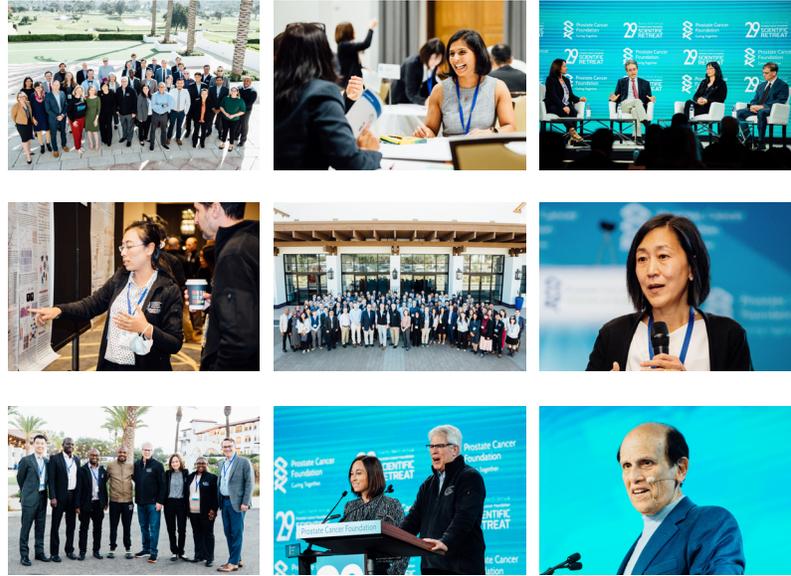


STATE *of the* SCIENCE REPORT



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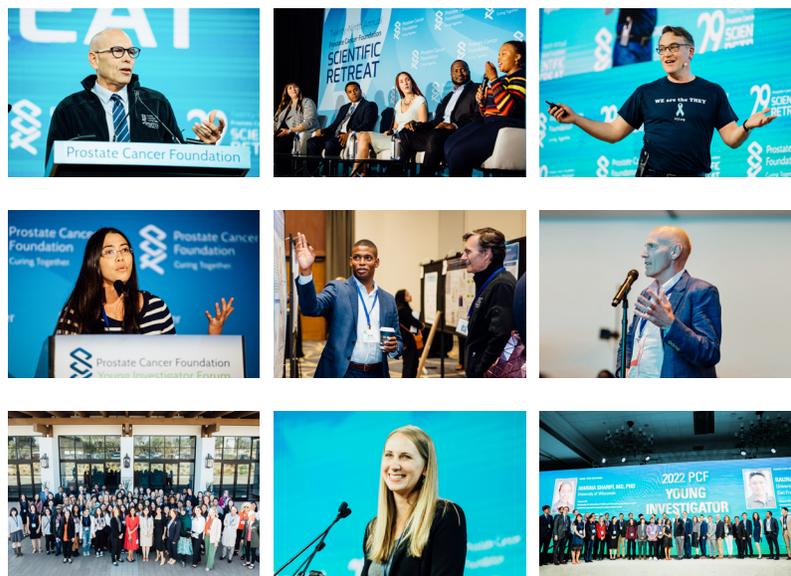
Twenty-Ninth Annual
Prostate Cancer Foundation
**SCIENTIFIC
RETREAT**

Highlights from
the 29th Annual
PCF Scientific Retreat
October 27-29, 2022

Provided compliments of the
Prostate Cancer Foundation



Prostate Cancer
Foundation
Curing Together.



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Introduction

The 29th Annual Prostate Cancer Foundation (PCF) Scientific Retreat was held on October 27 – 29, at the Omni La Costa Resort in Carlsbad, CA. This annual event is organized by PCF to bring together leading scientists and clinicians working in the field of prostate cancer research as well as other disciplines that may provide critical insights that could be used to forward prostate cancer research. The Retreat provides a platform for attendees to share their latest research findings, exchange ideas, and discuss new directions in the field.

The PCF Scientific Retreat typically lasts for two and a half days and includes keynote lectures, panel discussions, poster sessions, and other interactive events. Attendees include prostate cancer researchers from academia, industry, and government, as well as patient advocates and representatives from non-profit organizations.

The Retreat is considered one of the premier events in the field of prostate cancer research and has played a key role in advancing scientific knowledge and accelerating the development of new treatments for prostate cancer.

The 29th Annual PCF Scientific Retreat featured the following:

- 49 presentations and panels in the Plenary Session.
- 182 poster presentations.
- 25 different scientific disciplines related to prostate cancer research presented and discussed.
- 47% of speakers presented at a PCF Scientific Retreat for the first time.
- 1,110 individuals from 30 countries registered for the Retreat (648 in-person attendees + 462 virtual registrants), including 445 PhD, ScD, or DSc, 280 MD, MBBS, or DO, 144 MD/PhD, 4 JD, 40 PharmD, 1 DDS, 1 DSc/DMD, 1 DVM/PhD, 1 MD/PharmD, 1 PhD/DDS, 2 PhD/MBA, 1 PhD/PharmD, 2 MD/MBA, 1 MD/MBA/MS, 7 MD/MS, and 74 with Master's degrees (including MS, MBA, MBA/MSc), and 4 RN.
- Retreat registrants included 693 academic researchers or health care professionals, 318 biopharmaceutical industry professionals, 24 patients, survivors, caregivers, advocates or other interested members of the general public, and 31 undergraduate and high school students.
- 153 academic institutions, 62 biopharmaceutical companies, and 16 medical research foundations.
- NIH, NCI, Dept. of Defense, and Veterans Affairs research leaders from over 16 organizations.
- Attendance by 227 PCF Young Investigators.
- Attendance by 19 PCF Board of Director members and major donors.
- The 7th Annual PCF Women in Science Forum was held with over 308 attendees.

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 close to \$1 billion in support of cutting-edge research by more than 2,250 research projects at 245 leading cancer centers in 28 countries around the world. 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 creating a global public square for prostate cancer, in service to our mission of ending death and suffering from the disease. Learn more at pcf.org.

We thank the sponsors of the Retreat for their generous support: Janssen Oncology, Advanced Accelerator Applications, Amgen, Bayer, Daiichi Sankyo, Lantheus, Pfizer Oncology, Regeneron, Sanofi, AstraZeneca, Clovis Oncology, Astellas, Bristol-Meyers Squibb, Foundation Medicine, Genentech, Illumina, Merck, Exact Sciences, AdvanCell, Arvinas, Dendreon, Myovant Sciences, BAMF Health, ESSA Pharma, Sun Pharma, Harpoon Therapeutics, MacroGenics, XCellBio, and Oncternal Therapeutics.

PCF prepared the 2022 State of Science Report to summarize the scientific presentations from the Retreat in a manner accessible to the general public. We hope that global dissemination of this knowledge will aid in advancing understandings of current prostate cancer research, encourage discourse and the exchange of new ideas and information, inspire new research, and stimulate increased support for scientific research. Any questions about this report can be directed to Dr. Andrea Miyahira at amiyahira@pcf.org.

All of the presentations, panels, and discussions from the 29th Annual PCF Scientific Retreat, the PCF Women in Science Forum, and the PCF Young Investigator Forum, can be viewed here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/>.

Yours sincerely,



A handwritten signature in black ink, appearing to read 'C. Ryan'.

Charles J. Ryan, MD
President & CEO



A handwritten signature in black ink, appearing to read 'Howard R. Soule'.

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



A handwritten signature in black ink, appearing to read 'Andrea Miyahira'.

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

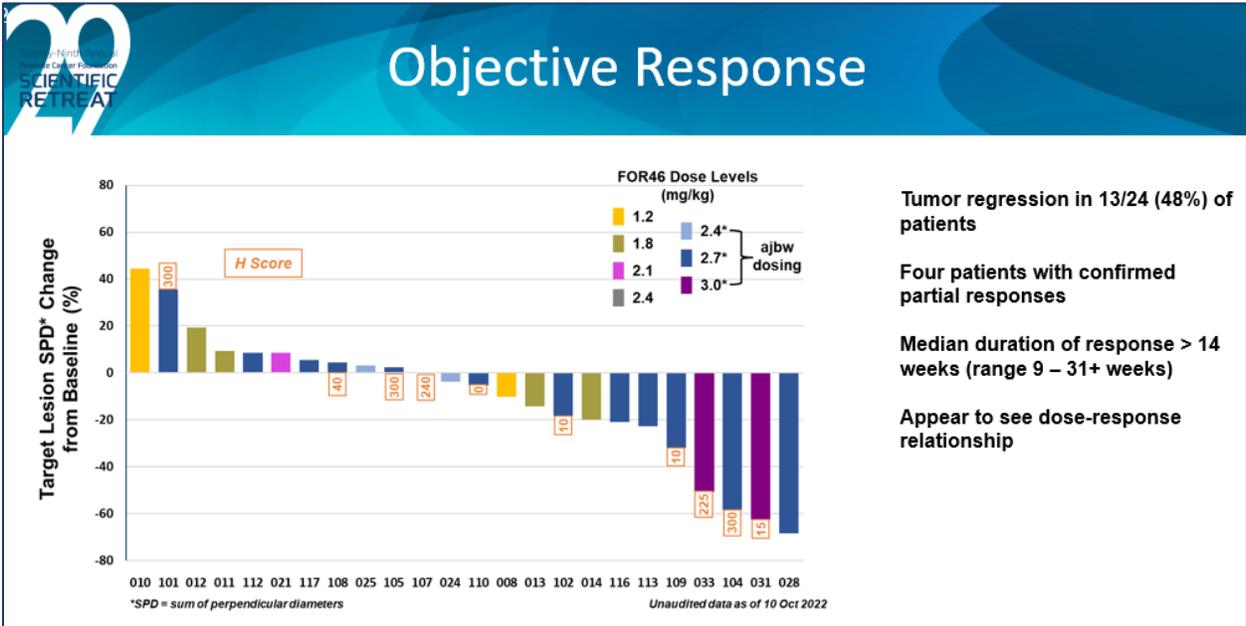
Session 1: Novel Clinical Trial Updates

Targeting a Tumor-Specific CD46 Epitope in Metastatic Castration Resistant Prostate Cancer

Rahul Aggarwal, MD
University of California, San Francisco

- There are currently no curative treatments for patients with metastatic castration-resistant prostate cancer (mCRPC). New treatments and new treatment targets are urgently needed.
- Dr. Rahul Aggarwal discussed the development of a novel therapy that targets CD46.
- CD46 is a normal protein expressed on many cell types, which acts to negatively regulate the innate immune system and is a part of a protein complex mediating cytoskeletal dynamics, invasion, and metastasis.
- Dr. Bin Liu (University of California, San Francisco) discovered a unique conformation of CD46 that is present at high levels on prostate cancer cells across the disease spectrum.
- Dr. Liu and colleagues developed an antibody that can specifically target this unique, cancer-specific conformation of CD46. This antibody does not interfere with the normal functions of CD46 and does not bind to CD46 on normal cells (except placental tissues and normal prostate cells).
- The CD46-targeting antibody was developed into an antibody-drug conjugate (ADC) named “FOR46”, a type of drug consisting of a tumor-targeting antibody attached to MMAE chemotherapy molecules. Each antibody can carry up to 3-4 MMAE molecules. After binding to CD46 on tumor cells, the ADC works by entering the cell and delivering the chemotherapy to kill the cell.
- Preclinical studies demonstrated promising activity for FOR46 against prostate cancer cell lines and animal models.
- Intriguingly, in preclinical studies, treatment of prostate cancer cells with androgen-targeted therapies increased the levels of CD46, which increased their sensitivity to FOR46. This suggests that improved efficacy may be achieved by combining androgen-targeted therapies with FOR46.
- Dr. Aggarwal led a phase 1 clinical trial to test the safety, establish an optimal dose of FOR46, and evaluate preliminary efficacy, in patients with mCRPC. Key eligibility criteria for this trial included progressive mCRPC, prior treatment with one or more androgen-targeted therapies, and no prior taxane chemotherapy for mCRPC. Prior chemotherapy in the castration-sensitive prostate cancer setting was allowed.
- Altogether, 51 patients were treated with FOR46 across 10 dose levels. The minimum expected effective dose, maximum tolerated dose, and recommended phase 2 dose levels were determined.
- Treatment-related adverse events (TEAEs) experienced by 10% or more of the study cohort were determined (across 10 dose levels). Overall, 65% of patients experienced Grade 2 or higher neutropenia, including 31% of patients with grade 4 severity; 1 patient experienced febrile neutropenia (2.0%). The severity of neutropenia was mitigated with the use of adjusted body weight dosing and growth factor support. Infusion-related reactions were common, though severity was predominantly limited to grade 1 to 2 with the use of pre-medication. Peripheral neuropathy was experienced by 39% of patients, with one Grade 3 event noted.

