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REVIEW ARTICLE

Deciphering Resistance: Beyond the Androgen Paradigm; Report From the 2025 Coffey-Holden Prostate Cancer Academy Meeting

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ABSTRACT

Introduction: The 12th Annual 2025 Coffey—Holden Prostate Cancer Academy (CHPCA) Meeting, "Deciphering Resistance: Beyond the Androgen Paradigm," was held at the University of California, Los Angeles (UCLA), Luskin Conference Center, in Los Angeles, CA, from June 19 to 22, 2025.

Methods: The CHPCA Meeting is a discussion-focused conference held annually by the Prostate Cancer Foundation (PCF), for in-depth academic analysis of emerging research with the greatest potential to drive new understandings and treatments for prostate cancer. The 2025 CHPCA Meeting included attendance by 79 academic investigators and 39 talks over 8 sessions.

Results: The session topics included: drug discovery in academia, non-apoptotic cell death mechanisms, understanding and overcoming treatment resistance, chromosomal instability (CIN) as a driver of metastasis and treatment resistance, targeting metastatic sites, immunotherapy sensitizers, and optimizing therapy delivery and biomedical engineering.

Discussion: This meeting report summarizes the presentations from the 2025 CHPCA Meeting. We hope that disseminating this information will directly contribute to novel research efforts and improved treatment strategies for patients with prostate cancer.

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1 | Introduction

The Prostate Cancer Foundation (PCF) is the world's leading philanthropic organization dedicated to funding life-saving prostate cancer research. Founded in 1993 by Mike Milken, PCF has been responsible for raising more than $1 billion in support of cutting-edge research by more than 2250 research projects at 245 leading cancer centers, with a global footprint spanning 28 countries. PCF supports the mission to accelerate research through global knowledge exchange efforts including seminars, working groups, and annual scientific conferences including the Coffey—Holden Prostate Cancer Academy (CHPCA) Meeting.

The CHPCA Meeting is an annual conference held by the PCF, based on the discussion-focused format of the former NCI Prouts Neck Meeting on Prostate Cancer, and named for the influential leaders Dr. Stuart Holden and the late Dr. Donald Coffey [1]. The purpose of the CHPCA is to encourage deep academic analysis of emerging research with the greatest potential to drive new understandings and treatments for prostate cancer [2–11].

The 12th Annual 2025 CHPCA Meeting was themed "Deciphering Resistance: Beyond the Androgen Paradigm," and was held at the UCLA Luskin Conference Center, in Los Angeles, CA, from June 19 to 22, 2025.

The 2025 CHPCA Meeting was attended by 79 academic investigators, of whom 40 were early career investigators (51%), meeting the Academy-format requirement that at least half of the attendees be early career investigators. There were 8 sessions totaling 39 talks, covering topics including drug discovery in academia, non-apoptotic cell death mechanisms, understanding and overcoming treatment resistance, chromosomal instability (CIN) as a driver of metastasis and treatment resistance, targeting metastatic sites, immunotherapy sensitizers, and optimizing therapy delivery and biomedical engineering.

2 | Distinguished Lecture: Drug Discovery in Academia: Some Success Stories

Dr. Michael Jung (UCLA) opened the meeting with a keynote lecture on the development of two FDA approved drugs for prostate cancer, enzalutamide and apalutamide. The medicinal chemistry journey began in 2003. Together with Dr. Charles Sawyers then at UCLA (now at Memorial Sloan Kettering), Jung and team set out to design a new class of androgen receptor (AR) antagonists that would be purely inhibitory regardless of receptor levels. The team began with RU-59063 [12], a thiohydantoin scaffold that functioned as a strong AR agonist, which the laboratory systematically modified and optimized. Nearly 170 analogs were generated, with each round of modification aimed at strengthening AR binding, blocking receptor nuclear translocation, and eliminating partial agonism while selecting for strong antagonists. From this effort emerged a series of compounds named the RD-series (Rationally Designed series). The first two lead compounds, RD-037 and RD-131, showed good activity but had very poor pharmacokinetic properties. Jung and colleagues then developed a more stable analog, RD-162, which demonstrated strong efficacy in pre-clinical models in vivo [13]. Mechanistic studies revealed that RD-162 prevented androgen binding, blocked AR nuclear translocation, and inhibited AR–DNA/coactivator interactions [13, 14]. The compound was further modified (RD-162') and licensed to Medivation where it became known as MDV3100 (enzalutamide) [13, 14].

The first-in-human studies, initiated around 2007–2008, revealed that patients experienced significant prostate specific antigen (PSA) declines and radiographic tumor responses [13]. On August 31, 2012, the FDA approved enzalutamide for men with metastatic castration-resistant prostate cancer (mCRPC) after chemotherapy. Just 2 years later, in September 2014, approval was extended to chemotherapy-naïve mCRPC, and subsequent studies demonstrated the efficacy and extended approvals in non-metastatic CRPC (nmCRPC) in 2018, in metastatic hormone-sensitive prostate cancer (mHSPC) in 2019, and non-metastatic HSPC with biochemical recurrence at high risk for metastasis in 2023. Enzalutamide's trajectory reflected both its potent pharmacology and the urgent clinical need, and it rapidly became a standard of care worldwide.

In parallel, Jung's group continued to innovate. Jung co-founded Aragon Pharmaceuticals in May 2009 to explore related but distinct scaffolds, including design, preparation, and testing of A52, which was named ARN-509, and later known as apalutamide [15]. The design goals were to retain potent AR antagonism, optimize pharmacokinetics, and reduce brain penetration to minimize central nervous system side effects, including the rare seizures observed with high-dose enzalutamide [15]. Preclinical and early clinical data supported its promise, and in 2013 Johnson & Johnson acquired Aragon to drive late-stage development. The SPARTAN trial led to FDA approval of apalutamide on February 14, 2018, for nmCRPC, while the TITAN trial established benefit in mHSPC, securing approval on September 17, 2019.

The dual success of enzalutamide (Xtandi®) and apalutamide (Erleada®) illustrates how rigorous, mechanism-driven medicinal chemistry coupled with strong academic–industry collaboration can deliver transformative therapies for cancer. Jung continues efforts on developing new molecules targeting additional critical pathways that regulate prostate cancer progression.

3 | Non-Apoptotic Cell Death Mechanisms

3.1 | The Discovery of New Non-Apoptotic Cancer Cell Death Phenotypes

Dr. Scott Dixon (Stanford University) discussed non-apoptotic cell death mechanisms and emphasized that apoptosis, a historically dominant cell death mechanism, represents only one of several regulated pathways through which cancer cells can die. He highlighted the rapid discovery of distinct, mechanistically diverse forms of cell death that are increasingly recognized as biologically and therapeutically important.

Among these, Dixon focused on ferroptosis, an iron-dependent, non-apoptotic form of cell death [16]. Ferroptosis is mechanistically defined by the lethal accumulation of lipid peroxides when antioxidant defenses, especially the glutathione–GPX4 axis, are compromised [16]. The pathway was initially identified through a phenotypic small-molecule screen of several hundred thousand compounds, which yielded two key inducers of cell death, erastin and RSL3. Subsequent characterization revealed

that these compounds trigger ferroptosis by inducing lipid peroxidation [16].

Dixon also discussed the current limitations of ferroptosis inducers, noting that while several compounds have been used in preclinical models, none have yet advanced into clinical trials. He presented efforts to optimize ferroptosis inducers for therapeutic application, highlighting compound 28, a derivative of RSL3 with improved pharmacokinetics [17]. Compound 28 covalently binds GPX4, induces ferroptosis, and has demonstrated promising therapeutic efficacy in preclinical studies [17].

Tegavivint (also known as tegatrabetan, BC2059) is a potential non-apoptotic cell death inducer in cancer [18]. Tegavivint has already been tested in patients and shown to be safe. Data suggests that tegavivint induces cell death via a mechanism distinct from ferroptosis, necroptosis, and pyroptosis, instead requiring the lipid metabolic enzyme *trans*-2,3-enoyl-CoA reductase [18]. Importantly, tegavivint is a drug candidate that has advanced into clinical trials for several indications, including non-small cell lung cancer, lymphoma, and hepatocellular carcinoma.

Dixon concluded by underscoring the importance of mapping the regulatory circuits of non-apoptotic cell death programs, advancing small-molecule inducers and inhibitors, and strategically leveraging these pathways both as tools to eliminate resistant cancer cells and as processes that must be controlled to prevent damage in degenerative disease contexts.

