this presentation?

- Prostate-specific membrane antigen (PSMA) has been recognized for decades as a highly promising target in prostate cancer, leading to the development of PSMA-directed *theranostics*, which pairs imaging and treatment using the same molecular target.
- Lutetium-177 (^{177}Lu)-PSMA-617 (Pluvicto®) is an FDA-approved radioligand therapy (RLT) for metastatic castration-resistant prostate cancer (mCRPC) that allows clinicians to selectively deliver beta particle radiation to prostate cancer cells while largely sparing normal tissue.
- Originally, ^{177}Lu-PSMA-617 was approved for use only after patients with mCRPC were treated with taxane chemotherapy.

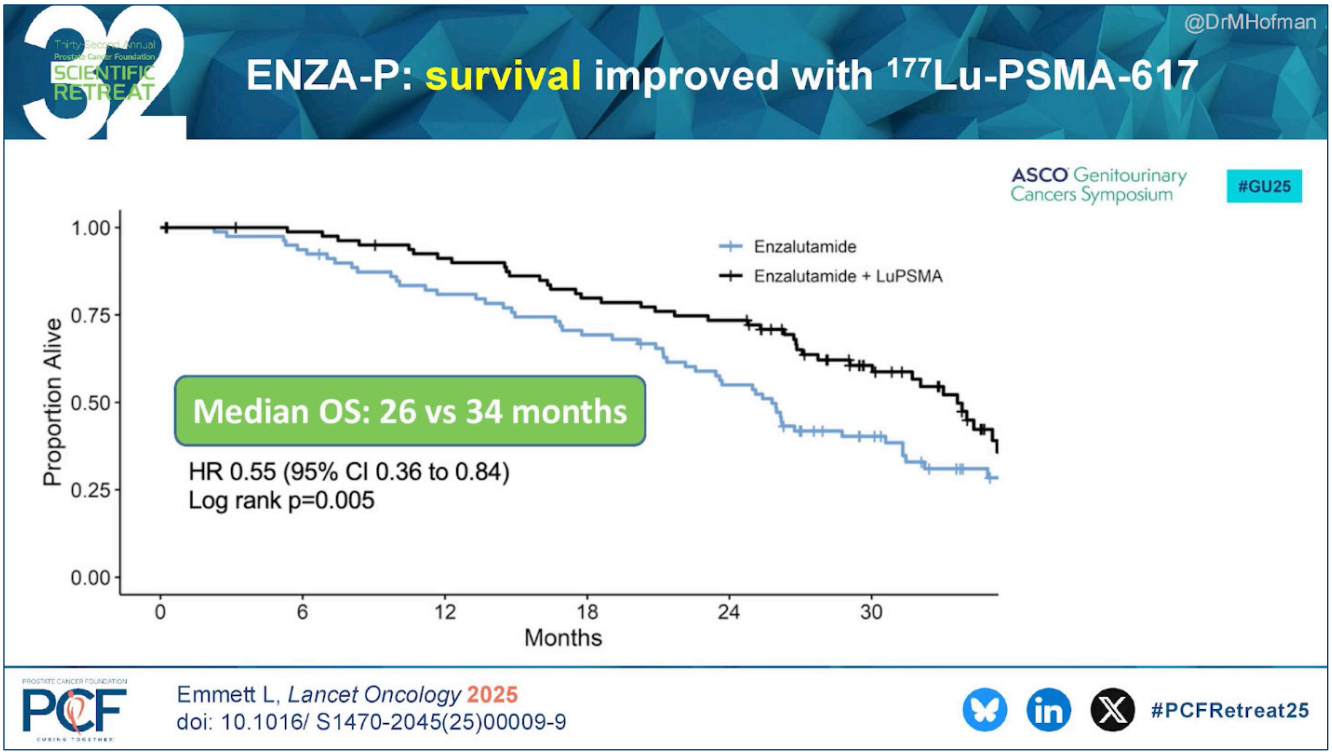
What progress or new findings were shared?

- Dr. Hofman gave a broad overview of advances in the field of PSMA-directed RLT, including the recent approval of ^{177}Lu-PSMA-617 in the prechemotherapy setting based on the results of the PSMAfore trial released in 2024.
- Recent randomized trials presented in 2025 showed that combining ^{177}Lu-PSMA-617 with other therapies, including androgen receptor pathway inhibitors (ARPIs), chemotherapy, PARP inhibitors, or immunotherapy, can improve outcomes compared with ^{177}Lu-PSMA-617 monotherapy.
- Updated results from the ENZA-p trial demonstrated that adding ^{177}Lu-PSMA-617 to enzalutamide in patients with mCRPC extended overall survival (OS) by 45% over enzalutamide alone while also preserving or improving patient-reported quality of life (**Figure**).
- In ENZA-p, advanced imaging metrics from PSMA PET scans, along with circulating tumor DNA (ctDNA) and other blood-based biomarkers, are increasingly able to predict which patients are most likely to respond to ^{177}Lu-PSMA-617. Patients with a larger volume of disease appeared to benefit more from the addition of ^{177}Lu-PSMA-617 to enzalutamide.
- Although ^{177}Lu-PSMA-617 combined with immunotherapy (ipilimumab [Yervoy®] and nivolumab [Opdivo®]) extended progression-free survival (PFS) over ^{177}Lu-PSMA-617 monotherapy in the EVOLUTION trial, more patients in the combination arm experienced grade 3 or 4 adverse events (29% vs 76%).
- Long-term follow-up of treated patients suggests that repeated cycles of ^{177}Lu-PSMA-617 can be administered safely over several years, although rare late toxicities such as myelodysplastic syndrome (MDS) can occur and are being actively monitored.
- New clinical trials are exploring next-generation approaches, including the combination of ^{177}Lu-PSMA-617 with the radiopharmaceutical radium-223 (Xofigo®) in the αLPHAβET trial or with the PARP inhibitor olaparib (Lynparza®) in the LuPARP trial. The αLPHAβET trial showed that the combination of both radiopharmaceuticals is safe.

Why do these findings matter?

- In the future, combination approaches involving ^{177}Lu-PSMA-617 may extend OS in patients with mCRPC.

- These advances show that RLT has evolved from a late-stage therapeutic option for heavily pretreated patients into a flexible, precision-based treatment that can be tailored to disease stage, tumor biology, and patient characteristics.



Terbium-161 PSMA: Does Auger Strike a Perfect Balance of Beta and Alpha?

James Buteau
Peter MacCallum Cancer Centre

What is the scientific background for this presentation?

- Although lutetium-177 (^{177}Lu)-PSMA-617 (Pluvicto®) is effective and well tolerated in mCRPC, most patients ultimately develop resistance, which is thought to be due to inadequate irradiation of very small tumor deposits or isolated cancer cells (called *micrometastases*).
- ^{177}Lu-PSMA-617 emits beta particles with a tissue penetration range of approximately 1 mm, leading to irradiation of normal cells alongside cancer cells.
- Terbium-161 (^{161}Tb) is a novel radionuclide with physical properties similar to ^{177}Lu, but it additionally emits Auger and conversion electrons, which deposit high-energy radiation over much shorter distances, potentially increasing tumor cell kill at the microscopic level.

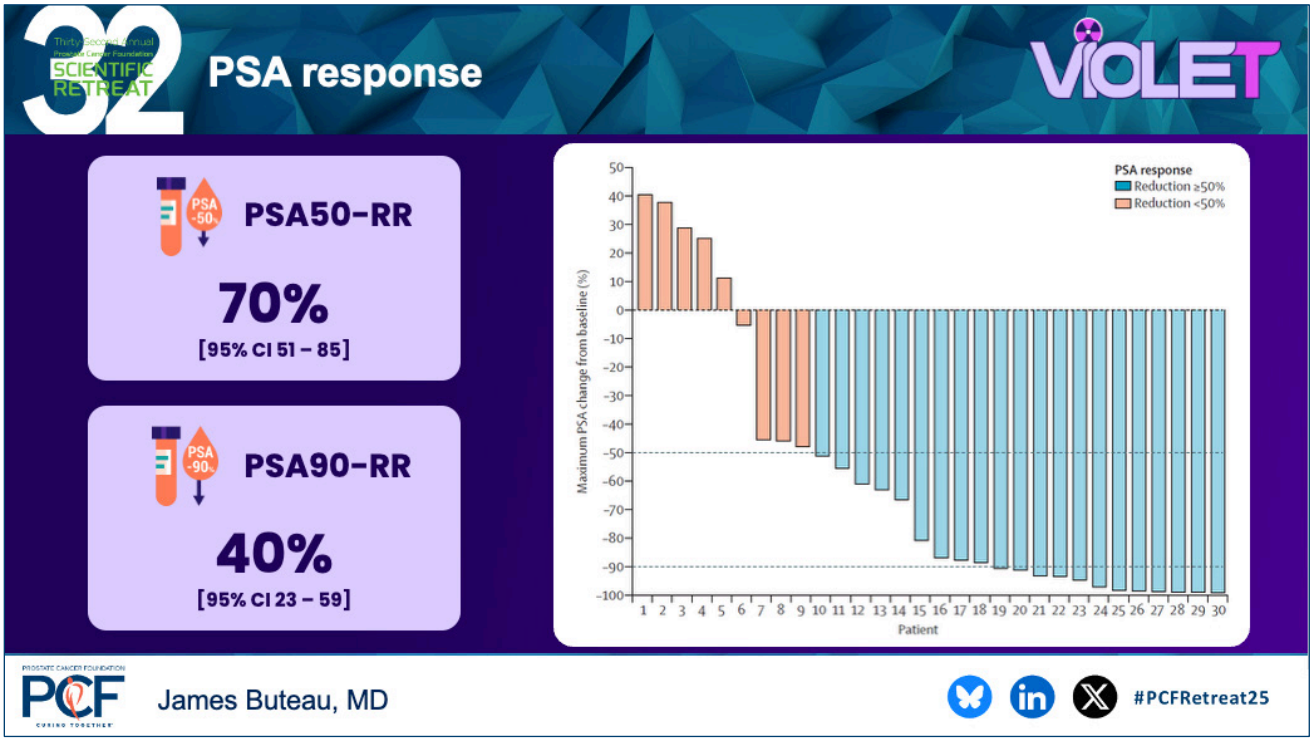
What progress or new findings were shared?

- Dr. Buteau presented results from the VIOLET trial, a first-in-human, phase 1/2 dose-escalation study of ^{161}Tb-PSMA in patients with metastatic castration-resistant prostate cancer (mCRPC) who had received an androgen receptor pathway inhibitor (ARPI) and taxane chemotherapy.

- Thirty patients were treated every 6 weeks for up to 6 cycles across 3 dose levels, with no dose-limiting toxicities observed and expansion of the highest dose cohort (7.4 GBq) based on a favorable safety profile.
- Treatment with ^{161}Tb-PSMA produced encouraging antitumor activity, with 70% of patients achieving ≥50% PSA decline and 40% achieving ≥90% PSA decline (**Figure**).
- Median progression-free survival (PFS) was 11.1 months, with overall survival (OS) data still maturing at the time of presentation.
- Dosimetry analyses showed high and prolonged radiation retention in tumor tissue with rapid washout from kidneys and salivary glands—organs that naturally attract PSMA-directed radioligand therapy (RLT)—resulting in absorbed doses comparable to those seen with ^{177}Lu-PSMA-617.

Why do these findings matter?

- These first-in-human data suggest that ^{161}Tb RLT is a safe and potentially effective treatment modality that, when targeted to PSMA, may result in antitumor activity in patients with mCRPC.



Novel Theranostic Agents for Neuroendocrine Prostate Cancer (TACTICAL Award)

Jason Lewis
Memorial Sloan Kettering Cancer Center

What is the scientific background for this presentation?

- Neuroendocrine prostate cancer (NEPC) is an aggressive, treatment-resistant subtype that often emerges through treatment-induced transdifferentiation of prostate adenocarcinoma and is associated with poor survival and few effective therapies. Transdifferentiation is a phenomenon in which cells change phenotype from one cell type to another, and in cancer, can be driven by treatment pressures.

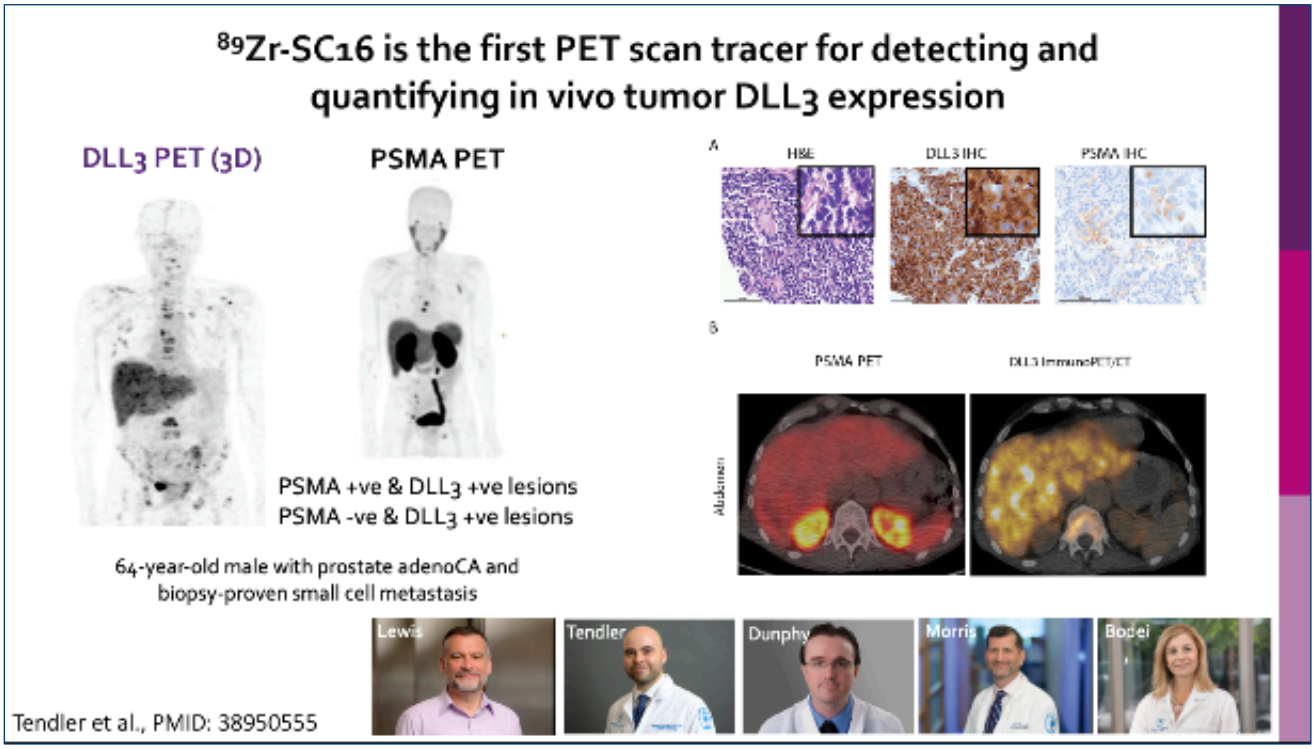
- Unlike adenocarcinoma, NEPC typically lacks androgen receptor (AR) and PSMA expression, making hormonally targeted agents and PSMA-directed RLT less effective against these tumor types.
- The cell-surface protein delta-like ligand 3 (DLL3) is highly expressed in poorly differentiated neuroendocrine tumors, including NEPC, making it a promising theranostic target.

What progress or new findings were shared?

- Dr. Lewis described the development and clinical translation of DLL3-targeted theranostics, building on prior work demonstrating high DLL3 expression in metastatic NEPC through autopsy and tissue profiling studies.
- DLL3-targeted PET imaging successfully identified DLL3-positive lesions in patients with NEPC, often revealing high variability within patients, with DLL3-positive tumor cells coexisting alongside PSMA-positive adenocarcinoma (**Figure**).
- Preclinical studies showed that DLL3-targeted radioligand therapy produced deep and durable tumor responses in NEPC models, consistent with the known radiosensitivity of neuroendocrine tumors.
- Molecular studies identified regulators of DLL3 expression, including ASCL1 and Notch signaling pathways, as well as additional candidate targets such as the *KMT2C* gene, suggesting potential strategies to modulate or expand DLL3-targeted therapy.
- Beyond prostate cancer, DLL3 expression and imaging were demonstrated in other aggressive neuroendocrine malignancies, including small cell lung cancer, gastrointestinal neuroendocrine carcinomas, and neuroblastoma, highlighting broader translational potential.
- To overcome barriers with previously developed anti-DLL3 antibodies, Dr. Lewis presented early data on next-generation anti-DLL3 antibodies and constructs that showed improved imaging performance and therapeutic promise.
- Finally, Dr. Lewis discussed a potential novel biomarker identified in NEPC, called GPC3, which is highly enriched in NEPC tumors, and has been studied as a potential RLT target in preclinical models.

Why do these findings matter?

- DLL3-directed theranostics offer a potential diagnostic and therapeutic strategy for patients with NEPC, a population with limited treatment options and poor outcomes.
- The ability to visualize and target biologically distinct, therapy-resistant tumor subclones could enable more precise treatment selection and combination strategies in advanced prostate cancer.



Radionuclides for the Theranostic Revolution: Matched Theranostic Pairs

Suzanne Lapi
University of Alabama at Birmingham

What is the scientific background for this presentation?

- Theranostics is a precision medicine strategy in which molecular imaging is first used to determine if a patient's cancer expresses a protein target, followed by treatment with a radioligand therapy (RLT) against the same target. Theranostics success depends not only on the biological target, but also on the chemical pairing between the targeting molecule and the radioactive isotope, as small changes in metal coordination can lead to large differences in biodistribution and efficacy.
- Ideally, imaging and therapeutic radiopharmaceuticals should be elementally matched, meaning they use chemically identical isotopes for diagnosis and treatment, because labeling the same target molecule with different isotopes (e.g., copper [Cu] vs lead [Pb]) can produce different tumor uptake and normal-organ exposure.

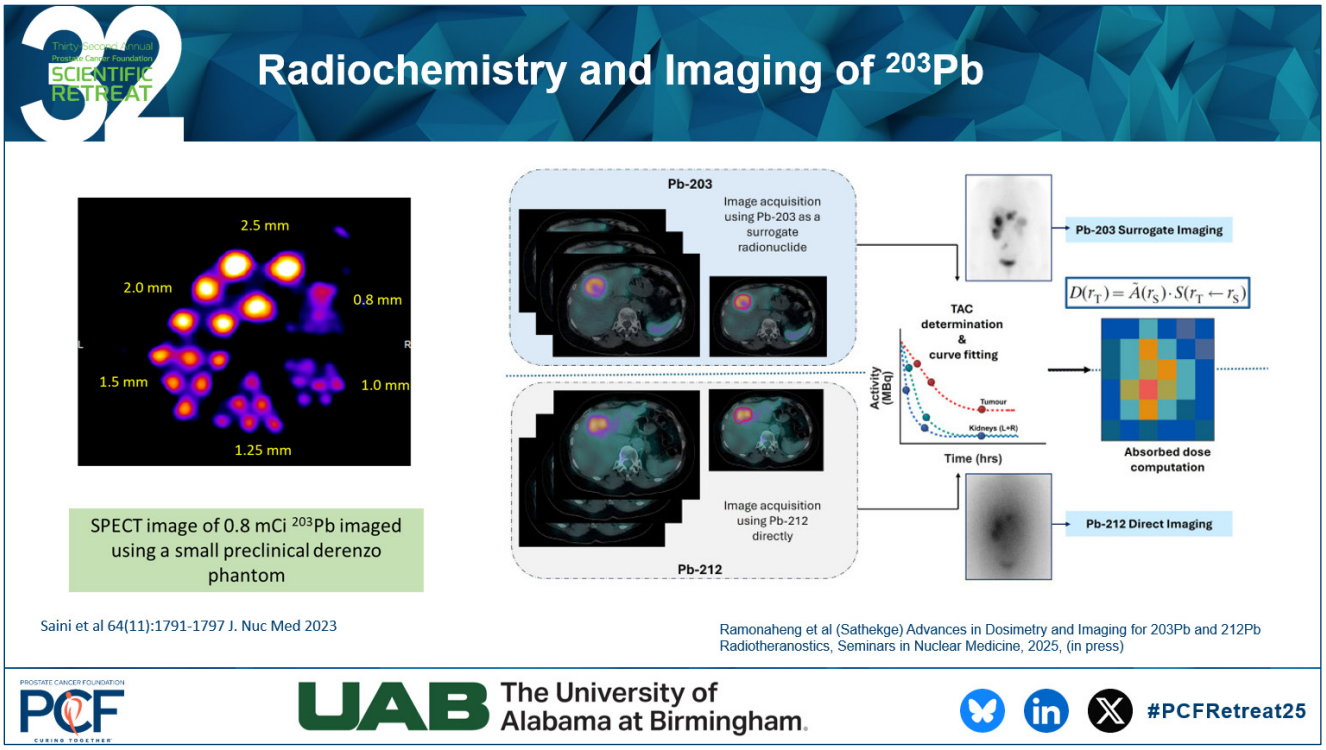
What progress or new findings were shared?

- Dr. Lapi described scalable cyclotron- and generator-based isotope production methods at her institution that enable reliable distribution of investigational radiopharmaceuticals for multicenter clinical trials.
- Advances in the production and clinical use of elementally matched theranostic pairs of imaging isotopes and therapeutic isotopes, including ^{64}Cu/^{67}Cu and ^{203}Pb/^{212}Pb, were described.
- Although SPECT imaging is classically considered to be less sensitive than PET imaging, using elementally matched pairs allowed researchers to achieve resolutions down to 1 mm with ^{203}Pb SPECT for ^{212}Pb-targeted radiopharmaceuticals (**Figure**).

- New isotope production strategies were presented for emerging imaging surrogates of RLTs such as ^{177}Lu and ^{161}Tb, including the use of long-lived parent molecules (such as neodymium-140, with a 3.4-day half-life) that, after reaching the target within the body, decay to short-lived isotopes that emit the signal for PET imaging (such as praseodymium-140, with a 3.4-minute half-life).

Why do these findings matter?

- Better-matched theranostic elemental pairs improve the ability to predict RLT efficacy and optimize dosing, supporting more personalized use of radiopharmaceuticals.
- Advances in isotope production and distribution are intended to reduce logistical barriers that have historically limited access to theranostics, enabling broader clinical adoption.



Session 2: Immunotherapy for Prostate Cancer

Training T cells for the Harsh New World (of Prostate Cancer) (TACTICAL Award)

Saul Priceman
University of Southern California

What is the scientific background for this presentation?

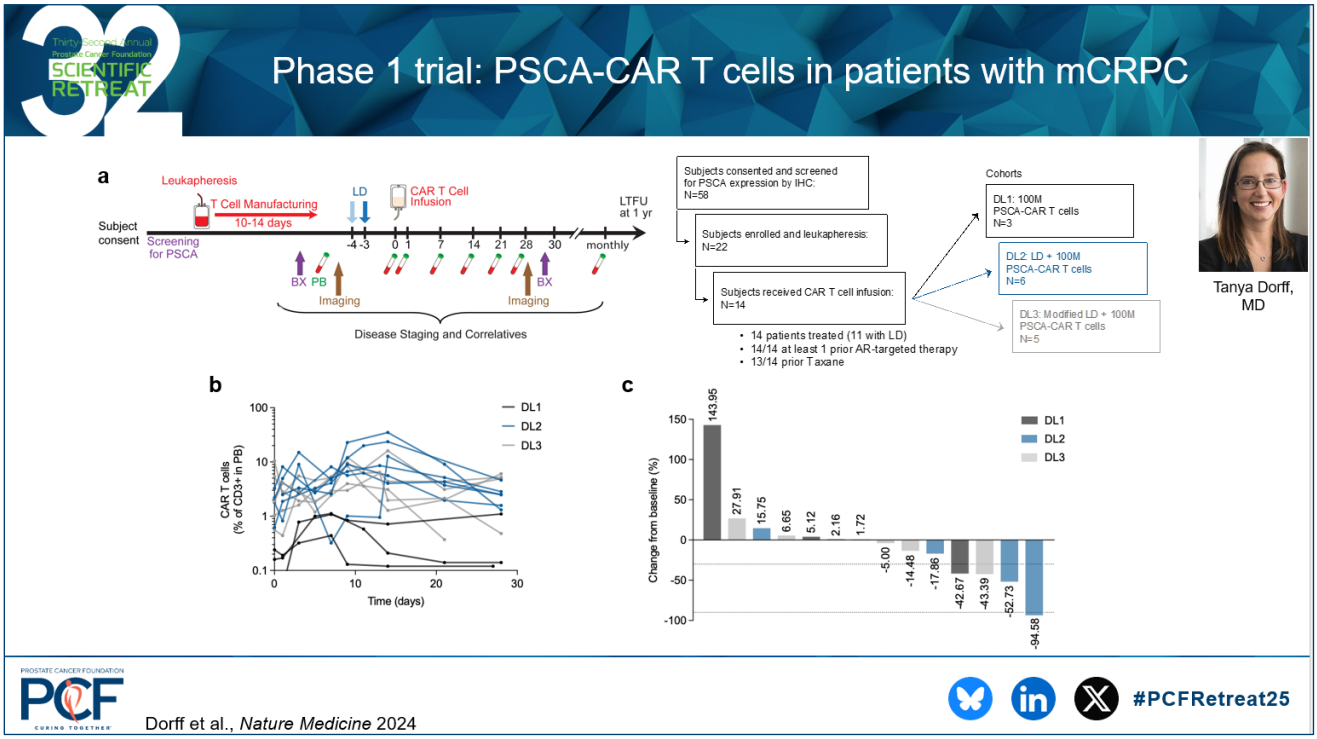
- Prostate tumors are typically immunologically "cold," with few infiltrating T cells and a highly immunosuppressive tumor microenvironment (TME), limiting the effectiveness of cellular immunotherapies used for other types of cancer.
- Overcoming barriers such as inadequate T-cell activation and infiltration is essential to enable effective T-cell–based therapies in metastatic castration-resistant prostate cancer (mCRPC).

What progress or new findings were shared?

- Preclinical studies in mouse models demonstrated that pretreatment with cyclophosphamide—a chemotherapy that depletes patient T cells (called *lymphodepletion*)—can promote T-cell infiltration into tumors, increasing the effectiveness of cellular immunotherapies such as chimeric antigen receptor T-cell (CAR-T) therapy.
- In a phase 1 clinical trial of prostate stem cell antigen (PSCA)-directed CAR-T therapy administered following lymphodepletion, treatment in patients with mCRPC resulted in PSA responses in about one-half of patients (**Figure**).
- Although early responses were observed, most were short-lived, likely reflecting limited CAR T-cell persistence and underscoring the need for next-generation engineering strategies.
- Dr. Priceman then described the collaborative TACTICAL Award research that is working to develop cellular immunotherapies for mCRPC with increased efficacy and decreased toxicity.
- Laboratory studies have shown that CAR-T cells that overexpress the transcription factor FOXO1—which is found at higher levels in young T cells and lower levels in older, dysfunctional T cells—reversed age-associated dysfunction and increased CAR T-cell longevity.
- Strategies targeting the TME were also highlighted, including the delivery of proinflammatory cytokines directly to the tumor, increasing T-cell populations and reducing immunosuppressive cell populations.
- Analyses of patient tumor samples revealed that the factors driving treatment effectiveness are different from those causing side effects, suggesting it may be possible to improve safety without reducing benefit.

Why do these findings matter?

- These data demonstrate that CAR T-cell therapy has antitumor activity in prostate cancer when both T-cell dysfunction and the suppressive tumor microenvironment are addressed.
- This work supports a rational path toward next-generation, combination-based cellular immunotherapies that may ultimately expand the role of T-cell–based treatments in advanced prostate cancer.



Pasritamig, a Differentiated, KLK2-Targeted T Cell Engager for Prostate Cancer

Charles Drake
Johnson & Johnson Innovative Medicine

What is the scientific background for this presentation?

- T-cell engagers are a newer class of immunotherapies designed to directly activate T cells within the tumor microenvironment (TME) by simultaneously binding CD3, a protein expressed on T cells, and a protein expressed primarily or exclusively on cancer cells called a *tumor-specific antigen*.
- Historically, cytokine release syndrome (CRS)—an inflammatory side effect that can lead to organ failure in some cases—has been a major limitation of T-cell engagers in solid tumors, restricting dosing, administration route, and outpatient use.