- At the time of this presentation, four patients remained on treatment. The median duration of treatment was 31 weeks, with five patients remaining on treatment for more than one year.
- CD46 expression was evaluated in archival tumor tissue samples from 12 patients. Of 11 evaluable samples, 92% were positive for CD46 expression.
- Most patients experienced a decline in PSA levels, with 37% of patients experiencing a decrease of 50% or more.
- Thirteen out of 24 (48%) patients with visible tumors on scans experienced tumor regressions (**Figure**).
- An example of one exceptional responder was presented. This patient experienced a 71% decrease in PSA and a decrease in tumor size on scans.
- In ongoing studies, the UCSF team, led by Robert Flavell, is developing a CD46-targeted PET imaging tracer. This tracer would allow the identification of patients whose tumors express CD46 and may be more likely to benefit from this treatment, as well as a standalone diagnostic. Preclinical and phase 1 studies of this PET tracer are promising.
- An ongoing clinical trial is using CD46 PET imaging to image patients before and after treatment with enzalutamide to determine whether enzalutamide increases CD46 levels on tumors.
- The team is also developing a CD46-targeted radioligand therapy in which radioactive isotopes are attached to the CD46 antibody as an alternative and possibly more effective treatment approach. Preclinical studies testing this treatment in prostate cancer models have been promising. A bi-specific T cell engaging immunotherapy using the CD46 antibody is also under development.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-1-novel-clinical-trial-updates/>**



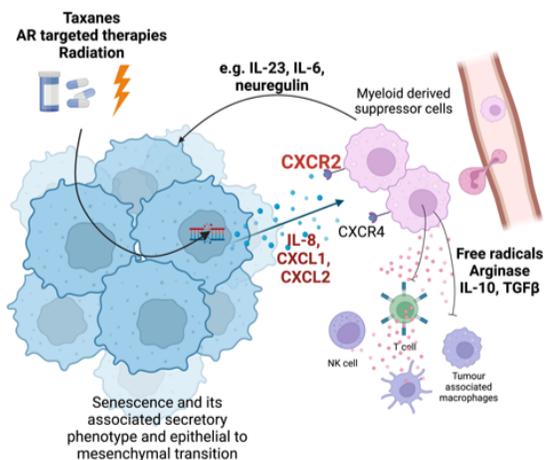
Targeting Myeloid Chemotaxis via CXCR2 Blockade as a Therapeutic Strategy in Advanced Prostate Cancer

Christina Guo, MD

Institute for Cancer Research; Royal Marsden Hospital, UK

- Myeloid cells are an immune cell subset with various functions in promoting tumor formation, growth, and resistance to existing cancer treatments.
- Profiling of prostate cancer patients has found that higher numbers of myeloid cells in blood and in tumors are associated with worse outcomes, including treatment resistance and shorter survival.
- The de Bono lab found that tumors from patients with metastatic castration-resistant prostate cancer (mCRPC) are highly infiltrated with inflammatory myeloid cells, which express the surface protein CXCR2, a G-protein coupled receptor to chemokines involved in myeloid cell migration.
- Prostate cancer cells were found to secrete the specific types of chemokines that attract inflammatory myeloid cells via CXCR2, into tumors. Once in tumors, these cells secrete factors that promote tumor growth and suppress anti-tumor immune cell activities (**Figure**).
- Based on these data, the de Bono lab hypothesized that targeting CXCR2 may be a promising new treatment approach in prostate cancer.
- The team initiated a phase 1, proof-of-concept, clinical trial to test the safety, determine an optimal dose, and evaluate preliminary efficacy of the CXCR2 antagonist, AZD5069, in combination with enzalutamide in patients with mCRPC (ACE Trial).
- Overall, 21 patients were treated with AZD5069 across 5 dose levels.
- Uncomplicated reversible neutropenia was the most commonly observed side effect. These studies demonstrated that the combination of CXCR2 inhibition and enzalutamide is well tolerated in patients with late-stage lethal prostate cancer.
- Five of 21 patients derived clinical benefit from this treatment, with 3 achieving objective partial responses.
- Blood and tumor biopsy samples were taken from patients before and after treatment to evaluate the biological effects of the therapy. Decreased numbers of myeloid cells were found in both tumors and blood from patients treated with increased dose levels of AZD5069.
- This study provides proof-of-mechanism and proof-of-concept evidence that inhibiting myeloid cell chemotaxis via CXCR2 blockade reduced tumor infiltration by myeloid cells in patients with late-stage mCRPC and may reverse resistance to existing treatment in some patients with late-stage lethal prostate cancer. Further studies are warranted.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-1-novel-clinical-trial-updates/>**

Myeloid inflammatory cells are recruited to the prostate tumor bed down chemokine gradients via CXCR2



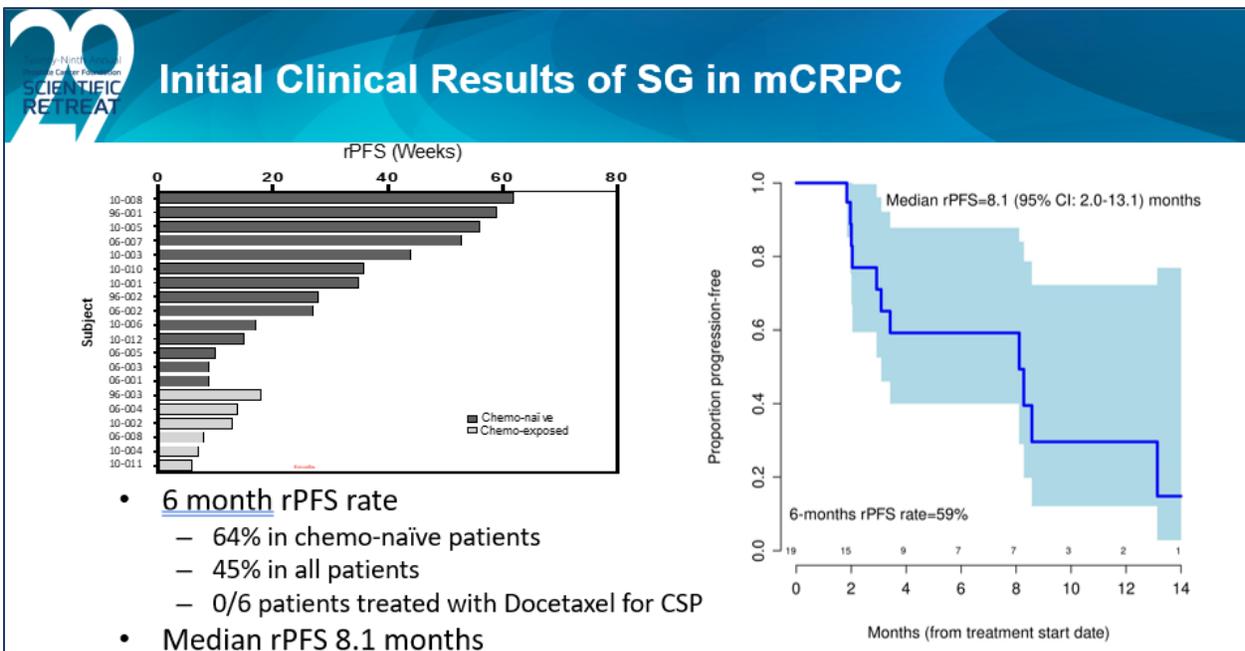
- PCa Rx induce the senescence associated secretory phenotype (SASP)
- Senescent epithelial cells release chemokines (e.g. IL-8/CXCL8, CXCL1, CXCL2) - high affinity ligands for CXCR2 G-protein coupled receptor
- Chemoattract myeloid inflammatory cells
- Secrete factors (e.g. IL-23, NRG1, IL-6) which fuel PCa growth and Rx resistance

Biomarker Results from Targeting TROP2 with Sacituzumab Govitecan in mCRPC

Joshua Lang, MD
University of Wisconsin

- Prostate cancer is a highly heterogenous disease, with multiple distinct molecular subtypes, variable responsiveness to androgen-targeted therapies, and variable clinical outcomes. There are also multiple mechanisms that can lead to treatment resistance.
- These variabilities underscore the need for biomarkers that can identify tumor subtypes and treatment resistance mechanisms, and predict treatment responses, in order to help clinicians choose the most appropriate therapeutic strategy for each patient.
- “Liquid biopsies” are blood draws from which circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) can be obtained to study disease biology and as clinical biomarkers.
- Dr. Joshua Lang and colleagues at the University of Wisconsin Circulating Biomarker Core (CBC) have developed microfluidics technology that can capture individual tumor cells from liquid biopsies and perform studies to evaluate single cell gene expression and genomic sequencing. A custom genomic sequencing test that evaluates mutations in 821 cancer-related genes was developed.
- This technology is being used to study biology and treatment resistance mechanisms in patient samples from 14 multi-site clinical trials. Over 650 patient samples from 23 different NCI Cancer Centers were evaluated in 2021.
- CTC profiling of samples from clinical trials testing androgen receptor (AR)-targeted therapies found that pre-treatment levels of AR-regulated gene expression are prognostic for radiographic progression-free survival and overall survival.

- CTCs were also used to identify patients with small cell/neuroendocrine prostate cancer (NEPC) and confirmed that these patients tend to respond poorly to AR-targeted therapies and have shorter overall survival.
- ctDNA and CTC analyses on liquid biopsies can also be integrated to identify the full spectrum of mCRPC subtypes.
- TROP2 is a protein expressed on prostate cancer and other cancer cell types. Dr. Lang and colleagues used CTC analyses to confirm that TROP2 is commonly expressed in metastatic prostate cancer, with highest the expression levels in luminal adenocarcinoma subtypes.
- TROP2 expression on CTCs was also associated with poorer overall survival.
- Sacituzumab Govitecan (IMMU-132) is a TROP2-targeted antibody-drug conjugate that has previously received FDA approval for patients with triple-negative breast cancer.
- Dr. Lang and colleagues initiated a phase 2 clinical trial to test IMMU-132 in patients with mCRPC progressing on enzalutamide or abiraterone. Twenty patients have been treated thus far; preliminary results from this trial were presented.
- Treatment-emergent adverse events (TEAEs) observed in >10% of the 20 treated patients were mostly Grades 1-2 and included decreased neutrophil count, nausea, alopecia, anemia, diarrhea, constipation, anorexia, fatigue, decreased white blood cells, decreased platelet count, hypoalbuminemia, vomiting, hyperglycemia, hyponatremia, and maculopapular rash. Grade 3 and 4 events included decreased neutrophil count (6 patients with Grade 3; 5 patients with Grade 4) and decreased white blood cells (1 patient with Grade 3; 2 patients with Grade 4) and were easily managed with GCSF (granulocyte colony-stimulating factor). Grade 3 anemia (3 patients) and diarrhea events (1 patient) were also observed.
- Overall, these TEAEs are consistent with what has been observed with IMMU-132 in other cancer clinical trials, but with higher frequencies of neutropenia, which may be associated with extensive bone metastatic disease.
- In preliminary analyses, median radiographic progression-free survival (rPFS; time from trial enrollment to the growth of tumors on scans) for patients in this trial was 8.1 months (**Figure**). While no PSA declines >50% were observed, PSA stabilization was observed in patients with rPFS times longer than 6 months.
- TROP2-expressing CTCs correlated with the duration of response to therapy. Genomic and gene expression signatures in liquid biopsies identified potential biomarkers of response and resistance.
- Overall, these studies demonstrate that TROP2 is broadly expressed in mCRPC and is a promising treatment target.
- These interim trial results suggest that IMMU-132 has activity in mCRPC, although validation in larger trials is needed. This trial is being expanded to include additional combination treatment arms.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-1-novel-clinical-trial-updates/>**

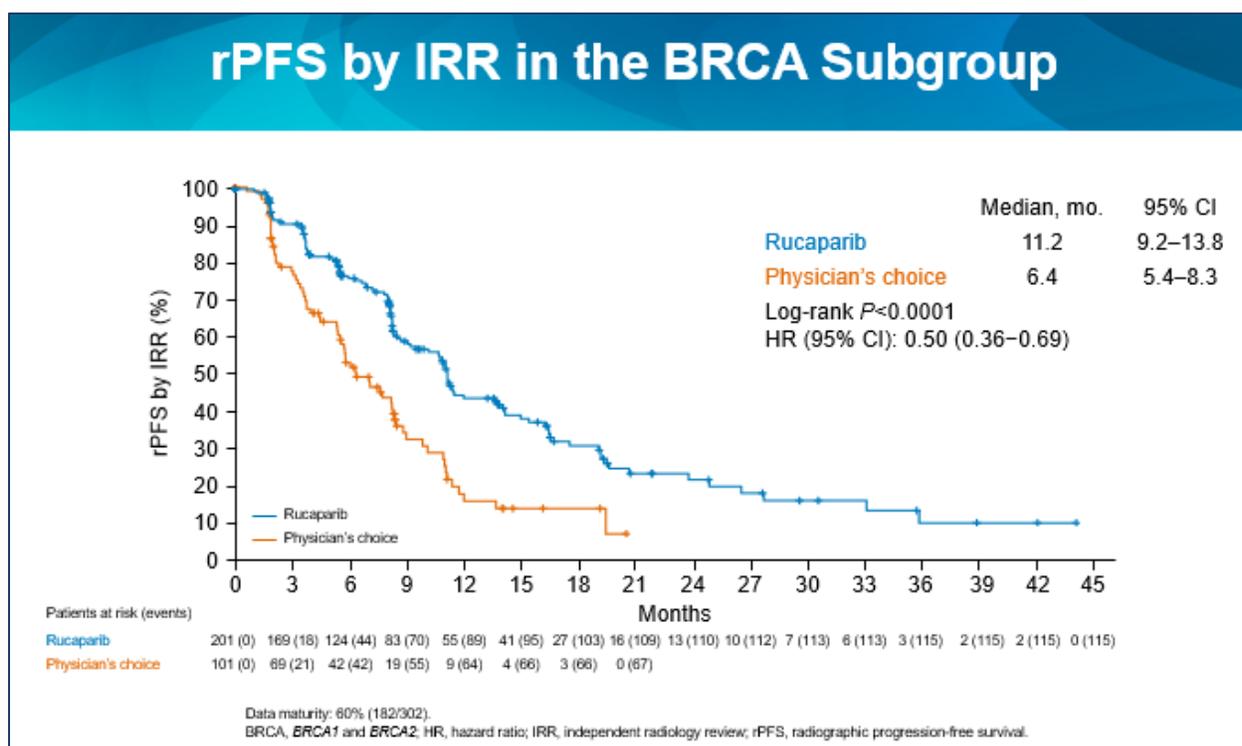


TRITON3: A Phase 3 Study of Rucaparib vs. Physician's Choice of Therapy in mCRPC associated with HRD