3.2 | Targeting Metabolic Cell Death in Cancer

Dr. Boyi Gan (University of Texas MD Andeson Cancer Center) discussed the conceptual and mechanistic understanding of regulated cell death pathways and their therapeutic implications in cancer, including prostate cancer. He began by framing cell death at the conceptual level, dividing it into two categories: cell suicide and cell sabotage [19]. Cell suicide pathways involve a cell deliberately initiating its own death for the benefit of the whole organism, as seen in apoptosis [19]. In contrast, sabotage pathways arise when homeostasis is disrupted by toxic metabolites or metal accumulation, leading to cell death with less clearly defined physiological benefit [19]. Examples of such pathways include ferroptosis, cuproptosis, and the recently described disulfidptosis.

Suicide pathways are usually mediated by well-defined executioner proteins, such as caspases in apoptosis or MLKL in necroptosis, whereas sabotage pathways often lack such key executioners. For instance, ferroptosis is triggered by lipid peroxidation [16], while cuproptosis results from copper overload that disrupts mitochondrial metabolism through aggregation of lipoylated proteins and iron-sulfur protein depletion [20]. Although the detailed molecular mechanisms of cuproptosis remain under investigation, copper appears to play a critical role in these downstream cellular events, ultimately driving cell death [20].

Gan further described disulfidptosis, identified in his lab [21]. This form of cell death arises from the overaccumulation of cystine imported through SLC7A11 [21]. Under normal reducing intracellular conditions, cystine is rapidly converted to cysteine for antioxidant defense. However, when glucose availability or NADPH is limited, this conversion is impaired, leading to cystine accumulation and aberrant disulfide bonding in cytoskeletal proteins, which disrupts actin structure and induces cell death [21]. Disulfidptosis can be triggered by glucose starvation or inhibition of thioredoxin reductase in cells with high expression of SLC7A11.

While ferroptosis, cuproptosis, or disulfidptosis inducers show strong potency in vitro, their single-agent activity in vivo is generally modest [22]. Thus, combination strategies are needed to enhance therapeutic efficacy [22]. Studies combining cell death inducers with radiotherapy, chemotherapy, and targeted therapy have demonstrated promise in overcoming therapy resistance, particularly in prostate cancer. For example, combining ferroptosis inducers with AR antagonists has shown potential in resistant settings [22]. There is also emerging evidence that metabolic cell death pathways can shape anti-tumor immunity, sometimes promoting immune activation but in other contexts fostering immunosuppression, underscoring the complexity of therapeutic application.

A major challenge for the field is the identification of biomarkers for these non-apoptotic pathways. Suicide mechanisms such as apoptosis are easily monitored using established markers like cleaved caspase-3, but sabotage pathways lack such defined executors, making it difficult to distinguish them from stress-induced processes. There is an urgent need to develop specific biomarkers to facilitate the exploration of these novel cell death mechanisms as therapeutic strategies.

3.3 | Engineering Innate Sensing Molecules to Modify the Tumor Microenvironment (TME)

Dr. Megan Molina (University of Washington) presented research on developing broadly applicable strategies to overcome cancer therapy resistance. While immune checkpoint blockade (ICB) has transformed treatment for certain malignancies, prostate cancer exhibits resistance attributed in part to the immunosuppressive TME which lacks sufficient T-cell infiltration [23]. Without dendritic cell priming and T-cell presence in the TME, robust anti-tumor immunity is unlikely. To overcome this issue, Molina advocated for strategies that engage the innate immune system to complement checkpoint inhibition.

Molina discussed programmed cell death as an immunological tool and outlined three canonical pathways: apoptosis as immunologically silent, and necroptosis and pyroptosis, both of which are inflammatory and immunogenic [24]. Harnessing these latter pathways could potentially trigger strong adaptive immune responses against tumors. Molina presented data on engineered molecules that allow controlled induction of necroptosis and pyroptosis. For instance, fusing death pathway proteins with FKBP12 domains, resulted in drug-activatable constructs: inducible caspase-1 for pyroptosis and RIPK3 for necroptosis [25]. Engineered fibroblasts expressing inducible caspase-1 were validated in vitro, where treatment with a dimerizer drug triggered rapid pyroptosis, gasdermin pore formation, and release of bioactive cytokines IL-1β and IL-18. In vivo studies using melanoma models demonstrated that these engineered cells followed by drug activation reduced tumor growth. Among tested constructs, caspase-1 plus IL-18 consistently showed the most potent anti-tumor effects,

occasionally leading to complete tumor regression and protection upon rechallenge. Increased dendritic cell activation and greater tumor antigen uptake were observed, supporting the concept that engineered pyroptosis can enhance antigen presentation and adaptive immunity.

Molina also presented preliminary data on the feasibility of delivering inducible pyroptosis machinery directly into T cells, with early indications of potential efficacy. Efforts are also underway to refine tumor specificity by developing logic-gated T cells and synthetic circuits to ensure targeted expression of pyroptotic cargo within tumors. These studies highlight the promise of combining inflammatory programmed cell death with existing immunotherapies to overcome resistance, particularly in cancers such as prostate.

3.4 | Death & Destruction: How Therapy-Induced Death Programs Anti-Tumor Immunity

Dr. Brian Ruffell (Moffitt Cancer Center) discussed the intersection of regulated cell death and tumor immunity, focusing on how cell death pathways regulate the immunogenicity of the anti-tumor response [26]. Previous studies have demonstrated death effector molecules can be potentially targeted to induce anti-tumor immunity [27, 28].

Ruffell presented his group's research on investigating whether engineered necroptosis could enhance anti-tumor immunity [29]. Using constructs to induce RIPK3- or MLKL-mediated necroptosis, they confirmed in vitro that dying tumor cells released molecules such as ATP and HMGB1, and that these could activate dendritic cells [29]. However, in multiple in vivo tumor models, including breast and colon cancer, inducing necroptosis paradoxically accelerated tumor growth rather than suppressing it [29]. Further studies revealed that necroptotic tumors exhibited reduced $CD8^+$ T-cell and NK-cell infiltration and impaired interferon-γ responses [29]. Instead, the dying cells triggered early neutrophil influx followed by macrophage recruitment, consistent with a wound-healing-like response that suppressed anti-tumor immunity [29]. Depleting macrophages and neutrophils partially reversed this phenotype [29]. Mechanistic studies revealed that necroptotic cells and neighboring live cells responding to necroptotic death produced high levels of chemokines such as CXCL1, CXCL2, and CCL2, recruiting suppressive myeloid cells [29]. This process was found to depend on IL-1α signaling through MyD88 [29]. IL-1α, usually localized in the nucleus under resting conditions, was specifically released during necroptosis but not apoptosis [29]. Chemotherapy was also found to induce IL-1α release in tumor cells that lost membrane integrity, suggesting cells were undergoing mixed modes of death. Importantly, neutralizing IL-1α reduced tumor growth and reversed myeloid-driven immunosuppression [29]. Chemotherapy-induced IL-1α release was found to reprogram macrophages, and loss of tumor IL-1α shifted them from an immunosuppressive to an immunostimulatory phenotype [29]. These findings support IL-1α as a key mediator linking necroptosis, myeloid recruitment, and impaired T-cell immunity. Consistent with this, high IL-1α expression correlated with worse outcomes in patients with breast and lung cancers treated with chemotherapy or immunotherapy, though it appeared less relevant in prostate cancer [29].

These studies highlight the translational implications of IL-1α neutralizing antibodies, already in early-phase clinical trials and their potential to improve outcomes when combined with chemotherapy. Related nuclear cytokines, such as IL-33, may also contribute to similar immune-suppressive mechanisms.

3.5 | Metabolic Vulnerabilities in Prostate Cancer: The Lipid Droplet Connection

Dr. Daniel Frigo (University of Texas MD Anderson Cancer Center) discussed his group's work on prostate cancer metabolism, focusing on how tumors regulate lipid processing and how this influences therapeutic vulnerability. Prostate cancer is marked by abnormal lipid metabolism, driven in part by AR activity, which promotes both lipid uptake and de novo lipogenesis [30]. While inhibitors of these pathways have entered clinical trials, their effectiveness as single agents have been limited due to compensatory metabolic adaptation.