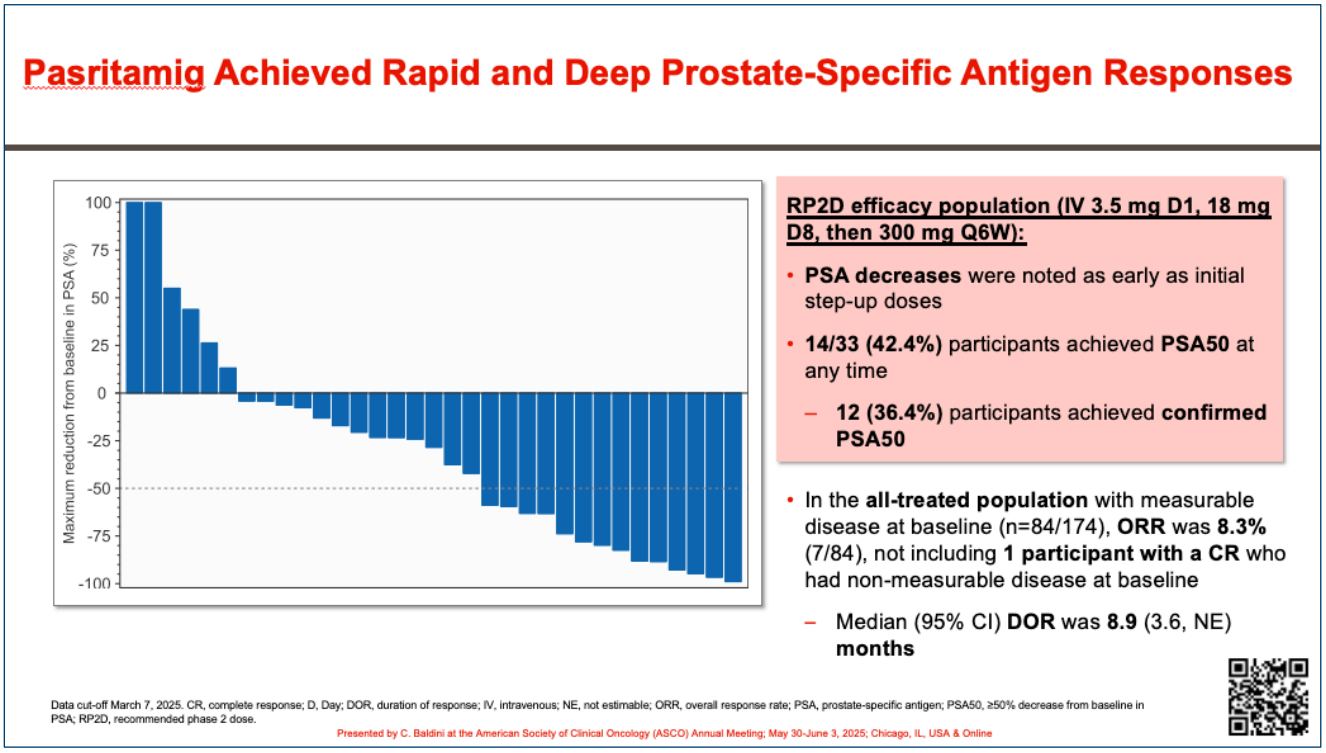
What progress or new findings were shared?

- Dr. Drake reviewed clinical progress with pasritamig, a CD3 T-cell engager, which targets the tumor-specific antigen KLK2, a protein expressed in prostate cancer cells with minimal expression in normal tissues.
- In a phase 1 study of pasritamig in patients with metastatic castration-resistant prostate cancer (mCRPC), treatment resulted in PSA declines of ≥50% in 42% of patients and objective responses on imaging in 8% of patients (**Figure**).
- A key clinical observation was that route of administration mattered: switching pasritamig from subcutaneous to intravenous dosing enabled higher drug exposure while markedly reducing the incidence of CRS.
- At the recommended phase 2 dose and schedule, CRS was uncommon, with less than 10% of patients experiencing grade 1 events, and no grade ≥2 CRS events. Furthermore, there were no treatment discontinuations due to toxicity.

- Unexpectedly, less frequent dosing (every 6 weeks) resulted in higher PSA response rates compared with more frequent dosing schedules, doubling the PSA response rate at 12 weeks compared with every-3-week dosing.
- Translational research data suggested that the more frequent dose schedule was less efficacious because ongoing T-cell activation can lead to cell death and T-cell exhaustion.

Why do these findings matter?

- Because of its favorable tolerability and antitumor activity, pasritamig may be explored in combination strategies, including with chemotherapy, androgen receptor pathway inhibitors (ARPIs), radioligand therapy, and other immunotherapies.
- Pasritamig's safety profile and potential for combination treatment support its potential use earlier in the disease course, including in settings such as biochemical recurrence, where immunotherapy may offer a second chance for durable disease control.



Session 3: Drugging the Epigenome to Target Lethal Disease

The Landscape of N6-Methyladenosine in Localized Primary Prostate Cancer and How These Modifications Can Drive Disease Aggressiveness

Housheng Hansen He
Princess Margaret Cancer Centre, University Health Network

What is the scientific background for this presentation?

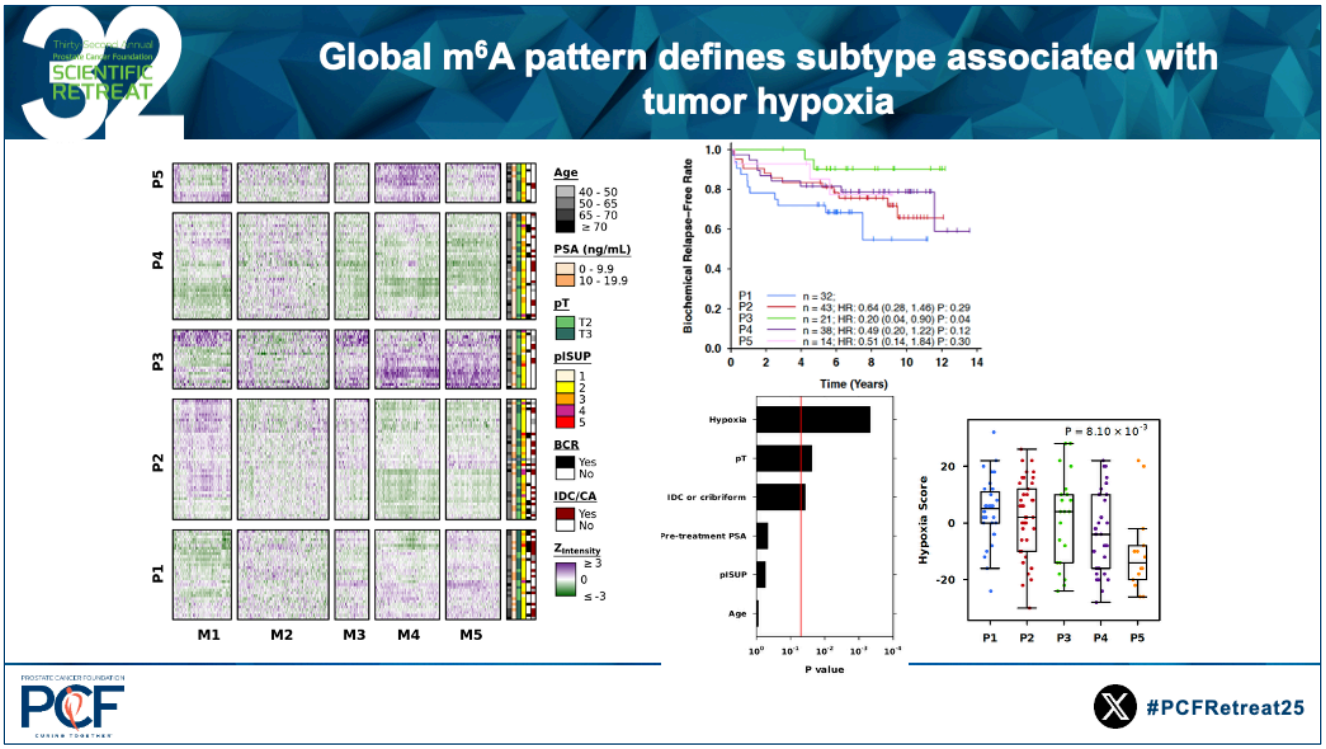
- RNA molecules can undergo chemical modifications after transcription (called *epigenetic* modifications), which regulate how RNA molecules are processed, translated, and degraded without altering their sequence.
- The most common internal RNA modification in human cells is N6-methyladenosine (m^6A) methylation, which can be added or removed by specific enzymes ("writers" or "erasers") and recognized by "reader" proteins.
- Dysregulation of m^6A modification can lead to a state called *hypermethylation* and has been implicated in cancer progression, including in prostate cancer.

What progress or new findings were shared?

- Dr. Hansen He reviewed analyses of patient samples which showed that hypermethylation of prostate cancer is associated with dysregulation of m^6A methylation.
- Using an m^6A profiling method developed by the investigators, m^6A modifications were mapped in 148 primary prostate tumors, identifying more than 32,000 m6A sites across more than 9500 genes.
- Oncogenes, such as *AR* and *MYC* were heavily m^6A-modified, whereas tumor suppressor genes (e.g., *TP53*, *PTEN*) showed few or no m6A modifications.
- Based on these data, patients could be stratified into 5 m^6A-based molecular subtypes, which showed significant differences in survival outcomes despite all patients being classified as intermediate risk by conventional criteria.
- The most aggressive m^6A subtype (P1 group in **Figure**) was strongly associated with tumor hypoxia (low oxygen levels), a known driver of prostate cancer progression and treatment resistance.
- Functional studies demonstrated that hypoxic conditions directly increased m^6A modification levels, suggesting a biological link between hypoxia and RNA methylation.
- Site-specific m^6A modification of the gene *VCAN* (a marker of fibroblast cells and a component of the extracellular matrix of the tumor microenvironment [TME]) increased protein translation and promoted tumor progression, even in the absence of supportive stromal cells.
- Early drug development efforts targeting m^6A regulators—particularly METTL3 inhibitors currently in phase 1 trials for hematologic malignancies—were highlighted as potential future strategies for prostate cancer.

Why do these findings matter?

- m^6A methylation patterns may serve as novel biomarkers to identify patients at higher risk of progression who are not distinguished by standard clinical features.
- The link between m^6A modification and tumor hypoxia raises the possibility of combination strategies that target both hypoxic signaling and RNA methylation to treat lethal prostate cancer.



Characterizing Lineage Plasticity Using Circulating Chromatin

Sylvan Baca
Harvard: Dana-Farber Cancer Institute

What is the scientific background for this presentation?

- Advanced prostate cancer can develop treatment resistance through *lineage plasticity*, a process in which androgen receptor (AR)–dependent prostate adenocarcinoma shifts to different cell states—most commonly neuroendocrine prostate cancer (NEPC).
- Lineage plasticity is driven largely by epigenetic reprogramming, including changes in DNA methylation, histone modifications, and chromatin accessibility, rather than new DNA mutations.
- Traditional tissue biopsies provide only a snapshot of this process, whereas liquid biopsy approaches offer the potential to track epigenetic changes across the entire tumor burden and over time.

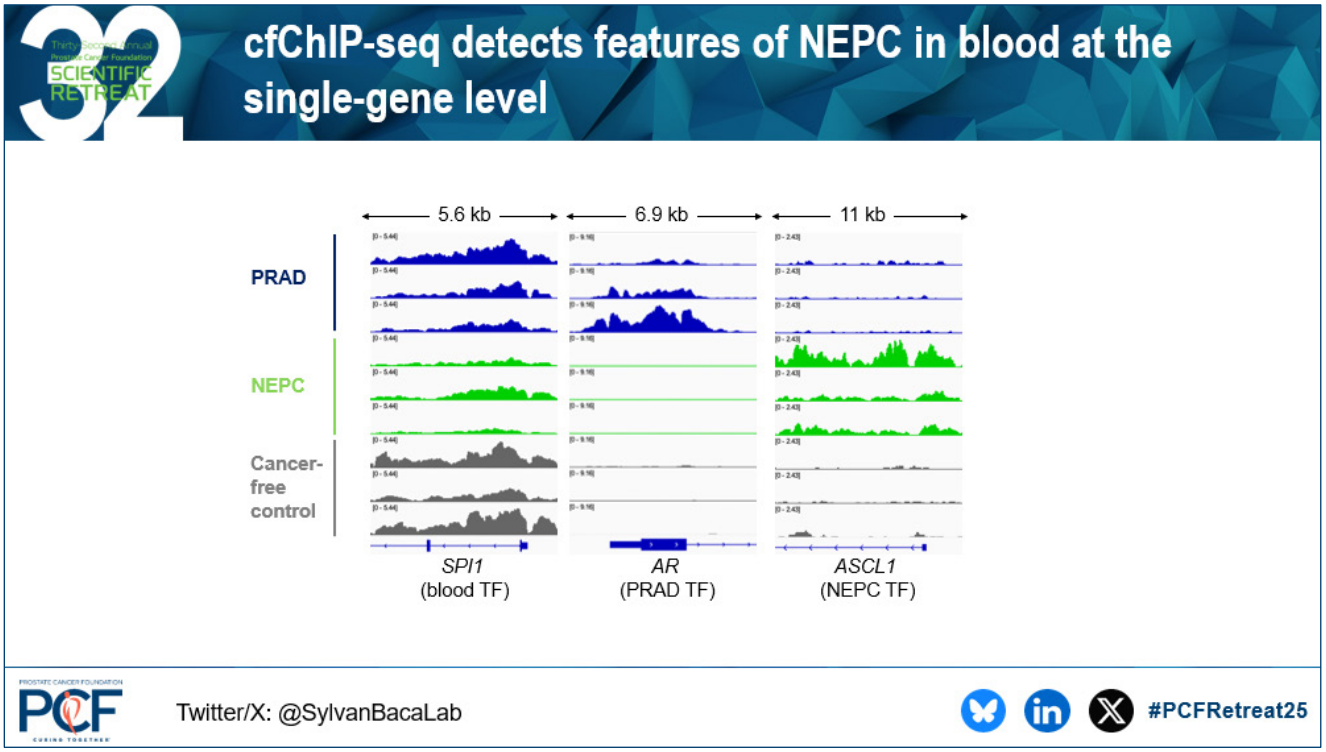
What progress or new findings were shared?

- Dr. Baca described the development of cell-free chromatin profiling (called *cfChIP-seq*), which enables analysis of histone modifications and DNA methylation patterns in tumor DNA shed into the blood by cancer cells without the need for a tissue biopsy.
- Distinct epigenetic signatures were identified that reliably distinguish hormone-driven prostate adenocarcinoma from NEPC, reflecting widespread changes in gene regulation during lineage transition.
- cfChIP-seq profiling provided information at the single-gene level, revealing loss of *AR*-associated signaling and gain of neuroendocrine drivers such as *ASCL1* during the transition from prostate adenocarcinoma to NEPC (**Figure**).

- Beyond lineage classification (e.g., differentiation of adenocarcinoma from NEPC), cfChIP-seq was also able to infer expression of therapeutic targets, including PSMA, delta-like ligand 3 (DLL3), and Nectin-4, based on promoter and enhancer activity detected in blood samples.
- Longitudinal sampling showed that some patients harbor mixed epigenetic signals, with coexisting adenocarcinoma and NEPC components, even after biopsy-confirmed NEPC diagnosis.
- In several cases, NEPC-associated epigenetic signals were detectable weeks or months before neuroendocrine differentiation was diagnosed by tissue biopsy, suggesting the possibility of early detection with cfChIP-seq.

Why do these findings matter?

- Blood-based assessment of lineage state and target expression could help guide treatment selection, particularly as cell surface protein–targeted therapies continue to expand.
- Early detection of lineage plasticity may enable earlier therapeutic intervention or combination strategies, potentially improving outcomes for patients with aggressive disease.



Utility of Epigenetic Profiling to Inform Resistance to ARPI

Wilbert Zwart
Netherland Cancer Institute

What is the scientific background for this presentation?

- Epigenetic modifications are reversible changes to DNA molecules or DNA-bound proteins that regulate gene expression without altering the DNA sequence.

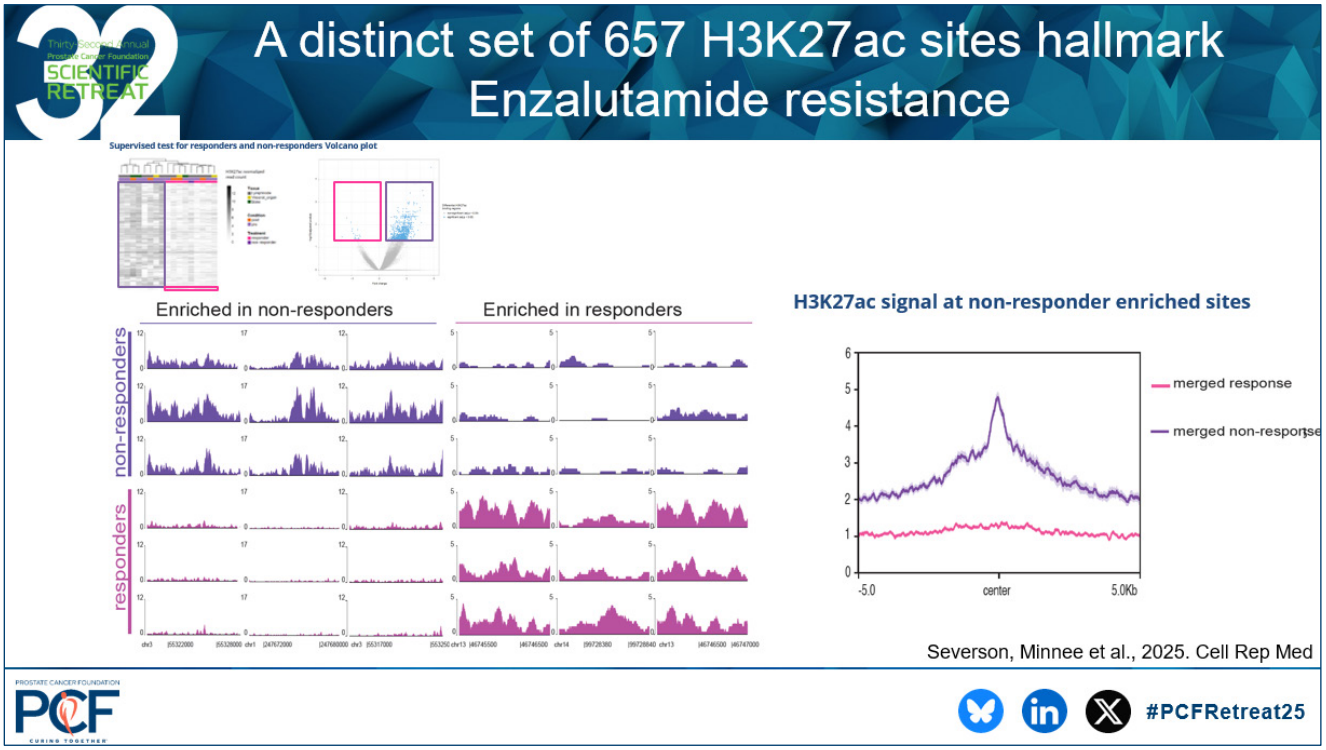
- In prostate cancer, the androgen receptor (AR) exhibits marked transcriptional plasticity (the ability of gene expression to change in response to various environmental stimuli) with epigenetic modifications to chromatin accessibility and DNA regions that increase expression (called *enhancers*) enabling tumors to develop resistance to hormonal therapies such as androgen receptor pathway inhibitors (ARPIs).
- Epigenetic profiling of clinical samples may identify predictive biomarkers associated with ARPI response and resistance and reveal new therapeutic vulnerabilities.

What progress or new findings were shared?

- Dr. Zwart presented results using patient samples from prostate cancer clinical trials in both the neoadjuvant and metastatic settings that incorporated epigenetic profiling before and after AR-targeted therapy.
- In a phase 2 study of patients receiving neoadjuvant ARPI therapy for high-risk prostate cancer, treatment with ARPIs induced widespread epigenetic reprogramming, with changes to the transcription factor FOXA1 and increased ARNTL expression.
- In laboratory studies, ARNTL knockout restored enzalutamide (Xtandi®) sensitivity in treatment-resistant cells, suggesting that ARNTL may be a novel therapeutic target in prostate cancer treated with ARPIs.
- In the metastatic setting, epigenetic profiling of acetylation of lysine residue 27 on histone 3 (H3K27ac)—an epigenetic modification that serves as a marker of AR enhancers and promoters—revealed a distinct set of H3K27ac sites that reliably distinguish enzalutamide responders from nonresponders (**Figure**).
- Researchers identified additional epigenetic drivers of resistance at H3K27ac sites associated non-response, and combination strategies pairing ARPIs with epigenetic modifiers targeting these markers (e.g., HDAC inhibitors) demonstrated enhanced antitumor activity in preclinical models.
- Dr. Zwart also highlighted early efforts to translate epigenetic profiling into minimally invasive blood-based assays, including cfChIP-seq, to monitor treatment response and resistance over time.

Why do these findings matter?

- These data show that epigenetic profiling can identify patients unlikely to benefit from ARPI therapy, enabling early treatment modifications.
- Resistance to ARPIs may be reversible by targeting epigenetic regulators that cancer cells become dependent on during therapy.
- Integrating epigenetic biomarkers into clinical trials could support more personalized treatment strategies, improving outcomes and avoiding ineffective therapies.



Targeting the Epigenome to Alter Lineage Plasticity

Michael Shen
Columbia University

What is the scientific background for this presentation?

- Epigenetic modifications are reversible chemical changes to DNA molecules or DNA-bound proteins (e.g., histones) that regulate gene expression without altering the DNA sequence.
- Epigenetic reprogramming plays an important role in the lineage plasticity (the ability of cancer cells to change their histology or molecular expression, often to evade treatment) that characterizes the transition from prostate adenocarcinoma to neuroendocrine prostate cancer (NEPC).
- NSD2 is a histone-modifying enzyme that regulates chromatin accessibility and gene expression and has been implicated in driving aggressive behavior and lineage changes in advanced prostate cancer.

What progress or new findings were shared?

- Dr. Shen presented epigenetic profiling data from genetically engineered mouse models and laboratory *organoid systems*—self-organizing, miniature, lab-grown organs that mimic the structure and function of human organs (**Figure**).
- Screening of epigenetic regulators of neuroendocrine differentiation identified NSD2 as a key driver of lineage plasticity in organoid models, with neuroendocrine cells showing high levels of NSD2-mediated epigenetic modifications (dimethylation of lysine residue 36 on histone 3 [H3K36me2] sites).
- When prostate cancer samples from patients were analyzed, NEPC had the highest NSD2 expression levels, followed by CRPC and then treatment-naïve prostate cancer. High NSD2 expression was associated with worse OS.

- In laboratory studies using mouse models and organoid systems, genetic knockdown or pharmacologic inhibition of NSD2 reduced expression of neuroendocrine lineage genes and reactivated canonical AR signaling, restoring sensitivity to enzalutamide (Xtandi®).
- Combination treatment with an NSD2 inhibitor and enzalutamide showed synergistic antitumor effects, significantly suppressing tumor growth compared with either agent alone.

Why do these findings matter?

- These studies demonstrate that NEPC differentiation is an epigenetically controlled and potentially reversible process, rather than an irreversible consequence of disease progression.
- Targeting NSD2 represents a novel therapeutic strategy to reverse neuroendocrine differentiation and resensitize tumors to AR-targeted therapies.

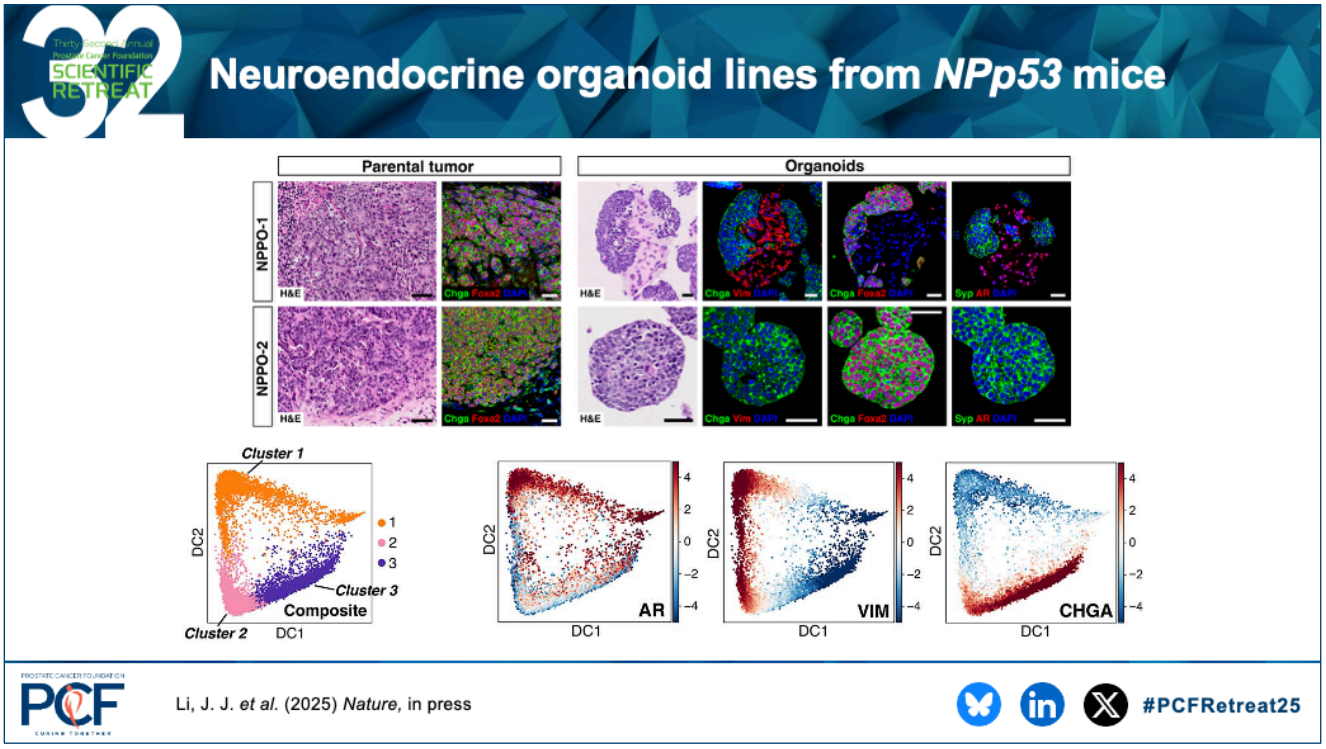


Figure source: Li JJ et al. *Nature*. 2026;649(8095):216-226.

Special Lectures

MYC Family Matters

Myles Brown
Harvard: Dana-Farber Cancer Institute

What is the scientific background for this presentation?

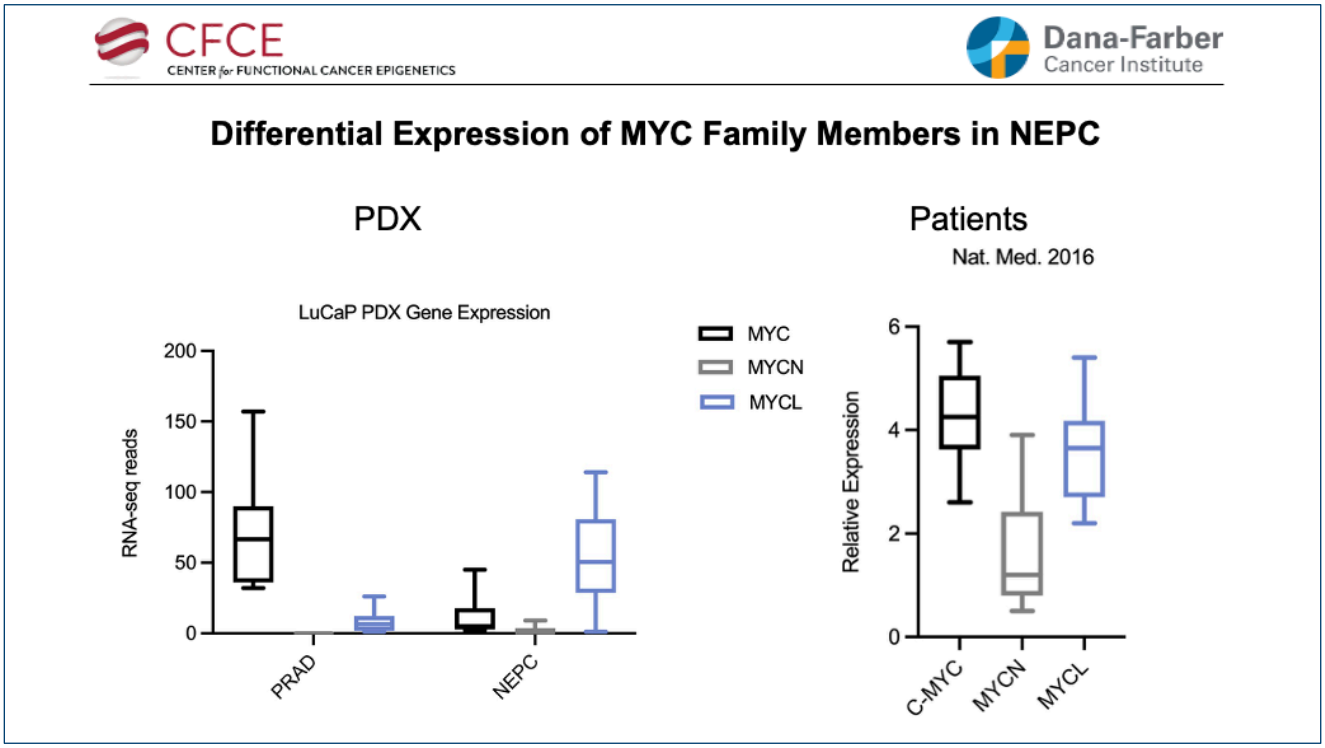
- Epigenetic studies evaluate reversible changes to DNA molecules or DNA-bound proteins that regulate gene expression without altering the DNA sequence.
- Prior epigenetic studies have shown that neuroendocrine prostate cancer (NEPC) more closely resembles other neuroendocrine cancers (e.g., small cell lung cancer) than prostate adenocarcinoma, suggesting overlapping transcription and chromatin regulation across different tumor types.
- The MYC family of oncogenic transcription factors (c-MYC, N-MYC, and L-MYC) play central roles in cancer progression.
- Studies have shown that MYC family members are expressed differently in NEPC relative to prostate adenocarcinoma.