Alan Bryce, MD
Mayo Clinic

- In 2020, the PARP-inhibitor rucaparib received accelerated FDA approval for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a second-generation androgen pathway-inhibitor (API) and taxane-based chemotherapy, and who have germline or somatic mutations in the DNA repair genes *BRCA1* or *BRCA2*.
- This approval was based on positive results from the single-arm phase 2 TRITON2 study, in which patients with mCRPC and a *BRCA* alteration treated with rucaparib had an overall response rate of 43.5% and a PSA response rate of 54.8%. In TRITON2, radiographic and PSA responses were observed in a limited number of patients with an *ATM* alteration.
- TRITON-3 is a randomized phase 3 confirmatory study required by the FDA to confirm the clinical benefit and safety of rucaparib in mCRPC in a randomized setting.
- Dr. Alan Bryce presented top-line efficacy and safety data from TRITON3.
- In TRITON3, patients with mCRPC and *BRCA1/2* or *ATM* alterations who had received one prior second-generation API and no prior taxane were randomized to receive rucaparib vs physician's choice of docetaxel or second-generation API (abiraterone acetate or enzalutamide, whichever the patient had not yet received). This represents the first study comparing a PARP inhibitor with docetaxel in mCRPC.
- The primary endpoint was radiographic progression free survival (rPFS; length of time from randomization to growth of tumors on scans) in patients with *BRCA1/2* mutations (~300 patients), and if statistically significant, in the entire cohort (*BRCA1/2* + *ATM* mutations; ~400 patients). Secondary endpoints included overall survival and overall response rates.

- rPFS was significantly improved by treatment with rucaparib vs. physician's choice in patients with *BRCA* alterations (median 11.2 vs. 6.4 months, respectively; **Figure**), as well as in the entire cohort (median 10.2 vs. 6.4 months, respectively). No significant differences between treatment arms were observed in the subgroup of patients with *ATM* mutations.
- The median treatment duration was 8.3 months for patients receiving rucaparib and 5.1 months for patients receiving physician's choice.
- Safety was compared between patients on rucaparib vs. physician's choice (docetaxel or second-generation API). At least one grade ≥ 3 TEAE was observed in 60% of patients receiving rucaparib vs. 53% of patients receiving physician's choice. Dose reductions or interruptions due to toxicities occurred in 60% of patients receiving rucaparib vs. 39% of patients receiving physician's choice. Treatment discontinuations due to toxicities occurred in 15% of patients receiving rucaparib vs. 21.5% of patients receiving physician's choice. There were no reported cases of myelodysplastic syndrome or acute myeloid leukemia.
- Overall, TRITON3 was a positive trial that met its primary endpoint of demonstrating that rucaparib significantly improves rPFS compared with standard-of-care (docetaxel or second-generation API) in patients with mCRPC, and confirmed the efficacy and safety results seen in TRITON2.
- This trial was the first to compare a PARP inhibitor with docetaxel as one of the standards of care and was the first clinical study in mCRPC to demonstrate superiority of a treatment compared to a docetaxel-containing control arm.
- Results from additional endpoints from the trial were presented at the 2023 ASCO GU Meeting.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-1-novel-clinical-trial-updates/>**



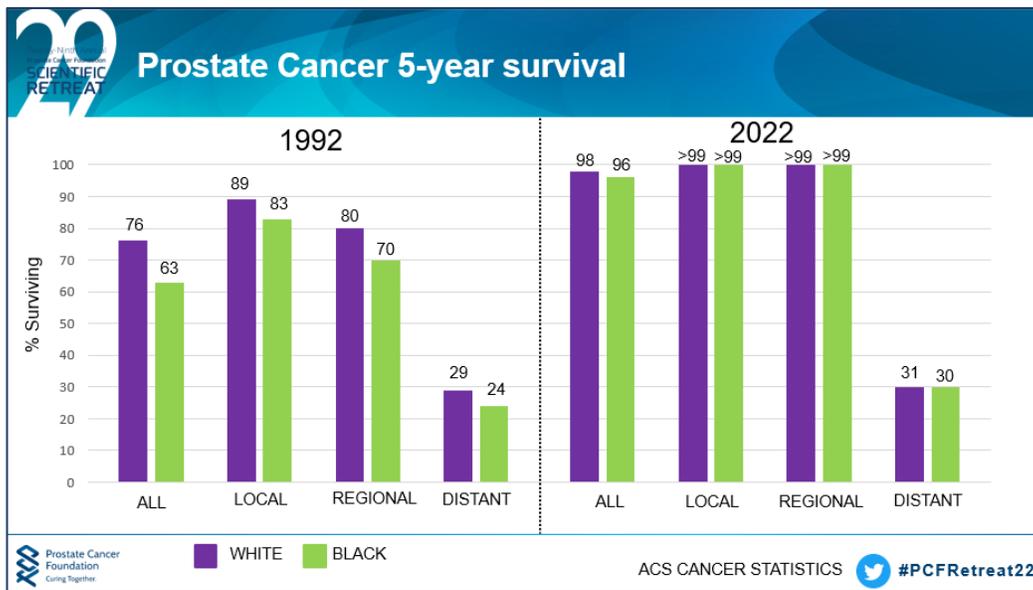
SPECIAL LECTURE: The Magic of Mayonnaise

Kenneth Pienta, MD Johns Hopkins University

- Over the past 20 years, significant progress has been made in prostate cancer screening and treatment. This has led to dramatically improved 5-year survival rates for patients diagnosed with localized or regional prostate cancer, and narrowed the racial disparities gap between Black and White patients. However, survival rates for patients diagnosed with distant metastatic prostate cancer have not significantly improved, and annual death rates from prostate cancer are unchanged.
- Dr. Kenneth Pienta discussed how team science can be applied to drive further improvements for patients and demonstrated the making of mayonnaise as a metaphor.
- The creation of multidisciplinary science teams requires the collision of people from very different fields.
- The building of effective team science collaborations requires trust, vision, self-awareness, emotional intelligence, mentoring, team evolution and dynamics, communication, recognition and sharing successes, solutions for conflict and disagreement, and navigating and leveraging networks and systems.
- Mayonnaise is a colloid, a type of substance that does not conform to standard conceptions of solids, liquids, or gases, and once created, cannot be separated back into their original components.
- Colloidal science requires risk taking, to meet as equals, open-mindedness, new ideas, respect and recognition of each person's contributions, patience, trust, understanding values, and the trading of ideas.

Let's not be satisfied:

- Be an explorer to disciplines you have not interacted with before.
- Make at least one first contact.
- Make some mayonnaise!
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/special-lecture-the-magic-of-mayonnaise/>**



PANEL: State of Science on Diet and Lifestyle in Lethal Prostate Cancer and Survivorship

Moderator: Lorelei Mucci, ScD
Harvard TH Chan School of Public Health

Panelists:

- William Aronson, MD (University of California, Los Angeles)**
- June M. Chan, ScD (University of California, San Francisco)**
- Christina Dieli-Conwright, PhD, MPH (Dana-Farber Cancer Institute)**
- Edward Giovannucci, MD, ScD (Harvard TH Chan School of Public Health)**

- This panel discussed the scientific evidence and recommendations on diet and other health habits for improving prostate cancer survival and survivorship.

Benefits of physical activity in patients with prostate cancer:

- Epidemiological studies have shown that physical activity, including vigorous activity and brisk walking, are beneficial for patients with prostate cancer. A recent systematic review estimated that vigorous activity reduces risk of prostate cancer mortality by ~30% and reduces risk of all-cause mortality by 40%. Other benefits include quality of life measures such as improvements in strength, depression, anxiety, sleep, and cognition.
- Benefits of physical activity demonstrated in randomized clinical trials in patients with prostate cancer include improved quality of life, physical function, muscle strength, and fitness. A randomized controlled trial that evaluated 3-week high-intensity interval training

vs. no intervention in men on active surveillance found benefits in cardiorespiratory fitness, PSA levels and PSA velocity. Other clinical outcomes remain to be evaluated.

- Ongoing clinical trials in patients with prostate cancer are evaluating combinations of aerobic and resistance exercise, as studies have suggested greater benefits when combining these exercise modalities, particularly for cardiovascular disease risk and muscle maintenance. Trials are also evaluating the impact of exercise on outcomes including cardiometabolic health, sarcopenia, sarcopenic obesity, insulin resistance biomarkers, and cardiovascular disease risk, as well as on clinical endpoints including survival and disease progression in patients on active surveillance.
- Physicians should discuss the benefits of exercise with their patients, particularly those undergoing ADT, which causes numerous negative side effects that can be counteracted by exercise.
- Exercise is beneficial and safe for patients with advanced, metastatic prostate cancer. Certain precautions must be taken, and physician oversight is advised in patients with disease in certain metastatic sites such as bone, particularly with resistance exercise. National and international working groups have put out recommendations for exercise safety in patients with advanced cancers.
- The panel recommends at least 30 minutes of brisk walking per day, or other related types of exercise, and every-other-day upper and lower body resistance training. While exercise is beneficial and safe, recommendations should be based on where patients are starting from and their risk for injury, with an overall goal of increasing fitness, strength and endurance.
- Other tips include finding an exercise that you enjoy and can stick with, and having exercise partners.
- Sustainability, access to areas to exercise, and finding the time to exercise can be a challenge, and can vary based on socioeconomic status, education, race/ethnicity, and geography. Remote-monitored high intensity interval exercise programs have been found to benefit patients with advanced prostate cancer. Virtual exercise programs are currently being tested in trials that focus on enrolling Black and Hispanic patients.

Obesity as a risk factor in prostate cancer:

- Obesity is an established risk factor for 13 types of cancers, but has not been definitively demonstrated to impact risk for prostate cancer.
- For instance, obesity during adolescence is associated with lower lifetime risk for prostate cancer, while weight gain during adulthood is a risk factor for advanced prostate cancer.
- Several studies have shown that obesity is a risk factor for prostate cancer mortality among patients, with stronger evidence shown for visceral obesity (or “belly fat”).
- Further studies are needed to definitively demonstrate whether obesity in general, or certain types of body fat such as visceral adiposity, increase risk for prostate cancer mortality.
- Although weight loss is not proven beneficial for prostate cancer, it is well known to be beneficial to reduce cardiovascular risk and should be encouraged for those who are overweight.