To explore alternative vulnerabilities, Frigo's lab studied lipid droplet homeostasis and the role of PNPLA2 (ATGL, Adipose triglyceride lipase), a lipase responsible for initiating triglyceride breakdown [31]. Elevated ATGL expression correlated with poor prognosis in advanced prostate cancer [31]. Functional experiments revealed that ATGL knockout impaired tumor growth in vitro and in castration-resistant models in vivo, an effect reversed by ATGL re-expression [31].

Importantly, ATGL loss sensitized prostate cancer cells to alternative forms of cell death (i.e., non-apoptotic). Mechanistically, lipidomics analyses revealed that ATGL inhibition caused profound changes to cellular lipid pools that tilted the metabolic state towards one that is vulnerable to oxidative stress. Frigo also pointed to evidence from the SELECT trial, where antioxidant supplementation with selenium and vitamin E unexpectedly increased prostate cancer risk, supporting the concept that neutralizing oxidative stress may facilitate disease progression [32, 33].

Overall, disruption of lipid droplet homeostasis through ATGL inhibition creates a metabolic state that primes prostate cancer cells for death, revealing a potential therapeutic strategy. Interventions that target lipid droplet homeostasis may therefore provide a novel avenue for treating advanced prostate cancer.

3.6 | The Role of the Detoxification Enzyme in Modulating Cell Death in Prostate Cancer

Dr. Shiqin (Laura) Liu (UCLA) presented research on the role of GSTP1 (glutathione S-transferase Pi 1) in regulating cell death pathways in advanced prostate cancer, with an emphasis on treatment-resistant disease [34–45].

Liu discussed an approach to identify new drivers and targets for advanced-treatment resistant prostate cancer using proteomic analyses to compare hormone-sensitive and oncogene-driven treatment resistant prostate cancer models [46]. The study identified more than 100 proteins that were elevated in neuroendocrine prostate cancer (NEPC). Among these, GSTP1 emerged as one of the top upregulated and druggable candidates. GSTP1 is a detoxification enzyme that conjugates glutathione to reactive molecules, thereby maintaining redox balance

[47, 48]. While GSTP1 has been previously studied in other cancer types and is frequently hypermethylated in localized prostate cancer, the group discovered that it is highly expressed in advanced prostate cancer [49–53].

Functional studies further supported the oncogenic role of GSTP1 in advanced prostate cancer. CRISPR-mediated knockout or knockdown of GSTP1 significantly decreased tumor growth in xenografts, as evidenced by reduced tumor volume and weight. In metastatic models, where labeled cells were injected into mice, GSTP1 loss substantially decreased metastatic burden, particularly in the liver and bone—two key metastatic sites in NEPC. These findings demonstrated that GSTP1 promotes both tumor growth and metastatic progression in advanced prostate cancer.

Liu shared data on the therapeutic potential of targeting GSTP1. Treatment with GSTP1 inhibitors in preclinical models significantly delayed tumor growth, reducing the expression of non-apoptotic cell death mediators. These findings suggest that GSTP1 inhibition may represent a novel therapeutic strategy for patients with metastatic, treatment-resistant prostate cancer.

In conclusion, GSTP1 is a critical driver of prostate cancer progression and metastasis, in part through its role in regulation of non-apoptotic cell death, and that pharmacological targeting of GSTP1 could open new therapeutic avenues for advanced disease.

4 | Understanding and Overcoming Treatment Resistance in Prostate Cancer

Overcoming resistance and anticipating resistance mechanisms to proactively target them is key to promoting remission and regression of cancer. Approaches discussed in this session aimed either at further elucidating the biology of therapeutic resistance or developing novel therapeutics that might leverage features of castrate resistant prostate cancer (CRPC).

Tumor heterogeneity allows for selection of resistant clones. Anticipating which therapeutics will drive selection of resistant clones, and what therapies those clones may be more sensitive to, can allow for combinatorial strategies to suppress malignancy. Modelling this in the laboratory can be difficult, and in the patient is often an insurmountable feat. CIN may obscure genomic drivers and searching for point mutations may better identify mediators of therapeutic resistance. Dr. Rohit Bose (University of California, San Francisco; UCSF) and his team looked at genomic patient data and specifically identified tumors that had high mutation burden and low CIN [54]. They noted that tumors can be driven independently by mutational instability or by CIN, but carry genomic alterations in similar genes, regardless. They then sought to simulate tumor evolution in the laboratory environment. To do so, they utilized a mismatch repair (MMR) deficient model to develop stochastically emergent tumors (SETs) grown in vivo. Treatment of these tumors with AR signaling inhibitors (ARSIs) revealed ZFHX3 loss as an ARSI sensitizer.

Dr. Remi Adelaiye-Ogala (University at Buffalo) continued the discussion on the determinants of therapeutic resistance. She emphasized that treatment resistance is multifactorial and complex, reflecting the existence of complexity within the tumor itself. She shared research from her team studying enzalutamide-resistant CRPC, which identified a genomically defined subset that overexpresses EVI1, an oncogenic nuclear transcription factor encoded by MECOM, that could be a new therapeutic target and may benefit from combined treatment strategies.

A common feature of CRPC is its continual dependency on AR-related signaling pathways. Dr. Steven Balk (Beth Israel Deaconess Medical Center) discussed mechanisms driving maintenance of these pathways in CRPC despite exposure to ARSIs like enzalutamide. While resistance mutations to next-generation AR inhibitors occur, they are rare, indicating the presence of other mechanisms of resistance. Balk and team demonstrated that ARv7, a splice variant of AR lacking the ligand binding domain, can drive AR activity independent of full-length AR. While ARv7 is induced by enzalutamide, its transcriptional activity depends on further adaptions. He noted that CRPC which is adapted to enzalutamide exhibits a global increase in chromatin accessibility, particularly at ARv7 binding sites. The chromatin accessibility appears to be dependent on the Nuclear Factor I family of transcription factors [55].

Dr. Adegboyega Oyelere (Georgia Institute of Technology) discussed his group's efforts which utilize traditional chemistry and thoughtful approaches to targeting resistant prostate cancer. First, they endeavored to overcome resistance by exploiting the continued expression or overexpression of AR in CRPC for selective delivery of complementary anti-cancer pharmacophores. In this approach they designed a dual acting anti-androgen-histone deactylase inhibitor and additionally ferroptosis inducing anti-androgens [56]. These compounds showed anti-tumor efficacy and may have increased safety compared to linking AR binding molecules to traditional cytotoxic therapy. Oyelere additionally expanded on the rational development of AR inverse-agonists. He and his group developed AR binders that induce AR nuclear localization, collapse AR dependent chromatin clusters, and thus shut down transcription of AR target genes [57].

Dr. Stuart Conway (UCLA) discussed how his medicinal chemistry lab has developed ways to capitalize on inherent cancer properties to improve the therapeutic index of drugs. He noted that hypoxia is common among solid tumors and thus allows for the use of bio-responsive chemistry that reacts selectively under these conditions. Specifically, his team has developed prodrugs that can fragment in hypoxic environments to release active agents. He provided a specific example of reducing the off-target toxicity of proteolysis targeting chimeras (PROTACs) by utilizing an indolequinone bio-reductive group to mask the E3 ligase ligand. This group could be reduced in a hypoxic environment to release the active PROTAC. He demonstrated two examples of PROTACs that selectively induce degradation of BRD4 in hypoxia [58].

5 | CIN as a Driver of Metastasis and Treatment Resistance

This session examined CIN as a unifying driver of prostate cancer progression, metastatic spread, and therapeutic resistance. Presentations spanned molecular mechanisms, genomic and epigenomic interactions, immune consequences, and novel therapeutic strategies to exploit CIN-driven vulnerabilities.

These talks demonstrated that CIN is more than a background feature of advanced prostate cancer; it is a dynamic, multifactorial process that shapes disease biology, therapeutic vulnerability, and immune interactions. By dissecting CIN molecular underpinnings and linking them to actionable biomarkers, this session detailed concrete translational strategies to potentially both counteract CIN-driven resistance and harness CIN-associated pathways for patient benefit.

5.1 | CIN in Prostate Cancer: The Original CIN of Metastasis

Dr. Isla P. Garraway (UCLA) outlined the central role of CIN in prostate cancer progression, a foundational driver of metastasis and treatment resistance [59–61]. CIN encompasses large-scale genomic alterations, such as whole-chromosome gains/losses, focal amplifications/deletions, and complex rearrangements, that arise from mitotic errors and impaired DNA repair. These structural aberrations are enriched in advanced disease, particularly in treatment-resistant metastases, and contribute to tumor heterogeneity and clonal selection under therapeutic pressure [62].