What progress or new findings were shared?

- In laboratory studies of patient samples and mouse models, c-MYC was often amplified in prostate adenocarcinoma, whereas L-MYC was overexpressed in NEPC (**Figure**).
- Dr. Brown explained that these results were validated in an autopsy series of patients with CRPC as well as in prostate cancer cell lines, which showed that NEPC cells may be uniquely dependent on L-MYC for survival.
- Overexpression of L-MYC in prostate adenocarcinoma models had minimal effect; however, in CRPC models, L-MYC expression suppressed both AR and c-MYC transcription within days.
- L-MYC expression alone did not cause resistance to enzalutamide (Xtandi®) in prostate adenocarcinoma cells. However, when L-MYC overexpression occurred alongside loss of the tumor suppressor genes *RB1* and *TP53*, L-MYC activated neuroendocrine gene expression and promoted resistance to enzalutamide.
- Chromatin accessibility studies showed that L-MYC expression increased open chromatin at neuroendocrine gene loci while closing enhancer regions at the *AR* gene.
- Cells that transitioned to an L-MYC–driven neuroendocrine state became dependent on continued L-MYC expression, with withdrawal of L-MYC leading to growth arrest or cell death.

Why do these findings matter?

- These data identify L-MYC as a lineage-specific driver of neuroendocrine differentiation and therapy resistance in a subset of advanced prostate cancers.
- Dependence on L-MYC signaling in NEPC raises the possibility that L-MYC–directed therapies or degraders could be effective in selected patients with NEPC.



Degrading MYC: Updates on Drugging the Key Undruggable Oncogene (TACTICAL Award)

Arul Chinnaiyan
University of Michigan

What is the scientific background for this presentation?

- Prostate cancer is largely driven by dysregulated proteins that control gene expression (called *transcription factors*). The *MYC* gene, which encodes a transcription factor, is one of the most frequently amplified and overexpressed oncogenes in cancers and is commonly dysregulated in metastatic castration-resistant prostate cancer (mCRPC).
- Despite its central role in cancer biology, MYC has long been considered "undruggable" because it lacks obvious binding pockets for small molecules, making it difficult to directly inhibit with traditional pharmacologic approaches.

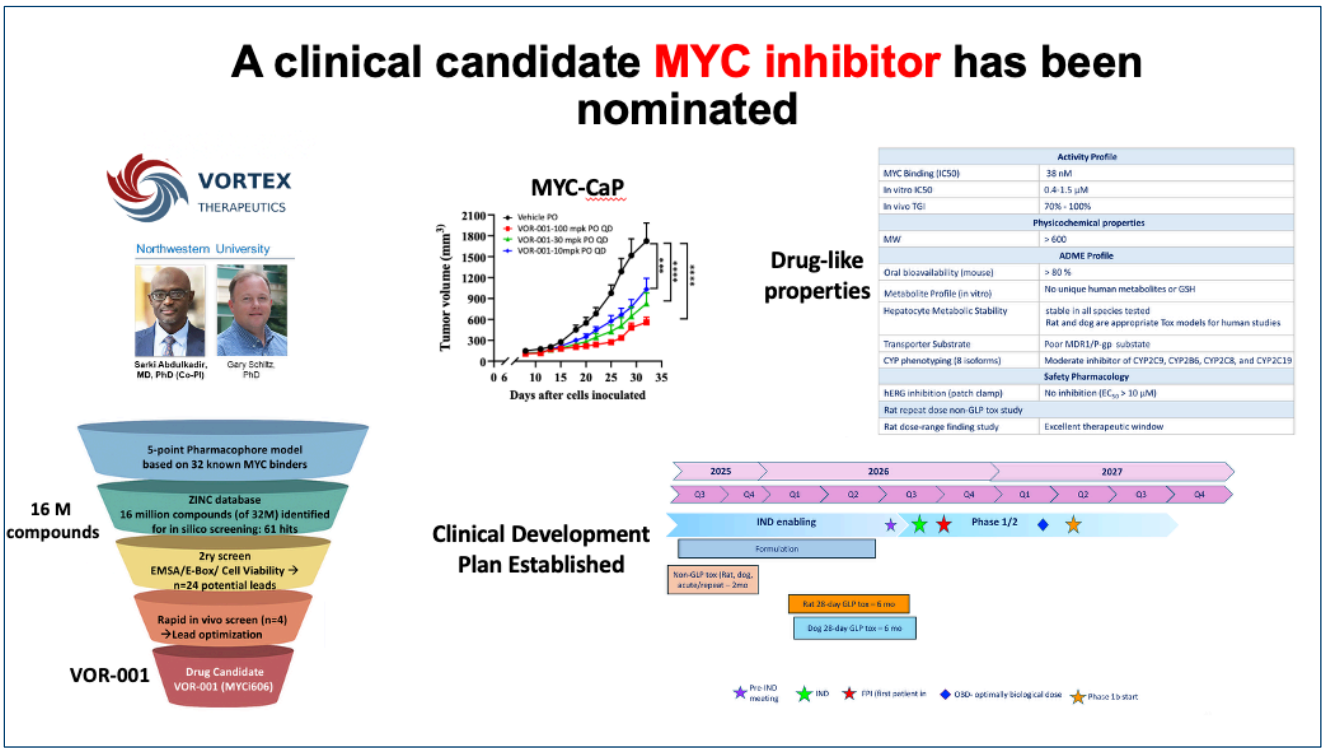
What progress or new findings were shared?

- Dr. Chinnaiyan began the presentation by reviewing the TACTICAL Award research that led to the development of multiple potential strategies to target MYC, including direct MYC inhibitors, MYC degraders, and compounds that suppress *MYC* expression by inhibiting DNA transcription or RNA translation.
- Dr. Chinnaiyan discussed Vortex Therapeutics, a company that was established to develop a MYC inhibitor. Following a computational model screening of 16 million compounds, a clinical candidate MYC inhibitor (VOR-001) with favorable drug-like properties and preclinical activity in prostate cancer was identified (**Figure**).
- Using DNA-encoded library screening—a method that rapidly tests billions of compounds attached to unique DNA "barcodes"—the team identified small molecules capable of binding MYC. These binders can then be engineered into PROTACs, which are specialized compounds that can link a target, in this case MYC, to the cell's protein-degradation system, triggering selective destruction of the MYC protein.

- The group also developed degraders targeting GSPT1, a protein involved in MYC translation. These compounds suppressed MYC levels and showed antitumor activity in prostate cancer mouse models.
- When the team used PROTACs to degrade p300/CBP—proteins that help control gene expression and interact with the androgen receptor (AR)—they unexpectedly observed a marked reduction in MYC protein levels. This finding suggests that targeting p300/CBP may indirectly suppress MYC, offering another strategy to inhibit MYC-driven tumors.
- The remainder of the presentation was focused on a novel class of molecules called *DALTACs*. Unlike PROTACs, which work by destroying proteins, DALTACs change how proteins interact with each other.
- DALTAC-1 is a DALTAC that binds the AR protein with p300, "gluing" the proteins together into a dysfunctional complex and preventing them from promoting cancer growth.
- In laboratory studies and mouse models of AR-expressing prostate cancer, DALTAC-1 significantly reduced MYC signaling and tumor growth.

Why do these findings matter?

- Demonstrating multiple viable strategies to inhibit or degrade MYC represents a major advance in overcoming the "undruggable" label.
- By selectively targeting AR complexes that promote cancer growth while sparing normal AR biology, DALTAC-based strategies may offer a way to suppress MYC-dependent tumor growth with improved specificity in AR-positive prostate cancer.



How Does Androgen Biosynthesis Occur Independent of CYP17A1 and CYP11A1?

Nima Sharifi
University of Miami

What is the scientific background for this presentation?

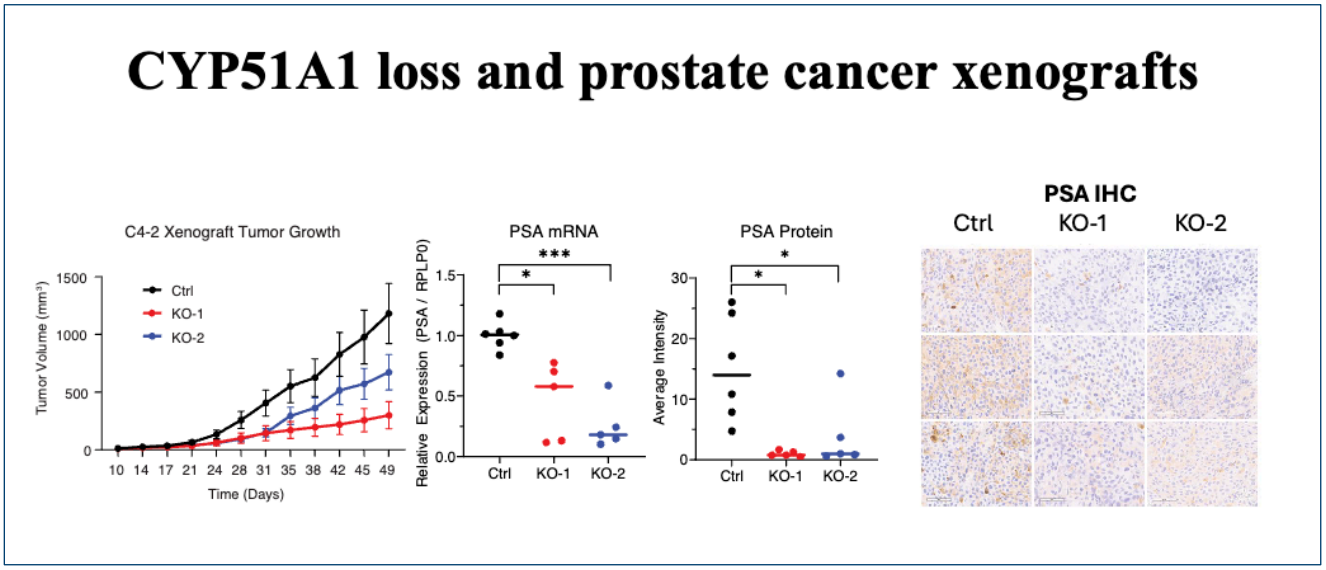
- Prostate cancer is typically a hormonally driven disease, making androgens such as testosterone the primary therapeutic target.
- Androgens and androgen precursor molecules are synthesized from cholesterol by the cytochrome P450 enzymes CYP11A1 and CYP17A1.
- Even with prostate cancer treatments that suppress androgen production—such as androgen deprivation therapy (ADT) and CYP17A1 inhibition (e.g., abiraterone [Zytiga®])—many patients continue to have detectable testosterone and dihydrotestosterone (DHT) levels in their prostate tissues, potentially leading to treatment resistance.

What progress or new findings were shared?

- In CRPC cell models, intracellular testosterone and DHT persisted despite androgen removal from the environment and CYP17A1 inhibition, indicating ongoing androgen synthesis within the cells themselves.
- Dr. Sharifi described the identification of an alternative androgen biosynthesis pathway that does not require CYP11A1 or CYP17A1 and instead uses oxidized forms of cholesterol (called *oxysterols*) as intermediates.
- The oxysterol 17,20-dihydroxycholesterol (DHC) was shown to serve as a substrate for androgen production, allowing for the generation of androgens and androgen precursors.
- Pharmacologic and genetic studies demonstrated that this pathway is independent of CYP17A1 and depends on another cytochrome P450 enzyme, CYP51.
- Systematic screening of all 57 human cytochrome P450 enzymes identified CYP51 as the sole enzyme capable of catalyzing androgen synthesis from DHC.
- In animal models of prostate cancer, loss of CYP51 delayed progression to castration-resistant disease and reduced tumor AR signaling (**Figure**).
- Liquid biopsy of circulating tumor DNA from 730 men with mCRPC revealed upregulation of the *CYP51* gene in ~17% of patients, suggesting a potential mechanism of treatment resistance.

Why do these findings matter?

- These data highlight a previously unrecognized, CYP17-independent pathway of androgen biosynthesis.
- CYP51-mediated androgen production may help explain residual AR signaling and resistance to current hormonal therapies in a subset of patients with mCRPC.



Trial Design and Objectives for Prostate Cancer: Recommendations from Prostate Cancer Clinical Trials Working Group 4

Andrew Armstrong
Duke University

Michael Morris
Memorial Sloan Kettering Cancer Center

What is the scientific background for this presentation?

- Over the past 25 years, the Prostate Cancer Working Groups (PCWG 1–3) established shared rules for how prostate cancer clinical trials define eligible patient populations, measure response to treatment, and determine disease progression, helping researchers standardize trials across institutions and countries.
- Earlier PCWG guidelines were developed in an era largely dominated by clinical biomarkers (e.g., PSA levels) and conventional imaging, before widespread use of PSMA PET imaging, liquid biopsies, and modern targeted therapies.
- Rapid advances in treatment options, imaging technologies, and biomarkers have created new challenges in how trials are designed and interpreted, prompting the need for updated guidance.

What progress or new findings were shared?

- PCWG4 was formed to provide consensus guidance on how prostate cancer trials should be designed, conducted, and interpreted in the modern era, with the goal of improving consistency across studies and accelerating the development of effective therapies.
- PCWG4 introduces a more patient-centered disease framework that avoids terms like “castration-resistant” and instead classifies prostate cancer disease state based on prior therapies received, tumor biology, imaging findings, and clinical behavior (**Figure**).
- The guidelines formally incorporate PSMA PET imaging into trial design, emphasizing that new imaging measures (such as standardized uptake values [SUVs] or total tumor volume) are still investigational and should be collected for analysis but not yet used as definitive endpoints.
- Under PCWG3, radiographic disease progression on bone scans required confirmation on a follow-up scan, meaning patients often had to wait for additional new lesions to appear before progression was formally declared; PCWG4 introduced the “rule of 5,” which allows

progression to be confirmed once more than 5 new lesions are observed, aiming to identify meaningful disease progression earlier and avoid unnecessary delays in treatment decisions.

- PCWG4 endorses the use of intermediate biomarkers—measures such as PSA changes and circulating tumor DNA levels that provide early signals of biological or treatment activity but do not by themselves prove long-term benefit—to support early "go/no-go" decisions in clinical trials, meaning determining whether a therapy shows enough promise to continue development or should be stopped before larger, more resource-intensive studies are launched.
- The recommendations stress that discordance between PSA changes and imaging progression is common (occurring in roughly 20%–25% of patients) and clinically important, reinforcing the need for regular imaging rather than reliance on PSA alone.

Why do these findings matter?

- PCWG4 provides a modern roadmap for designing prostate cancer trials that better reflect how the disease is diagnosed, monitored, and treated today.
- By aligning trial end points more closely with patient outcomes and emerging technologies, these guidelines aim to speed drug development while improving the ability to identify which patients are most likely to benefit from new therapies.
- The framework is intended as a bridge to future trial designs, supporting data collection that will enable even more precise, biology-driven endpoints in the next generation of prostate cancer studies.

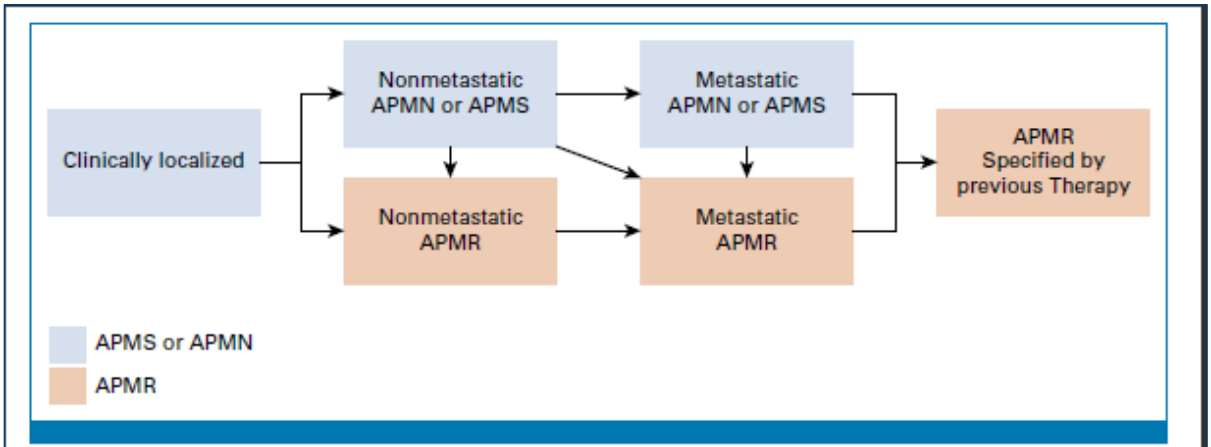


FIG 1. Prostate cancer clinical state model, a framework for patient treatment and drug development, updated for Prostate Cancer Clinical Trials Working Group 4. Combination therapy is considered one line of therapy. Androgen pathway modulation includes ADT and ARPI. Within each state, specify where relevant: (1) genotype (germline, somatic), (2) imaging modality used to define metastasis (PET, CT/MRI/bone scan), (3) disease characteristics and biomarkers critical for risk stratification, including pathology and immunohistochemistry, and (4) previous therapies and outcome including lack of exposure (treatment-naïve), exposed but not resistant, and resistant. APMN/S is the preferred term for hormone-/castration-naïve/castration-sensitive disease (HSPC, CSPC), whereas APMR is the preferred term for castration-/hormone-resistant prostate cancer (CRPC/HRPC). Mapping of previous PCWG3 disease states to the current PCWG4 state model is shown in Appendix Table A1. ADT, androgen deprivation therapy; APMN/S, androgen pathway modulation–naïve/sensitive; APMR, androgen pathway modulator–resistant; ARPI, androgen receptor pathway inhibitor; CSPC, castration-sensitive prostate cancer; CT, computed tomography; HSPC, hormone-sensitive prostate cancer; MRI, magnetic resonance imaging; PCWG, Prostate Cancer Clinical Trials Working Group; PET, positron emission tomography.

Figure source: Armstrong AJ et al. *J Clin Oncol.* Published online February 26, 2026. doi:10.1200/JCO-25-02834

Integrating Tissue-Based Insights to Optimize ARPI+PARPI Combination Therapy in HSPC

Patrick Pilie
University of Texas MD Anderson Cancer Center

What is the scientific background for this presentation?

- Combination therapy with an androgen receptor pathway inhibitor (ARPI)—which blocks androgen signaling in prostate cancer—and a poly (ADP-ribose) polymerase (PARP) inhibitor—which prevents cancer cells with defective DNA repair mechanisms from fixing DNA damage—has shown clinical benefit in advanced prostate cancer, with the strongest effects in patients with *BRCA* mutations, which are associated with double-stranded DNA breaks.
- Preclinical and clinical data suggest that AR pathway inhibition itself can induce cellular stress and vulnerability to PARP inhibition, even in tumors without known homologous recombination repair (HRR) mutations, delay resistance to antiandrogen therapy, and revert neuroendocrine transition in a subset of lethal prostate cancer.
- Applying this combination earlier in the disease course, particularly in high-risk localized prostate cancer, may increase benefit—but requires better tools to identify which patients truly need treatment with combination therapy.

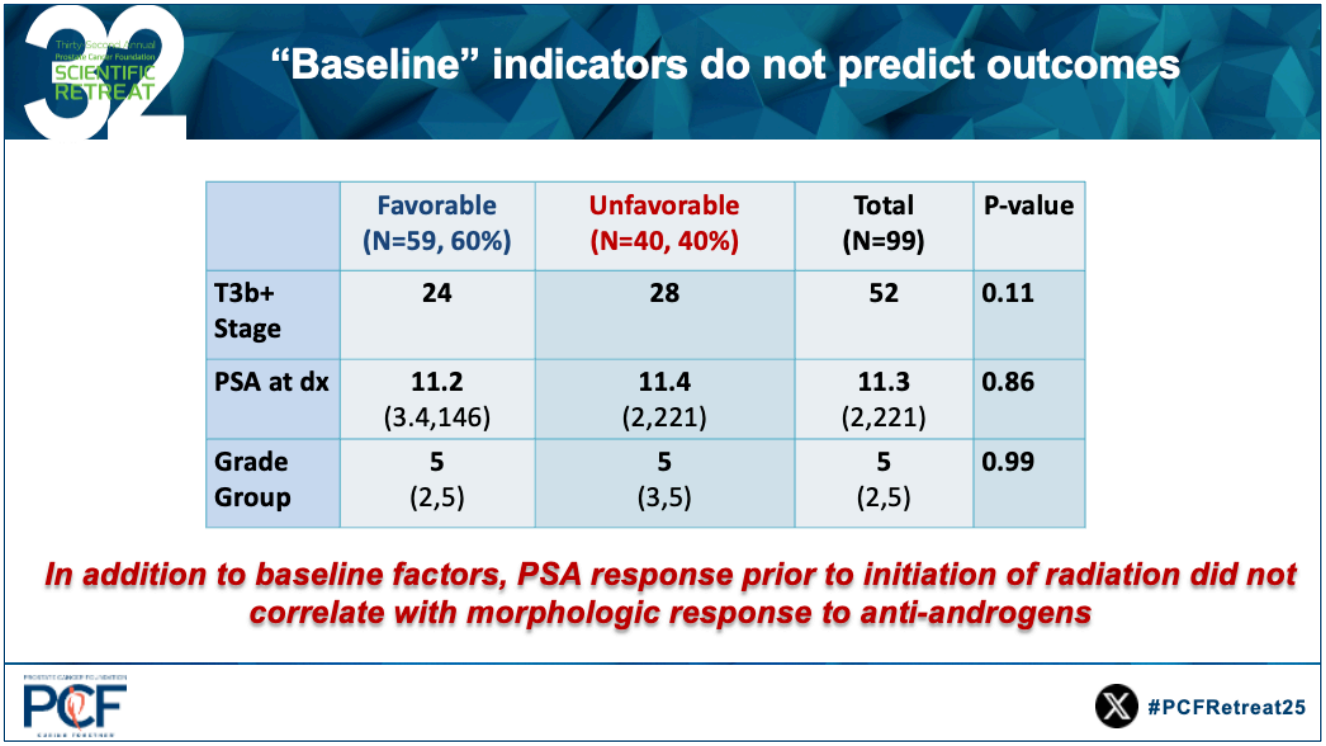
What progress or new findings were shared?

- Dr. Pilié presented early results from a clinical trial in men with high-risk localized prostate cancer (n = 99 patients to date).
- Participants received neoadjuvant apalutamide (Erleada®) and androgen deprivation therapy (ADT) prior to radiation therapy (RT), and based on results from an on-treatment biopsy, were classified as favorable or unfavorable response to antiandrogen therapy. Patients with favorable risk went on to receive apalutamide and ADT for another 18 months, whereas patients with unfavorable risk were randomized to apalutamide and ADT with or without the PARP inhibitor niraparib (Zejula®).
- After about 3 months of neoadjuvant treatment, approximately 60% of patients showed a favorable response on biopsy (determined by lower tumor cell density and morphology, suggestive of response to hormonal therapy), and about 40% had unfavorable tumor biology.
- Traditional baseline clinical features (i.e., T stage, PSA level at diagnosis, grade group) and PSA response with treatment did not predict which patients would have unfavorable on-treatment tumor morphology (**Figure**).
- Early clinical outcomes showed that all relapse events thus far occurred in the unfavorable morphology group, including multiple patients with emerging neuroendocrine metastatic disease.
- Paired baseline, on-treatment, and post-treatment tissue biopsies—along with serial blood sampling—are being banked to study links between AR signaling, DNA damage response pathways (which are classic markers of PARP inhibitor sensitivity), TME changes, and resistance.

Why do these findings matter?

- These data suggest that short-term response of the tumor to ARPI—measured directly in tissue—can more accurately identify patients at risk for recurrence relative to conventional clinical markers.

- Adaptive, tissue-guided strategies may allow patients at the highest risk for relapse to receive intensified treatment regimens while sparing others unnecessary toxicities from combination therapies.



From Mesopotamia to the Great Lakes "The 6000 Miles Journey": Prostate Cancer Then & Now (PCF Women in Science Lifetime Achievement Award Lecture)

Maha Hussain
Northwestern University/Robert H. Lurie Comprehensive Cancer Center

What is the scientific background for this presentation?

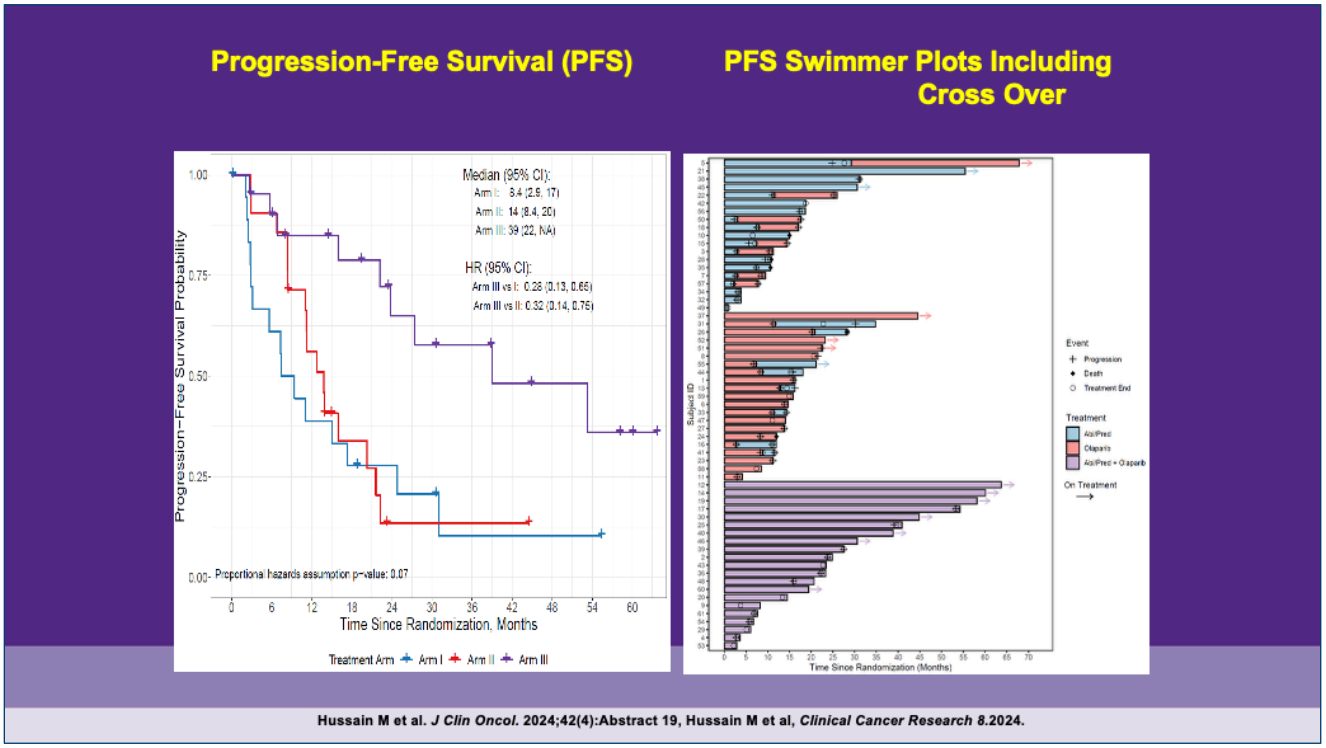
- In 2025, Dr. Maha Hussain became the first-ever recipient of the Prostate Cancer Foundation (PCF) Women in Science Lifetime Achievement Award, which recognizes the commitment, scientific achievements, and leadership of women in the field.
- Dr. Hussain framed her presentation around her personal journey in science and medicine, beginning with her training at a time when metastatic prostate cancer care was largely palliative and the field of genitourinary (GU) oncology was still emerging.
- She highlighted that when she entered the field, there were very few medical oncologists focused on prostate cancer—and even fewer women in GU oncology, underscoring how both the science and the workforce have evolved alongside each other.
- Using milestones from her own career, Dr. Hussain traced how prostate cancer care evolved from late-stage, symptom-driven treatment to earlier intervention with therapies targeting the biologic drivers of prostate cancer, thus impacting patients' outcomes across all states of disease.

What progress or new findings were shared?