Dietary recommendations:

- A number of well-done epidemiology studies have provided strong evidence to make dietary recommendations for patients with prostate cancer; these highly overlap with recommendations for cardiovascular health.
- These recommendations include: limiting foods that are high in saturated fat, salt, and added sugar; moderate alcohol consumption; avoiding processed and red meats; and eating a diet high in fiber, liquid non-tropical plant oils, whole grains, vegetables, beans and fruit.
- Rather than focusing on individual foods, there is increasing evidence that dietary patterns may be more important, such as avoiding patterns that increase levels of inflammation and insulin. An example of a healthy dietary pattern is the Mediterranean diet.
- Vegan and plant-based diets: While there aren't enough vegans in existing large population studies to examine the epidemiologic impact on disease outcomes, healthy vegan/plant-based diets appear to improve the biomarkers associated with heart-healthy diets.
- The role of individual dietary factors remains unclear. However, there may be benefits with Vitamin D sufficiency, coffee, tomato products, and omega-3 fatty acids found in fish. More studies are needed to definitively demonstrate the benefits of these factors.
- Multiple epidemiologic studies and clinical trials have evaluated the benefits of exercise and/or dietary factors in prostate cancer survivorship and clinical outcomes. Overall, the panel recommends achieving a healthy weight with exercise based on what a patient can safely achieve and adhere to, to increase fitness and reduce obesity. A healthy diet that follows heart-healthy dietary guidelines is recommended. More studies are needed to definitively show survival and clinical outcomes benefits with these lifestyle interventions in patients with prostate cancer, across the disease spectrum.
- **The full panel discussion can be viewed here:** <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/panel-state-of-science-on-diet-and-lifestyle-in-lethal-prostate-cancer-and-survivorship/>

KEYNOTE ADDRESS

Michael Milken
Founder and Chairman
Prostate Cancer Foundation

This presentation can be watched in full at:

<https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/keynote-address/>

PANEL: State of Clinical Therapy for Advanced Prostate Cancer

Moderator: Charles J. Ryan, MD
Prostate Cancer Foundation

Panelists:

Jessica Hawley, MD, MS (University of Washington; Fred Hutchinson Cancer Center)

Renu Eapen, MBBS, FRACS (Urol) (Peter MacCallum Cancer Centre, Melbourne; University of Melbourne)

Felix Feng, MD (University of California, San Francisco)

Michael Haffner, MD, PhD (University of Washington; Fred Hutchinson Cancer Center)

Ana Kiess, MD, PhD (Johns Hopkins University)

Colin Pritchard, MD, PhD (University of Washington; Fred Hutchinson Cancer Center)

- This panel discussed an atypical and complex clinical case of a patient with prostate cancer. The clinical findings and strategy were discussed, and panelists weighed in on recommendations as well as new standards of care that may be applied in the current era of therapy and diagnostics.
- The patient presented in 2021 with a PSA of 53, and two previous negative TRUS biopsies when his PSA was 6 and 11. He was treated with a course of antibiotics, but after re-check, his PSA was 71. Subsequent imaging with MRI, CT, and bone scans found that the patient had metastatic disease, with bulky pelvic and retroperitoneal lymphadenopathy.
- Diagnostic tools that could be applied in 2022 would include the use of prostate MRI, transperineal biopsies, which have a much lower risk of sepsis and provide better sampling of the entire prostate, urine biomarker tests such as 4K, and PSMA PET scans.
- Pathology on the retroperitoneal mass biopsy revealed an ampicrine carcinoma, a rare subtype of prostate cancer with overlapping features of neuroendocrine and adenocarcinoma that is characterized by the co-expression of both androgen signaling and neuroendocrine markers.
- Genomic analysis of this tumor found a *TMPRSS2-ERG* fusion, a *TP53* mutation, and additional alterations in tumor tissue. The patient did not have genomic alterations that would have made them eligible for PARP-inhibitors or pembrolizumab.
- The patient was treated with carboplatin + docetaxel, then 10 fractions of palliative radiation therapy, followed by abiraterone acetate + prednisone. He currently has an undetectable PSA and low tumor burden on scans. However, his most recent scan found stable to mildly increased pelvic lymph node sizes.
- The panel discussed considering future treatment with immunotherapy or PSMA-targeted radionuclide therapy (Pluvicto). Currently, the wait times for Pluvicto are many months, and the patient has already been placed on a wait list and anticipates starting Pluvicto in two to three months following this presentation.
- Additional recommendations include PSMA PET and FDG PET to evaluate whether all disease sites are PSMA-positive, as an indicator of how successful treatment with PSMA-targeted therapy will be.
- Overall, the panel discussed recommendations and new strategies for diagnosis and treatment of patients with atypical and complex prostate cancer cases. Recent improvements in diagnostics, therapies, and biomarker-driven patient management

strategies will continue to improve the outlook for all patients with advanced prostate cancer, including those with rare subtypes.

- **The full panel discussion can be viewed here:** <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/panel-state-of-clinical-therapy-for-advanced-prostate-cancer/>

Session 2: Impact of Molecular and Genomic Factors on Prostate Cancer Disease Etiology and Health Disparities

Immunogenomic Landscape of African American Prostate Cancer

Tamara Lotan, MD
Johns Hopkins University

- Prostate cancer disparately affects Black individuals, with almost twice the incidence rate and more than twice the mortality rate, compared with White individuals. The reasons for these racial disparities are complex and multi-factorial.
- Studies have suggested that biological and genetic differences may contribute to prostate cancer racial disparities. For instance, higher levels of inflammation and immune-related gene expression are present in African American prostate cancer cases.
- Dr. Tamara Lotan discussed a study investigating biological differences in prostate cancer from Black vs. White patients.
- A cohort of 200 self-identified African American and 200 self-identified White patients with prostate cancer was developed. Prostate cancer surgical samples were obtained, and an array of studies was performed to profile gene expression patterns, genomic alterations (**Figure**), epigenetic patterns, and the types and numbers of immune cells in tumors.
- No differences in the overall number of somatic (tumor) copy number alterations were observed by race or ancestry.
- Higher numbers of somatic copy number alterations were associated with a more immunosuppressive tumor microenvironment. This association was independent of race.
- Some immune gene expression differences between African American and White prostate cancer were found to be likely due to differences in germline copy number variations. These genes included the chemokine isoforms MIP-1 α and MIP-1 β , which were more highly expressed in African-American prostate cancer cases and had higher copy numbers in these cases. MIP-1 α and MIP-1 β play a role in recruiting immune cells to sites of infection and immune activity.
- Additional new somatic copy number alterations that vary by the percentage of African ancestry were identified on chromosomes 6, 11, and 12.
- Further studies are needed to understand if and how these differences contribute to prostate cancer racial disparities.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-2-impact-of-molecular-and-genomic-factors-on-prostate-cancer-disease-etiology-and-health-disparities/>**

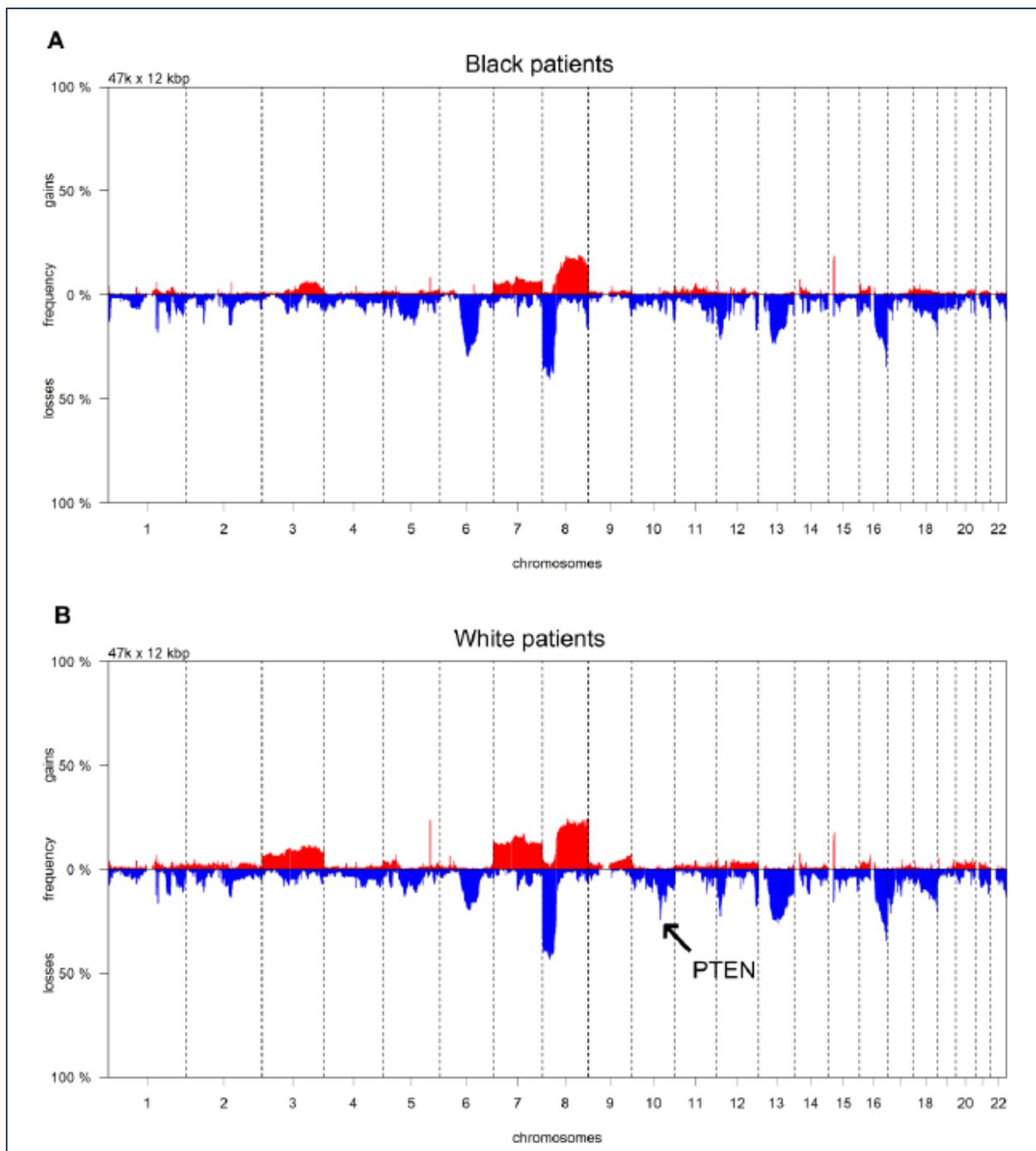


Figure: Landscape of copy number loss (blue) and gain (red) in primary prostate tumors from self-identified Black (top) and White (bottom) patients (Vidotto T et al., *JCI Insight*, *In Press*, 2023).

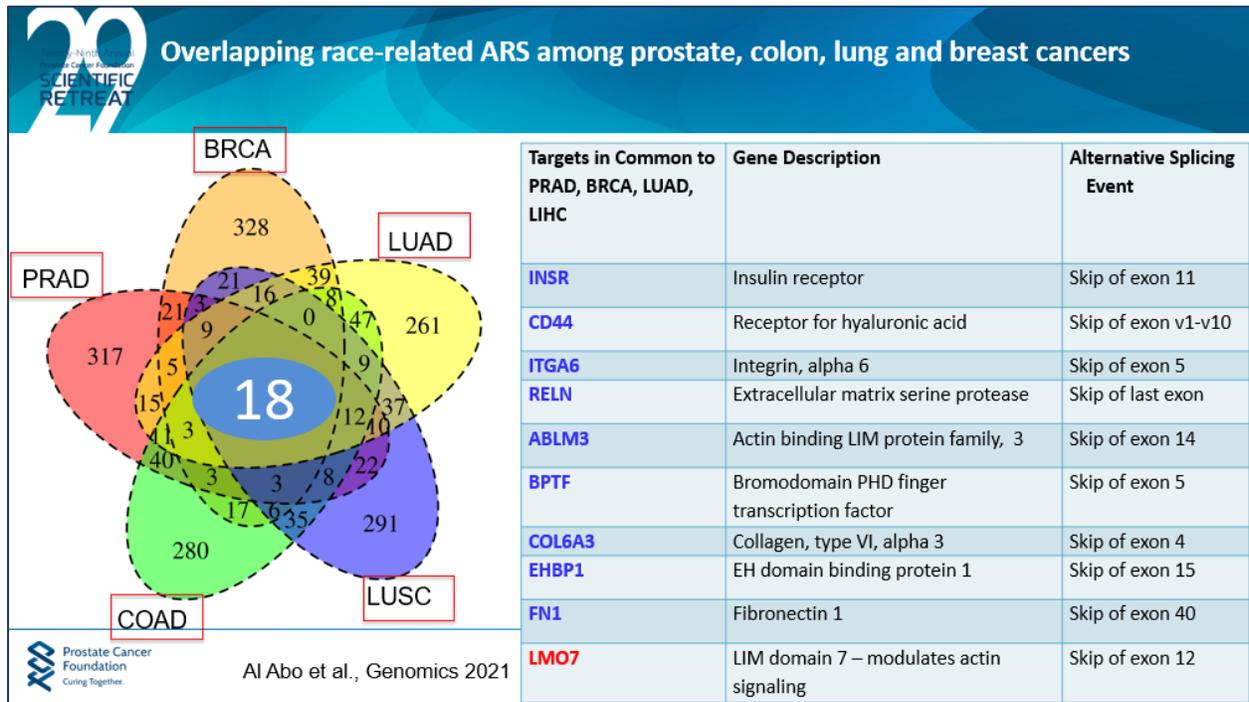
Alternative RNA Splicing in African American Prostate Cancer

Steven Patierno, PhD **Duke University**

- There is an unequal burden of cancer among minoritized and marginalized populations and the medically vulnerable and underserved, with African American populations disparately affected by prostate and other cancers.
- Compared with European Americans, African Americans are more likely to have an earlier age at prostate cancer diagnosis, a more advanced stage at diagnosis, greater risks of early recurrence, higher rates of metastasis, and shorter overall survival.
- Equal access health systems reduce some of these disparities, but do not eliminate them.
- There are multi-level contributors to cancer health disparities, including societal-level cultural frameworks driven by racism and poverty, institutional-level environments such as healthcare access, and neighborhood-level social and physical environments, such as socioeconomic status and diet. These may all interact in a complex manner with ancestry-related genetics and biology to impact disease risk and outcomes.
- “Race” and “ethnicity” are not biological, but are socio-cultural constructs. However, racial ancestry does affect phenotypic and genetic diversity and may impact disease risk, biology, and outcomes.
- Dr. Steven Patierno discussed studies on how alternative gene splicing may contribute to prostate cancer disparities.
- Genes are not continually encoded in the human genome, but instead have non-coding regions (introns) inserted into a gene’s DNA code; these introns must be removed (spliced out) during RNA transcription to produce a properly functioning protein. Coding regions (exons) can also be rearranged and included or excluded during this process, to create different protein variants with specific and unique functions. Alternative RNA splicing is the main mechanism of molecular diversity, responsible for how ~20,000 genes in the human genome can make over 250,000 proteins.
- RNA sequencing was performed on prostate cancer biopsy and adjacent normal prostate tissue samples from a cohort of self-identified African American and White patients with prostate cancer.
- Over 2,500 differentially spliced genes were identified in African American vs. White American prostate cancer biopsy samples. About one-third of these were also differentially spliced in adjacent normal prostate tissue, suggesting germline genetics may have impacted these splicing variations.
- One gene found to be differentially spliced between African American vs. White American prostate cancer was PI3K-delta, with a short variant present at significantly higher levels in African American prostate cancer. This short variant could drive increased aggressiveness in experimental models and was associated with worse survival in patients.
- A study was done using data from The Cancer Genome Atlas (TCGA) to evaluate racial differences in RNA splicing across multiple cancer types. Hundreds of differentially spliced RNAs were identified in cancers from White American vs. African American patients. Several race-related differently spliced genes were associated with prostate cancer patient survival.
- 18 race-related differently spliced genes were identified that overlapped across prostate, colon, lung and breast cancers (**Figure**). These 18 genes have all been previously found to have a role in cancer biology. For instance, a shorter splice variant of LMO7 was found to

increase cell migration and metastasis, and was associated with shorter time to recurrence in patients with prostate cancer.