Garraway placed these findings in the context of her work from the U.S. Department of Veterans Affairs (VA) Multi-OMICS Analysis Platform for Prostate Cancer (VA-MAPP). VA-MAPP, a PCF/VA-supported national biorepository, aggregates clinical, molecular, and imaging data from high-risk localized and metastatic prostate cancer patients across the VA system (> 50,000 samples from > 5000 patients). Diagnostic prostate needle biopsy remains a key entry point for molecular profiling in prostate cancer, and comparative transcriptomic analyses of high-grade localized (M0) and metastatic (M1) tumors, as well as mCRPC, identified mitotic and chromosomal segregation genes as leading-edge features distinguishing metastatic disease [63]. These findings pointed to a CIN gene expression signature (CIN70), previously validated in other malignancies [64], as a candidate biomarker in prostate cancer. She discussed insights from genomic sequencing datasets showing how CIN intersects with key molecular subtypes of prostate cancer, which further destabilize the genome and confer aggressive phenotypes [62, 63, 65]. Emerging single-cell analyses reveal that CIN can evolve dynamically within individual tumors, creating subclonal diversity that fuels resistance to systemic therapies such as ARSIs and chemotherapy.

Translational opportunities center on detecting CIN and monitoring its trajectory. Garraway described approaches using copy number alteration and/or aneuploidy RNA-based signatures, circulating tumor DNA profiling, and image-based aneuploidy assessment. These tools, integrated with other omics layers, may help stratify patients for intensified therapy or early intervention. Ultimately, understanding the "when" and "how" of CIN emergence could enable strategies to prevent metastatic seeding or to target CIN-high tumors with agents exploiting their genomic instability [66].

5.2 | Long Molecule Genomic Scars in DDR-Deficient Cancer: Biomarkers and Treatment Opportunities

Dr. Nadeem Riaz (Memorial Sloan Kettering Cancer Center; MSKCC) presented recent work leveraging long-read sequencing to capture large-scale genomic alterations, "genomic scars," that result from defects in homologous recombination (HR) DNA repair [67]. These scars include complex structural variants, templated insertions, and other features that are not readily resolved by short-read sequencing [68]. By applying these methods to tumors with *BRCA1/2* loss, his group identified subtype-specific structural rearrangement patterns, which in turn have predictive and prognostic implications.

For example, *BRCA2*-deficient tumors often display patterns of large deletions and duplications, while *BRCA1* loss is more frequently associated with complex rearrangements. These distinct signatures correlate with differences in therapeutic sensitivity, particularly to PARP inhibitors (PARPi) and platinum-based chemotherapy and may also inform radiotherapy response. Riaz emphasized that identifying HR-deficient (HRD) tumors through scar profiling can help refine patient selection for DNA damage response (DDR)-targeted therapies.

Therapeutically, Riaz discussed moving beyond synthetic lethality toward "synthetic cytotoxicity" or strategically combining HRD-directed therapies (e.g., PARPi) with DNA-damaging agents like ionizing radiation to achieve supra-additive tumor cell kill [69]. He presented examples in which HRD-positive models, particularly those with defined structural scar patterns, responded more effectively to PARPi + radiation combinations than to either therapy alone. The potential to layer immunotherapy onto these regimens, guided by the specific genomic scar profile, was also discussed, with early-stage studies exploring PARPi + ICB in select DDR-deficient settings [70, 71].

Finally, Riaz noted the potential to apply scar-based biomarkers beyond prostate cancer, as similar patterns are emerging in breast, ovarian, and pancreatic cancers, reinforcing the broad relevance of these approaches.

5.3 | CIN Drives Prostate Cancer Evolution via Stage-Dependent Epigenetic Dysregulation

Dr. Paul Boutros (UCLA) presented an integrated view of how CIN interacts with the epigenome, TME, and host factors to shape prostate cancer evolution. Drawing on a decade of research from his group and collaborators, he traced a progression of findings linking hypoxia to genomic instability, beginning with studies demonstrating that low-oxygen conditions synergize with CIN to promote aggressive phenotypes [72]. Hypoxia leaves a durable genomic "scar" and exerts strong proteomic effects [73], with weaker correlations observed across different cancer types, and notable associations with patient age and ancestry. In prostate cancer, these effects are detectable even in noninvasive biospecimens such as urine.

Recent work has illuminated a mechanistic connection between hypoxia, CIN, and RNA modification: hypoxia influences CIN through m6A-dependent proteome reshaping, altering protein translation and stability [74]. This occurs alongside widespread production of circular RNAs, some of which can give rise to peptides, potentially adding another layer of biological complexity [75]. The germline genome further shapes these processes, modulating how CIN-driven events manifest in individual patients [76].

To interrogate the interplay between CIN and epigenetic regulation, Boutros described analyses of over 3000 prostate methylomes spanning normal tissue, localized disease, and metastases. These studies reveal that interactions between DNA methylation patterns and copy-number alterations (CNAs) drive evolutionary trajectories, contributing to inter-patient heterogeneity in tumor behavior. Such methylation–CNA interactions may help explain why patients with similar genomic alteration profiles can have markedly different clinical courses. Importantly, some of these epigenetic states appear partially reversible, for example, exercise interventions have been shown to modify TME features in ways that could counteract CIN-related progression, raising the possibility of non-pharmacologic modulation of tumor evolution [77].

The emerging picture is one in which localized prostate cancer lethality arises not from a single mutational event, but from the convergence of clonal genomic drivers, CIN, hypoxia-induced proteomic shifts, germline-shaped epigenomic landscapes, and TME dynamics. This multilayered complexity, Boutros argued, underscores the need for integrative biomarker strategies that account for both genomic and epigenomic context, and for therapeutic approaches, potentially including lifestyle modifications, that address the full spectrum of CIN's biological consequences.

5.4 | Immune Sensing of DNA Damage for Cancer Prevention and Therapy

Dr. Gaorav Gupta (University of North Carolina at Chapel Hill) discussed how DNA damage serves as a double-edged sword in oncology, capable of eliciting both pro- and anti-tumor immune effects depending on timing, context, and underlying tumor biology [78]. Drawing largely from his group's work in breast cancer, he outlined parallels and implications for prostate and other solid tumors.

Gupta emphasized that the immune consequences of DNA damage are not uniform: acute, high-amplitude "burst" signals can activate potent antitumor immunity, while chronic, low-level ("smoldering") signaling may instead foster immune tolerance or suppression. In murine models, CRISPR-engineered tumors with p53 deficiency and MYC overexpression revealed that DNA damage–induced necroptosis, a form of programmed inflammatory cell death, can drive robust immunosurveillance [79, 80].

Combining radiation therapy (RT) with ICB such as anti-PD-1 in these models enhanced tumor clearance and immune infiltration, particularly when necroptosis was engaged. Mechanistic experiments showed that this synergy required a novel MRE11/ZBP1-dependent necroptosis pathway, which facilitates the transfer of double-stranded DNA and cGAS into macrophages, thereby priming innate immune activation. These findings suggest that necroptosis is not merely a byproduct of DNA damage, but an active conduit for amplifying immunogenicity in the TME [79].

Gupta also highlighted clinical-trial efforts in breast cancer aimed at optimizing RT–immunotherapy combinations, focusing on dose and schedule to maximize immunostimulatory potential without tipping into tolerance [81]. Translational endpoints, including tumor biopsies, circulating tumor DNA, and immune-cell profiling, are being leveraged to correlate necroptosis induction with therapeutic responses.

The overarching message was that DNA damage-induced necroptosis can be harnessed both for immunoprevention, blunting progression from early lesions, and for enhancing immunotherapy efficacy in established cancers [82]. Identifying when and how to trigger "burst"-type damage signaling, while avoiding maladaptive chronic activation, may allow clinicians to better exploit DDRs for durable cancer control.

5.5 | Overcoming Tumor Resistance to STING Agonists Through cGAS Inhibition

Dr. Samuel Bakhoum (Dartmouth Geisel School of Medicine) addressed why many tumors fail to respond durably to STING agonists [83] and outlined a mechanistic strategy to restore responsiveness by modulating the cGAS–STING axis. He began by situating cGAS expression and detection within published human tissue studies and antibody-validation controls, emphasizing the need for rigorous assay standards when interpreting cGAS staining in clinical specimens. He then revisited canonical features of CIN such as lagging chromosomes and micronuclei [84], as persistent sources of cytosolic DNA that chronically stimulate cGAS–STING signaling in cancer [61, 85].