- Regarding metastatic prostate cancer care, Dr. Hussain described how long-standing questions raised in the 1980s and 1990s—such as the benefit of combining androgen deprivation therapy (ADT) with other agents or introducing chemotherapy earlier in the disease course—were initially controversial but later validated through rigorous trials.
- Beginning around 2015, multiple randomized studies demonstrated that treatment intensification in metastatic hormone-sensitive prostate cancer (mHSPC) using doublet and triplet combinations with ADT, docetaxel chemotherapy, and ARPIs, significantly improved OS.
- Dr. Hussain highlighted landmark trials such as PEACE-1, ENZAMET, and ARASENS, emphasizing how these studies reshaped standards of care across disease volume and risk groups.
- In later-stage disease (metastatic castration-resistant prostate cancer [mCRPC]), she reviewed how the treatment landscape expanded to include chemotherapy, ARPIs, radioligand therapy (RLT), immunotherapy, and targeted therapies, reflecting decades of cumulative progress.
- Dr. Hussain also discussed how collaborative efforts such as the PCF-SU2C Prostate Cancer Dream Teams revealed potential clinically actionable genomic alterations in advanced prostate cancer, enabling the development of PARP inhibitors and precision-based treatment strategies.
- Drawing on her own investigator-initiated work in the BRCAAway trial, she also highlighted evidence that combining PARP inhibitors with ARPIs (Arm III in **Figure**) may be more effective than sequential therapy (e.g., ARPI followed by PARP inhibitor or vice versa), informing ongoing trial designs.

Why do these findings matter?

- This presentation illustrates how step-wise scientific advances, persistence in clinical research, and multidisciplinary workforce growth together transformed prostate cancer care over several decades.



Hussain M et al. *J Clin Oncol.* 2024;42(4):Abstract 19, Hussain M et al, *Clinical Cancer Research 8.*2024.

From Bench to Business: Bridging Biomedical Research and Entrepreneurial Drug Development

Arie Belldegrun
University of California, Los Angeles (UCLA)

What is the scientific background for this presentation?

- Dr. Arie Belldegrun is a urologic oncologist who is the Director of the UCLA Institute of Urologic Oncology as well as an entrepreneur and investor in industry ventures intended to address unmet needs in prostate cancer and other malignancies. He has also played a central role in founding and leading multiple biotechnology companies focused on translating immuno-oncology research into approved therapies.
- Dr. Belldegrun framed his talk around a career spent bridging academic discovery and entrepreneurial drug development (**Figure**).
- Institutional ecosystems that support collaboration, risk-taking, and commercialization of biomedical research—particularly at academic centers—were highlighted as central drivers of innovation in prostate cancer and beyond. These environments were emphasized as critical to enabling the rapid translation of high-risk scientific concepts into clinically meaningful therapies.

What progress or new findings were shared?

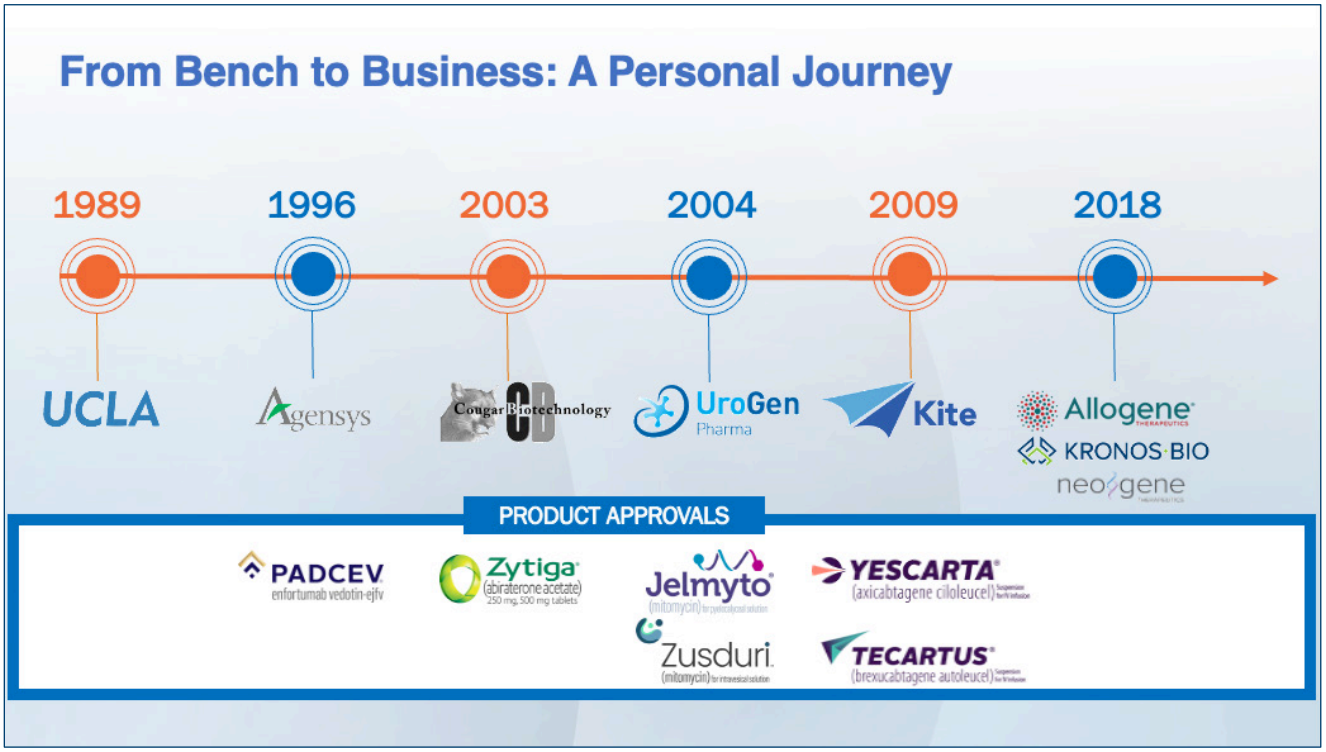
- Dr. Belldegrun discussed his early work in cancer immunology at the National Institutes of Health, including studies of tumor-infiltrating lymphocytes and cytokine-based therapies, which laid the foundation for later immunotherapy advances.
- Together with other investigators, Dr. Belldegrun founded Agensys in the mid-1990s, where differential gene expression approaches enabled the identification of multiple cancer targets. This work led to the development of early antibody-drug conjugates that ultimately

contributed to therapies now used worldwide, including enfortumab vedotin-ejfv (Padcev®) for bladder cancer.

- After Agensys was acquired by Astellas, Dr. Belldegrun's company Cougar Biotechnology developed abiraterone acetate (Zytiga®) for advanced prostate cancer. Through close collaboration between urologists and medical oncologists, the program progressed from in vitro studies to phase 3 clinical trials within a few years, reshaping the treatment paradigm for the disease. Cougar Biotechnology was acquired by Johnson & Johnson in 2009.
- Building on his immunotherapy expertise, Dr. Belldegrun cofounded Kite Pharma in 2009, focusing on CAR T-cell therapy and establishing the first large-scale manufacturing infrastructure for engineered cellular immunotherapies. Kite's CAR-T programs produced practice-changing clinical results, including durable remissions in patients with otherwise lethal cancers, ultimately leading to FDA approvals and global adoption. Kite was later acquired by Gilead Sciences.
- Recognizing the need for more scalable and accessible cell therapies, Dr. Belldegrun emphasized the development of next-generation approaches, including "off-the-shelf" allogeneic CAR T-cell therapies designed to enable earlier use in disease and broader patient access. In 2018, he co-founded Allogene Therapeutics with Dr. David Chang to develop the next generation of off-the-shelf CAR T therapies using healthy donor–derived T cells.
- Dr. Belldegrun highlighted recent clinical progress at Allogene, including encouraging data presented in patients with very advanced kidney cancer, supporting the potential of allogeneic immunotherapy approaches across multiple tumor types.
- Following Kite's acquisition, Dr. Belldegrun launched Vida Ventures, which supports a broad portfolio of biotechnology companies across oncology and immunology, including platforms focused on prostate cancer and other areas of high unmet need.
- Dr. Belldegrun also presented new data from a recently completed phase 1 trial in prostate cancer by Halda Therapeutics, evaluating an innovative therapeutic modality known as RIPTAC™ (Regulated Induced Proximity Targeting Chimeras). This technology is designed to precisely redirect immune activity toward tumor cells through controlled proximity-based mechanisms, representing a novel immune-engaging approach distinct from traditional CAR T therapies.
- Halda was recently acquired by Johnson & Johnson, underscoring the strategic importance of next-generation immunotherapy platforms and the successful translation of high-risk scientific concepts into impactful therapeutic programs.
- Throughout the presentation, Dr. Belldegrun emphasized that many of these advances originated as high-risk ideas with limited early clinical data but were pursued through rigorous science, interdisciplinary collaboration, and close alignment with patient needs.

Why do these findings matter?

- Dr. Belldegrun's career arc illustrates how the integration of scientific discovery, clinical insight, and entrepreneurship can dramatically accelerate the development and delivery of transformative therapies to patients.
- Many of the treatments discussed—spanning hormonal therapies, targeted agents, cellular immunotherapies, and emerging immune-engaging technologies—have reshaped standards of care and extended survival for patients with advanced cancers, including prostate cancer.


From Bench to Business: A Personal Journey
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Panel Discussion: Luminaries in Prostate Cancer—How the Past Informs Our Future

Moderator

Phillip Koo
Prostate Cancer Foundation

Panelists

Maha Hussain
Northwestern University

Oliver Sartor
Tulane University

Cora Sternberg
Weill Cornell Medicine

Introduction

- The Luminaries in Prostate Cancer panel discussion was moderated by Phillip Koo, Prostate Cancer Foundation (PCF) Chief Medical Officer, and was intended to discuss recent clinical advances in prostate cancer as well as the future direction of medicine across all fields of prostate cancer diagnosis and care.

How has advanced prostate cancer care evolved, and where is it headed?

- Panelists reflected on the dramatic shift in prostate cancer care, from an era with few effective systemic therapies to one with multiple life-prolonging options, particularly for advanced and metastatic disease.
- Survival gains over the past 2 decades were attributed to earlier treatment, combination approaches, improved biomarkers, and next-generation imaging, rather than individual treatment or diagnostic advances alone.
- Despite progress, the panel emphasized that prostate cancer remains a heterogeneous disease, with outcomes varying widely based on biology, disease burden, and access to care.
- Looking ahead, panelists agreed that future gains will depend on better patient selection, biomarker integration, and thoughtful sequencing of therapies.

What future opportunities exist from the urologic oncologist perspective?

- The panel was joined by Dr. Jim Hu, who was able to provide a surgeon's perspective on the changing field of prostate cancer.
- Panelists discussed how advances in robotic-assisted prostatectomy have improved surgical precision and recovery, but emphasized that technical capability must be paired with careful patient selection and shared decision-making.
- Special attention was given to younger patients with prostate cancer, for whom decisions around prostatectomy must balance long-term cancer control with potential impacts on urinary, sexual, and overall quality of life.
- The panel highlighted ongoing challenges and opportunities in prostate cancer screening, including how to better identify clinically significant disease while minimizing overdiagnosis and overtreatment.
- Panelists emphasized the importance of multidisciplinary teams collaborating to help patients navigate increasingly complex treatment choices—integrating clinical risk, imaging, pathology, and patient preferences—at the earliest stages of care.

How can radiation oncology shape the next decade of care?

- Dr. Neha Vapiwala joined the panel to discuss the evolving field of radiation oncology in prostate cancer.
- Panelists discussed how advances in radiation delivery and imaging have enabled more precise targeting, allowing clinicians to better tailor treatment fields and doses while minimizing side effects and expanding the opportunities for combining RT with novel agents (e.g., T-cell engagers, CAR-T therapy).
- The role of RT in earlier disease settings was emphasized, including its use in combination with systemic therapy for high-risk localized disease and in patients with limited metastatic burden (i.e., oligometastatic disease).
- Decision-making around when to escalate RT intensity versus when to de-escalate was highlighted as a key opportunity, particularly as genomic classifiers and imaging tools improve risk stratification (e.g., the PORTOS signature).
- Panelists noted that radiation oncologists increasingly serve as partners in multidisciplinary treatment planning, helping clinicians and patients weigh trade-offs between surgery, RT, and combination approaches based on long-term outcomes and quality of life.

What are the biggest opportunities in medical oncology?

- Dr. Emmanuel Antonarakis supported the medical oncology discussion, which was focused on the expanding range of nonhormonal systemic treatment options, which could provide particular benefit in biochemical recurrence or oligometastatic disease.
- The panel underscored that PSA alone is no longer sufficient to guide systemic therapy decisions, pointing to the need for better biomarkers to inform when to start, stop, or change treatment while preserving quality of life.
- Minimal residual disease (MRD)—which refers to a very small number of cancer cells remaining in the blood after treatment, typically only detectable with highly sensitive sequencing tests—is a concept used to guide treatment escalation and de-escalation in other cancer types but has not yet made its way into the clinic for prostate cancer. In the future, incorporating MRD could help with decision making in patients with prostate cancer who are responding to treatment by conventional clinical markers (e.g., PSA levels).
- Panelists emphasized the potential benefits of investigating the treatment of earlier disease states with intensified but limited-duration systemic therapy.
- Challenges in treatment sequencing were highlighted, particularly how earlier use of potent therapies may influence resistance patterns and limit future options.

How will nuclear medicine redefine detection and treatment?

- Dr. Michael Hofman joined the panelists to discuss how PSMA-based theranostics have changed prostate cancer diagnosis and treatment.
- At the most basic level, PSMA PET imaging has fundamentally changed prostate cancer staging, often identifying disease earlier and more accurately than conventional imaging, leading to more informed decision making but also more complexity due to the lack of level 1 evidence in this space.
- The group emphasized that increased sensitivity raises new clinical questions, particularly when early detection should lead to treatment escalation versus careful observation.
- Nuclear medicine was highlighted as a growing therapeutic discipline, with PSMA-directed RLT offering a targeted treatment option for advanced disease and potential expansion into earlier settings.

- Panelists stressed the importance of integrating nuclear medicine findings into multidisciplinary decision making, ensuring that imaging results inform—rather than dictate—treatment choices.

Session 4: Updates from Industry Clinical Trials

PSMAddition: Initial Results from the Phase III Trial of Lu-177-PSMA-617 in Metastatic Hormone Sensitive Metastatic Prostate Cancer

Oliver Sartor
Tulane University

What is the scientific background for this presentation?

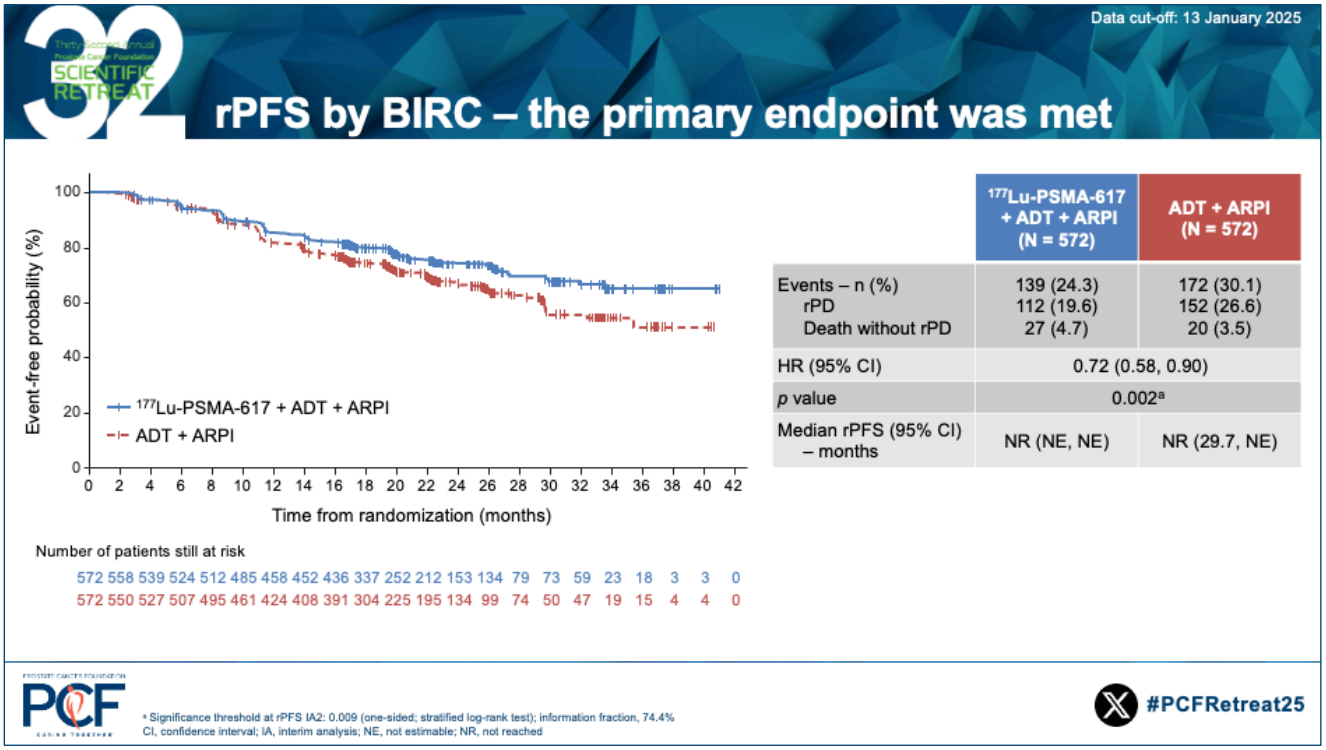
- Prostate specific membrane antigen (PSMA)-targeted radioligand therapy (RLT) with lutetium-177–PSMA-617 (^{177}Lu-PSMA-617 [Pluvicto®]) is an established, FDA-approved treatment for patients with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) in the post-chemotherapy setting or the pre-chemotherapy setting based on the VISION and PSMAfore trials, respectively.
- A key unanswered question has been whether moving ^{177}Lu-PSMA-617 earlier, into the metastatic hormone-sensitive prostate cancer (mHSPC) setting, could further delay disease progression when combined with standard androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPIs).

What progress or new findings were shared?

- Dr. Sartor presented initial results from PSMAddition, the first phase 3 trial testing ^{177}Lu-PSMA-617 in patients with mHSPC receiving ADT + ARPI.
- The trial randomly assigned 1144 patients with PSMA-positive mHSPC to receive either ^{177}Lu-PSMA-617 + ADT + ARPI or ADT + ARPI alone.
- At the second interim analysis (median follow-up, 23.6 months), the addition of ^{177}Lu-PSMA-617 to ADT + ARPI significantly improved the primary outcome of radiographic progression-free survival (rPFS) by 28% compared with ADT + ARPI alone (**Figure**).
- The rPFS benefit was consistent across most clinical subgroups, including disease volume, age, and prior local therapy, suggesting broad activity in this population.
- An early, prespecified interim analysis of overall survival (OS) showed a favorable trend, but results remain immature and are expected to be influenced by crossover from the control arm.
- Secondary endpoints—including time to PSA progression and time to mCRPC—generally favored the ^{177}Lu-PSMA-617 combination.
- Safety findings were consistent with the known profile of ^{177}Lu-PSMA-617, with higher rates of dry mouth, fatigue, nausea, and low-grade cytopenias in the combination groups, but low rates of treatment discontinuation and no unexpected toxicities.
- Patient-reported outcomes showed no clinically meaningful differences in time to worsening of quality of life or pain at this early time point.

Why do these findings matter?

- PSMAddition provides the first evidence from a randomized controlled trial that PSMA-directed RLT can improve disease control when added to standard therapy in mHSPC.
- If confirmed with longer follow-up, these results could expand the role of RLT earlier in the disease course, potentially delaying progression to castration-resistant disease.



Development of Xaluritamig, a STEAP1-Targeted T-Cell Therapy, for Prostate Cancer

Judd Englert
Amgen

What is the scientific background for this presentation?

- Prostate cancer has shown limited benefit from existing immunotherapies, in part because most tumors have few active T cells and a strongly immunosuppressive tumor microenvironment.
- A bispecific T-cell engager is a type of immunotherapy designed to physically link a patient's own T cells to cancer cells by binding to both a target on the tumor and to a protein on T cells, helping activate the immune system to directly kill cancer cells.
- STEAP1 (six-transmembrane epithelial antigen of the prostate 1) is a cell-surface protein that is highly expressed in most prostate adenocarcinomas but has low expression in normal tissues, making it an attractive therapeutic target.
- Because STEAP1 expression does not completely overlap with PSMA expression, targeting STEAP1 could serve as a complementary approach in patients with PSMA-positive disease and as an alternative option for those with low or absent PSMA expression.

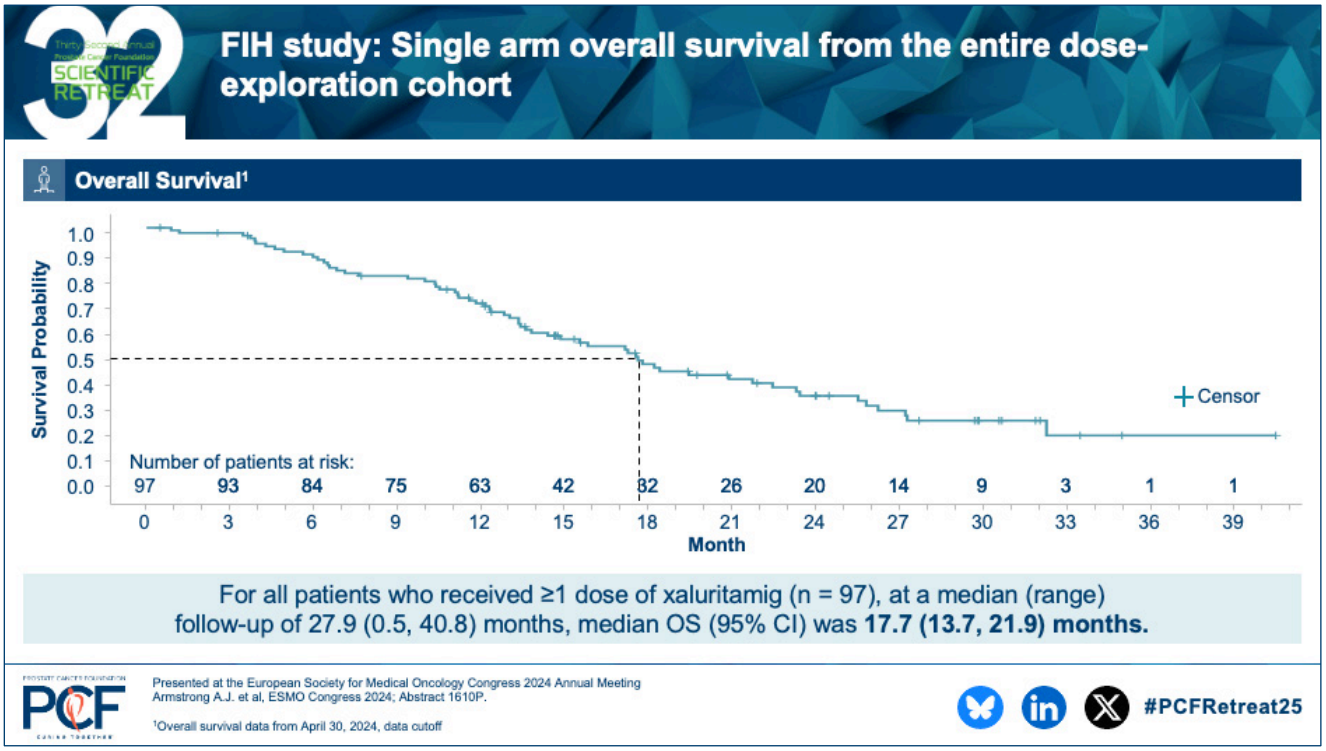
What progress or new findings were shared?

- Xaluritamig is a first-in-class, off-the-shelf XmAb® designed to bind STEAP1 on prostate cancer cells and CD3 on T cells, redirecting a patient's own T cells to kill tumor cells.
- In an ongoing, first-in-human (FIH) study, a preliminary analysis of 97 patients with heavily pretreated metastatic castration-resistant prostate cancer (mCRPC) showed potential antitumor activity with xaluritamig, including deep PSA declines and radiographic responses, even in difficult-to-treat sites such as liver metastases.

- After a median follow-up of 27.9 months, the median overall survival (OS) was 17.7 months in patients who received at least 1 dose of xaluritamig (**Figure**).
- Cytokine release syndrome (CRS)—a potentially serious side effect with T-cell engagers wherein the immune system mounts a systemic inflammatory response—occurred primarily during the first treatment cycle and was mostly low grade and manageable with step-up dosing and steroids.
- Dr. Englert also described 2 ongoing or planned phase 3 trials evaluating xaluritamig in patients with prostate cancer: one in mCRPC patients already treated with taxane chemotherapy (XALute study) and one in combination with abiraterone in mCRPC patients who have not yet received chemotherapy (Xalience study).

Why do these findings matter?

- Preliminary data from the ongoing FIH study suggest that a STEAP1-targeted T-cell engager therapy may be able to activate meaningful immune responses in prostate cancer—a disease long considered resistant to immunotherapy.
- The potential ability to induce rapid and deep responses in heavily pretreated patients highlights the potential of xaluritamig to address a major unmet need in advanced prostate cancer.
- If confirmed in phase 3 trials, this approach could introduce a new class of immunotherapy for prostate cancer and help move immune-based treatments earlier in the disease course.



A Phase 3 Study of Capivasertib + Abiraterone vs Placebo + Abiraterone in Patients with PTEN Deficient De Novo Metastatic Hormone-Sensitive Prostate Cancer: CAPItello-281

Daniel George
Duke University

What is the scientific background for this presentation?

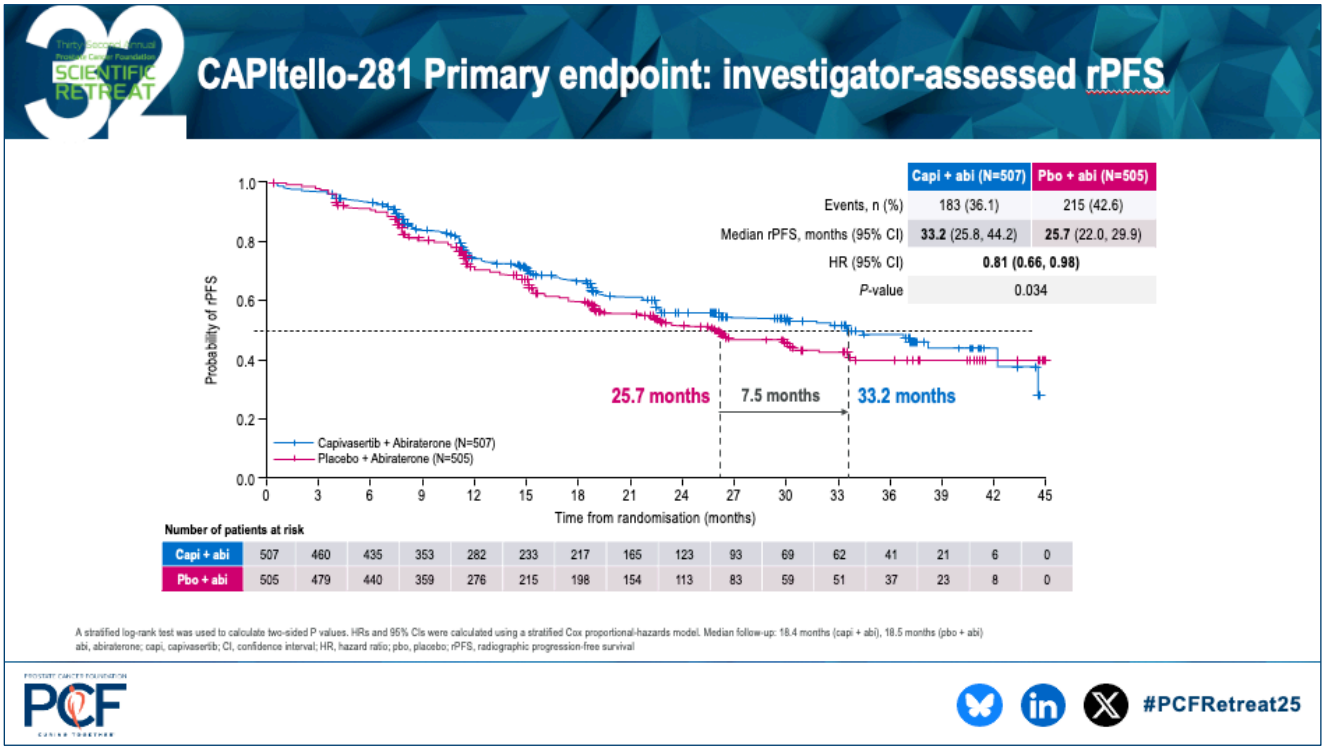
- *PTEN* deficiency is common in prostate cancer and is associated with more aggressive disease and poorer outcomes, particularly in patients with advanced disease.
- *PTEN* deficiency leads to activation of the PI3K–AKT protein signaling pathway, which provides an alternative proliferative drive that cannot be suppressed by androgen receptor (AR)-directed therapy, providing a strong biologic rationale for combining androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPIs) with AKT-targeted therapy to overcome resistance to hormonal treatment.

What progress or new findings were shared?