- Ongoing studies are evaluating the biological and clinical impacts of different race-related RNA splicing variants. Ultimately, RNA splicing variants may have potential as biomarkers for precision medicine approaches for all patients whose cancer expresses the pathological splice variant.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-2-impact-of-molecular-and-genomic-factors-on-prostate-cancer-disease-etiology-and-health-disparities/>**



Epidemiology: Are Biologic Impacts Due to Ancestry vs Socio-Economic impacts of Racism?

Folakemi Odedina, PhD
Mayo Clinic

- Black patients experience significant prostate cancer disparities, with significantly higher incidence and mortality rates compared to White patients. Prostate cancer racial disparities are multi-faceted and are largely driven by structural inequities, social injustices, institutional racism, and inequitable social determinants of health.
- Dr. Folakemi Odedina discussed studies on how the socio-economic impacts of racism interact with ancestry to drive prostate cancer disparities in patients of African descent.

- Race is a social construct that is distinct from ancestry and biology. Race defines systemic racism or structural inequities and can be used to operationalize racial and ethnic health disparities. Ancestry in contrast, is the lineage encoded in a person's DNA.
- The ten countries with the highest prostate cancer mortality rates are all Black nations in Africa and the Caribbean (Zimbabwe, Barbados, Haiti, Zambia Jamaica, Trinidad and Tobago, Bahamas, Dominican Republic, Saint Lucia, and Côte d'Ivoire). Thus, understanding and addressing prostate cancer disparities requires a global approach.
- Health outcome disparities are largely due to effects of racism, discrimination and segregation, structural inequities, social injustice, adverse differences in social determinants of health, disparities in health care access across the cancer continuum of care, and lack of diversity in the health care workforce. Ultimately these socioeconomic factors influence tumor biology in a complex manner that results in health disparities.
- Studies have found that when socioeconomic factors are equitable, racial disparities in prostate cancer mortality are significantly reduced.
- Contributors to disparities in prostate cancer incidence remain more complex, and may be due to interactions between stressors caused by racist systems and ancestry. For instance, racist laws, policies, economic systems, and other forms of structural racism have resulted in poor environmental and neighborhood exposures that disparately affect Black populations and negatively impact their biology and health.
- The Prostate Cancer Transatlantic Consortium (CaPTC) was formed in 2005 as a global effort to study prostate cancer disparities in countries that are historically connected by the transatlantic slave trade. Understanding the roles of different contributors to prostate cancer disparities in different countries, such as systemic racism vs. poverty, will help to improve understandings of why Black men have an increased incidence of prostate cancer.
- CaPTC has performed several studies to evaluate the interactions between ancestry and prostate cancer disparities.
- In one study, alterations in DNA repair genes, *BRCA2* and *ATM* were identified in high frequency in prostate cancer samples from a Nigerian patient cohort and from African American patients in TCGA (The Cancer Genome Atlas). Alterations in these genes were less frequent in European American prostate cancer samples from TCGA.
- Another CaPTC study found an enrichment with immune-inflammatory microenvironment in Nigerian prostate cancer samples.
- An ongoing CaPTC study is evaluating the association between cortisol and testosterone in African-ancestry patients with prostate cancer.
- These data are being used to develop comprehensive models to determine the biologic impacts of ancestry vs. the social determinants of health (including structural inequities, societal injustices, racism, discrimination, segregation), which contribute to prostate cancer disparities. Few studies have tested interventions to reduce inequities in prostate cancer among Black men; these are urgently needed.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-2-impact-of-molecular-and-genomic-factors-on-prostate-cancer-disease-etiology-and-health-disparities/>**

The complexity of health disparity and the need for a unique approach to better understand and address complex chronic diseases underscore the need for team science research that is ***multilevel, collaborative, translational, and global.***

The Prostate Cancer Transatlantic Consortium (CaPTC)

members work collaboratively to address prostate cancer in Black men connected by the Transatlantic Slave Trade



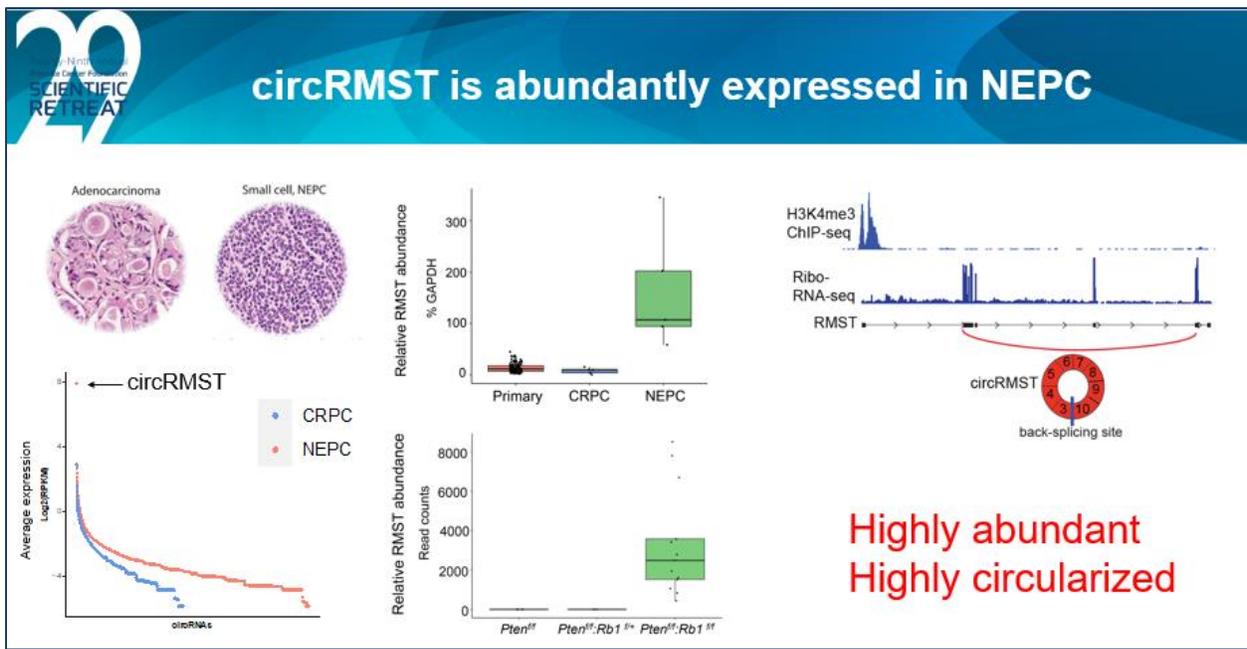
Session 3: Neuroendocrine Prostate Cancer

Circular RNA in NEPC and CRPC

Hansen He, PhD

Princess Margaret Cancer Centre, Canada

- Neuroendocrine prostate cancer (NEPC) is a highly aggressive subtype of castration resistant prostate cancer (CRPC) that is characterized by loss of prostate cell features and gain of neuroendocrine cell features. There are currently no effective treatments for patients with NEPC.
- Circular RNA (circRNA) is a recently discovered class of RNA that is circularized. While circRNA can be transcribed into proteins, it can also perform various regulatory non-coding functions including regulating gene transcription, acting as a scaffold for proteins, and as a sponge for soaking up RNA and proteins.
- Dr. Hansen He discussed the roles of circRNA in NEPC biology.
- A study performed in NEPC samples identified a circularized form of the RMST gene (circRMST) as one of the most abundant circRNAs in NEPC (**Figure**). circRMST was not present or present at only very low levels in adenocarcinoma-CRPC and primary prostate cancer samples (**Figure**), suggesting it has a role specific to NEPC.
- circRMST was also highly expressed in a subtype of small cell lung cancer (SCLC) that is driven by the ASCL1 oncogene. SCLC also has a neuroendocrine phenotype and shares some molecular features with NEPC.
- Studies in NEPC and SCLC models found that circRMST was required for optimal tumor growth and promotes ASCL1 expression and neuroendocrine cell fate specification. circRMST was found to interact directly with critical NEPC oncogenes SOX2 and NKX2-1.
- circRMST also repressed anti-tumor immune activity in NEPC and SCLC models.
- Together, these data suggest that circRMST drives progression of adenocarcinoma to NEPC by activating ASCL1 through SOX2 and NKX2-1, and by suppressing anti-tumor immune responses.
- The potential for circRMST as a biomarker for early detection of NEPC, and as a therapeutic target, deserve further study.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-3-neuroendocrine-prostate-cancer/>**



The Role of ASCL1 in NE Reprogramming of Prostate Cancer

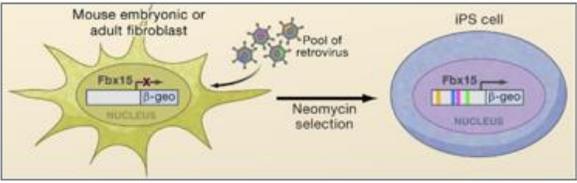
John Lee, MD, PhD

Fred Hutchinson Cancer Center

- Neuroendocrine prostate cancer (NEPC) is an untreatable and highly aggressive form of castration-resistant prostate cancer (CRPC) that arises in a subset of patients after treatment with anti-androgen therapy. NEPC is characterized by the expression of neuroendocrine cell genes and often the loss of typical prostate cell features such as the androgen receptor (AR).
- Various molecular features have been ascribed to NEPC, including loss of AR expression and/or signaling and loss of tumor suppressor genes *PTEN*, *TP53*, and *RB1*. However, the development of NEPC is not consistently associated with or driven by these features, and the molecular drivers of NEPC remain unclear.
- Dr. John Lee discussed studies on the roles of the neural transcription factors ASCL1 and NeuroD1 in driving prostate adenocarcinoma transformation into NEPC.
- A novel “pooled candidate” method was used to identify drivers of NEPC. Eight candidate NEPC driver oncogenes and/or genetic alterations were together found to drive reprogramming of prostate adenocarcinoma cell lines into an AR-negative NEPC phenotype (*RB1*-deletion, a *TP53* mutation, *N-MYC*, *ASCL1*, *SRRM4*, *NR0B2*, *BCL2* and a *KRAS* mutation).
- Of these eight factors, the neural transcription factor ASCL1 was minimally required for the expression of neuroendocrine lineage genes and reprogramming of prostate adenocarcinoma cells into NEPC. However, other oncogenic factors (*RB1*-deletion, a *TP53* mutation, *N-MYC*, *SRRM4*, and *BCL2*) were needed in addition to ASCL1 to maintain NEPC cell survival and growth.
- Another neuronal transcription factor, NeuroD1, was able to replace the function of ASCL1 in driving NEPC; other neuronal transcription factors were unable to do so.

- ASCL1 or NeuroD1 were found to alter the epigenomic landscape of AR, by epigenetically suppressing AR-target genes and an AR-activating genomic alteration commonly seen in CRPC.
- Overall, these data demonstrate that ASCL1 and NeuroD1 are critical drivers of AR silencing and the development of NEPC from prostate adenocarcinoma.
- Additional studies to better understand the mechanisms of these factors, as well as how the NEPC state is maintained, are ongoing.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-3-neuroendocrine-prostate-cancer/>**

Reprogramming AR-active prostate cancer (ARPC) to NEPC using a pooled candidate factor approach – à la Yamanaka



Takahashi K and Yamanaka S. *Cell*. 2006.
Commentary by Rodolfo KT and Eggen K. *Cell*. 2006.