A central hypothesis is that chronic STING activation can paradoxically blunt antitumor interferon outputs via adaptive mechanisms, including selective desensitization ("IFN-selective tachyphylaxis") and autophagy-dependent degradation of STING protein. While acute activation of STING can promote anti-tumor immunity via type I interferon signaling, chronic, persistent stimulation—as often seen in CIN-high tumors—can lead to adaptive desensitization of the pathway and reduced interferon output [85, 86]. This tolerance state, driven by tumor-intrinsic factors, may contribute to the limited efficacy observed in some clinical trials of STING agonists.

One therapeutic avenue of interrupting chronic cGAS–STING stimulation is to "reset" pathway responsiveness, creating a therapeutic window for re-engagement with a STING agonist. Importantly, tumor-intrinsic STING signaling would be a critical determinant of this benefit, underscoring the need for biomarker strategies to identify patients whose tumors exhibit features of chronic activation.

Finally, Bakhoum pointed to a biomarker strategy integrating staining patterns and pathway activity to identify patients with evidence of chronic activation who may be least likely to respond to immediate STING agonism but may benefit from this proposed "reset-then-re-challenge" approach. The overarching message reframes certain STING-refractory cancers as chronically activated yet functionally tolerized, and posits specific actions to break tolerance and re-enable productive innate immune signaling.

6 | Targeting the Metastatic Sites

Metastatic prostate cancer remains a significant clinical challenge, with most cancer-related deaths attributable to metastatic disease. The process of metastasis involves a

complex cascade of events where cancer cells disseminate from the primary site, survive in circulation, establish dormant micrometastases at distant sites, and eventually emerge as clinically detectable lesions. Understanding the molecular mechanisms that govern each phase of the metastatic cascade has become crucial for developing effective therapeutic interventions that can prevent or delay disease progression. Recent research has revealed that successful metastatic colonization requires cancer cells to overcome multiple biological barriers, including immune surveillance, metabolic stress, and hostile microenvironments, while maintaining the plasticity necessary to adapt to new tissue contexts. The bone microenvironment, being the predominant site of prostate cancer metastasis, presents unique challenges and opportunities for therapeutic targeting, as cancer cells must compete with normal hematopoietic processes while establishing their metastatic niche.

6.1 | Evolutionary Ecology of Metastatic Recurrence

Dr. Sarah Amend (Johns Hopkins University) discussed how cancer can be viewed as "a disease of uncontrolled proliferation by transformed cells subject to evolution by natural selection" [87]. This evolutionary ecology framework applies principles from evolutionary biology to understand how interactions shape cancer cell populations through selection and adaptation [87].

Research by Amend and colleagues revealed that cellular stress induces a transient adaptive state characterized by dramatically altered morphology, eventual repopulation capability, and progressive increases in DNA content following stress release. This phenomenon, observed across multiple cell lines, tumor types, and therapeutic stressors, represents a fundamental adaptive mechanism that cancer cells employ to survive treatment [88].

A particularly striking finding by Amend's group was the identification of cells with increased genomic content (IGC) as pioneering cancer cells that seed metastatic sites early in disease progression. The presence and number of IGC cells in primary prostate tumors predicts metastatic recurrence and CRPC development [89], while their presence in bone marrow disseminated tumor cells (DTCs) correlates with decreased progression-free survival [90].

Studies have demonstrated that genotoxic chemotherapy induces mitotic bypass and endocycling, leading to increased cellular motility and functional deformability. These endocycling cancer cells exhibit hyper-elastic properties that facilitate their role as pioneering metastatic cells. Remarkably, the majority (70%–80%) of bone marrow DTCs in pre-clinical mouse models are IGC cells, supporting their role as the primary drivers of metastatic seeding.

This evolutionary framework suggests that pioneering cancer cells function as ecosystem engineers, secreting high levels of senescence-associated secretory phenotype (SASP) factors and cytokines that prime the metastatic niche for future tumor growth. This hypothesis proposes that eliminating pioneering cancer cells could prevent ecosystem priming and alter metastatic recurrence patterns.

6.2 | Lineage Plasticity and Dormancy in Metastatic Progression

Lineage plasticity, defined as the ability of cells to change from one identity to another in response to microenvironmental signals or drug treatment, represents a fundamental mechanism underlying therapeutic resistance and metastatic progression [91]. This phenotypic change can occur through alterations at genomic, transcriptional, and epigenetic levels.

Dr. Michael Shen (Columbia University) discussed research on NSD2, which has been identified as a master regulator of prostate cancer metastasis, with NSD2 expression serving as a prognostic indicator in CRPC [92]. Targeting NSD2 can reverse plasticity in CRPC with neuroendocrine differentiation, leading to reversion of plasticity and activation of canonical AR signaling. This creates opportunities for combination therapy, as demonstrated by the synergy between NSD2 inhibitors and enzalutamide.

Central to understanding metastatic progression is the concept of cellular dormancy, a reversible quiescent state that is conceptually distinct from tumor mass dormancy. Cellular dormancy underlies the clinical phenomenon where metastases can emerge years or even decades after primary tumor treatment and apparent cure [93]. This dormant state represents a critical vulnerability in cancer progression, as dormant cells can maintain viability while remaining undetected by conventional imaging and resistant to therapies that target actively proliferating cells. The ability of cancer cells to transition between dormant and proliferative states through lineage plasticity mechanisms has profound implications for therapeutic strategy, suggesting that successful treatment of metastatic disease requires targeting both active tumor growth and dormant cell populations that serve as seeds for future recurrence.

6.3 | Epigenetic Regulation of Cancer Cell Dormancy

Dr. David Jarrard (University of Wisconsin) discussed how the epigenetic mechanisms underlying cancer cell dormancy, particularly in the context of androgen deprivation therapy (ADT), represent a critical area for therapeutic intervention. While endocrine therapy remains the backbone of prostate cancer treatment, the recognition of ADT-induced long-term complications and therapeutic resistance has highlighted the need for combination approaches that synergistically target multiple pathways. The TREATS (Targeting Responses to Early ADT in Tumors Synergistically) program demonstrated that ADT induces sensitivity to metabolic inhibitors such as 2-deoxyglucose and that combining ADT with metformin decreases androgen-dependent prostate cancer growth through mTOR inhibition [94, 95]. Clinical data showing improved overall survival in patients on metformin when starting ADT established the translational potential of targeting metabolic vulnerabilities created by ADT [96]. These findings set the stage for investigating histone-modifying enzymes (HMEs) as complementary targets that could enhance ADT efficacy through epigenetic modulation.

A central theme involves HMEs as cancer targets. These enzymes, which regulate post-translational modifications, represent an active area of drug development due to their increased expression in tumors and tissue-restricted nature. Research by

Jarrad and colleagues has revealed dysregulated acetylation and sirtuin enzyme activity in CRPC development, with particular emphasis on upregulated P300/CBP activity driven by SIRT2 downregulation [97]. This loss of SIRT2 occurs in approximately 66% of human CRPC cases and serves as a potential biomarker for therapeutic intervention, as demonstrated by increased acetyl-p300 levels in circulating tumor cells (CTCs) from CRPC patients [98].

More recently, EZH1 has been identified as a key player in the early response to ADT. EZH1 and EZH2 are both PRC2 subunits but serve distinct functions: EZH1 is highly expressed in differentiated or quiescent cells and functions in stem cell maintenance and dormancy with weaker H3K27me3 methyltransferase activity, while EZH2 is highly expressed in proliferating cells and acts as a stronger H3K27me3 methyltransferase that frequently functions as an oncogene [99]. EZH1 expression increases early after ADT and accumulates K27 methylation, potentially maintaining cancer stem cell survival in a dormant state. The clinical relevance is demonstrated by EZH1 protein levels in ADT-treated specimens predicting PSA failure. Valemetostat, a dual EZH1/EZH2 inhibitor approved for refractory T-cell leukemia/lymphoma, showed synergistic improvement when combined with ADT. This dual targeting approach addresses both the dormancy-maintaining function of EZH1 and the proliferative drive of EZH2, suggesting that combination therapy targeting both pathways may prevent tumor relapse by eliminating cancer stem cells in dormancy.