- Dr. George presented results from CAPItello-281, a phase 3 trial evaluating the AKT inhibitor capivasertib (Truqap®) + abiraterone (Zytiga®) + ADT versus placebo + abiraterone + ADT in 1012 patients with *PTEN*-deficient newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC).
- The study demonstrated a statistically significant improvement in the primary outcome of radiographic progression-free survival (rPFS), with the addition of capivasertib extending median rPFS by 7.5 months relative to placebo (hazard ratio, 0.81 [95% CI, 0.66-0.98]; *P* = .034; median, 33.2 vs 25.7 months) (**Figure**).
- Benefit was observed across subgroups, regardless of age, disease risk, metastatic volume, baseline prostate-specific antigen (PSA) levels, and Gleason score.
- In an exploratory analysis, patients with higher levels of *PTEN* deficiency in their tumors tended to have poorer outcomes in the control arm and more benefit from capivasertib than patients with lower levels of *PTEN* deficiency and hence more tumor cells with functioning *PTEN*.
- Overall survival (OS) results were not mature at the time of the presentation and will continue to be evaluated with further follow-up.
- Safety findings were consistent with the known profile of capivasertib, including manageable metabolic effects (high blood sugar levels), diarrhea, and skin rash.
- In discussion, Dr. George emphasized that patients with *PTEN*-deficient disease often have an accelerated disease course, reinforcing the need for early identification and aggressive management.

Why do these findings matter?

- CAPItello-281 provides phase 3 evidence that targeting AKT signaling can meaningfully improve disease control in a biomarker-selected population of patients mHSPC.
- *PTEN* deficiency, which is present in about one-quarter of patients with mHSPC, may be a new predictive biomarker that can guide treatment intensification in prostate cancer.
- The study highlights the broader shift toward biology-driven treatment intensification, moving beyond a one-size-fits-all approach to managing advanced prostate cancer.



CAN-2409 with Radiotherapy for Localized Prostate Cancer: A Phase 3, Randomized, Placebo-Controlled Clinical Trial

Paul Peter Tak
Candel Therapeutics

What is the scientific background for this presentation?

- Localized prostate cancer treated with radiation therapy (RT) with curative intent still carries a ~30% risk of disease recurrence and progression, particularly in patients with intermediate- and high-risk disease (about 70% of the population with localized prostate cancer).
- Traditional systemic immunotherapies have had limited success in prostate cancer, in part because prostate tumors are often immunologically “cold,” with low levels of immune activation.
- Aglatimagene besadenovec (CAN-2409 or aglatimagene) is an experimental, gene-based immunotherapy injected directly into tumors that uses a modified replication-defective virus to introduce a gene encoding HSV-thymidine kinase into tumor cells. When combined with an oral antiviral drug (valacyclovir), this causes cancer cells to die in a way that results in a specific antitumor immune response.
- The goal of treatment with aglatimagene combined with standard-of-care RT with curative intent in patients with intermediate- or high-risk localized prostate cancer is to prevent cancer recurrence while minimizing treatment-related side effects.

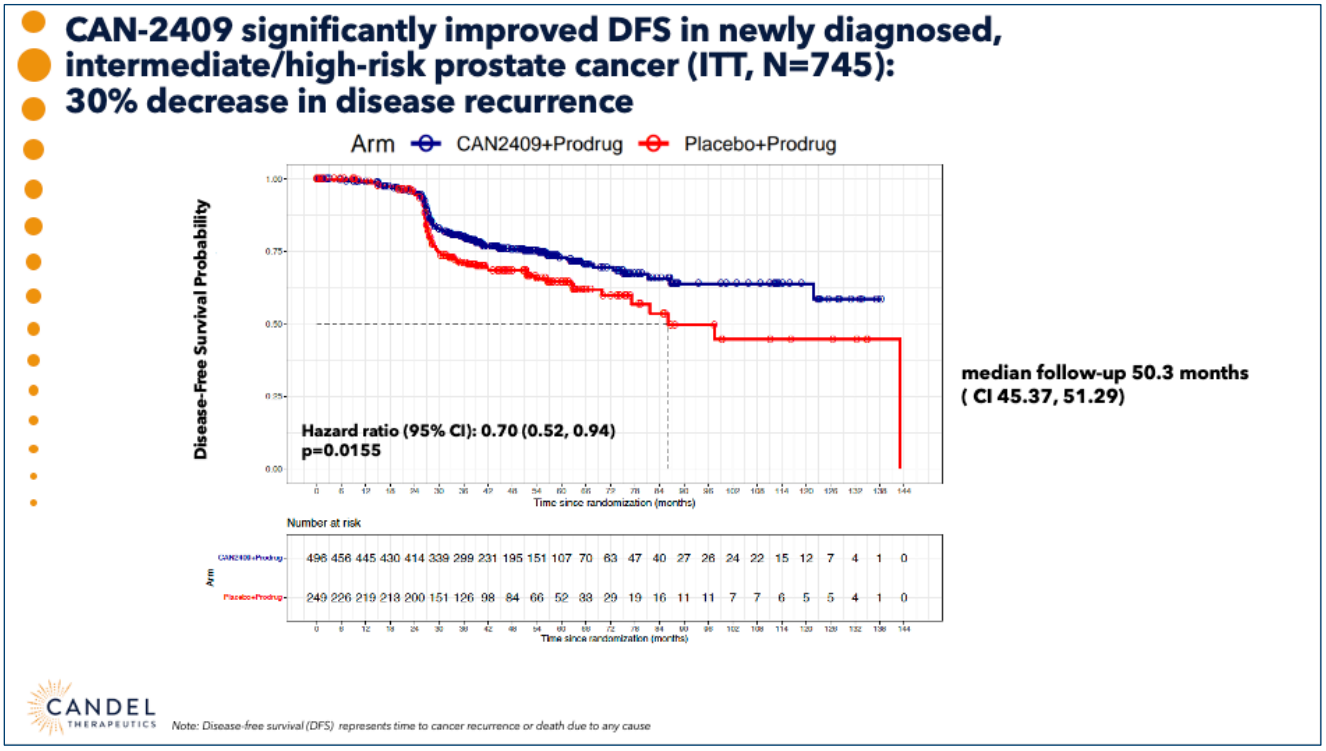
What progress or new findings were shared?

- Dr. Tak presented results from a randomized, phase 3, placebo-controlled trial evaluating CAN-2409 plus standard RT in patients with newly diagnosed intermediate- or high-risk localized prostate cancer.

- A total of 745 patients were randomly assigned to receive CAN-2409 + valacyclovir or placebo + valacyclovir, with or without short-term androgen deprivation therapy (ADT).
- After a median follow-up of 50.3 months, patients treated with CAN-2409 had a 30% lower risk of disease recurrence (*P* = .0155) (**Figure**).
- Benefit was observed across multiple subgroups, including patients receiving short-term androgen deprivation therapy and those with favorable or unfavorable intermediate-risk disease, independent of the type of external beam RT (e.g., either conventional or moderate hypofractionated EBRT).
- Secondary analyses showed significantly higher rates of patients achieving very low PSA nadirs (<0.2 ng/mL) and significantly higher rates of negative prostate biopsies at 2 years in the aglatimagene group compared with placebo.
- Treatment was generally well-tolerated, with a favorable safety profile and no unexpected toxicities. The most common side effects in the aglatimagene group were chills, fever, and flu-like symptoms, which were mostly mild to moderate in severity.

Why do these findings matter?

- These results suggest that adding a locally injected immunotherapy to standard of care RT can meaningfully improve outcomes in patients with intermediate- or high-risk localized prostate cancer treated with curative intent.
- If adopted into practice, this approach could offer patients a new option to reduce recurrence risk while maintaining acceptable tolerability and quality of life.



Session 5: Artificial Intelligence and Machine Learning to Better Inform Patient Outcomes

Pathology Deep Learning Tools for Localized Prostate Cancer

Tamara Lotan
Johns Hopkins University

What is the scientific background for this presentation?

- Prostate cancer diagnosis and risk assessment are based largely on examination of tumor tissue under a microscope (called *histopathology*). The most widely used system, Gleason scoring, assigns grades based on how abnormal the cancer cells look and how they are arranged, but grading can vary across pathologists.
- Recent advances in digital pathology, in which traditional glass microscope slides are scanned into high-resolution digital images, allow biopsy samples to be analyzed by computer algorithms rather than by individual pathologists.
- There is growing interest in whether AI tools applied to digital pathology images can match or exceed traditional grading systems and genomic classifiers in predicting a patient's risk for metastasis and disease progression.

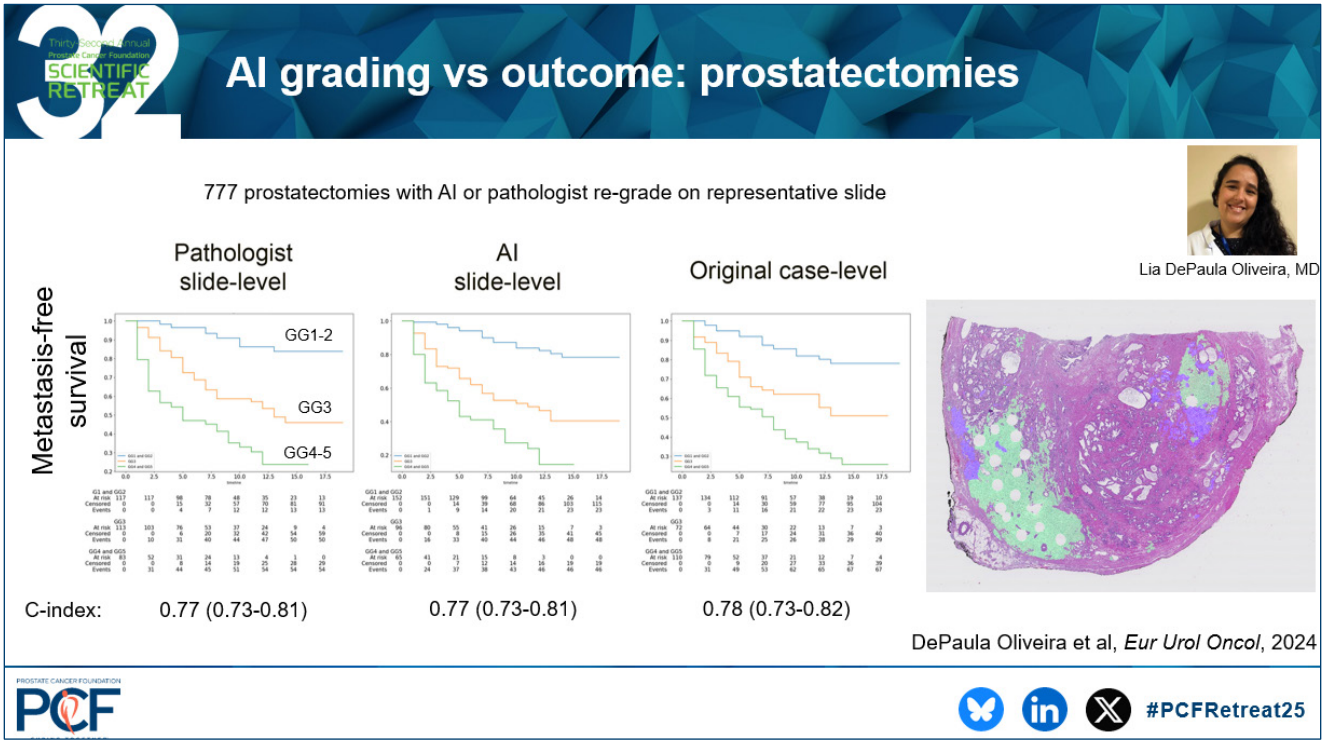
What progress or new findings were shared?

- Because many AI algorithms for grading prostate cancer have been developed using highly curated datasets, Dr. Lotan and her team sought to validate these tools in real-world clinical settings to determine whether AI grading performs reliably across diverse patient populations.
- Using more than 800 biopsy samples from the RESPOND cohort study, which enrolled African Americans with prostate cancer, researchers showed that AI grading algorithms had strong agreement with expert pathologists.
- When samples from patients undergoing active surveillance for Gleason Grade Group (GG) 1 prostate cancer were evaluated by AI algorithms or pathologists, AI-based upgrading (to GG ≥2) predicted a significantly increased risk of future grade reclassification on a subsequent biopsy, whereas pathologist upgrading alone did not.
- Using prostatectomy samples, AI-based grade performed comparably to pathologist grading for predicting metastasis-free survival (**Figure**).
- A deep learning "metastasis risk" classifier trained on prostatectomy slides outperformed or matched established genomic classifiers (e.g., Decipher, Prolaris) in predicting the risk of metastasis.
- The metastasis risk classifier also showed prognostic value when adapted to smaller tissue samples and to needle biopsy specimens, demonstrating that risk of metastasis can be predicted directly from routine histology.
- AI tools were also developed for specific tasks, such as automated detection of lymph node metastases and exploratory classification of neuroendocrine prostate cancer (NEPC).

Why do these findings matter?

- AI tools can function as pathologist-supervised assistants, improving efficiency and consistency in grading, tumor quantification, and lymph node screening without replacing human expertise.
- Predicting metastasis risk directly from standard prostate biopsy and prostatectomy slides could reduce reliance on costly genomic assays and expand access to advanced risk stratification.

- AI-based risk models may eventually move beyond traditional Gleason grading to more biologically meaningful outcome-driven classifications that better inform treatment decisions.



Navigating the Prostate Cancer Journey with Genetic Testing, RNA, AI, and MRD

Hosein Kouros-Mehr
Myriad Genetics

What is the scientific background for this presentation?

- Prostate cancer is a highly heterogeneous disease; tumors vary widely in their underlying biology, growth patterns, and response to therapy, making it difficult to predict outcomes using traditional clinical features alone.
- Genomic tests and molecular profiling have improved risk assessment, but additional discrimination among risk groups in prostate cancer could be beneficial.
- Advances in molecular residual disease (MRD) testing and artificial intelligence (AI) create opportunities to personalize oncology clinical decision-making and extract biologically meaningful information directly from routine clinical data, including standard pathology images and clinical records.

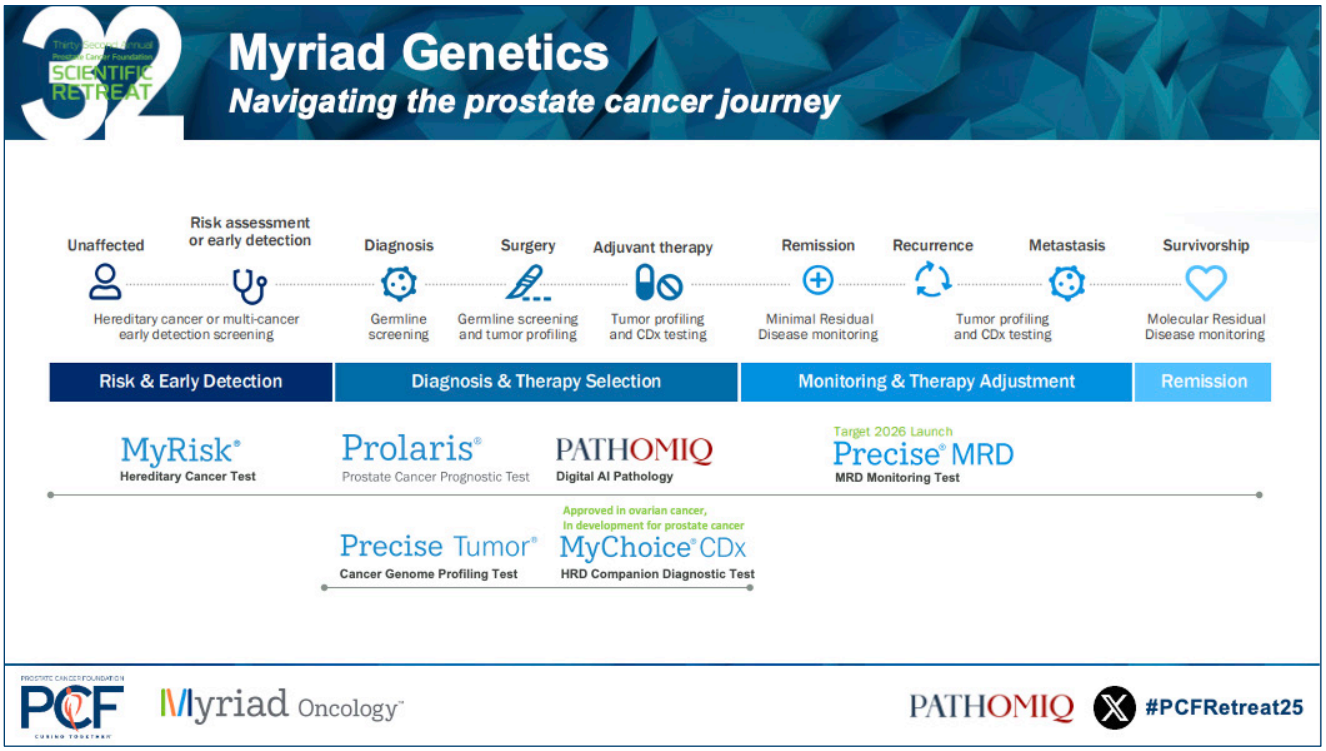
What progress or new findings were shared?

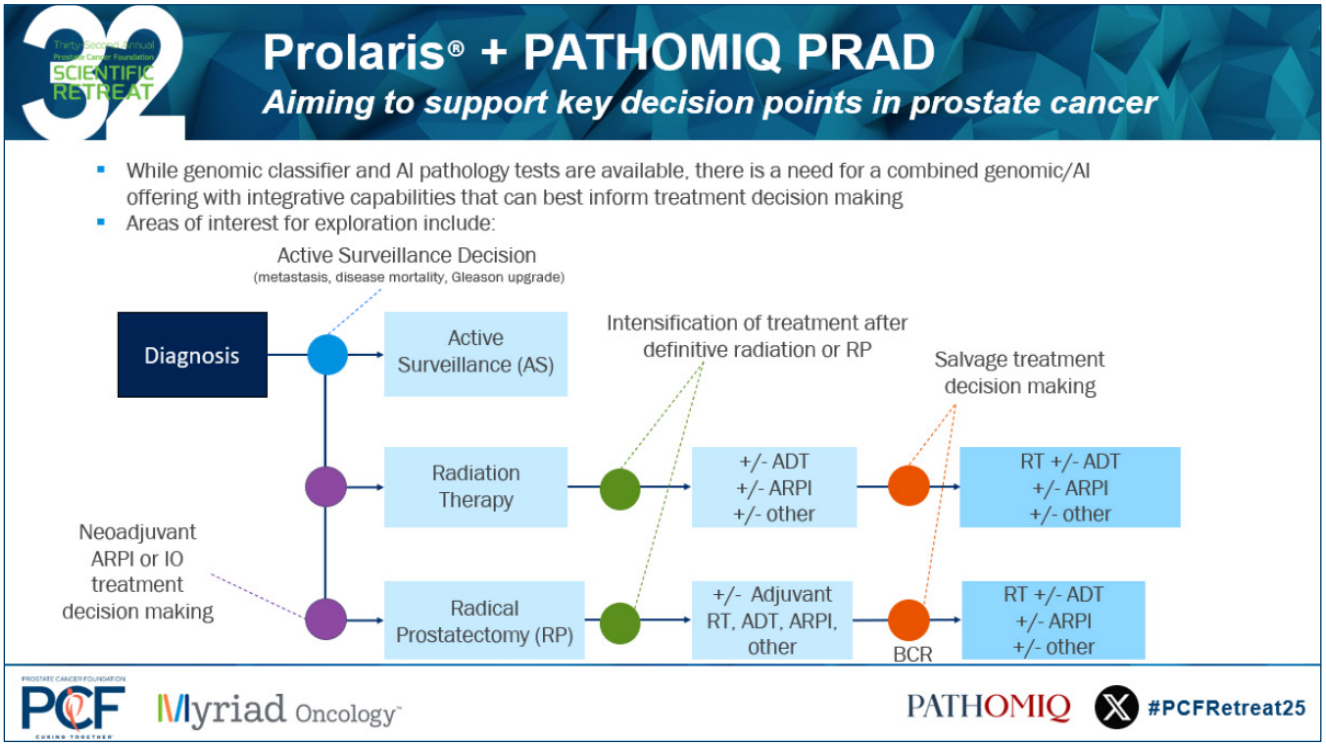
- Dr. Kouros-Mehr discussed combining the Prolaris test, a commercially available genomic assay that measures expression of cell cycle progression genes to estimate prognosis, with AI-derived features generated from routine pathology slides using the Pathomiq platform. He also presented preliminary ctDNA data from an ultrasensitive, tumor-informed MRD test showing high sensitivity in localized prostate cancer.

- Prolaris provides a molecular risk score based on how actively tumor cells are dividing, while Pathomiq analyzes subtle visual patterns in standard prostate cancer samples that may reflect tumor biology/architecture not captured by gene expression alone. Pathomiq has been shown to be broadly predictive of outcomes at various points in the prostate cancer treatment journey (**Figures**).
- When the Prolaris score was combined with Pathomiq's AI-derived imaging analysis, the integrated model improved prediction of adverse outcomes compared with either approach alone, suggesting that genomic and image-based data provide complementary information.
- The combined approach strengthened discrimination between lower- and higher-risk patients, improving the ability to identify individuals more likely to develop metastasis or experience disease progression.

Why do these findings matter?

- This multimodal strategy demonstrates how AI-based image analysis can enhance, rather than replace, established genomic tests by adding additional layers of biologic insight from tissue already obtained in routine care.
- Integrating multiple data types—clinical, imaging, and molecular—may enable more personalized treatment strategies and better identification of patients who need intensified therapy.
- Additionally, MRD testing in genitourinary cancers allows the identification of residual tumor cells at an earlier stage than standard imaging, which may allow personalized cancer treatment decision making in the future. Additional studies are pending.





Digital Pathology for Patient Management and Treatment Decisions in Prostate Cancer and Urologic Oncology

Andre Esteva
Artera

What is the scientific background for this presentation?

- Artificial intelligence (AI) in medicine has evolved from simple pattern-recognition tools to sophisticated deep learning systems capable of analyzing medical images, pathology slides, and multimodal clinical data.
- In oncology, deep learning AI systems are increasingly being explored not just for image interpretation, but for integrating diverse data types—including pathology, genomic data, and clinical features—to predict outcomes and guide treatment.
- However, many AI systems are trained on limited datasets or evaluated retrospectively, raising important questions about generalizability, clinical validation, and real-world implementation.

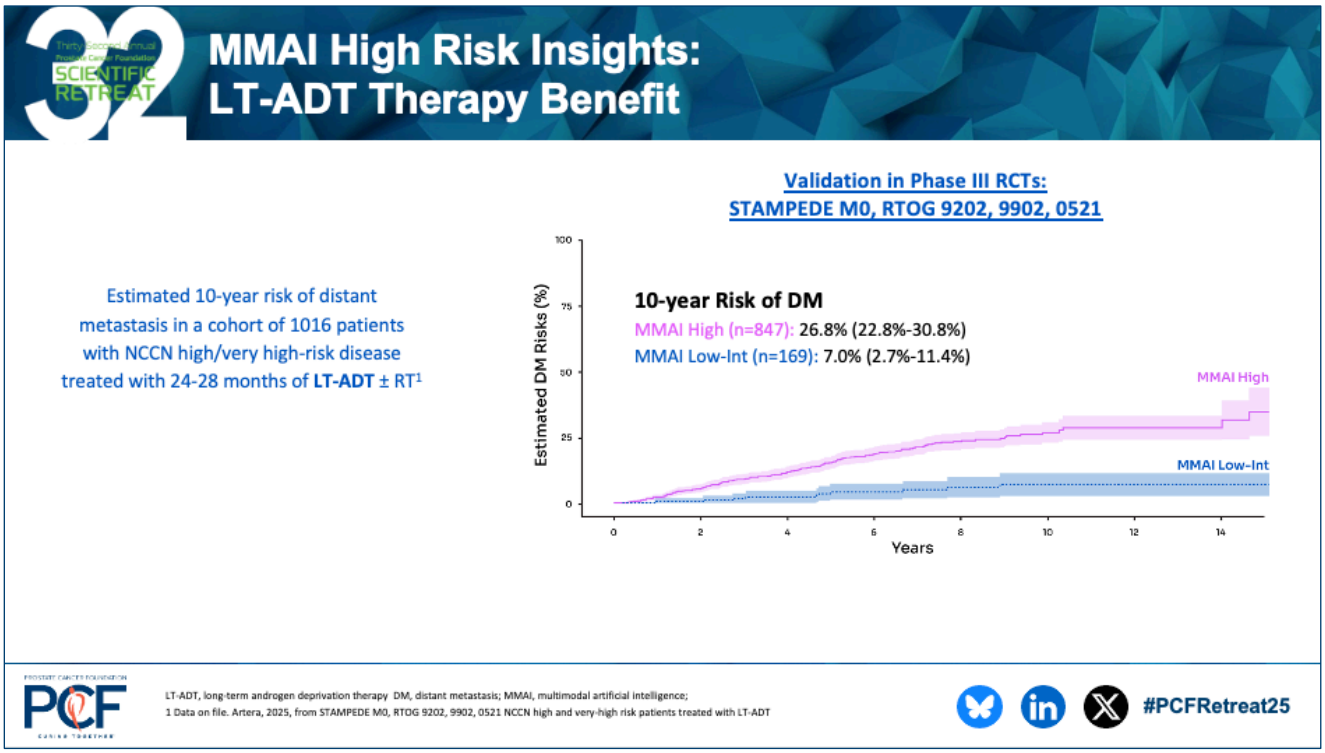
What progress or new findings were shared?

- Dr. Esteva described the development of large-scale foundation models, which are AI systems trained on vast amounts of general data so it can later be adapted to many specific medical tasks with relatively little additional training.
- ArteraAI, a foundation model, was trained on millions of medical images, including histopathology slides, using self-supervised learning approaches that allow models to learn generalizable visual features before being fine-tuned for specific clinical tasks.
- In clinical validation studies, the model was tested in independent patient cohorts to determine whether its predictions were meaningfully associated with real-world outcomes, such as disease progression or metastasis, confirming that the algorithm provides prognostic information beyond traditional clinical and pathologic features.

- Using samples from large randomized phase 3 trials, the ArteraAI platform independently predicted risk of metastasis and identified patient subgroups more likely to benefit from treatment intensification, even after accounting for standard clinical factors such as Gleason grade, PSA level, and tumor stage (**Figure**).
- In analytical validation studies, the team evaluated how consistently and accurately the AI model performed across technical variables—such as differences in slide preparation, scanning platforms, and institutions.
- The ArteraAI model demonstrated stable performance across different slide scanners, staining conditions, and laboratory sites, with minimal variation in predictive accuracy, supporting the technical robustness and reproducibility required for clinical deployment.

Why do these findings matter?

- Large foundation models trained on diverse datasets may improve the reliability and scalability of AI tools in oncology, reducing dependence on narrowly curated training cohorts.
- Rigorous validation—including prospective testing—is essential to ensure that AI systems perform consistently across populations and health systems.
- These advances suggest that AI may increasingly function as a clinical support tool, augmenting physician expertise and helping interpret complex cancer data.



Computational Approaches for PSA Trajectories to Guide Therapy

Julian Hong
University of California, San Francisco

What is the scientific background for this presentation?

- Prostate cancer clinical trials often take years to complete, delaying drug approvals and keeping patients on potentially suboptimal therapies while final outcomes mature.

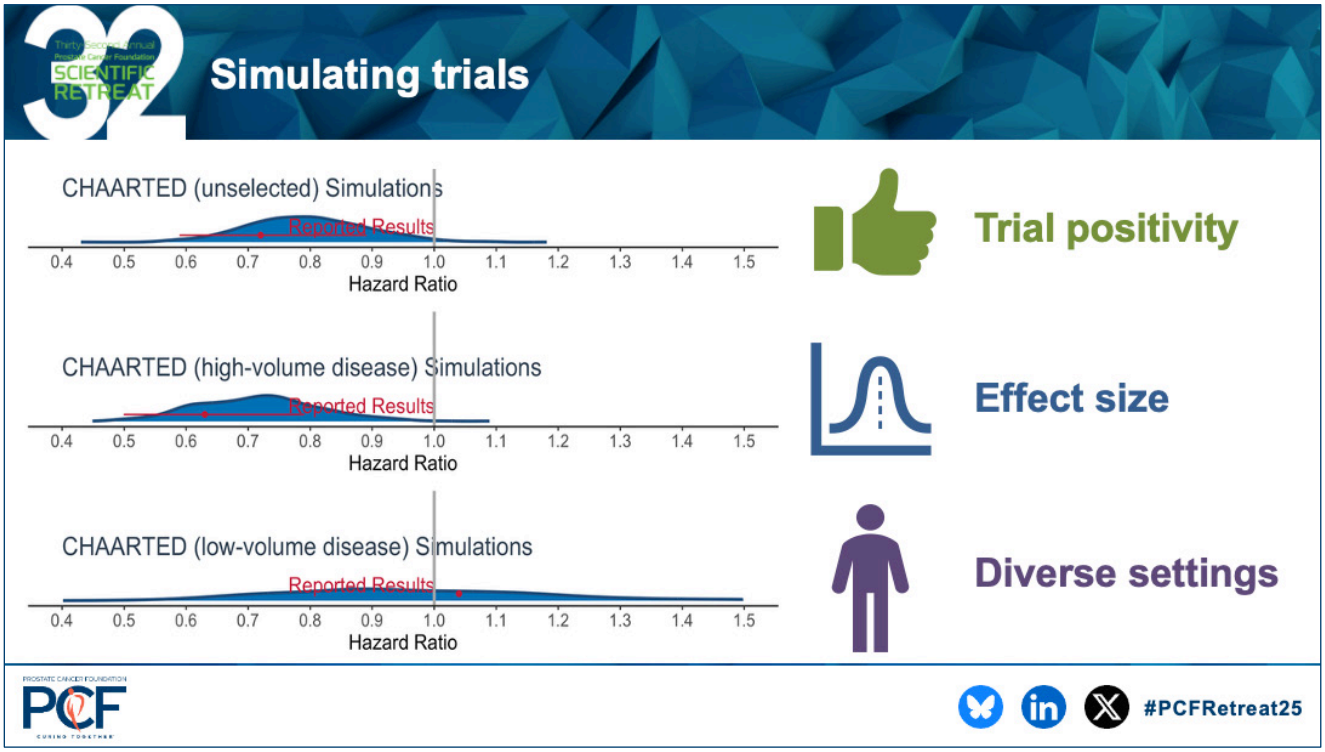
- Prostate-specific antigen (PSA) levels are routinely used to monitor treatment responses in clinical trials, but researchers often rely on single PSA values to determine treatment efficacy.
- PSA trajectories—how PSA rises or falls over time—may contain more detailed information about tumor biology and treatment response than isolated measurements.