Candidate Factor LV Pool
shRB1
TP53 R175H
MYCN
ASCL1
SRRM4
NR0B2
BCL2
KRAS G12V

Each factor introduced at a MOI of 4, based on titers on the specific cell line

Scheme for AR+/NE- to AR-/NE+ prostate cancer reprogramming

Day 0
300K cells per well in RPMI + 10% FBS and transduce with LV pool

Refresh media every 3-4 days

Day 3
Split cells, seed in 10 cm plates in N-SCM

Day 14
Collection of cells for analysis

PSMA Heterogeneity in NEPC and CRPC

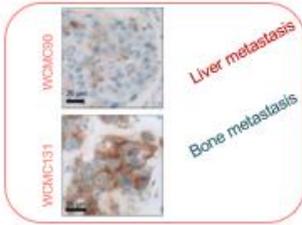
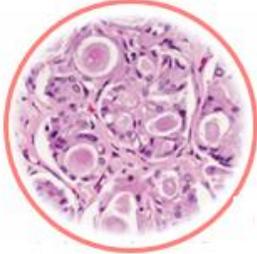
Himisha Beltran, MD
Dana-Farber Cancer Institute

- Prostate specific membrane antigen (PSMA) is a protein expressed on most prostate cancer cases and has proven to be a valuable target for imaging and therapeutics. However, PSMA is not uniformly expressed on all tumor cells or in all patients, thus not all patients will benefit from PSMA-targeted therapy.
- For instance, about 13% of patients with castration-resistant prostate cancer (CRPC) are ineligible for treatment with the recently FDA-approved PSMA-targeted radionuclide ¹⁷⁷Lu-PSMA-617 (Pluvicto®) due to low/no PSMA expression in their tumors.

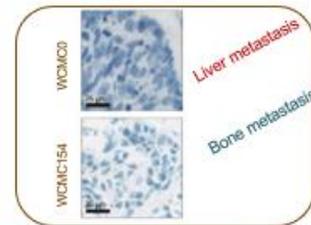
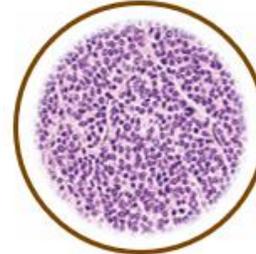
- Dr. Himisha Beltran discussed studies to understand PSMA heterogeneity in advanced prostate cancer, and to identify improved clinical strategies for imaging and treatment of PSMA-low tumors.
- PSMA expression is thought to be regulated by the androgen receptor (AR). PSMA is commonly lost in small cell/neuroendocrine prostate cancer (NEPC), which are often AR-negative (**Figure**). However, the mechanisms driving loss of PSMA expression and whether all NEPC are PSMA-negative, are unknown.
- A study evaluating PSMA expression in patients with AR-positive CRPC found lower levels of PSMA in liver metastases than in other metastatic sites.
- In mouse models, tumors from PSMA-low liver metastases went on to generate PSMA-low metastases at various sites. This suggests that PSMA is epigenetically suppressed, and that this may be stably passed on, no matter where in the body the new metastatic site develops.
- Whether epigenetic suppression of PSMA may contribute to inferior outcomes seen in patients with liver metastases treated with ^{177}Lu -PSMA-617 deserves investigation.
- Studies in NEPC models and patients with NEPC found that most, but not all, NEPC tumors are PSMA-negative.
- A study to identify regulators of PSMA expression in NEPC found that the HOXB13 transcription factor bound directly to the PSMA gene enhancer and could turn on PSMA expression.
- These data suggest that some NEPC patients may benefit from PSMA PET imaging and treatment with ^{177}Lu -PSMA-617 and that a diagnosis of NEPC should not automatically disqualify them from this consideration.
- Whether there are better ways to image PSMA-low CRPC and NEPC is an important question.
- ^{18}F -fluciclovine PET (Axumin) is an alternative PET imaging method that visualizes prostate tumors due to their higher amino acid transporter expression. PSMA-low CRPC and NEPC tumors were found to have high amino acid transporter expression and could be imaged with ^{18}F -fluciclovine PET.
- Dr. Beltran and colleagues are initiating a pilot clinical study at Dana-Farber Cancer Institute to evaluate ^{18}F -fluciclovine PET imaging for PSMA-low CRPC and NEPC.
- Ultimately, combined imaging biomarkers may help to better identify specific CRPC subtypes for more precise therapy.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-3-neuroendocrine-prostate-cancer/>**

PSMA can be 'lost' in AR-negative small cell neuroendocrine prostate cancer (NEPC)

CRPC-AdPC (AR⁺)



CRPC-NEPC (AR⁻)



**Are all NEPC tumors
PSMA -negative?**

Session 4: Single Cell Sequencing

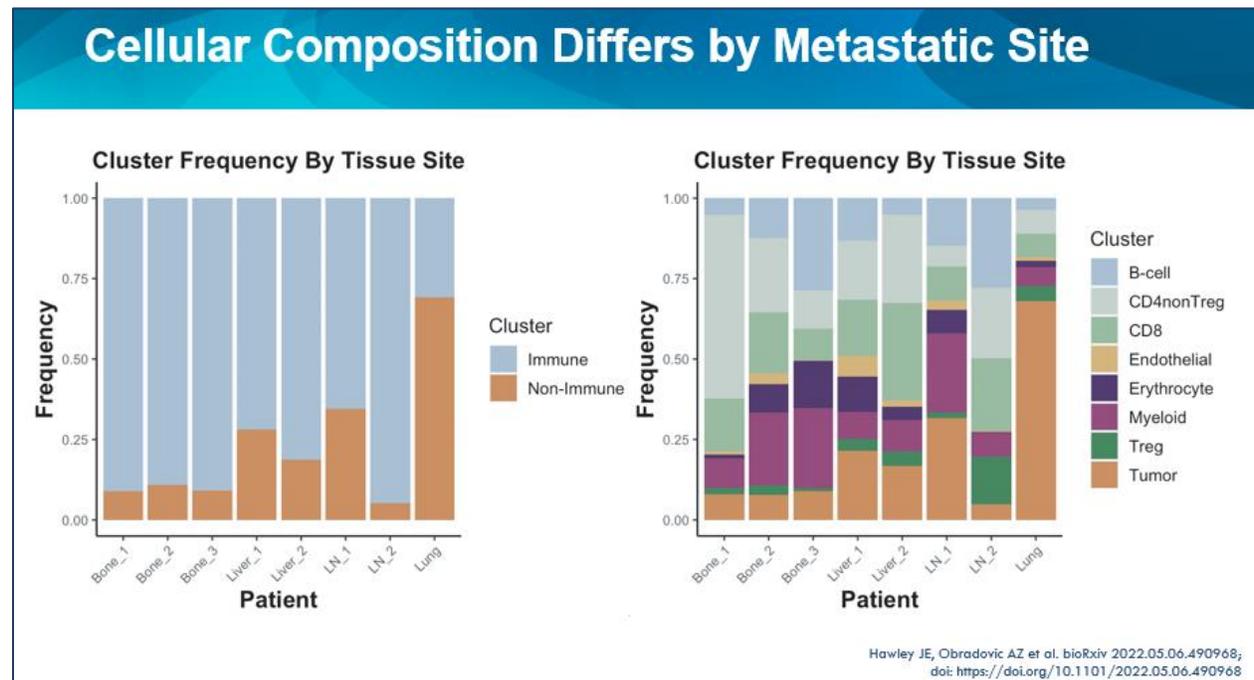
Longitudinal Single-Cell Analysis of Metastases from Men with mHSPC Treated with ADT and Anti-PD-1

Jessica Hawley, MD, MS

University of Washington; Fred Hutchinson Cancer Center

- Dr. Jessica Hawley discussed investigations into immune and tumor cell changes during treatment with prostate cancer.
- The Prime-Cut Trial was designed based on observations that treatment with androgen deprivation therapy (ADT) causes an influx of immune cells into the prostate tumor microenvironment.
- This trial is testing the combination of ADT, with phasic addition of the anti-PD1 immunotherapy cemiplimab after >4 weeks, followed by the addition of docetaxel chemotherapy after another 6 weeks, in patients with newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC) who had not received ADT in the prior 6 months. Patients undergo metastatic biopsies at baseline, just prior to the start of cemiplimab (to evaluate the effects of ADT alone), and just prior to the start of docetaxel (to evaluate the effects of ADT + cemiplimab).
- Preliminary results were reported from the first 10 patients enrolled on this trial. Biopsies have been obtained from various metastatic sites, including bone, liver, lung, and lymph node.
- Single cell RNA sequencing was performed on the metastatic biopsy samples to evaluate cell identity, function, and gene expression of tumor, immune, and other cells, in different metastatic sites and at different stages of this iterative combination therapy.
- Overall, immune cell subpopulations were found to differ by metastatic site (**Figure**), with lung metastases appearing most immune-depleted.
- The addition of cemiplimab immunotherapy to ADT was associated with a significant increase in the numbers of T cells in tumors.
- Tumor cell biology also differed across different metastatic sites and changed with therapy.
- The team investigated whether any baseline immune or tumor features were associated with clinical outcomes.
- The presence of CD8 T cell and regulatory T cell (Treg) populations at baseline were found to be associated with PSA responses. These were the same immune cell types that were expanded after ADT + cemiplimab combination therapy.
- Conversely, the presence of a CD4 T cell population at baseline was associated with late progression (patients who respond at first, but then progress).
- Tumor cell phenotypes that were associated with PSA response vs. with late progression were also identified. These phenotypes were validated to associate with clinical outcomes in larger prostate cancer datasets from TCGA.
- Possible druggable targets in these different tumor phenotypes were identified. For example, TOP2A and CD33 were identified as possible druggable targets in the tumor cell phenotypes associated with late progression.
- The changes seen in the metastatic tumor microenvironment after ADT were different from those seen in prior studies in the primary tumor microenvironment after ADT.

- Overall, these studies demonstrate the phenotypic changes in tumor and immune cells after treatment with ADT and with ADT + cemiplimab. Whether the baseline features identified that associated with outcomes may serve as predictive biomarkers for identifying patients who may most benefit from this treatment approach, deserve further study. These studies may also serve as rationale for testing new immunotherapy approaches in patients with prostate cancer.
- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-4-single-cell-sequencing/>

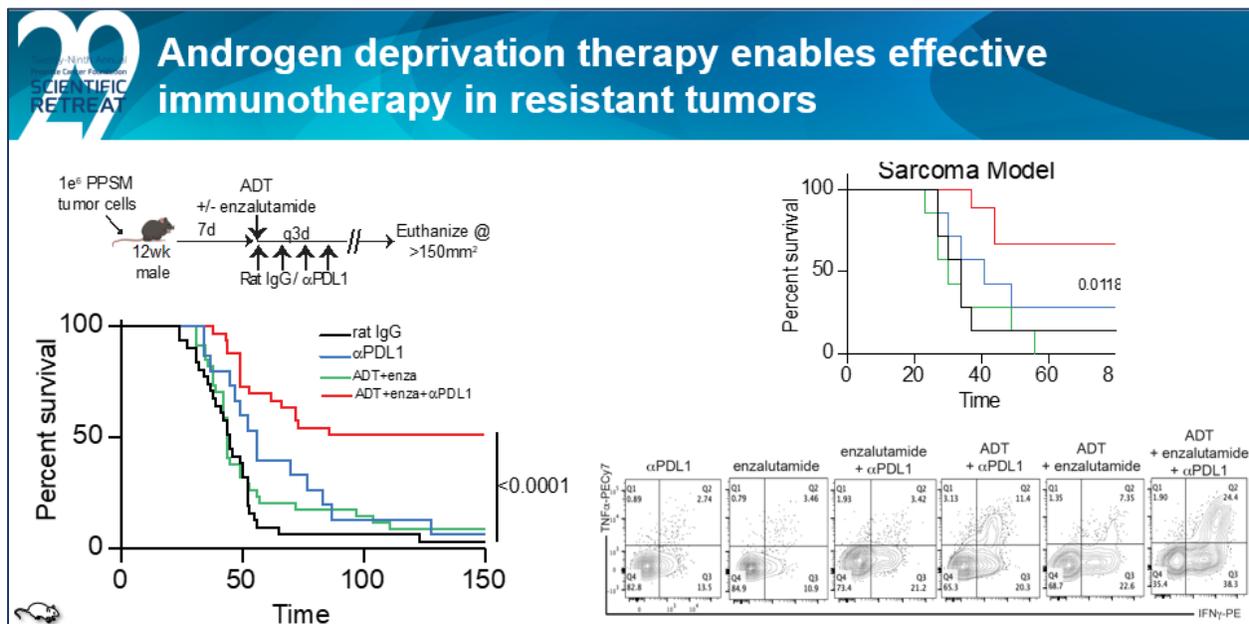


Harnessing Single Cell Analysis of the Tumor Microenvironment to Improve Immunotherapy Approaches in Prostate Cancer

Amy Moran, PhD
Oregon Health Sciences University

- Studies have found that male and female sex hormones can regulate the immune system.
- Dr. Amy Moran discussed studies on how androgens impact immune cells and responses to cancer immunotherapy.
- Dr. Moran partnered with Dr. Julie Graff, who was leading a clinical trial to evaluate the efficacy of combining the immunotherapy pembrolizumab with the anti-androgen therapy enzalutamide, in patients with metastatic castration-resistant prostate cancer (mCRPC).
- Pre-pembrolizumab treatment metastatic tumor biopsies were obtained from eight patients on this trial, including three who had experienced PSA responses following pembrolizumab treatment and five who had no PSA responses. Single cell gene expression analyses were performed on these biopsy samples to evaluate whether any immune features associated with response to this treatment combination.