6.4 | The Metastatic Niche: Bone Microenvironment and Tumor-Host Interactions

Dr. Yibing Kan (Princeton University) discussed how the bone microenvironment represents the most common site of prostate cancer metastasis, affecting most patients with advanced disease. Understanding the cellular and molecular components of this metastatic niche has been advanced by innovative techniques, including metastatic niche labeling with membrane-penetrating secreted mCherry, which enables identification and characterization of the cellular components within complex metastatic tissues [100].

A key discovery was the identification of a unique macrophage population in the bone metastatic niche displaying a heme metabolism signature. These iron-recycling macrophages, termed iMacs (Iron-recycling EBI Macrophages), are derived from erythroblastic islands and play a crucial role in both tumor growth and cancer-associated anemia. The re-routing of iMacs from erythroblastic islands to tumors inhibits erythropoiesis, providing a mechanistic explanation for the anemia commonly observed in patients with bone metastases.

Research by Kang's group and others revealed that tumor cells exposed to hypoxia in the iron-rich bone metastatic environment undergo adaptive changes, mimicking erythroblasts in response to hypoxic conditions [101, 102]. This plasticity represents another layer of adaptation that cancer cells employ to survive and thrive in the challenging bone microenvironment. This study provides both mechanistic insights into cancer-associated anemia and identifies potential therapeutic targets within the bone metastatic niche.

6.5 | Therapeutic Implications and Future Directions

The convergence of epigenetic regulation, lineage plasticity, microenvironmental interactions, and evolutionary adaptation reveals that successful targeting of metastatic sites requires abandoning single-agent approaches in favor of combination strategies. The identification of EZH1 as a dormancy regulator, NSD2 as a plasticity controller, and iron-recycling macrophages as niche facilitators demonstrates that metastatic progression depends on coordinated multi-cellular processes. This understanding necessitates therapeutic strategies that simultaneously disrupt dormancy maintenance, prevent adaptive plasticity, and remodel the metastatic microenvironment. The evolutionary framework further emphasizes that cancer's adaptive capacity must be anticipated and countered, suggesting that future therapies should exploit rather than simply challenge cancer's evolutionary constraints. These insights fundamentally shift the therapeutic paradigm from targeting static cancer cell populations to disrupting dynamic, adaptive metastatic ecosystems.

7 | Immunotherapy Sensitizers

In the last two decades, we have seen an explosion of immunotherapy strategies for treatment of the most aggressive types of cancer, from vaccines, to ICB, T cell engagers (TCE), and cellular immunotherapies (like T-cell receptor [TCR]-based T cell, chimeric antigen receptor [CAR]-based T cell, and tumor-infiltrating lymphocyte [TIL] therapies) [103]. Melanoma, hematological malignancies like lymphoma and leukemia, kidney cancers, and other cancer types have benefited from the advances in our understanding of how the immune system “sees” and eliminates cancer and even regulates the therapeutic responses of other modalities including chemotherapy, radiation, and targeted therapies. Prostate cancer was the first solid cancer with an FDA-approved immunotherapy, a dendritic cell-based vaccine called Sipuleucel-T, which showed modest but promising therapeutic potential for immunotherapy to target this disease [104, 105]. Unfortunately, owing in part to its low mutational burden and immunologically “cold” TME, prostate cancer has not benefited from immunotherapies including ICB [106], and will likely require novel combinatorial therapies to improve outcomes [107]. We are at the early stages of applying these and other immunotherapies to prostate cancer, with some successes and many revealed challenges, including with cellular immunotherapies [108]. There is still so much to be learned about advanced prostate cancer disease progression to best apply these immunotherapies for robust and durable responses.

7.1 | What Do T Cells “See” Inside the Tumor?

Tumor mutational burden is linked, albeit imperfectly, with therapeutic responses to ICB [109]. A classic example of this is in melanoma, which has a high mutational burden—primarily resulting from ultraviolet (UV) radiation-induced DNA damage—leading to the formation of neoantigens that enhance T cell activation [110]. These neoantigens can stimulate robust endogenous immunity and underlie responses to ICB. Interrogating the T cell landscape has been critical in understanding predictors of effective immunotherapy for melanoma and may provide insights into other cancer types, like prostate cancer.

Dr. Cristina Puig-Saus (UCLA) discussed a study in which analysis of blood and tumors of melanoma patients treated with anti-PD-1 ICB using whole-exome sequencing and RNA-sequencing defined non-synonymous mutations and putative neoantigens, shedding light on successful anti-tumor T cell generation in patient responders that are lacking in non-responders [111]. Beyond higher mutational loads in responding patients in line with previous literature, T cell responses were found to be polyclonal and reactive to a limited set of immunodominant mutations in responders versus non-responders. Moreover, a good concordance with neoantigen-specific T cells from blood and tumors suggest that monitoring these T cells in blood might serve as a minimally invasive source for therapeutic development of TCR-based T cell therapies.

Identifying the "right" neoantigen and how best to monitor T cell responses in patients have challenged the field in terms of predicting responses to immunotherapy and for the development of T cell therapies. Whether these therapies are tailored towards high mutational burden tumor types is also understudied. Dr. Stephen Schoenberger (La Jolla Institute) presented recent platform optimization to test neoantigen-specific T cells in low tumor mutational burden tumor types, which suggested that this type of work may span all tumor types [112]. The Identify-Prioritize-Validate (IPV) platform has enabled rapid prioritization of neoantigen-specific TCRs from blood and may hold promise for systematically validating clinically actionable mutations and the TCRs that recognize them, further enabling cancer vaccine and TCR-based T cell therapy development.

7.2 | What Constitutes a Productive T Cell-Immune Response in Prostate Cancer?

The interplay between the tumor and lymphoid tissue is critical for a productive anti-tumor T cell response. Typically, T cells are trained in the lymphoid tissue, particularly in tumor-draining lymph nodes, where professional antigen presenting cells like dendritic cells present tumor antigens to T cells that migrate through the blood to the tumor, differentiate to effector T cells and kill tumor cells. The state of those T cells, and the microenvironment they encounter once inside the tumor, are critical determinants of the anti-tumor immune response.

Dr. Haydn Kissick (Emory University) presented recent studies which found that stem-like CD4 T cells that reside in the tumor-draining lymph node limit effector CD8 T cell responses to the tumor ("restricted state"), through regulatory T cell (Treg) activity [113]. Depletion of these Tregs allowed Tbet+ CD4 T cells to differentiate into IFNy-producing Th1 cells that enable PD1+ TCF1+ CD8 T cell differentiation in the lymph node ("active state"), enhancing their functionality and response to ICB. Forced Tbet expression alone in CD4 T cells recapitulated this phenotype in mouse tumor models, and in agreement, expression of the Th1 transcription factor, Tbet, predicted response to ICB in patients. While these stem-like T cells are abundant in the tumor-draining lymph nodes in patients, the rare stem-like T cell population in some cancers like prostate cancer limit their therapeutic potential. Many questions remain, including (1) how to install the T cell machinery (i.e., tertiary lymphoid structures) [114] to generate productive anti-tumor T cell immunity inside prostate cancers, (2) how to bolster stem-like T cells that give rise to effector cells inside tumors, and (3) how do some TMEs prevent this complex machinery that drives anti-tumor immunity and response to ICB.

7.3 | What Are the Barriers to Effective Immunotherapies in Prostate Cancer?

ICB therapy is not alone in its challenges in treating prostate cancer, with adoptive T cell therapies and other immunotherapies also facing difficulties in clinical translation. It is clear now that the immune system in prostate cancer patients warrants further interrogation before effectively applying immunotherapy treatments. The unique TME in prostate cancer, rich in myeloid cell populations with varying pro-tumor functionalities, is a major culprit in the so-called "immunologically cold" disease. Single-cell transcriptomics and functional studies have further supported this phenomenon.