What progress or new findings were shared?

- Dr. Hong's overarching goal was to develop a computational method that uses PSA trajectories from clinical trials to provide an early readout of potential trial-level outcomes, shortening the time required to interpret whether a trial is likely to be positive.
- In large clinical trials, PSA values are often collected at about 30-day intervals. Using these data from large clinical trials, the computational model was trained to recognize key features of PSA levels (e.g., absolute values, relative changes, trajectory patterns) along with baseline clinical variables that can influence clinical trial outcomes.
- Once the model was trained, researchers then used that model to simulate the outcomes of other clinical trials to validate that the model could actually predict trial positivity.
- In the validation analysis, the computational model simulated final clinical trial results using only the first 4 months of trial data. Researchers found that the simulated results closely overlapped with the actual published results, correctly identifying whether trials were positive and approximating the magnitude of treatment benefit.
- Importantly, in the CHAARTED trial, which evaluated the benefit of adding docetaxel to androgen deprivation therapy (ADT) in patients with metastatic hormone-sensitive prostate cancer (mHSPC), the model reproduced the known finding that treatment benefit was concentrated in patients with high-volume disease, demonstrating that the simulation approach could capture subgroup-specific treatment effects (**Figure**).

Why do these findings matter?

- This work demonstrates that 4 months of PSA data may be sufficient to generate an early estimate of whether a clinical trial will ultimately show a survival benefit, potentially shortening trial interpretation timelines from years to months.
- Early trial-level prediction could inform go/no-go decisions (e.g., determining whether a trial should continue on), reduce time patients spend on ineffective therapies, and accelerate drug development pipelines.
- Beyond PSA modeling, this approach represents a broader strategy of using complex longitudinal clinical data to simulate and expedite clinical trial readouts, with potential applications across different disease settings and therapeutic modalities.



Empowering VA Practitioners with Data to Optimize their Care of Veterans with Prostate Cancer

Antonio Fojo
Columbia University

What is the scientific background for this presentation?

- In prostate cancer care, therapies are often discontinued when prostate-specific antigen (PSA) levels begin to rise, even though the treatment may still be providing clinical benefit.
- Tumor behavior during treatment reflects a mixture of treatment-sensitive tumor cells that die in response to therapy and treatment-resistant tumor cells that continue to grow, meaning that tumor progression may be caused by the growth of tumor cell subsets rather than complete treatment failure.

What progress or new findings were shared?

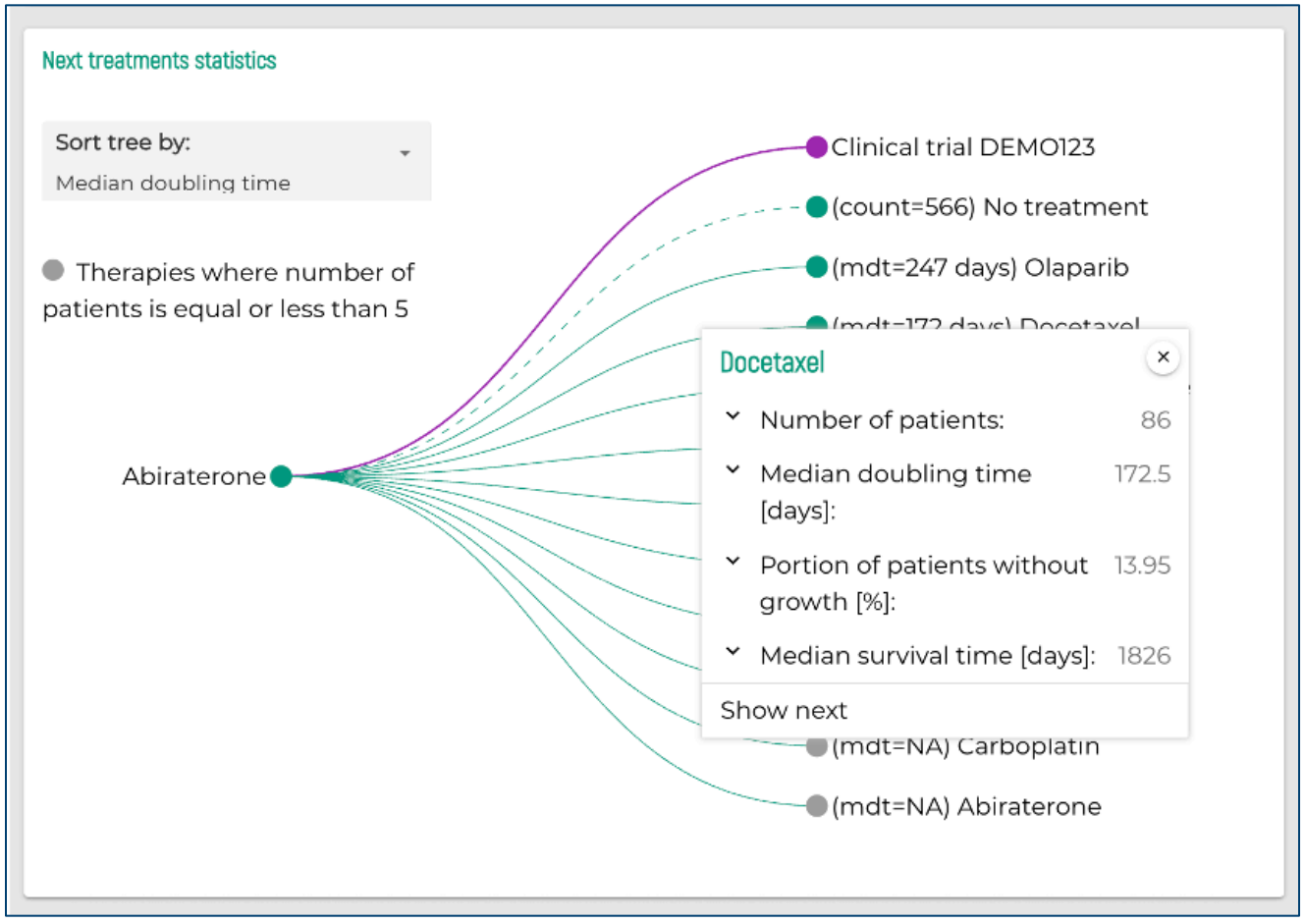
- Dr. Fojo presented a mathematical model that analyzes changes in PSA over time to estimate 2 key components of tumor behavior: the portion of cancer cells that are shrinking in response to treatment (represented by *d* for decay) and the portion that are continuing to grow despite therapy (represented by *g* for growth).
- By fitting this equation to a patient's actual PSA measurements, the model can calculate the rates of tumor regression and tumor growth that best explain the observed PSA pattern.
- The tumor growth rate (*g*) can be converted into a tumor doubling time and was shown to correlate strongly with overall survival (OS) across different cancer types, whereas the regression rate (*d*) was not predictive of OS.
- Based on these findings, the team developed a clinical decision-support tool, CanTA, currently designed for use within the Veterans Affairs (VA) health system. The tool calculates an individual patient's tumor growth rate and doubling time, compares it with

similar “digital twins”—patients with similar tumor growth rates and treatment histories—and displays expected growth-rate patterns for potential next-line therapies (**Figure**).

- The system allows clinicians to evaluate the extent to which a rising PSA is a result of meaningful acceleration of tumor growth or whether continued benefit from the current therapy is likely, helping avoid premature treatment changes.
- Ongoing work aims to incorporate genomic data, including mutations such as in the tumor suppressor gene *TP53*, where preliminary analyses showed significantly higher tumor growth rates in mutation-positive tumors, with plans for confirmation using VA datasets.

Why do these findings matter?

- Tumor growth rate provides a continuous, biology-based measure of treatment effect that correlates with OS and may detect emerging resistance earlier than conventional progression criteria.
- This approach may help optimize sequencing decisions, prevent unnecessary early discontinuation of effective therapies, and generate new hypotheses for prospective validation.



Session 6: Novel Technology for Circulating Biomarker Development

PC-SYNERGY: Biological and Therapeutic Insights from a Metastatic Prostate Cancer Atlas at Single Cell Resolution (TACTICAL Award)

Peter Nelson
Fred Hutchinson Cancer Center

What is the scientific background for this presentation?

- Advanced prostate cancer is highly heterogeneous, meaning different tumor cells within the same patient can look and behave very differently, contributing to treatment resistance and disease progression.
- Many novel and emerging therapies (e.g., radioligand therapies, antibody–drug conjugates, CAR T cells, and bispecific T-cell engagers) rely on targeting specific proteins on the tumor cell surface, making it critical to understand how consistently these targets are expressed across tumors.
- Traditional biopsies sample only a small area of the tumor and therefore often fail to capture this complexity, creating a need for more comprehensive approaches that provide insight into the heterogeneous gene expression patterns and cell surface target activity across cancer cells within a single patient.

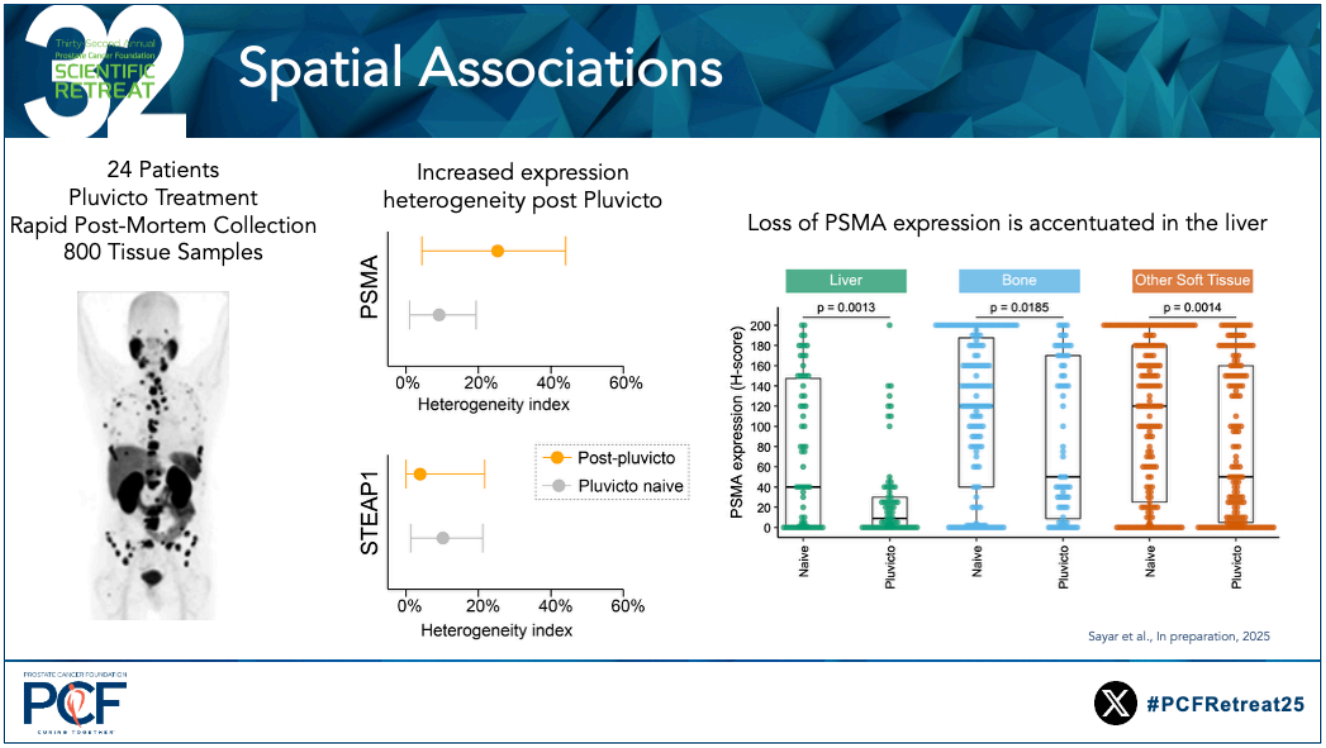
What progress or new findings were shared?

- Dr. Nelson presented early results from the PC-SYNERGY initiative, which is building a large single-cell and spatial atlas of metastatic prostate cancer using tissue biopsies and liquid biopsies, which analyze circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) released into the bloodstream by cancers.
- This approach allows researchers to study individual cancer cells and their surrounding environment in detail, rather than averaging signals across an entire tumor, helping reveal hidden differences that can drive treatment resistance.
- Analysis of more than 160 metastatic tumors and over 1 million cancer cells—including 824,000 prostate cancer cells—showed substantial differences in tumor type both across different patients and within individual patients, including mixtures of androgen receptor (AR)–driven and neuroendocrine tumor states within the same person and, in some cases, within the same tumor.
- Researcher's analyses revealed that tumor type is often driven by epigenetic changes—meaning reversible changes to DNA molecules or DNA-bound proteins that regulate gene expression—rather than new genetic mutations, helping explain how cancers can rapidly shift behavior under treatment pressure.
- Detailed mapping of treatment targets expressed on cancer cell surfaces (e.g., PSMA, DLL3) showed that expression varies widely by tumor type, metastatic site, and prior therapy, with liver metastases often showing lower PSMA expression.
- Post-treatment analyses, including samples from patients treated with lutetium-177–PSMA-617 (Pluvicto®), demonstrated increased target heterogeneity and frequent loss of PSMA expression, particularly in liver lesions, suggesting a potential mechanism of treatment resistance (**Figure**).

Why do these findings matter?

- These results show that tumor heterogeneity can be a barrier to durable responses from targeted therapies and helps explain why single-agent treatments often fail over time.

- This work provides a foundation for developing biomarker-driven clinical trials and more personalized treatment strategies using treatment combinations for patients with advanced prostate cancer.



Profiling Prostate Cancer Phenotypes from Cell-Free DNA through Advanced Machine Learning

Gavin Ha
Fred Hutchinson Cancer Center

What is the scientific background for this presentation?

- In advanced prostate cancer, obtaining tumor tissue from metastatic sites is often difficult, invasive, and may not fully represent all areas of disease. As a result, researchers are increasingly interested in whether blood-based tests can provide similar biological information.
- Prostate cancer can change its biological identity (called tumor *phenotype*) over time. For example, tumors that initially depend on androgen receptor (AR) signaling may later evolve into neuroendocrine prostate cancer (NEPC), a more aggressive and treatment-resistant subtype. Detecting these shifts traditionally requires tissue biopsy.
- When cancer cells die, they release fragments of DNA into the bloodstream. These fragments—called circulating tumor DNA (ctDNA)—carry not only genetic mutations but also information about how DNA was packaged in the tumor cell (called *epigenetics*).

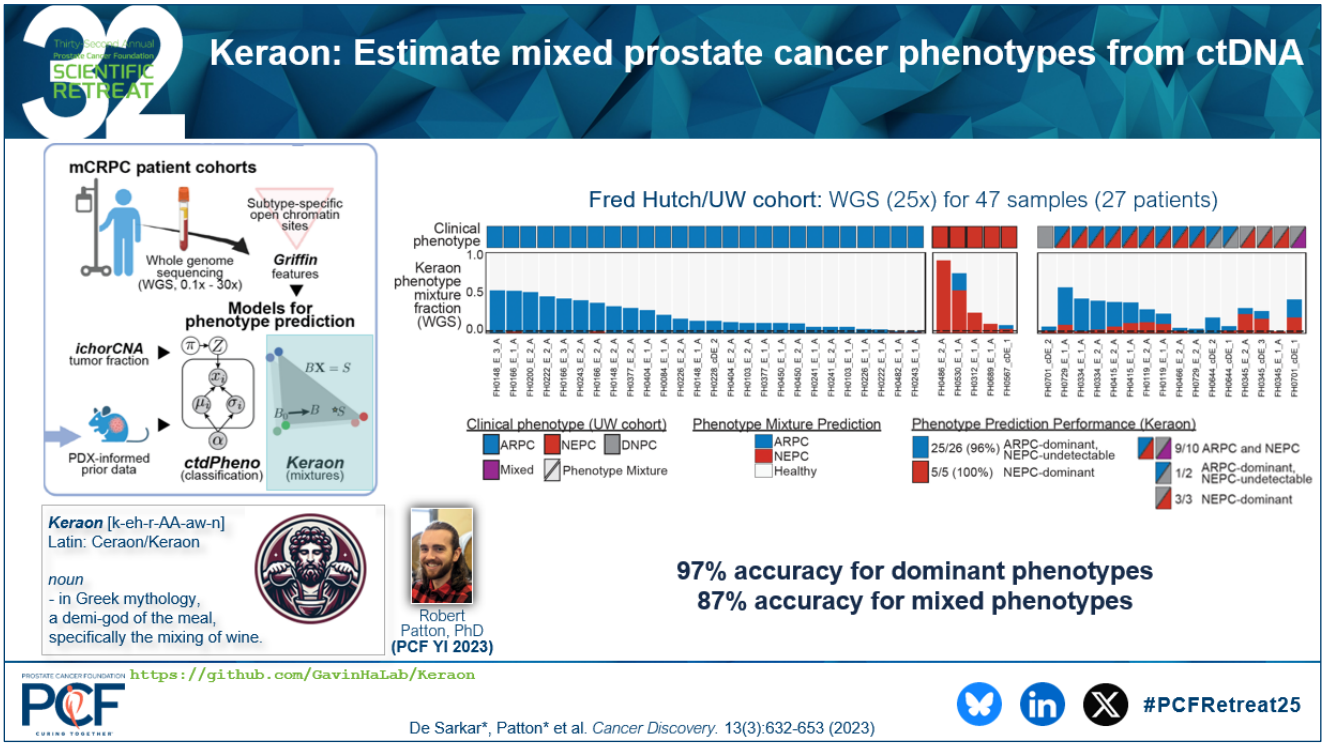
What progress or new findings were shared?

- Dr. Ha's overarching goal is to determine whether whole-genome sequencing of ctDNA—combined with advanced computational modeling—can be used to infer tumor phenotype and gene activity from a simple blood sample.

- The team first used ATAC-seq (a laboratory method that identifies regions of open or "accessible" chromatin, meaning DNA regions that are actively being expressed in cells) in laboratory studies to define differences between AR-positive prostate cancer and NEPC.
- They showed that these differences in chromatin accessibility are reflected in ctDNA fragmentation patterns, meaning that the way DNA breaks apart in the bloodstream can reveal whether a tumor has an AR-driven or neuroendocrine phenotype.
- The group developed a computational tool, Keraon, that analyzes ctDNA fragmentation data to estimate whether a tumor is AR-dominant, neuroendocrine, or a mixture of both.
- In validation studies, the Keraon model achieved approximately 97% accuracy in identifying dominant tumor phenotypes and 87% accuracy in detecting mixed phenotypes (**Figure**).
- Dr. Ha also presented a deep learning framework trained to predict gene expression of more than 18,000 genes directly from ctDNA fragments. Predicted gene expression levels strongly correlated with tissue biopsy sequencing results, including for key prostate cancer markers such as AR and neuroendocrine-associated genes.
- In a clinical cohort of patients treated with ^{177}Lu-PSMA-617 (Pluvicto®), the team used sequencing to measure how much tumor DNA was present in blood at baseline. Higher tumor fraction and certain gene expression signatures—such as elevated cell-cycle progression scores—were associated with shorter overall survival (OS).

Why do these findings matter?

- These results demonstrate that ctDNA fragmentation patterns can provide insight into tumor biology beyond simple mutation detection, including tumor phenotype and gene activity, without requiring repeat biopsies.
- Being able to identify mixed tumor phenotypes or early neuroendocrine transformation from a blood test could help guide therapy selection and monitor treatment resistance more dynamically.
- If validated in larger prospective studies, these computational approaches could enhance patient stratification in clinical trials and support more personalized treatment strategies in advanced prostate cancer.



High Purity Circulating Tumor Cell RNA-Sequencing in Advanced Prostate Cancer

Marina Sharifi
University of Wisconsin

What is the scientific background for this presentation?

- Metastatic castration-resistant prostate cancer (mCRPC) is a biologically heterogeneous disease, meaning that tumors can adopt different *lineage states* (such as androgen receptor [AR]–driven adenocarcinoma or neuroendocrine prostate cancer [NEPC]) that influence treatment response and prognosis.
- Although tissue biopsy remains the gold standard for determining tumor lineage states, repeated biopsies are invasive and often impractical, especially in patients with bone-predominant or visceral metastases.
- Liquid biopsies, including circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs), offer a minimally invasive way to monitor tumor evolution over time using a blood sample; however, technical challenges include low tumor purity and contamination with normal blood cells.

What progress or new findings were shared?

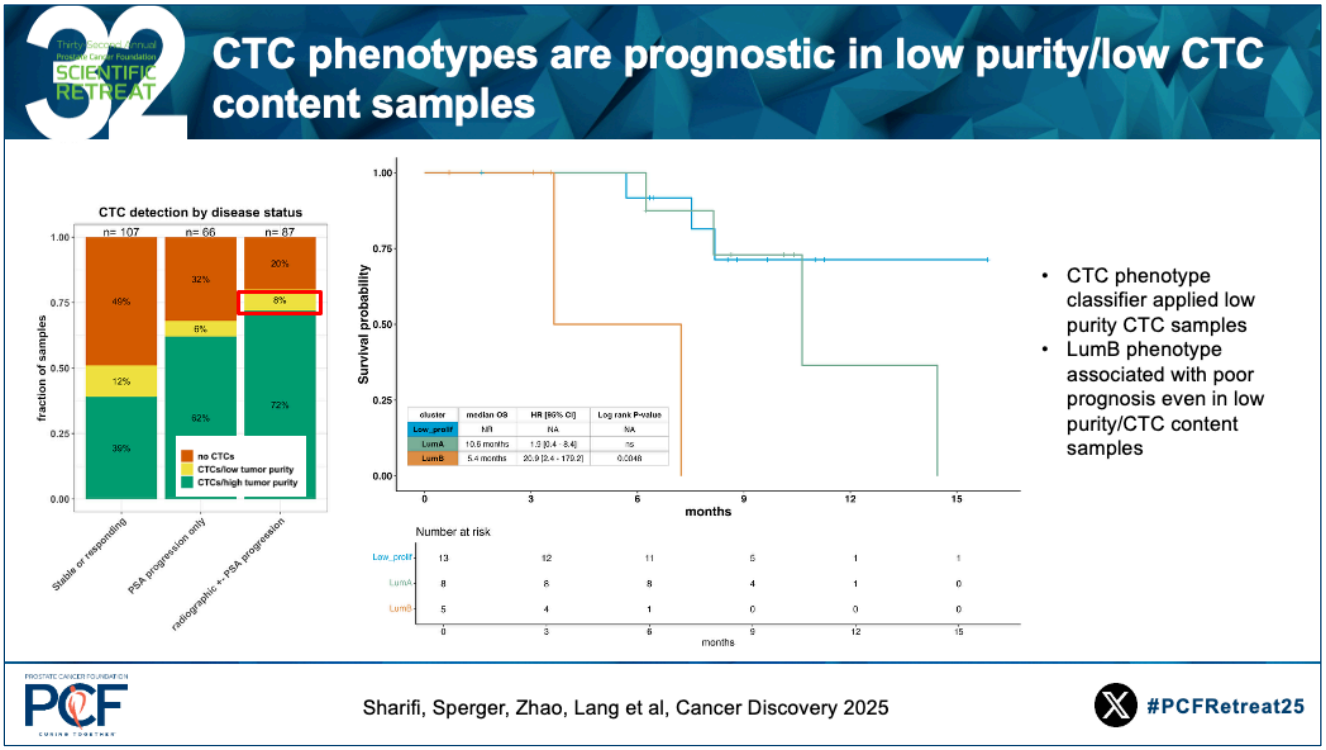
- Dr. Sharifi's team wanted to develop a high-purity CTC RNA sequencing approach capable of accurately profiling tumor phenotypes in patients with metastatic prostate cancer, overcoming the limitations of low tumor content in standard liquid biopsy approaches.
- A specialized technique that increases the relative amount of tumor cells in a blood sample led to high tumor purity in approximately 70% of liquid biopsy samples from patients with progressive metastatic prostate cancer, enabling reliable RNA sequencing of CTCs.
- RNA sequencing (sometimes called *transcriptomic analysis*) identified 4 distinct CTC phenotypes: luminal A–like (high AR signaling, low proliferation); luminal B–like

(moderate/high AR signaling, high proliferation); low proliferation (low AR signaling, low neuroendocrine features); and neuroendocrine (low AR signaling, high proliferation, high neuroendocrine features).

- The Luminal B and neuroendocrine phenotypes were associated with significantly shorter overall survival (OS).
- Importantly, the Luminal B phenotype remained prognostic even in samples with low tumor purity, suggesting that the CTC classifier is robust and clinically applicable across samples with varying CTC content (**Figure**).
- The frequency of CTC phenotypes varied by metastatic site, with luminal B being most common in patients with liver metastases.
- Longitudinal CTC RNA sequencing in liquid biopsies captured phenotype transitions during therapy, suggesting that this technique may be used to monitor changes in tumor phenotype that may influence treatment decision making.

Why do these findings matter?

- High-purity CTC RNA sequencing provides a minimally invasive method to classify prostate cancer lineage states in real time, without requiring repeat tissue biopsies.
- Detection of phenotype shifts during treatment suggests that liquid biopsy–based transcriptional profiling could help identify emerging resistance states and guide therapy changes earlier.
- Overall, this work supports integrating CTC-based transcriptional profiling into clinical trials and longitudinal monitoring strategies to better match therapies to evolving tumor biology.



Circulating Tumour DNA Genomic Correlatives in mCRPC Treated with LuPSMA or Cabazitaxel from the Randomised Phase II TheraP Trial (ANZUP 1603)

Edmond Kwan
Monash University, Australia

What is the scientific background for this presentation?

- Researchers are interested in whether circulating tumor DNA (ctDNA)—which is released into the bloodstream by cancer cells—can be analyzed to better predict prostate cancer treatment response and disease behavior.
- Studying ctDNA within randomized controlled trials allows researchers to evaluate these blood-based markers in a well-defined setting, where treatments and outcomes are systematically compared, helping clarify whether ctDNA provides meaningful predictive or prognostic information.

What progress or new findings were shared?

- The TheraP trial (ANZUP 1603) was a randomized phase 2 study in heavily pretreated metastatic castration-resistant prostate cancer (mCRPC) that compared lutetium-177–PSMA-617 (^{177}Lu-PSMA-617 [Pluvicto®]) with cabazitaxel (Jevtana®) chemotherapy and showed higher objective response rates, longer progression-free survival (PFS), and better quality of life with ^{177}Lu-PSMA-617.
- In the TheraP trial, patients were selected using two different PET scans—one that shows how much PSMA a tumor expresses (PSMA PET) and another that shows how metabolically active the cancer is (FDG PET).
- Using these detailed imaging data, researchers evaluated whether ctDNA levels and specific genetic changes detected within ctDNA could help explain why some patients responded better to ^{177}Lu-PSMA-617 while others benefited more from chemotherapy, and to explore why resistance eventually developed.
- Patients with low or undetectable ctDNA levels had the greatest benefit from ^{177}Lu-PSMA-617, including markedly better PFS compared with cabazitaxel, supporting ctDNA level as a potential predictive biomarker for improved response with ^{177}Lu-PSMA-617 relative to cabazitaxel.
- Combining ctDNA detection status with average PSMA PET detection levels further stratified outcomes: patients with undetectable ctDNA levels and high average PSMA expression levels detected on imaging experienced the most benefit from ^{177}Lu-PSMA-617 (Figure).
- In patients with high ctDNA levels, alterations in the tumor suppressor *PTEN* gene were associated with greater relative benefit from ^{177}Lu-PSMA-617 versus cabazitaxel. The difference appeared driven largely by particularly poor outcomes for *PTEN*-altered patients treated with cabazitaxel.
- Dr. Kwan also noted that ctDNA analysis identified treatment-emergent genetic changes associated with hematologic malignancies (called *clonal hematopoiesis*) at an approximately 3.2-times higher rate with ^{177}Lu-PSMA-617 versus cabazitaxel.