- Two subsets of CD8 T cells were observed in these samples, which corresponded with responders vs. non-responders. T cells from responders tended to have reduced androgen receptor (AR) activity.
- AR was found to be expressed in T cells infiltrating primary prostate tumors from archival samples.
- Experiments in blood samples from healthy donors found that AR expression was increased when T cells became activated. However, AR appears to suppress the activities of T cells, as T cells produced higher levels of the immune-activating protein IFN-gamma when treated with enzalutamide or when AR was deleted. AR activity was also negatively associated with IFN-gamma expression in another mCRPC patient cohort.
- These data suggest that AR activity may limit the efficacy of immunotherapies. Dr. Moran and team found that higher AR activity was associated with lower IFN-gamma expression in CAR T cells developed for lymphoma, and with poor responses to immunotherapy in patients with melanoma. However, no correlation between AR activity and IFN-gamma expression or CD8 T cell activity was observed in a cohort of patients with prostate cancer treated with the immunotherapy ipilimumab.
- In mouse prostate cancer and sarcoma models, combining anti-PDL1 immunotherapy with ADT + enzalutamide was highly synergistic (**Figure**).
- Together, these studies demonstrate that AR represses T cell intrinsic IFN-gamma expression and suggest that combining immunotherapy with AR-targeted therapies may improve patient outcomes. Further investigations into the potential of this treatment strategy are warranted.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-4-single-cell-sequencing/>



SPECIAL LECTURE:

The Global Public Square of Prostate Cancer

Charles J. Ryan, MD
Prostate Cancer Foundation

This presentation can be viewed in full at:

<https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/special-lecture-the-global-public-square-of-prostate-cancer/>

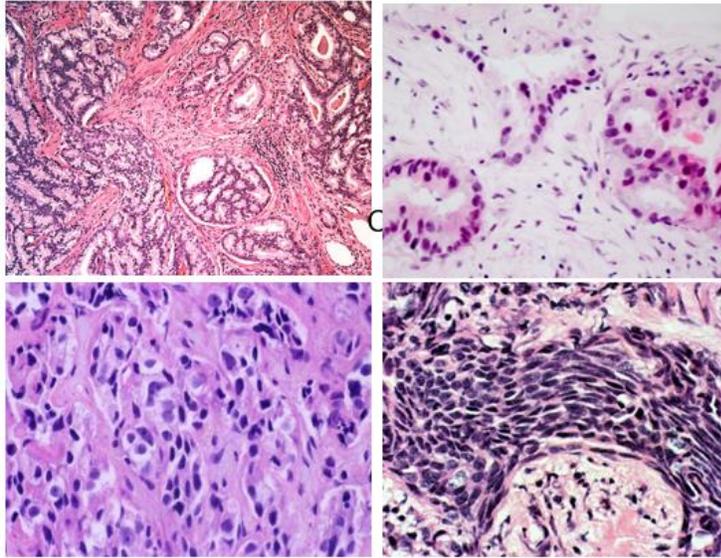
Session 5: Lessons from Primary Prostate Cancer

Molecular Signatures to Risk-Stratify Intermediate-Risk Primary Prostate Cancer

Jiaoti Huang, PhD
Duke University

- Several methods have been developed to predict clinical prognosis in patients with newly diagnosed prostate cancer. These include Gleason/ISUP grading by pathologists, and the molecular tests Decipher, Prolaris, and Oncotype DX, that evaluate tumor gene expression patterns.
- The molecular tests use aggregated tumor samples and are unable to carefully evaluate heterogeneous tumor features. Thus, they may miss the presence of small numbers of tumor cells with more aggressive features.
- Dr. Jiaoti Huang discussed the use of single cell sequencing methods to evaluate tumor heterogeneity in primary prostate cancer.
- A study was performed to analyze gene expression at the single cell level in prostate cancer samples from across the disease spectrum, from primary prostate cancer to castration-resistant prostate cancer (CRPC) and neuroendocrine prostate cancer (NEPC) (Figure).
- When single cell gene expression data from all tumor cases were combined, three major groups of tumor cells were identified that originated mostly from CRPC and NEPC cases. Importantly, ~0.5% of tumor cells from primary prostate cancers had gene expression patterns that were similar to adenocarcinoma-CRPC, suggesting the presence of a minor population of pre-existing hormonal therapy-resistant cells in primary cancer.
- A 51-gene signature was developed to identify the CRPC-like cells in primary prostate cancer. This signature correlated with higher Gleason grade and poorer clinical outcomes in other prostate cancer patient cohorts, suggesting it may have prognostic potential.
- Together, these data demonstrate that significant cellular heterogeneity exists in primary prostate cancer, including the presence of a subset of cells that share molecular features with advanced, therapy-resistant CRPC. These pre-existing cells may contribute to therapy resistance and may carry important prognostic significance.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-5-lessons-from-primary-prostate-cancer/>**

Single cell RNA sequencing of prostate cancer of early and advanced stages



1. Primary adenocarcinoma
2. Castration resistant PCa
3. Metastatic CRPC
4. Small cell carcinoma

Cheng et al: Eur Urol. 2022 May;81:446-455.

Cellular Origins of Therapy Resistance / Biologic Features in Primary Prostate Cancer that may Inform Outcome or Therapy Response

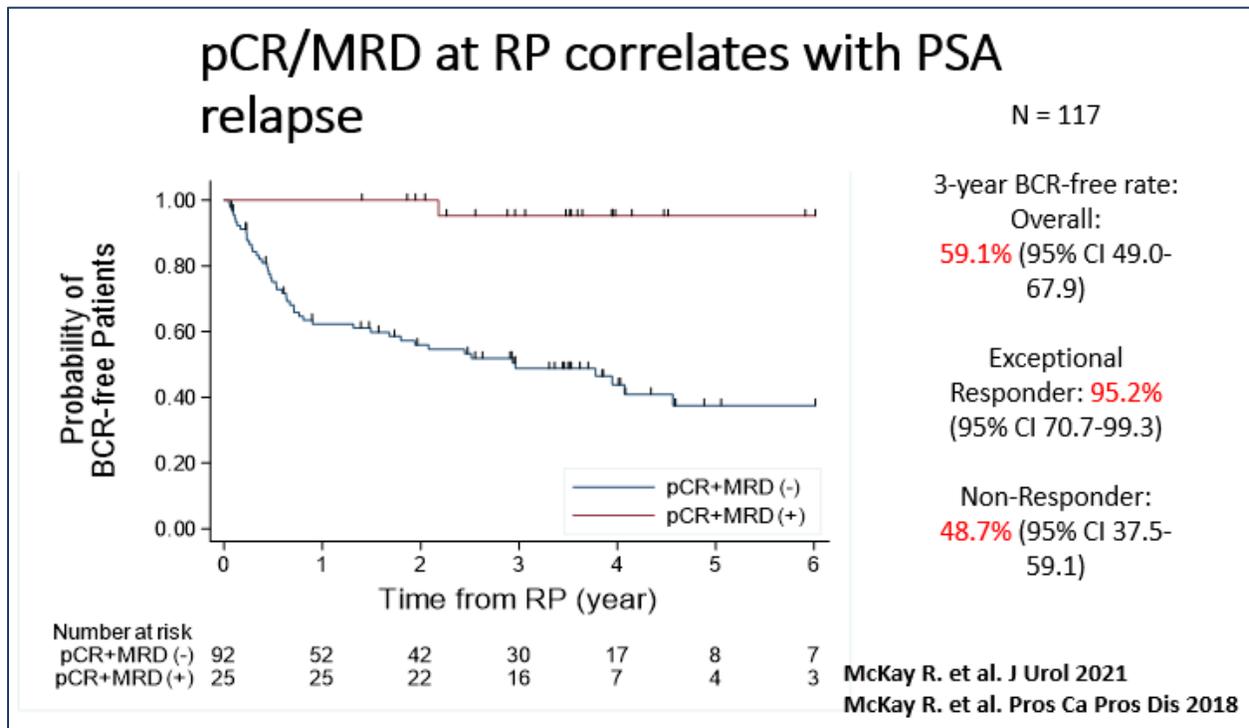
Mary-Ellen Taplin, MD

Dana-Farber Cancer Institute

Presented on behalf of Dr. Taplin by Steven Balk, MD, PhD (Beth Israel Deaconess Medical Center)

- Approximately 30% of patients diagnosed with localized prostate cancer are at high risk for relapse after primary treatment. Strategies to better identify and treat these patients are greatly needed.
- Neoadjuvant treatments are systemic therapies given prior to surgery, and are standard of care in cancers such as breast cancer; however, no neoadjuvant therapies have yet been proven effective in pivotal trials in patients with localized prostate cancer.
- The pathological endpoints of residual cancer burden (RCB) and pathological complete response (pCR) have been validated as surrogates for risk of relapse and other clinical outcomes such as overall survival (OS) in neoadjuvant breast cancer clinical trials. The clinical importance of pathological endpoints are not yet validated for prostate cancer.
- Dr. Mary-Ellen Taplin discussed contemporary neoadjuvant hormone therapy trials in patients with localized prostate cancer. While past trials which tested androgen deprivation therapy (ADT) alone failed to meet clinical significance, contemporary trials are testing more intense androgen-inhibiting treatment strategies, which combine ADT with second-generation androgen receptor (AR)-targeting agents, in better-selected patient populations.
- One recent neoadjuvant trial found that patients with localized prostate cancer who received ADT + abiraterone had better reductions in tissue androgen levels, and were more likely to have a pathological complete response (pCR) (10% vs. 4%) and minimal residual disease (MRD; 14% vs. 0%), compared with patients who received ADT alone.

- Similar results were seen in neoadjuvant trials testing other AR-targeting agents such as enzalutamide or apalutamide combined with ADT vs, ADT alone: better pathologic responses were typically seen with more intense androgen-inhibiting therapy regimens. Across these trials, ~10% of patients who received more intense AR-inhibiting therapy experienced pCR, and 20-40% experienced MRD (≤ 5 mm residual cancer).
- A study that evaluated long-term outcomes in patients previously enrolled in three different prostate cancer neoadjuvant trials found a significant correlation between pCR/MRD and PSA relapse: the PSA relapse rate at 3 years was 8% in patients who had experienced pCR or MRD after neoadjuvant treatment vs. 41% in patients who had not experienced pCR or MRD (**Figure**).
- A study that compared the long-term outcomes of neoadjuvant-treated patients with a matched cohort of patients that received surgery alone, found that neoadjuvant-treated patients had longer times to PSA recurrence and longer metastasis-free survival times. Of note, in this analysis, there were more patients with high-grade prostate cancer in the neoadjuvant-treated group than the surgery alone group.
- Studies are ongoing to develop biomarkers that will help to identify patients who are most likely to benefit from neoadjuvant treatment.
- Tumor genomics studies found that mutations in the *SPOP* gene were associated with pCR or MRD with neoadjuvant therapy, while *ERG*-mutations or *PTEN*-loss were associated with non-response. DNA repair gene alterations were not associated with responses.
- Studies on tumor gene expression found that high expression of androgen-regulated genes was associated with better responses to neoadjuvant therapy while high expression of TGF- β -regulated genes was associated with non-response.
- Ongoing studies are evaluating the impact of neoadjuvant therapy on immune responses and how they associate with clinical responses.
- The phase 3 PROTEUS trial is testing the efficacy of neoadjuvant apalutamide + ADT vs placebo + ADT in patients with localized or locally advanced prostate cancer who are candidates for radical prostatectomy. This trial will also validate whether the pCR/MRD pathological endpoints can predict metastasis-free survival; if proven, this will open the door to many more trials in this setting as pCR/MRD can be evaluated immediately after surgery, while conventional clinical trial endpoints take many years. The PROTEUS trial has completed accrual; results are expected in late 2023.
- The GUNS trial is multi-arm neoadjuvant trial testing high-intensity anti-androgen treatment plus various additional treatments in patients with localized prostate cancer, based on tumor genomic alterations. These include apalutamide (AR-axis alterations), docetaxel (tumor suppressor gene mutations), rucaparib (DNA repair gene alterations) and atezolizumab (MMR or *CDK12* mutations).
- The phase 2 Neptune trial is testing neoadjuvant olaparib + ADT in patients with high-risk localized prostate cancer who have germline or tumor alterations in *BRCA1/2*.
- A phase 2 trial led by Dana-Farber Cancer Institute will test the combination of neoadjuvant ADT + darolutamide + the CDK4/6-inhibitor abemaciclib.
- Altogether, these studies suggest that neoadjuvant treatments may be promising for patients with high-risk localized prostate cancer. Studies are ongoing to prove the efficacy of neoadjuvant treatments, validate the clinical pathological responses, and identify biomarkers and optimal neoadjuvant approaches for individual patients.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-5-lessons-from-primary-prostate-cancer/>**