Dr. Lawrence Fong (Fred Hutchinson Cancer Center) presented a recent study from his group, in which single-cell profiling was performed on tumors from patients with localized (ADT-naïve), ADT treated hormone-sensitive, and ADT-treated castration-resistant disease [115]. Of the vast heterogeneity of myeloid cell subsets found in these tumors, a subpopulation of $SPP1^{hi}$ tumor-associated macrophages (TAMs) emerged as a dominant fraction of cells, with increasing numbers during disease progression to castration-resistance. These cells correlated with reduced numbers of antigen presenting dendritic cells as well as increased numbers of exhausted CD8 T cell subsets. Leveraging mouse models of castration resistance disease, $SPP1^{hi}$ TAMs also showed high percentages following progression and were functionally immunosuppressive, driving resistance to ICB. Importantly, these cells correlated with high adenosine pathway (i.e., A2AR) activation, shown to shift away from cytotoxic T cells towards immune tolerance phenotypes [116]. Based on preclinical studies showing that A2AR blockade restored T cells inside prostate tumors and response to ICB, a clinical trial was recently initiated combining the small molecule A2AR inhibitor, Ciforadenant, with ICB in patients with CRPC. Early data from the trial show promising increased responses to ICB from historical data, and a potential clinical path forward using this combination to improve responses to immunotherapy in prostate cancer.

Immunosuppressive TAMs have been reported extensively in prostate cancer to drive tumor progression and resistance to therapy including ICB. In parallel to the adenosine pathway study above, Dr. Sangeeta Goswami (University of Texas MD Anderson Cancer Center) discussed recent data implicating a key epigenetic regulator, EZH2, in regulating disease progression and the tumor-immune microenvironment. Earlier studies by Goswami and colleagues found that EZH2 inhibition increases CD8 T cells inside prostate tumors and attenuates Tregs, with EZH2 inhibition improving responses to anti-CTLA4 ICB in mouse models [117]. In patients treated with this combination, TAMs appear as a critical regulator of responses, enriched in patients who lack response. These studies highlight the importance of reversing myeloid-mediated immunosuppressive to reactive T cell immunity and enhance responses to immunotherapy.

7.4 | Immunotherapy on the Horizon for Prostate Cancer

Beyond depleting heterogeneous myeloid/macrophage subsets in tumors or leveraging their plasticity to shift pro-inflammatory/anti-tumor myeloid cell populations away from their immunosuppressive phenotypes, recent studies have expanded the engineering of T cells, including CAR-engineered T cells, to engineering myeloid cells to target tumors. CAR-engineered macrophages have been developed by various research groups including with industry involvement, with varying results to date. These therapeutic cells mediate anti-tumor immunity via phagocytosis, cytokine production, and remodeling of the TME for increased antigen presentation. The first of its kind phase 1 trial was recently published with HER2-CAR macrophages for patients with HER2+ advanced solid tumors, demonstrating safety, tolerability, and correlatives including trafficking of CAR-macrophages to tumors, beneficial changes in the TME, and expansion of CD8 T cells inside tumors [118]. However, limited therapeutic activity was observed, highlighting a need for improvements in this cell therapy platform for meaningful clinical responses. Further characterization of the $SPP1^{hi}$ TAMs driving immunosuppressive tumors showed that these cells highly express TREM2, offering a new target for CAR-macrophage development. Preliminary work presented by Dr. Jennifer Guerriero (Brigham and Women's Hospital; Harvard Medical School) supports the use of TREM2-CAR monocyte therapy to replace immunosuppressive macrophages in the TME, offering a new way to shift the myeloid cell landscape in tumors, which can be combined with ICB and other immunotherapies to target solid cancers including prostate cancer.

In summary, the hostile and immunosuppressive TME in prostate cancer must be interrogated and overcome to facilitate immunotherapies that effectively target this disease. Next-generation immunotherapy approaches including combinatorial therapies to elicit ICB responses are being evaluated, as well as CAR-engineered effector cells, including T cells and myeloid cells, which are an active area of pursuit. While challenges exist, technological and bioengineering advances in recent years are spawning new promise for redirecting anti-tumor immunity in the fight against advanced prostate cancer.

8 | Optimizing Therapy Delivery and Biomedical Engineering

8.1 | Engineered Nanobodies to Direct and Visualize Immunity

Dr. Novalia Pishesha (Boston Children's Hospital) discussed her group's work on developing nanobody-based platforms to precisely control and monitor immune responses. Nanobodies are small, single-domain fragments of antibodies derived from alpacas. They are structurally simpler than conventional antibodies, which makes them easier to produce, engineer, and adapt for therapeutic or diagnostic applications.

Nanobody-antigen-drug conjugates can also be used to induce antigen-specific immune tolerance. This strategy is designed to address autoimmune diseases such as multiple sclerosis and rheumatoid arthritis, where the immune system mistakenly attacks the body's own tissues. The approach involves engineering nanobodies that bind to major histocompatibility complex Class II molecules on antigen-presenting cells [119, 120]. These conjugates are linked to disease-relevant peptides, such as myelin peptides in the case of multiple sclerosis or collagen peptides in the case of rheumatoid arthritis, along with immunosuppressive agents. Once delivered to antigen-presenting cells, the conjugates reprogram these cells into a tolerogenic state [120]. This process enables the immune system to selectively eliminate autoreactive T cells or convert them into suppressive phenotypes, while leaving protective immunity intact. Pishesha presented data demonstrating that in mouse models of multiple sclerosis, a single injection of these nanobody conjugates reversed paralysis within 24 h and maintained recovery for over one hundred days. In models of rheumatoid arthritis, the same technology successfully halted the progression of joint inflammation.

Pishesha also shared work on developing nanobody-based imaging agents that allow non-invasive monitoring of immune responses. By creating nanobodies that specifically recognize disease-related T cell receptors and attaching them to imaging probes, the team was able to visualize the migration of autoreactive T cells within living animals using positron emission tomography (PET) imaging. This method provides a powerful way to track immune cell behavior during disease and treatment.

These data demonstrate the versatility of nanobody platforms for both therapeutic intervention and diagnostic imaging. While the current focus is on autoimmune diseases, the same strategies may eventually be applied to cancer and other immune-related disorders, underscoring a broad potential for clinical translation.

8.2 | Chemical Strategies to Expand the Therapeutic Window for Targeted Radiotherapy

Dr. Michael Evans (UCSF) shared his work on advancing radiopharmaceuticals from imaging applications toward therapeutic use. He provided an overview on the major resurgence around targeted radiotherapy, with growing numbers of regulatory approvals, increased academic output, and significant industry investment. Historically, the field prioritized low molecular weight radioligands such as peptides and small molecules, which clear quickly from circulation and therefore have lower toxicity [121]. However, this rapid clearance also limits tumor retention of radiation, which reduces therapeutic impact [121]. Current therapies provide survival benefits but are not consistently curative, despite that ionizing radiation has very few absolute resistance mechanisms [122].

To address these challenges, Evans' lab has focused on developing catalytically activated membrane-binding peptides. These small "restricted interaction peptides" circulate in an inactive form but are triggered by tumor-associated proteases to undergo structural changes, anchoring radioactive payloads within tumor membranes [123, 124]. This approach combines safety—through rapid systemic clearance—with efficacy, by prolonging radiation persistence in tumors. Preclinical studies have shown that this method improves tumor uptake and retention compared with traditional receptor-targeted agents. Early clinical

investigations with peptide-based imaging probes in prostate cancer patients confirmed tumor localization and persistence in vivo. Therapeutic versions carrying copper-67 significantly delayed tumor growth in animal models at doses ineffective with conventional approaches.

These findings establish an adaptable platform with broad potential across cancer types. By utilizing protease activity and membrane anchoring, Evans seeks to expand the range of actionable targets for radiopharmaceutical therapy and advance the field toward more effective, durable treatments.

8.3 | Hope, Hype, and Cancer Biology: Clinical Utility and Liquid Biopsies

Dr. Joshua Lang (University of Wisconsin) discussed the development of a microfluidic technology that uses surface tension and magnetic particles to capture and purify rare CTCs from blood. This method eliminates traditional centrifugation and washing steps, to improve recovery of rare events while achieving high purity. The platform enables the isolation of CTCs with purities greater than fifty percent, often exceeding what can be achieved with tissue biopsies, and allows for unbiased downstream molecular analysis.

Lang also shared a clinical study of 117 patients with advanced prostate cancer with more than 200 longitudinal samples collected for transcriptomic analysis [125]. The team identified four distinct subgroups of CTCs: luminal A-like, luminal B-like, low-proliferation, and small-cell NEPC [125]. These subgroups reflected biologically and clinically meaningful differences [125]. Patients with neuroendocrine or luminal B-like features had markedly shorter survival times compared with those in the luminal A-like or low-proliferation categories [125]. Importantly, the luminal B-like subgroup emerged as an independent prognostic factor across multiple clinical datasets [125].