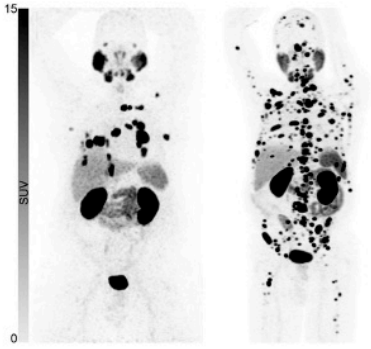
Why do these findings matter?

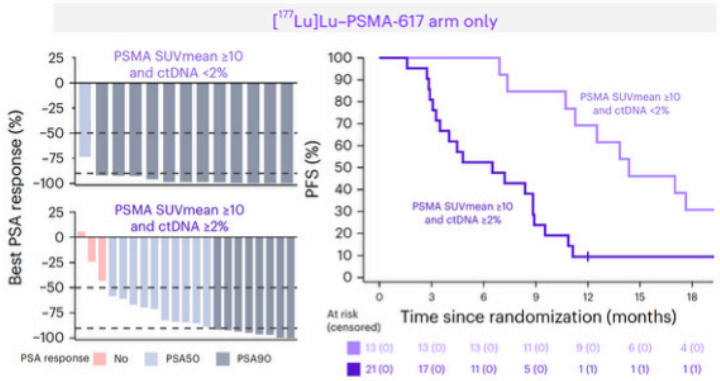
- These analyses suggest ctDNA levels could help identify which PSMA-positive mCRPC patients are most likely to benefit from ^{177}Lu-PSMA-617 versus cabazitaxel, moving liquid biopsy from “prognostic only” toward “treatment-informing” use.

- Pairing ctDNA with PSMA PET metrics may better capture tumor biology than either alone, potentially improving trial stratification and real-world treatment sequencing decisions.
- The increased risk for clonal hematopoiesis with ^{177}Lu-PSMA-617 highlights the importance of long-term monitoring as radioligand therapy is tested earlier in disease progression.

Combining ctDNA detection with PSMA SUVmean further stratifies LuPSMA outcomes

High PSMA SUVmean ≥10





Subgroup		*n*	PSA50 (%)	PSA90 (%)	mPFS, months (95% CI)	HR (95% CI)	*P*
PSMA SUVmean ≥10	ctDNA <2%	13	100	92	14 (11–NR)	Ref.	Ref.
	ctDNA ≥2%	21	86	38	6.5 (3.5–9.5)	3.3 (1.5–7.3)	0.0034
PSMA SUVmean <10	ctDNA <2%	3	100	66	15 (9.8–NR)	Ref.	Ref.
	ctDNA ≥2%	59	49	24	3.2 (3.0–5.1)	3.3 (1.0–11)	0.048

Session 7: Emerging Roles and Strategies to Harness the Host Microbiome in Cancer

The Role of the Microbiome in Host Androgen Production and Therapeutic Resistance in CRPC

Karen Sfanos
Johns Hopkins University

What is the scientific background for this presentation?

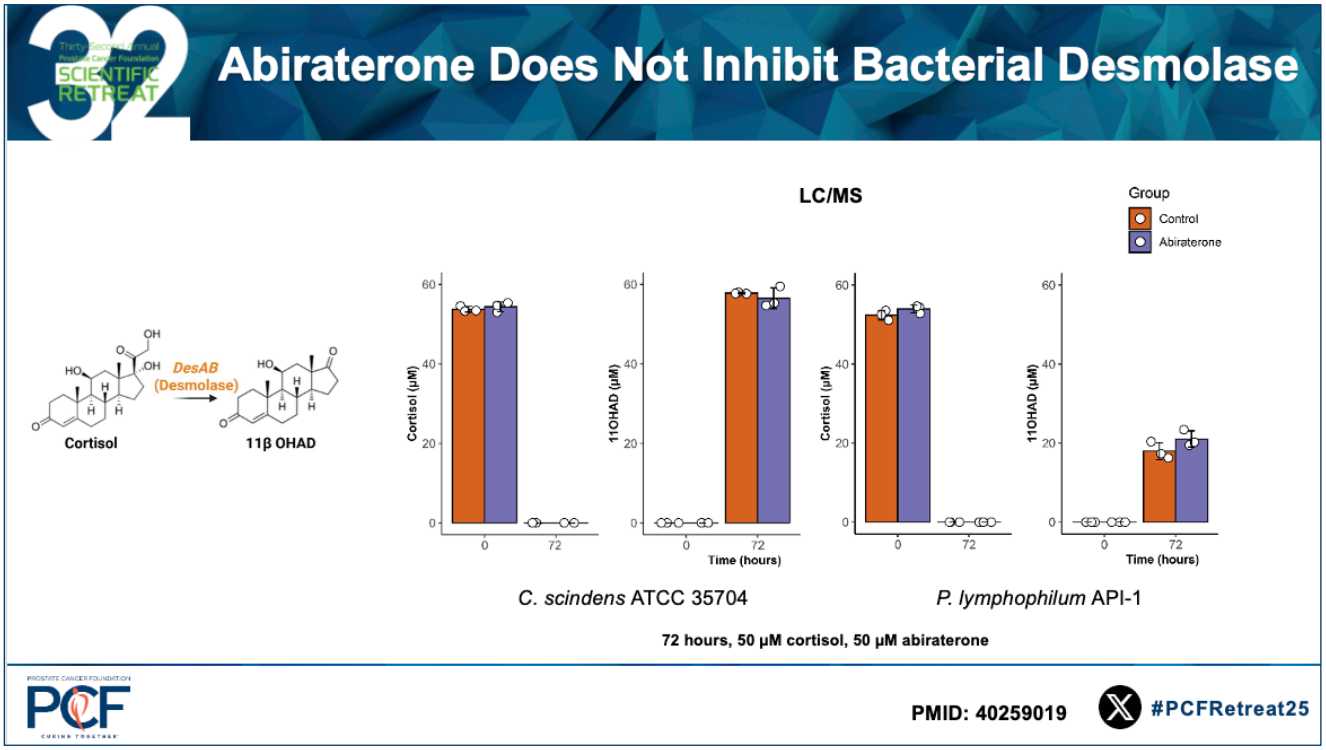
- Prostate cancer is a hormonally driven disease, largely fueled by hormones called androgens—such as testosterone—which belong to a broader class of molecules known as steroids.
- The human gut microbiome contains bacteria capable of metabolizing steroid hormones, and certain gut bacteria can convert steroid precursors into biologically active androgen-like compounds.

What progress or new findings were shared?

- Dr. Sfanos discussed how certain gut bacteria, including strains of *Clostridium scindens*, possess an enzyme similar to the human enzyme CYP17A1, which is capable of converting glucocorticoids such as cortisol and prednisone into androgenic compounds, including 11β-hydroxyandrostenedione (11β-OHAD) and delta-1 adrenosterone.
- Importantly, these bacterial enzymes are not inhibited by the CYP17A1 inhibitor, abiraterone (Zytiga®), meaning that even when human androgen production is blocked, bacteria in the gut may still generate androgen receptor (AR)–activating compounds (**Figure**).
- Laboratory experiments confirmed that these androgenic metabolites produced by bacteria can act as potent AR agonists in prostate cancer cell lines, stimulating androgen-responsive genes.
- When fecal samples from patients treated with abiraterone were evaluated, the levels of bacteria capable of producing androgenic metabolites were found to be increased in patients whose cancer was progressing on treatment in comparison to patients who were not being treated with abiraterone.
- Because abiraterone blocks a key steroid-producing enzyme, it disrupts normal hormone balance, requiring patients to take a replacement glucocorticoid (usually prednisone). Based on past research and the findings of Dr. Sfanos' team, an ongoing clinical trial is now testing whether switching to dexamethasone—a glucocorticoid less susceptible to this bacterial metabolism—can improve treatment response.

Why do these findings matter?

- These results suggest that the gut microbiome may serve as an alternative source of androgen production in men receiving androgen-targeted therapy, potentially contributing to therapeutic resistance.
- Modifying glucocorticoid selection or targeting bacterial steroid-converting enzymes may represent novel strategies to enhance or prolong response to androgen-targeted therapies.



Gut Reactions: How the Gut Microbiome Controls Effectiveness of Anti-Breast Cancer Drug Tamoxifen

Elizabeth Bess
University of California, Irvine

What is the scientific background for this presentation?

- Tamoxifen treats estrogen receptor (ER)–positive breast cancer by blocking estrogen signaling, which many breast tumors depend on for growth. This is similar to how androgen-targeted therapy is used in prostate cancer to inhibit androgen receptor (AR) signaling.
- Tamoxifen is often used for long periods of time, from 5 to 10 years, to prevent breast cancer recurrence.
- Tamoxifen is a prodrug, meaning it must be chemically converted in the body into more active forms to work well.

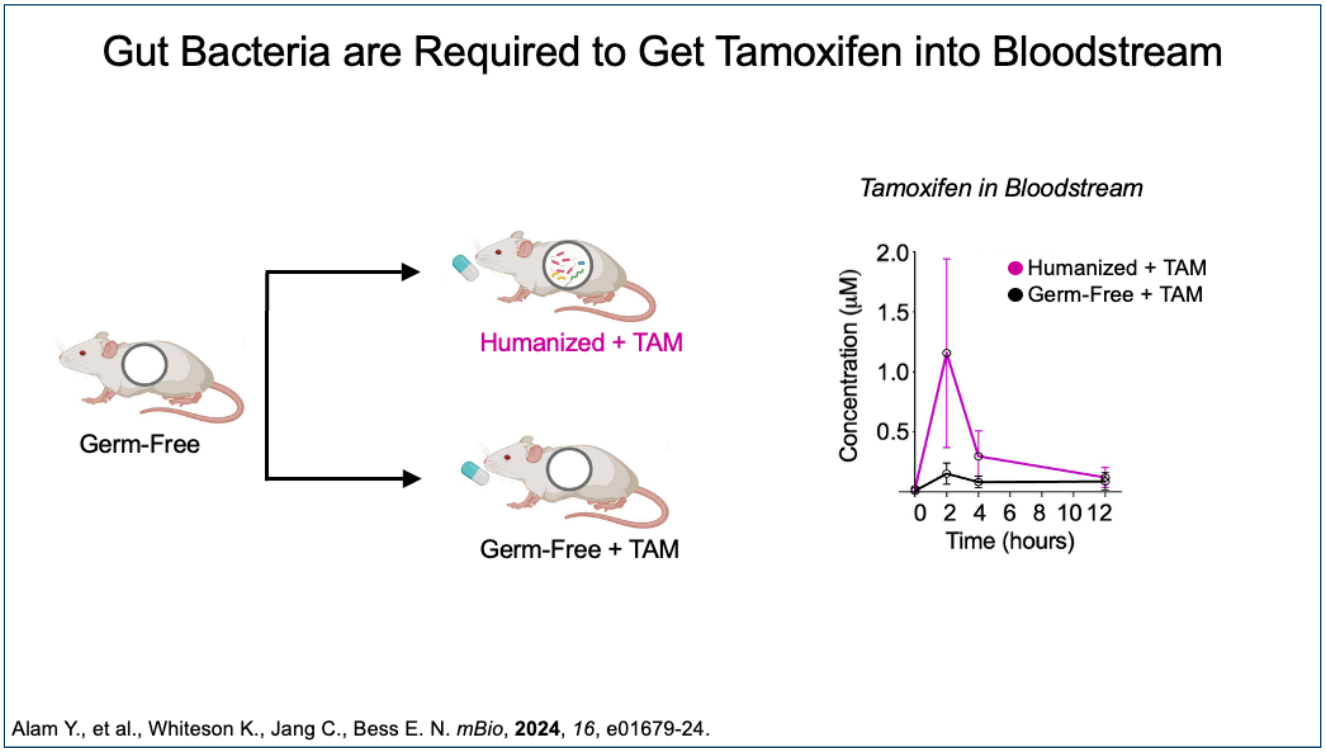
What progress or new findings were shared?

- Dr. Bess described research intended to determine whether gut bacteria influence the metabolism of tamoxifen into its active metabolites, potentially contributing to variability in treatment response.
- In preclinical experiments comparing tamoxifen metabolite levels in germ-free mice (raised without bacteria) versus mice colonized with human gut microbiota, the presence of gut microbes was necessary to achieve detectable systemic levels of tamoxifen and its active metabolites (**Figure**).
- Furthermore, antibiotic-treated mice demonstrated significantly reduced circulating levels of tamoxifen and its metabolite, supporting the conclusion that gut bacteria contribute to tamoxifen bioactivation.

- Mechanistically, the team focused on a process called glucuronidation, in which the liver attaches a sugar molecule to tamoxifen metabolites to facilitate elimination. Certain gut bacterial enzymes—particularly β-glucuronidases (GUS enzymes)—can remove this sugar tag, thereby reactivating the drug and allowing it to be reabsorbed into circulation.
- Longitudinal studies showed that extended tamoxifen exposure could alter microbial metabolic activity, even when the overall bacterial composition appeared relatively stable. This suggests that bacterial function, rather than simply bacterial presence, may influence tamoxifen metabolism.

Why do these findings matter?

- Microbiome-derived biomarkers—such as the presence or abundance of specific β-glucuronidase genes—could potentially help identify patients more likely to achieve optimal tamoxifen activation.
- The work also raises clinically relevant considerations, including the potential impact of antibiotic exposure and dietary factors on tamoxifen metabolism.
- More broadly, this research reinforces the concept that the microbiome can directly affect hormone-based cancer therapies, a principle that may extend beyond breast cancer to other hormonally driven malignancies such as prostate cancer.



Alam Y., et al., Whiteson K., Jang C., Bess E. N. *mBio*, **2024**, *16*, e01679-24.

Session 8: Exercise Interventions for Patients with Prostate Cancer

Exercise and Prostate Cancer: Bridging Epidemiology and Clinical Impact

June Chan
University of California, San Francisco

What is the scientific background for this presentation?

- Despite national recommendations encouraging at least 150 minutes of moderate-intensity exercise per week, only a minority of older men meet these activity targets.
- Studies have shown that men who engage in more physical activity after being diagnosed with prostate cancer have improved overall survival (OS) and prostate cancer–specific survival.
- However, most of these data come from observational cohort studies, which demonstrate associations but cannot definitively establish that exercise directly alters disease outcomes.

What progress or new findings were shared?

- Dr. Chan emphasized the need for moving beyond observational data to randomized controlled trials designed to test whether structured exercise programs can be safely implemented and produce measurable clinical and physiologic benefits in men with prostate cancer.
- In the ASX trial, 51 men with low to moderate baseline fitness who were undergoing active surveillance for localized prostate cancer were randomized to receive standard of care or a remotely supervised walking program using individualized heart rate targets.
- After 16 weeks in the ASX trial, men randomized to the walking program had a 14% improvement in cardiorespiratory fitness, whereas fitness declined slightly in the control group (**Figure**).
- Participants receiving the ASX walking intervention also reported reduced fear of cancer progression and improvements in certain urinary symptoms, suggesting both psychological and physiologic benefits.
- Dr. Chan also presented findings from the INTERVAL-GAP4 trial in 145 men with metastatic prostate cancer, in which supervised high-intensity interval training (HIIT) combined with resistance training was compared with a self-directed exercise program.
- The supervised exercise program resulted in sustained improvements in aerobic capacity and muscle strength over 12 months compared with usual care.

Why do these findings matter?

- These studies demonstrate that structured exercise interventions are feasible, safe, and capable of improving measurable physiologic outcomes (e.g., fitness, strength, metabolic health) in men across the prostate cancer continuum—from active surveillance to metastatic disease.
- Importantly, this work reframes exercise not simply as supportive care, but as a potential disease-modifying intervention that can improve both quantity and quality of life in patients with prostate cancer

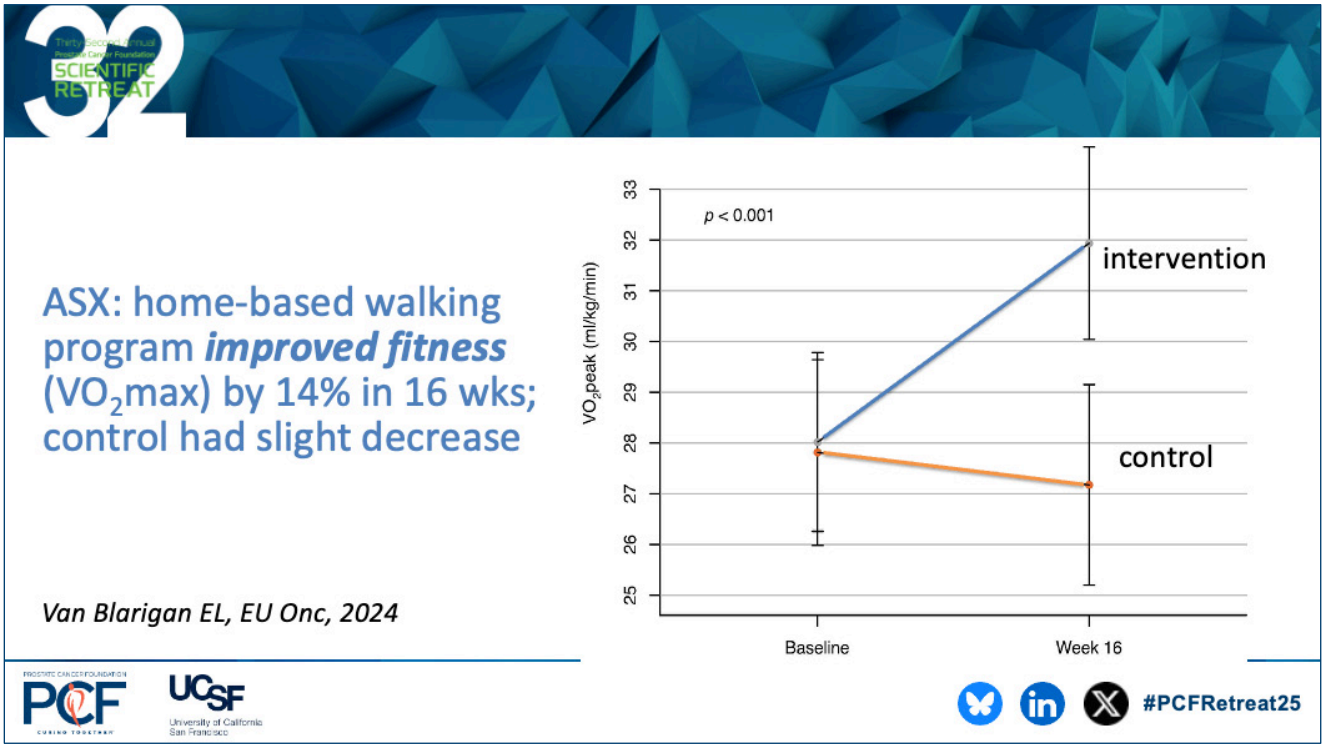


Figure source: Van Blarigan EL et al. *Eur Urol Oncol.* 2024;7(3):519-526.

Better Together: The Benefits of Team-Based Exercise for Couples Coping with Prostate Cancer

Kerri Winters-Stone
Oregon Health & Science University

What is the scientific background for this presentation?

- Cancer can impact the health of both patients and their spouses because physical and mental health are interconnected between partners. Changes in communication, intimacy, and relationship quality can influence both psychological well-being and biologic markers of chronic illness in partners, making it important to consider the health of both spouses and relationships to optimize the health of the couple.
- Traditional exercise interventions in oncology have focused primarily on the patient alone, but since couples' health and behaviors are strongly linked, exercising together may amplify the physical and relationship benefits of being active.

What progress or new findings were shared?

- Dr. Winters-Stone described the development of Exercising Together©, a strength-training intervention in which prostate cancer survivors train as a team with their spouse, using various teamwork techniques to promote motivation, support, communication, and shared accountability.
- In an initial pilot study, couples participating in partnered exercise demonstrated better adherence compared with usual care, with 100% retention in the partnered group, 75% adherence to twice-weekly training, and no adverse events.
- Prostate cancer survivors who participated in the partnered intervention reported increased physical activity and improvements in body composition, becoming leaner with a greater

proportion of muscle relative to fat, and both survivors and partners improved physical function.

- Partners in the Exercising Together arm also experienced psychosocial benefits, including increased affectionate behavior and fewer depressive symptoms, supporting the concept that team-based exercise can improve both survivor and partner outcomes.
- A larger 12-month randomized controlled trial of 294 couples compared partnered group exercise with supervised separate exercise and home-based exercise programs to disentangle the effects of team-based participation versus supervised group dynamics.
- Retention in the partnered exercise group was 96% (**Figure**). Other trial results are being analyzed.
- Preliminary feasibility and implementation studies of Exercising Together during radiation therapy for prostate cancer demonstrated high retention and strong class ratings, and an ongoing trial in radiation oncology is evaluating clinic-based Exercising Together versus usual care.
- Recognizing that not all men have partners, Dr. Winters-Stone also highlighted research on group-based exercise among prostate cancer survivors, noting that cancer-related loneliness is common (even among married men) and that exercising with other survivors may reduce loneliness and improve mental health.

Why do these findings matter?

- These data suggest that exercise interventions targeting the couple—rather than the patient alone—may improve adherence, physical health, mental health, and relationship quality, pointing to the interconnectedness within couples.
- Team-based exercise may enhance motivation and self-efficacy, increase training intensity through social support, and generate broader physiological benefits that extend beyond traditional fitness outcomes.

Exercising Together Trial

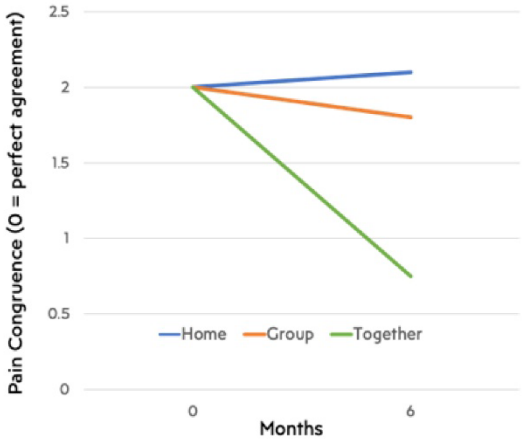
Winters-Stone, PI; Funding: R01CA218093; NCT03630354

- Comparison of Exercising Together (partnered training in a group) to survivor or spouse only group exercise programs and to individual home-based exercise
- 12-month RCT in couples coping with prostate, breast or colon cancer (n=294 couples); < 3 yrs post dx
- *Primary Endpoint*: Symptom congruence, relationship quality
- *Secondary Endpoints*: inflammation, lipids, insulin-family proteins, body composition, physical functioning

RETENTION and ADHERENCE in Prostate Couples (n=117)

Group	Retention	Adherence
Home (unsupervised)	88%	83%
Separate (supervised, group)	92%	81%
Partnered (supervised, group)	96%	82%
Total	92%	82%

Preliminary findings on symptom congruence



Winters-Stone et al, Trials 22(1):579, 2021

Session 9: AI-Driven Precision Medicine/R&D Efforts in Academia and BioPharma

Picking Pockets in the Disordered Androgen Receptor N-Terminal

Andrew Allen
Peptone

What is the scientific background for this presentation?

- Many biologically important cancer proteins lack obvious binding pockets or structural features that make them accessible to conventional therapeutics.
- Furthermore, many of these proteins are "disordered," meaning their structure has not been solved because the shape of the protein changes frequently.
- The androgen receptor (AR) protein—which plays a key role in prostate cancer progression and resistance to hormonal therapies—has a disordered protein domain that is critical for AR function. This domain is present even in treatment-resistant forms of AR, such as AR-V7.

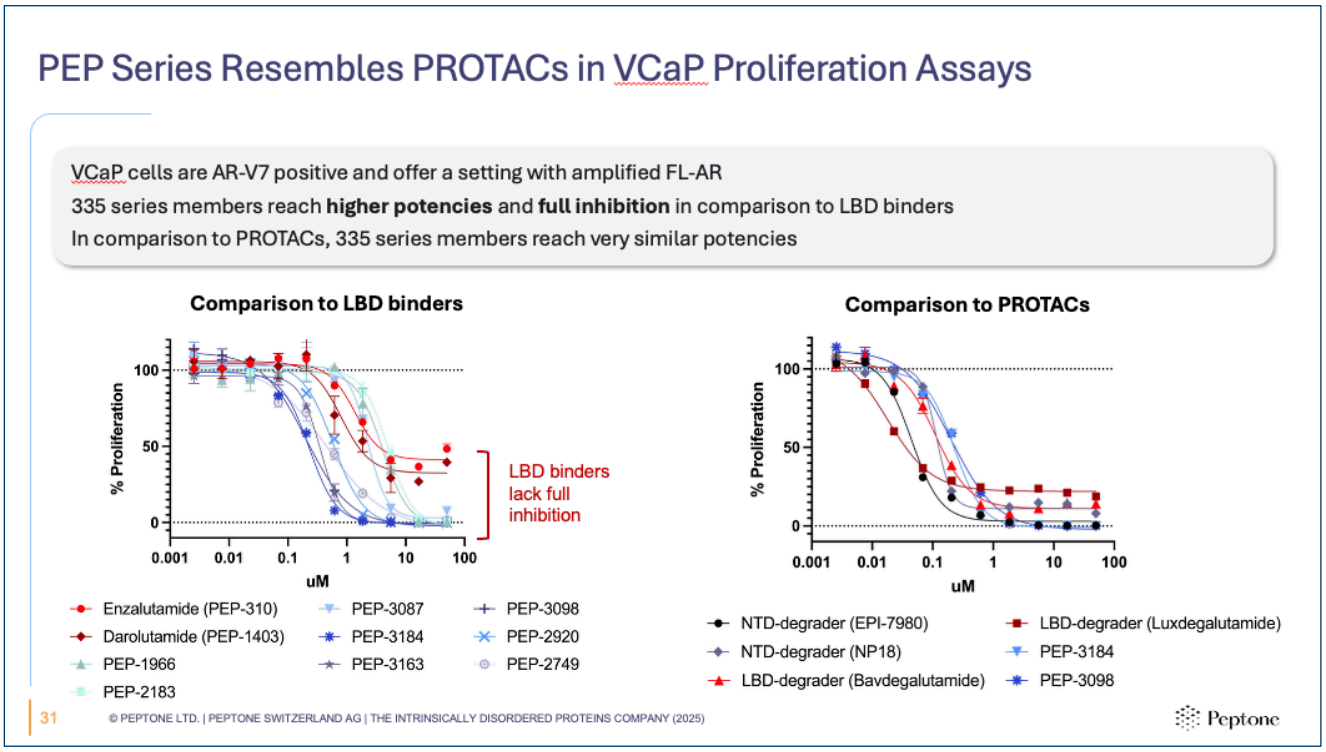
What progress or new findings were shared?

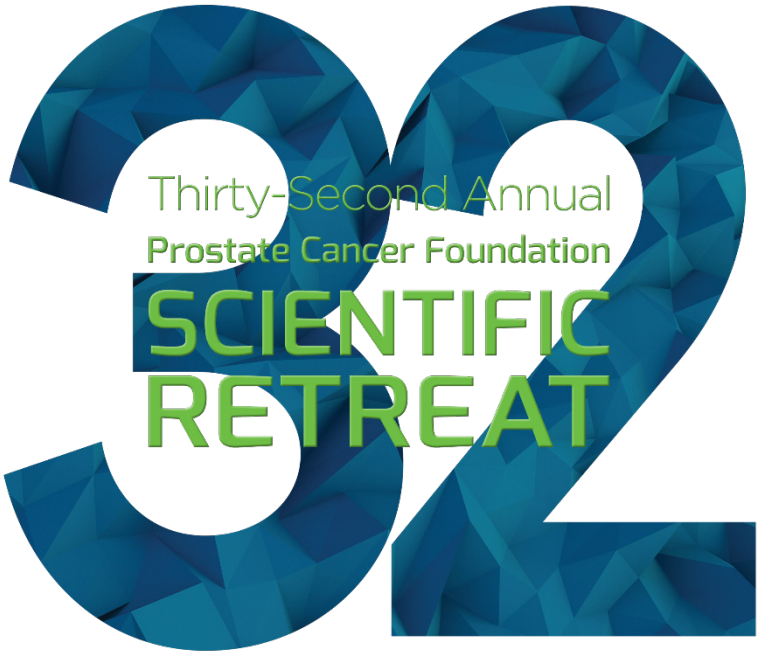
- Dr. Allen described Peptone's ultra-fast hydrogen-deuterium exchange mass spectrometry (UF-HDX-MS) platform, a technique that measures how different regions of a protein briefly open, close, or interact.
- The UF-HDX-MS platform generates experimental structural data for disordered protein regions and enables identification of "invisible" druggable pockets that cannot be resolved using typical structural biology methods
- These experimental structural data are then combined with computational simulations and artificial intelligence (AI)-based modeling to build a detailed map of all the shapes the disordered protein can adopt.
- This approach identified several promising drug candidates, including the PEP-335 series, which binds to the disordered N-terminal domain (NTD) region of the AR and showed very strong activity in prostate cancer cell models, performing better than standard AR-targeted drugs.
- The PEP compounds were active in prostate cancer models driven by treatment-resistant AR, including the mutated AR-V7 or amplified AR expression (**Figure**).
- Additional studies, including nuclear magnetic resonance (NMR), showed that the PEP compounds bind to a specific region within the NTD of the AR that blocks AR dimerization (the process by which two AR molecules pair to activate gene expression), without interfering with androgen binding at the ligand-binding domain (the site where most AR-targeted treatments bind and where treatment resistance can develop).
- Currently, Peptone is planning to perform preclinical toxicology and pharmacology studies in 2026 for an investigational new drug (IND) submission to the FDA, which will allow the launch of an early-phase clinical trial in patients with heavily pretreated advanced prostate cancer.