Genomic analysis supported these classifications, demonstrating distinct patterns of alterations in tumor suppressor genes such as *RB1*, *PTEN*, and *TP53*. Integration of CTC phenotypes with genomic profiles revealed that patients with high-risk signatures experienced significantly worse outcomes, even in the absence of obvious genomic drivers. These findings suggest that CTC analysis provides clinically relevant prognostic information beyond conventional markers such as PSA.

Lang concluded with defining the clinical niche that may benefit from these CTC classifiers and how to further integrate them with circulating tumor DNA and immune profiling. The goal is to define clinically actionable biomarkers that not only stratify patients for therapy but also uncover new therapeutic targets.

8.4 | Isolating Rare Tumor Cells, Cell Clusters, and Extracellular Vesicles Using Magnetic Levitation

Dr. Gozde Durmus (Stanford University) described the development of a magnetic levitation platform for isolating and analyzing rare cells and extracellular vesicles [126]. Inspired by early demonstrations of magnetic levitation of biological material, Durmus adapted the concept to create a simple, low-cost, and portable system capable of levitating individual cells in a paramagnetic medium between opposing magnets. The position at which a cell equilibrates reflects its density with high sensitivity, enabling label-free separation and characterization.

Application of the technology to blood demonstrated that normal red blood cells, white blood cells, and cancer cells each display distinct levitation profiles [126]. Because cancer cells are generally less dense than healthy blood cells, they can be distinguished and enriched without the need for molecular markers. By integrating imaging with the levitation platform, Durmus was able to sort not only single CTCs but also clusters, and to classify them into epithelial, mesenchymal, or hybrid states [126]. This magnetic levitation approach avoids potential bias introduced by antibody-based capture methods and has proven particularly useful in cases such as renal cell carcinoma, where conventional markers fail to detect CTCs reliably [126].

Beyond rare cell isolation, Durmus extended the magnetic levitation platform to extracellular vesicles [127]. Recognizing the challenge of directly levitating nanometer-scale vesicles, a strategy was devised in which vesicles are bound to engineered beads with distinct fluorescent labels [127]. The levitation device then sorts the beads, indirectly separating vesicle subtypes [127]. This method achieves yields comparable to ultracentrifugation while preserving structural integrity and requiring only microliter-scale plasma volumes [127].

The platform is being advanced toward clinical applications, including monitoring treatment response through changes in CTC subtypes. A start-up company has been established, LevitasBio, to distribute the levitation technology to other researchers for cancer and extracellular vesicle studies, with the goal of broadening its impact in both basic science and translational medicine.

8.5 | Nanoparticle-Mediated Delivery of Gene Editing Reagents Configured for Disruption of Oncogenic Drivers

Dr. Steven Jonas (UCLA) discussed nanotechnology-enabled approaches to advance precision medicine with a focus on three areas: technologies for diagnostics, tools for data interpretation and discovery, and methods to act upon precision medicine data by enabling gene and cell therapy approaches.

Jonas shared research on the design of lipid nanoparticle (LNP) delivery systems for genome editing applications [128]. Inspired by the family of a child with a high-risk alveolar rhabdomyosarcoma driven by a fusion oncogene who asked whether genome editing tools could be used to directly disrupt the genetic driver of her disease, Jonas and team began developing CRISPR-based reagents packaged into LNP delivery vehicles to silence oncogenes at the DNA or RNA level. These LNPs combine ionizable lipids, helper lipids, sterols, and polyethylene glycol-modified components to ensure stability, circulation, and effective endosomal escape [128]. Using microfluidic mixing platforms, the team systematically screened formulations for optimal delivery efficiency. Early studies have demonstrated robust delivery of genome-editing reagents, including knockdown of specific oncogenic targets like c-Myc in prostate cancer cells, with functional consequences observed in cell assays that measure invasion, colony formation, and growth.

Future work aims to enhance specificity by decorating nanoparticles with targeting ligands using click chemistry, enabling selective delivery to cancer cells while sparing normal tissue. Jonas emphasized the translational potential of this approach, noting the precedent of applying LNPs in widely used messenger RNA vaccines. These delivery strategies could form the foundation for next-generation therapies in prostate cancer and other malignancies, while also underscoring the importance of patient-inspired innovation in guiding new research directions.

8.6 | Advancing Prostate Cancer Research Through Dual Innovations: 3D Biofabricated Models and Trop2-Expressing Extracellular Vesicles for Liquid Biopsy

Dr. Utkan Demirci (Stanford University) presented recent work the utility of extracellular vesicles as diagnostic and monitoring tools for cancer. Unlike CTCs or circulating tumor DNA, extracellular vesicles are secreted very early in tumor development, sometimes from a single transformed cell. Such early release makes extracellular vesicles particularly promising for early cancer detection. Existing methods to isolate extracellular vesicles include ultracentrifugation or antibody-based magnetic capture which may pose challenges due to heterogeneity and low yield [129, 130].

To address these issues, Demirci and team developed a size-based separation technology that enables high-yield capture of extracellular vesicles from very small plasma volumes, as low as 50 μL [131]. Compared with standard commercial tools, the method achieved 6–10-fold higher yields of RNA and protein from prostate cancer plasma samples, making it suitable for downstream sequencing and molecular analysis [131]. Importantly, the platform allows fractionation of vesicles into different size ranges, which can reveal biologically meaningful differences in cargo and function [131]. Proteomic studies across prostate cancer cell lines demonstrated distinct protein distributions in vesicles of different sizes, suggesting links between vesicle biogenesis, tumor subtype, and metastatic potential [131].

Demirci also described research focused on creating three-dimensional hydrogel-based optical fibers capable of both culturing prostate cancer cells and sensing molecular changes in real time [132, 133]. By integrating nanoparticles and optical readouts, these "living fibers" mimic tubular tissue structures, allow continuous monitoring of vesicle secretion, and reveal how tumor models respond to drug treatment without destroying the culture [132, 133]. Early experiments demonstrated that changes in light transmission correlate with drug-induced cell viability and resistance patterns [132, 133].

Finally, Demirci shared efforts to apply their vesicle isolation platform to prostate cancer patient plasma samples. Using an assay for Trop-2, a marker previously linked to aggressive disease, they identified cases where conventional measures such as PSA underestimated risk. Elevated Trop-2 levels on vesicles flagged patients with clinically significant prostate cancer despite low standard scores.

Demirci hopes to make these vesicle isolation and analysis tools widely accessible to both clinical and research laboratories, enabling automated, unbiased, and scalable approaches for early detection and disease monitoring [134].

9 | Conclusion

The attendees at the 2025 CHPCA Meeting asked over 415 questions during the 39 presentations. The purpose of the CHPCA Meeting is to drive extensive discussion and accelerate new research and collaboration efforts that will ultimately result in treatments and strategies that end death and suffering from prostate cancer; we hope that summarizing the presentations in this meeting report will support this goal.

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Disclosure

Generative AI tools (ChatGPT) were used to assist in preparation of parts of this manuscript. All content was carefully reviewed and edited by the authors and referenced speakers, to ensure accuracy and integrity. For more information on the extent and nature of AI usage, please contact the authors.

Conflicts of Interest

R.R.M. has held consulting or advisory roles with Ambrx, Arcus, AstraZeneca, Aveo, Bayer, Blue Earth Diagnostics, Boundless Bio, Bristol Myers Squibb, Calithera, Caris, Dendreon, Daiichi Sankyo, Eli Lilly, Eisai, Exelixis, Janssen, Merck, Myovant, Neomorph, Nimbus, Novartis, Pfizer, Sanofi, SeaGen, Sorrento Therapeutics, Telix, and Tempus. S.J.P. is a scientific advisor and/or receives royalties from Imugene Ltd, Adicet Bio, Port Therapeutics, and Celularity. A.E.R. has consulted and received personal fees from Astellas, AstraZeneca, Bayer, Blue Earth, BillionToOne, Boston Scientific, Janssen, Lantheus, Pfizer and Veracyte. P.T.T. has consulted and has received personal fees from NATSAR Pharmaceuticals, Johnson and Johnson, Regeneron, Bayer Healthcare, Lantheus, Novartis, Pfzier and RefleXion Medical Inc. PTT also has a patent for 9114158 issued to Natsar Pharmaceuticals with royalties paid from Natsar Pharmaceuticals. None of the other authors declare any potential conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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