Why do these findings matter?

- The integration of experimental protein structure data with AI-driven modeling demonstrates that disordered proteins—long considered "undruggable"—can be systematically evaluated for druggable pockets.
- Targeting the disordered domain of AR represents a fundamentally different therapeutic strategy that may overcome resistance to existing therapies, including in AR-V7–driven

disease. Combinations of AR NTD inhibitors with AR ligand-binding domain inhibitors (such as enzalutamide) may also prove interesting, given the opportunity for additive or even synergistic effects.





APPENDIX I:

32nd ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT

Prostate Cancer Foundation
Young Investigator Forum

OCTOBER 22, 2025

PROGRAM AGENDA

Prostate Cancer Foundation
Young Investigator Forum

AGENDA

YOUNG INVESTIGATOR FORUM

Wednesday, October 22, 2025
***All times in U.S. PDT**

6:30 AM **Registration**

Location: Poinsettia Foyer

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

Location: Poinsettia 1

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

Location: Poinsettia 2 & 3

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

Howard Soule
Prostate Cancer Foundation
Andrea Miyahira
Prostate Cancer Foundation

Session 1: Science Communication: Necessary Skills in an Anti-Science Era
8:10 AM - 9:00 AM

8:10 AM - 8:40 AM **Cory Abate-Shen**
Columbia University

Introduced by Howard Soule

8:40 AM - 9:00 AM Discussion

Wednesday, October 22, 2025

Session 2: Science and Job Success: Survival of the Fittest Requires a Team
9:00 AM - 10:00 AM

9:00 AM - 9:45 AM **Kenneth Pienta**
Johns Hopkins University

Introduced by Howard Soule

9:45 AM - 10:00 AM Discussion

Session 3: Scoring with Confidence: Practical Heuristics for Grant Review as a Young Investigator
10:00 AM - 10:30 AM

10:00 AM - 10:20 AM **Edmond Kwan**
Monash University, Australia

Introduced by Andrea Miyahira

10:20 AM - 10:30 AM Discussion

Session 4: Introduction to High Achieving PCF Young Investigators
10:30 AM - 11:30 AM

Moderator: Howard Soule
Prostate Cancer Foundation

10:30 AM - 10:40 AM ***An All-in-One 'Living Drug' CAR T Cell Platform for Advanced Prostate Cancer***
Nour Shobaki
University of Pennsylvania

10:40 AM - 10:45 AM Discussion

10:45 AM - 10:55 AM ***Disabling the AR Neo-Enhanceosome by Targeting p300/CBP***
Jie Luo
University of Michigan

10:55 AM - 11:00 AM Discussion

11:00 AM - 11:10 AM ***Prostate Cancer Around the Globe: Disease Burden and Health Systems Levers***
Chris Dee
Memorial Sloan Kettering Cancer Center

11:10 AM - 11:15 AM Discussion

11:15 AM - 11:25 AM ***NSD2 Targeting Reverses Lineage Plasticity and Drug Resistance in Advanced Prostate Cancer***
Jia Li
Columbia University
11:25 AM - 11:30 AM Discussion

Group Photo
11:30 AM - 11:45 AM

Lunch
11:45 AM - 12:45 PM

Lunch Location: Orchid Terrace

12:45 PM - 1:00 PM **Move to Session 5**

Location: Poinsettia 2 & 3

Session 5: PANEL: Early and Mid-Career Advancement
1:00 PM - 2:15 PM

1:00 PM - 2:00 PM

Moderator: Burcu Darst (Fred Hutchinson Cancer Center)

Panelists:
Ping Mu (Yale University)
Saul Priceman (University of Southern California)
Alexandra (Sasha) Sokolova (Oregon Health & Science University)
Tanya Stoyanova (University of California, Los Angeles)

Introduced by Andrea Miyahira

2:00 PM - 2:15 PM Discussion

Session 6: Mentoring the Next Generation
2:15 PM - 3:00 PM

2:15 PM - 2:45 PM **Vanessa Hayes**
The University of Sydney, Australia

Introduced by Howard Soule

2:45 PM - 3:00 PM Discussion

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

Location: Poinsettia 1

Session 7: PCF Young Investigator Speed Networking 12.0
3:15 PM - 5:30 PM

Location: Poinsettia 1

Moderators:
Martin Bakht (Dana-Farber Cancer Institute)
Estefania Labanca (University of Texas MD Anderson Cancer Center)
Nour Shobaki (University of Pennsylvania)

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**

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

Reception Location: Orchid Terrace

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

Dinner Location: Orchid Terrace

***** 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.

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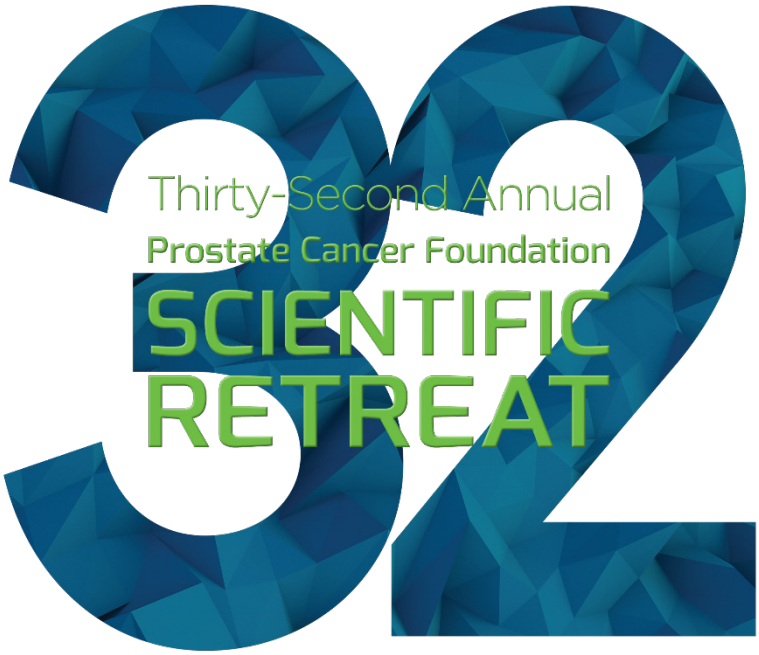


APPENDIX II:

32nd ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT

Prostate Cancer Foundation
Gender Equity Networking Initiative

OCTOBER 24, 2025

PROGRAM AGENDA

Prostate Cancer Foundation
Gender Equity Networking Initiative

The 10th Annual PCF Gender Equity Networking Initiative (GENI) Forum

Thursday, October 23, 2025
***All times in U.S. PDT**

Omni La Costa Resort
Carlsbad, California

Location: Poinsettia 2 & 3

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 build a supportive 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 women prostate cancer researchers and clinicians, and identify opportunities for further training, mentoring and synergy of a stellar network of women prostate cancer researchers and clinicians.

6:30 AM	**Registration**	Poinsettia Foyer
7:00 AM – 7:45 AM	**Breakfast, Coffee and Networking**	Poinsettia 1
7:45 AM	**Move to Poinsettia 2 & 3**	

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

Andrea Miyahira (Prostate Cancer Foundation)
Amina Zoubeidi (Vancouver Prostate Centre)

Session 1: Keynote: Opening Doors to Career Advancement: Turning Passion into Profession
8:05 AM – 8:55 AM

8:05 AM - 8:35 AM **Electra Paskett, PhD, FACE, FAACR, FASCO**
Marion N. Rowley Professor of Cancer Research and Director, Division of Cancer Prevention and Control, Department of Internal Medicine, Distinguished Professor, College of Medicine;
Professor, Division of Epidemiology, College of Public Health;
American Cancer Society Professor;
Deputy Director for Population Sciences and Community Outreach;
Director, Center for Cancer Prevention and Survivorship, Comprehensive Cancer Center;
Founding Director, Center for Community Outreach and Engagement, James Cancer Hospital
Ohio State University

Introduced by Susan Halabi

8:35 AM - 8:55 AM Questions

Session 2: Beyond Mentoring: Coaching Essentials for the Scientific Community
8:55 AM - 10:05 AM

8:55 AM - 9:35 AM **Heather Brod**
Heather Brod, MA, PCC
Heather Brod LLC

Introduced by Sarah Amend

Scientists are trained to reduce bias through observation and inquiry. Though when it comes to professional development, the default modes of mentoring and advising offer a limited perspective. Coaching offers another path. As a developmental process that mirrors the habits of science, it helps people examine their thinking, trust themselves, and take ownership of their growth. In this session, participants will learn foundational coaching skills and how to put them into practice to build individual capacity and strengthen how the scientific community develops and supports its members.

9:35 AM - 10:05 AM Questions

Session 3: Panel Discussion: Navigating in Uncertain Times
10:05 AM – 11:20 AM

Introduction by Ayesha Shafi

Moderator: Lisa Chesner (University of California, San Francisco)

Panelists:
Elisabeth I. Heath (Mayo Clinic)
Kara Maxwell (University of Pennsylvania)
Lorelei Mucci (Harvard T.H. Chan School of Public Health)
Susan Slovin (Memorial Sloan Kettering Cancer Center)

Session 4: Introduction to Students
11:20 AM – 11:30 AM

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

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 Orchid Terrace
11:45 AM – 12:30 PM

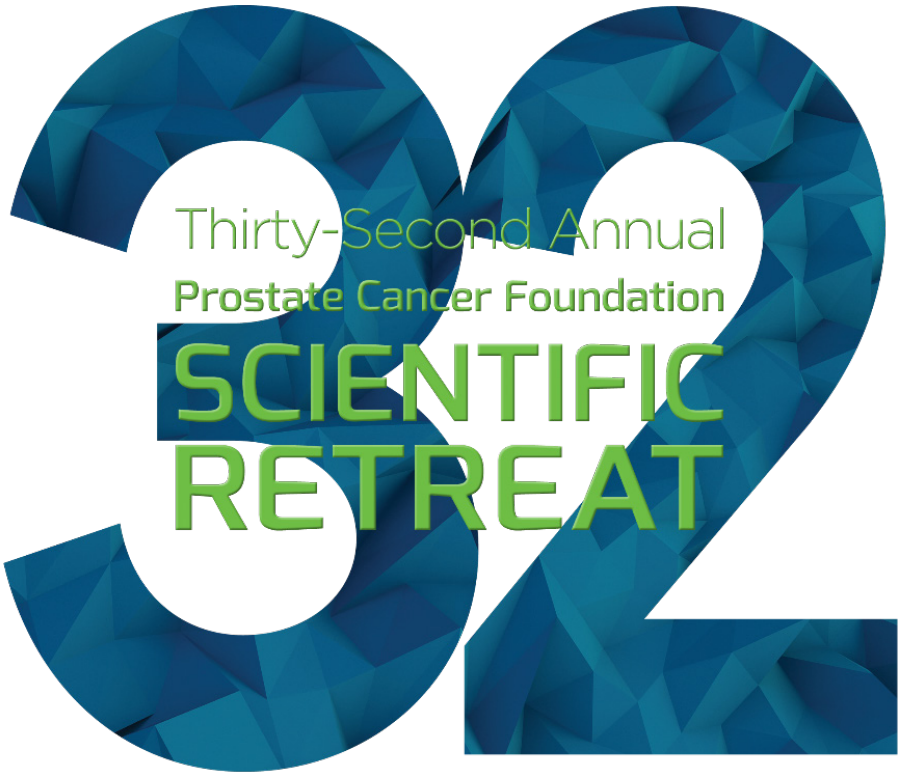
***** Meeting Adjourned *****

The 32nd 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 (Bethesda, MD)
Andrea Miyahira (Prostate Cancer Foundation)
Amrita Sawhney (Novartis)
Ayesha Shafi (Center for Prostate Disease Research (CPDR); USU Walter Reed Surgery)
Amina Zoubeidi (Vancouver Prostate Centre)



APPENDIX III:

32nd ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT

OCTOBER 23-25, 2025

PROGRAM AGENDA

AGENDA

Thursday, October 23, 2025

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: Theranostics: New Targets, New Atoms
1:05 PM - 2:25 PM

Moderator: Michael Hofman
Peter MacCallum Cancer Centre

1:05 PM - 1:20 PM ***Prostate Cancer Theranostics: What's Hot in 2025?***
Michael Hofman
Peter MacCallum Cancer Centre

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

1:25 PM - 1:40 PM ***Terbium-161 PSMA: Does Auger Strike a Perfect Balance of Beta and Alpha?***
James Buteau
Peter MacCallum Cancer Centre

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

1:45 PM - 2:00 PM ***Novel Theranostic Agents for Neuroendocrine Prostate Cancer (TACTICAL Award)***
Jason Lewis
Memorial Sloan Kettering Cancer Center

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

2:05 PM - 2:20 PM ***Radionuclides for the Theranostic Revolution: Matched Theranostic Pairs***
Suzanne Lapi
University of Alabama at Birmingham
2:20 PM - 2:25 PM **Discussion**

Session 2: Immunotherapy for Prostate Cancer
2:25 PM - 3:45 PM
Moderator: Nour Shobaki
University of Pennsylvania

2:25 PM - 2:40 PM ***Training T cells for the Harsh New World (of Prostate Cancer) (TACTICAL Award)***
Saul Priceman
University of Southern California
2:40 PM - 2:45 PM **Discussion**

2:45 PM - 3:00 PM ***Harnessing AR-V7 for Therapeutic and Preventive Prostate Cancer Vaccination***
Inês Mota
Weill Cornell Medicine
3:00 PM - 3:05 PM **Discussion**

3:05 PM - 3:20 PM ***Pasritamig, a Differentiated, KLK2-Targeted T Cell Engager for Prostate Cancer***
Charles Drake
Johnson & Johnson Innovative Medicine
3:20 PM - 3:25 PM **Discussion**

3:25 PM - 3:40 PM ***CD28-Targeted T Cell Engagers in Prostate Cancer***
Bilal Siddiqui
University of Texas MD Anderson Cancer Center
3:40 PM - 3:45 PM **Discussion**

Session 3: Drugging the Epigenome to Target Lethal Disease

3:45 PM - 5:05 PM

Moderators: Amina Zoubeidi
Vancouver Prostate Centre
Michael Shen
Columbia University

3:45 PM - 4:00 PM ***The Landscape of N6-Methyladenosine in Localized Primary Prostate Cancer and how these Modifications can Drive Disease Aggressiveness***
Housheng Hansen He
Princess Margaret Cancer Centre, University Health Network

4:00 PM - 4:05 PM **Discussion**

4:05 PM - 4:20 PM ***Characterizing Lineage Plasticity using Circulating Chromatin***
Sylvan Baca
Harvard: Dana-Farber Cancer Institute

4:20 PM - 4:25 PM **Discussion**

4:25 PM - 4:40 PM ***Utility of Epigenetic Profiling to Inform Resistance to ARPI***
Wilbert Zwart
Netherland Cancer Institute

4:40 PM - 4:45 PM **Discussion**

4:45 PM - 5:00 PM ***Targeting the Epigenome to Alter Lineage Plasticity***
Michael Shen
Columbia University

5:00 PM - 5:05 PM **Discussion**

SPECIAL LECTURE

5:05 PM - 5:20 PM

MYC Family Matters

Myles Brown
Harvard: Dana-Farber Cancer Institute

Introduction by Himisha Beltran
Harvard: Dana-Farber Cancer Institute

5:20 PM - 5:25 PM
Discussion

SPECIAL LECTURE
5:25 PM - 5:40 PM

How Does Androgen Biosynthesis Occur Independent of CYP17A1 and CYP11A1?

Nima Sharifi
University of Miami

Introduction by Howard Soule
Prostate Cancer Foundation

5:40 PM - 5:45 PM
Discussion

SPECIAL LECTURE
5:45 PM - 6:00 PM

Trial Design and Objectives for Prostate Cancer:
Recommendations from Prostate Cancer Clinical Trials Working Group 4

Andrew Armstrong
Duke University

Michael Morris
Memorial Sloan Kettering Cancer Center

Introduction by Howard Soule
Prostate Cancer Foundation

6:00 PM - 6:05 PM
Discussion

Thursday, October 23, 2025

SPECIAL LECTURE
6:05 PM - 6:20 PM

Integrating Tissue-Based Insights to Optimize ARPi+PARPi Combination Therapy in HSPC

Patrick Pilie
University of Texas MD Anderson Cancer Center

Introduction by Christopher Logothetis
University of Texas MD Anderson Cancer Center

6:20 PM - 6:25 PM
Discussion

Dinner
6:45 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 24, 2025

6:30 AM - 7:15 AM ***Breakfast***
Location: Costa Del Sol Patio

7:15 AM - 7:30 AM **Move to Group Photo** Costa Del Sol Foyer

Group Photo
7:30 AM - 7:45 AM

Location: Costa Del Sol Foyer

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

GENERAL SESSIONS
Location: Costa Del Sol Ballroom

KEYNOTE ADDRESS
8:00 AM - 9:00 AM

Michael Milken
Founder and Chairman
Prostate Cancer Foundation

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

PCF Women in Science
Lifetime Achievement Award Lecture
9:00 AM - 9:30 AM

From Mesopotamia to the Great Lakes "The 6000 Miles Journey"
Prostate Cancer Then & Now

Maha Hussain
Northwestern University

Introduction by Andrea Miyahira
Prostate Cancer Foundation

9:30 AM - 9:35 AM
Discussion

Dr. Felix Feng Legacy Lecture
9:35 AM - 9:50 AM

The Ongoing Legacy of Felix Feng Team Science

Daniel Spratt
Case Western University

Introduction by Howard Soule
Prostate Cancer Foundation

9:50 AM - 9:55 AM
Discussion

SPECIAL LECTURE
9:55 AM - 10:25 AM

From Bench to Business: Bridging Biomedical Research and Entrepreneurial Drug Development

Arie Belldegrun
University of California, Los Angeles

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

10:25 AM - 10:30 AM
Discussion

SPECIAL LECTURE
10:30 AM - 11:00 AM

CEO's Address

Gina Carithers
Prostate Cancer Foundation

Introduced by Howard Soule
Prostate Cancer Foundation

Lunch
11:00 AM - 12:00 PM

Location: Costa Del Sol Patio

12:00 PM - 12:15 PM **Move to Session**

Location: Costa Del Sol Ballroom

PANEL DISCUSSION: Luminaries in Prostate Cancer: How the Past Informs our Future
12:15 PM - 1:15 PM

Moderator: Phillip Koo
Prostate Cancer Foundation

Panelists:
Maha Hussain (Northwestern University)
Oliver Sartor (Tulane University)
Cora Sternberg (Weill Cornell Medicine; New York-Presbyterian)

12:15 PM - 12:25 PM Look back on advanced prostate cancer and where we are headed from here

12:25 PM - 12:35 PM Panel plus **Jim Hu** (Weill Cornell Medicine) – Future opportunities in urologic oncology

12:35 PM - 12:45 PM Panel plus **Neha Vapiwala** (University of Pennsylvania) – Future opportunities in radiation oncology

12:45 PM - 12:55 PM Panel plus **Emmanuel Antonarakis** (University of Minnesota) – Future opportunities in medical oncology

12:55 PM - 1:05 PM Panel plus **Michael Hofman** (Peter MacCallum Cancer Centre) – Future opportunities in nuclear medicine

1:05 PM - 1:15 PM Open Q&A

Session 4: Updates from Industry Clinical Trials
1:20 PM - 3:00 PM

Moderator: Howard Soule
Prostate Cancer Foundation

1:20 PM - 1:35 PM ***PSMAddition: Initial Results from the Phase III Trial of Lu-177-PSMA-617 in Metastatic Hormone Sensitive Metastatic Prostate Cancer***
Oliver Sartor
Tulane University

1:35 PM - 1:40 PM **Discussion**

1:40 PM - 1:55 PM ***Development of Xaluritamig, a STEAP1-Targeted T-Cell Therapy, for Prostate Cancer***
Judd Englert
Amgen
1:55 PM - 2:00 PM **Discussion**

2:00 PM - 2:15 PM ***A Phase 3 Study of Capivasertib + Abiraterone vs Placebo + Abiraterone in Patients with PTEN Deficient De Novo Metastatic Hormone-Sensitive Prostate Cancer: CAPItello-281***
Daniel George
Duke University
2:15 PM - 2:20 PM **Discussion**

2:20 PM - 2:35 PM ***Co-Targeting EZH2 and AR in Patients with mCRPC***
Douglas Laird
Pfizer
2:35 PM - 2:40 PM **Discussion**

2:40 PM - 2:55 PM ***CAN-2409 with Radiotherapy for Localized Prostate Cancer: A Phase 3, Randomized, Placebo-Controlled Clinical Trial***
Paul Peter Tak
Candel Therapeutics
2:55 PM - 3:00 PM **Discussion**

Session 5: Artificial Intelligence and Machine Learning to Better Inform Patient Outcomes

3:00 PM - 4:40 PM

Moderator: Tamara Lotan
Johns Hopkins University

3:00 PM - 3:15 PM ***Pathology Deep Learning Tools for Localized Prostate Cancer***
Tamara Lotan
Johns Hopkins University
3:15 PM - 3:20 PM **Discussion**

3:20 PM - 3:35 PM ***Navigating the Prostate Cancer Journey with Genetic Testing, RNA, AI, and MRD***
Hosein Kouros-Mehr
Myriad Genetics
3:35 PM - 3:40 PM **Discussion**

3:40 PM - 3:55 PM ***Digital Pathology for Patient Management and Treatment Decisions in Prostate Cancer and Urologic Oncology***
Andre Esteva
Artera
3:55 PM - 4:00 PM **Discussion**

Friday, October 24, 2025

4:00 PM - 4:15 PM ***Computational Approaches for PSA Trajectories to Guide Therapy***
Julian Hong
University of California, San Francisco
4:15 PM - 4:20 PM **Discussion**

4:20 PM - 4:35 PM ***Empowering VA Practitioners with Data to Optimize their Care of Veterans with Prostate Cancer***
Antonio Fojo
Columbia University
4:35 PM - 4:40 PM **Discussion**

SPECIAL LECTURE
4:40 PM - 4:55 PM

Prostate Cancer Genomics from High-Risk Populations: Lessons from African-Ancestry Patients

Franklin Huang
University of California, San Francisco

Introduced by Howard Soule
Prostate Cancer Foundation

4:55 PM - 5:00 PM
Discussion

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

Dinner & Awards Ceremony
7:00 PM - 9:00 PM

Location: Costa Del Sol Ballroom

PCF Awards Ceremony
7:45 PM - 8:45 PM

2025 ASCO-Felix Feng Young Investigator Award

2025 HBCU-PCF Recognition Award

2025 PCF Young Investigator Awards

2025 PCF Challenge Awards

2024 PCF Challenge Awards

2025 PCF-Foundation Medicine Collaborative Research Awards

2024 PCF-Pfizer Visiting Professorship Awards

Saturday, October 25, 2025

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 6: Novel Technology for Circulating Biomarker Development
7:00 AM - 8:40 AM

Moderators: Himisha Beltran
Harvard: Dana-Farber Cancer Institute
Alexander Wyatt
University of British Columbia

7:00 AM - 7:15 AM ***Boosting Liquid Biopsy Signal through New Technology***
Francesca Demichelis
University of Trento, Italy

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

7:20 AM - 7:35 AM ***PC-SYNERGY: Biological and Therapeutic Insights from a Metastatic Prostate Cancer Atlas at Single Cell Resolution (TACTICAL Award)***
Peter Nelson
Fred Hutchinson Cancer Center

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

7:40 AM - 7:55 AM ***Profiling Prostate Cancer Phenotypes from Cell-Free DNA through Advanced Machine Learning***
Gavin Ha
Fred Hutchinson Cancer Center

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

8:00 AM - 8:15 AM ***High Purity Circulating Tumor Cell RNA-Sequencing in Advanced Prostate Cancer***
Marina Sharifi
University of Wisconsin

8:15 AM - 8:20 AM **Discussion**

8:20 AM - 8:35 AM ***Circulating Tumour DNA Genomic Correlatives in mCRPC Treated with LuPSMA or Cabazitaxel from the Randomised Phase II TheraP Trial (ANZUP 1603)***
Edmond Kwan
Monash University, Australia

8:35 AM - 8:40 AM **Discussion**

SPECIAL LECTURE
8:40 AM - 8:55 AM

Degrading MYC: Updates on Drugging the Key Undruggable Oncogene (TACTICAL Award)

Arul Chinnaiyan
University of Michigan

Introduced by Howard Soule
Prostate Cancer Foundation

8:55 AM - 9:00 AM
Discussion

Session 7: Emerging Roles and Strategies to Harness the Host Microbiome in Cancer
9:00 AM - 10:00 AM

Moderator: Karen Sfanos
Johns Hopkins University

9:00 AM - 9:15 AM ***The Role of the Microbiome in Host Androgen Production and Therapeutic Resistance in CRPC***
Karen Sfanos
Johns Hopkins University

9:15 AM - 9:20 AM **Discussion**

9:20 AM - 9:35 AM ***Androgen Deprivation Therapy Enables Fungal Translocation into the Prostate Tumor Microenvironment, Promoting Cancer Progression***
Andrea Alimonti
Institute of Oncology Research (IOR), Switzerland

9:35 AM - 9:40 AM **Discussion**

9:40 AM - 9:55 AM ***Gut Reactions: How the Gut Microbiome Controls Effectiveness of Anti-Breast Cancer Drug Tamoxifen***
Elizabeth Bess
University of California, Irvine

9:55 AM - 10:00 AM **Discussion**

Session 8: Exercise Interventions for Patients with Prostate Cancer
10:00 AM - 11:20 AM

Moderators: June Chan
University of California, San Francisco
Christina Dieli-Conwright
Harvard: Dana-Farber Cancer Institute

10:00 AM - 10:15 AM ***Exercise and Prostate Cancer: Bridging Epidemiology and Clinical Impact***
June Chan
University of California, San Francisco
10:15 AM - 10:20 AM **Discussion**

10:20 AM - 10:35 AM ***Development of Exercise in Localized Prostate Cancer***
Lee Jones
City of Hope
10:35 AM - 10:40 AM **Discussion**

10:40 AM - 10:55 AM ***Better Together: The Benefits of Team-Based Exercise for Couples Coping with Prostate Cancer***
Kerri Winters-Stone
Oregon Health & Science University
10:55 AM - 11:00 AM **Discussion**

11:00 AM - 11:15 AM ***Prescriptive Exercise as the World's Best Drug to Enhance Prostate Cancer Survivorship***
Christina Dieli-Conwright (Virtual Presentation)
Harvard: Dana-Farber Cancer Institute
11:15 AM - 11:20 AM **Discussion**

Session 9: AI-Driven Precision Medicine/R&D Efforts in Academia and BioPharma
11:20 AM - 1:05 PM

Moderator: Marco Gottardis
Gottardisbiotech LLC

11:20 AM - 11:25 AM ***Introduction***
Marco Gottardis
Gottardisbiotech LLC

11:25 AM - 11:40 AM ***AI for Prostate MRI-Based Cancer Detection and Risk Prediction***
Keyan Salari
Massachusetts General Hospital
11:40 AM - 11:45 AM **Discussion**

Saturday, October 25, 2025

11:45 AM - 12:00 PM ***An Innovative Suite of AI Models for Mapping Lineage Plasticity and Identifying Therapeutic Vulnerabilities in Prostate Cancer***
Ping Mu
Yale University

12:00 PM - 12:05 PM **Discussion**

12:05 PM - 12:20 PM ***Generative AI for the Development of Novel Cancer Therapeutics***
Alex Therien
Generate Biomedicines

12:20 PM - 12:25 PM **Discussion**

12:25 PM - 12:40 PM ***Picking Pockets in the Disordered Androgen Receptor N-Terminal***
Andrew Allen
Peptone

12:40 PM - 12:45 PM **Discussion**

12:45 PM - 1:00 PM ***Discovery and Optimization of ERG Bifunctional, Stapled Peptide Degraders using Generative AI–Driven Multi-Property Modeling***
Jonathan Hurov
Parabilis Medicines

1:00 PM - 1:05 PM **Discussion**

Closing Remarks

1:05 PM - 1:10 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)

Himisha Beltran (Harvard: Dana-Farber Cancer Institute)
June Chan (University of California, San Francisco)
Christina Dieli-Conwright (Harvard: Dana-Farber Cancer Institute)
Marco Gottardis (Gottardisbiotech LLC)
Michael Hofman (Peter MacCallum Cancer Centre)
Fatima Karzai (Bethesda, MD)
Phillip Koo (Prostate Cancer Foundation)
Karen Sfanos (Johns Hopkins University)
Michael Shen (Columbia University)
Alexander Wyatt (Vancouver Prostate Centre)
Amina Zoubeidi (Vancouver Prostate Centre)

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

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