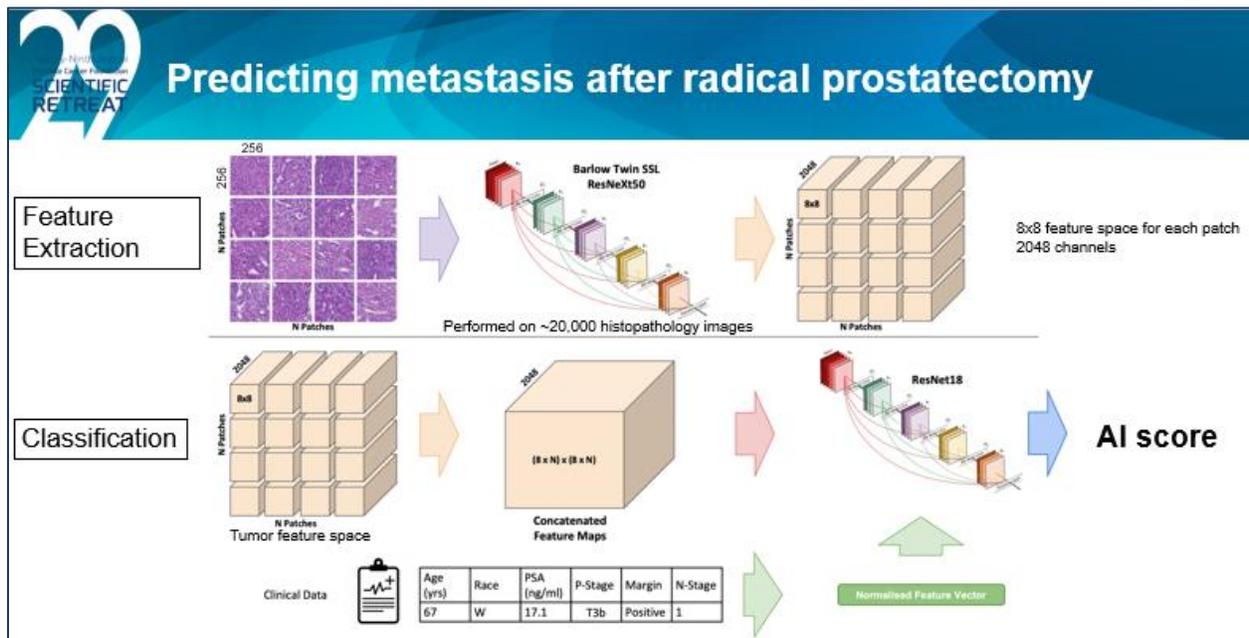
Predicting Prostate Cancer Outcome and Molecular Subtype with Artificial Intelligence

Tamara Lotan, MD
Johns Hopkins University

- Pathology data have been used to direct prostate cancer diagnosis and clinical management for over 50 years. Gleason grading methods were first described in 1966, and remain largely unchanged. While very helpful, pathology assessments are semi-quantitative, based entirely on tumor architecture with no assessment of nuclear and cytologic features, and have some degree of interobserver variability.
- Dr. Tamara Lotan discussed studies to develop machine learning and artificial intelligence (AI) technologies that may offer faster and improved cancer diagnosis and prognostication.
- Prior efforts to develop AI pathology tools have focused on tumor diagnosis and grading, and validation is based on pathologist-determined “ground truth”.
- Dr. Lotan and colleagues are developing AI pathology tools that are benchmarked against clinical outcomes (**Figure**).
- Pathology slides from a cohort of 724 patients who underwent radical prostatectomy and had long-term clinical follow-up data, 158 of whom developed metastases, were used to train an AI algorithm to predict metastasis after radical prostatectomy. The AI algorithm was then tested in a cohort of 181 patients who underwent radical prostatectomy, 40 of whom developed metastases.
- The AI algorithm had an 87.1% accuracy rate for predicting metastases using standard whole slide radical prostatectomy images and an 87.7% accuracy rate using tumor microarray images (~1 mm² samples of tumors). Accuracy increased to ~90% when

combined with clinical parameters (age, race, pre-op PSA, pathologic stage, and margin status) and Gleason grading. In comparison, the accuracy of predicting metastases using standard clinical parameters and pathology grading was ~85%.

- There are multiple molecular subtypes of prostate cancer, that can be identified by genomic sequencing or gene expression analyses. While tumor morphology can sometimes reflect molecular alterations in some cancer types, this is not observable in prostate cancer.
- A proof-of-principle study was done to investigate whether AI can be used to predict prostate cancer molecular subtypes from standard pathology slides.
- Pathology slides from 224 patients with tumor genomics data were used to train an AI algorithm to predict the presence of *ERG* mutations. The AI algorithm had an accuracy rate of 78-89% in different validation cohorts. In a separate but similar study, an AI algorithm was developed that had an accuracy rate of 83% for predicting the presence of *BRCA2*-alterations.
- Together, these data demonstrate the potential for AI and deep learning tools for predicting metastatic outcomes in patients with localized prostate cancer, using diagnostic tumor tissues as small as 1 mm². In addition, it may be possible to develop AI algorithms that can predict common tumor genomic alterations. Because not all patients have access to tumor genomic sequencing, such a tool would allow many more patients to access tumor molecular profiling and precision medicine using pathology slides.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-5-lessons-from-primary-prostate-cancer/>**



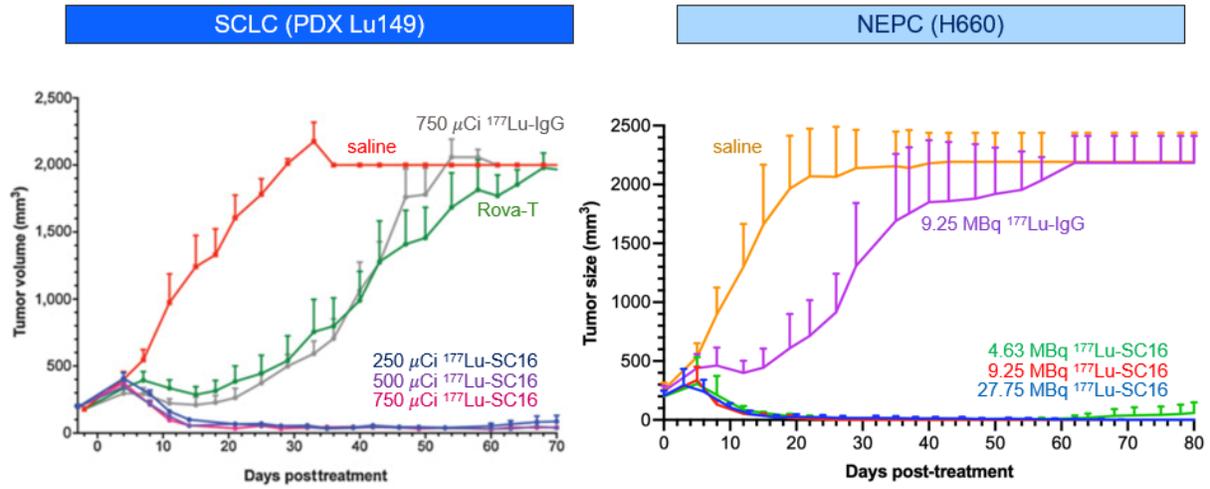
Lineage Plasticity in Cancers of the Lung and Prostate

Charles Rudin, MD, PhD

Memorial Sloan Kettering Cancer Center

- Lineage plasticity is a phenomenon in which cells can change their phenotype and take on characteristics of cells from other tissues. This is a normal process in early development, but these mechanisms are hijacked by cancer cells as a common mechanism for acquiring treatment resistance.
- Lineage plasticity leads to the development of small cell lung cancer (SCLC) from lung adenocarcinoma and to neuroendocrine prostate cancer (NEPC) from prostate adenocarcinoma. SCLC and NEPC are both “neuroendocrine” phenotypes, meaning they have lost adenocarcinoma features and gained features of neuroendocrine cells.
- Similar molecular mechanisms, including loss of the tumor suppressor genes *TP53* and *RB1*, contribute to the development of SCLC and NEPC. These cancer types may also share therapeutic vulnerabilities.
- To study the transition from lung adenocarcinoma to SCLC, Dr. Charles Rudin and team evaluated lung tumors that had both adenocarcinoma and SCLC regions. Several mechanisms were identified that contribute to this transition, stepwise.
- A CRISPR gene-deletion screen performed to identify vulnerabilities and chemo-sensitizing targets in SCLC, identified XPO1 as a novel target in SCLC.
- XPO1 was highly upregulated in SCLC and NEPC samples.
- Treatment with an XPO1-inhibitor slowed growth of SCLC and NEPC tumors in mice, and further synergized with platinum chemotherapy.
- XPO1-targeted treatments are available, such as Selinexor which is FDA-approved for multiple myeloma. These studies provide rationale for clinical trials testing these treatments in patients with NEPC and SCLC.
- Additional shared potential therapeutic targets in NEPC and SCLC include SOX2 and DLL3.
- A prior DLL3-targeted antibody-drug conjugate, Rova-T, showed initial efficacy but clinical development was halted due to significant toxicities.
- Dr. Rudin and colleagues are developing a novel DLL3-targeted radioligand treatment that consists of a DLL3-targeted antibody attached to the radioisotope 177-luteium. This treatment was highly effective in preclinical SCLC and NEPC models (**Figure**).
- In addition, Dr. Rudin and colleagues are developing a DLL3-targeted PET imaging strategy, that can be used to identify patients with SCLC and NEPC, and to select patients for treatment with DLL3-targeted treatments. Promising results have been seen with this imaging agent in first-in-human studies.
- These studies may ultimately lead to new treatments for these highly lethal cancer subtypes, as well as other aggressive neuroendocrine cancers.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-5-lessons-from-primary-prostate-cancer/>**

Targeting DLL3 in SCLC and NEPC : ^{177}Lu radioconjugate therapy



Tully et al. *Clin Cancer Res.* 2022
 Korsen et al. *Proc Natl Acad Sci U S A.* 2022

Session 6: Genetic, Epigenetic, Epitranscriptomic and Post-Translational Mechanisms and Clinical Heterogeneity in Prostate Cancer

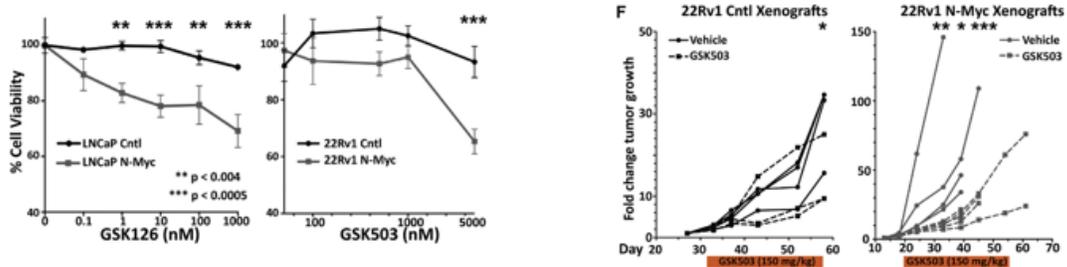
Genetic Determinants of Clinical Heterogeneity in Prostate Cancer

Brian Robinson, MD
Weill Cornell Medicine

- Approximately 75% of patients with localized prostate cancer have multifocal disease, meaning multiple separate primary tumors, in the prostate at the time of diagnosis. These can vary in clinical and molecular features including location, size, grade, genomic alterations, and potential to progress to metastatic and lethal disease. The clinical behavior of tumors and their morphology do not always correspond with molecular alterations.
- Dr. Brian Robinson discussed studies on the genomic and epigenomic heterogeneity of prostate cancer.
- Tumors progress and become metastatic or resistant to treatments by adapting to their environment. Often, this is through the acquisition of genomic alterations. However, tumors can change phenotypes and behavior through epigenomic alterations.
- Epigenomics is a major mechanism that regulates cell phenotype and behavior by chemically modifying DNA to promote or prevent gene transcription.
- Whether tumor cells can be reverted to a previous state, such as resensitization to a treatment they have become resistant to, is a question of interest. While genomic alterations cannot be “undone,” it may be possible to reverse epigenetic alterations.
- CHD1 is a chromatin remodeling protein that regulates epigenomics. Loss of CHD1 is seen in about 10% of prostate cancer cases, suggesting that CHD1 is a tumor suppressor gene.
- Loss of CHD1 resulted in increased expression of AR-driven oncogenic pathways in prostate cancer cells, and promoted tumor growth in prostate cancer mouse models.
- SPOP is a tumor suppressor gene that is commonly lost with CHD1. Loss of SPOP also promoted tumor growth in prostate cancer mouse models. Studies in both patients and mouse models have found that SPOP-mutant prostate cancer is much more sensitive to treatment with ADT than SPOP-normal prostate cancer.
- Neuroendocrine prostate cancer (NEPC) is a highly aggressive form of advanced castration-resistant prostate cancer (CRPC) that have lost prostate cell features and gained features of neuroendocrine cells. NEPC can be driven by genomic alterations such as mutations in *N-MYC* and loss of *RB1*. NEPC also commonly overexpresses the epigenomic regulatory protein EZH2.
- How best to identify NEPC remains to be determined, as not all tumors with NEPC-behavior express conventional neuroendocrine genes or have NEPC-associated genomic alterations.
- Epigenetic treatments, such as inhibitors of EZH2 or Aurora Kinase, are being studied for their potential to prevent progression to NEPC and/or to restore sensitivity to AR-targeted therapy. Preclinical studies have found that EZH2 inhibitors prevent NEPC cell growth (**Figure**).
- Whether epigenetic modifiers can be used to prevent prostate cancer development in the first place, warrants further study.

- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-6-genetic-epigenetic-epitranscriptomic-and-post-translational-mechanisms-and-clinical-heterogeneity-in-prostate-cancer/>

Cell viability and growth rate reduced with inhibition of histone methyltransferase EZH2



Dardenne et al. 2016 *Cancer Cell*.

Session 7: Next Generation Prostate Cancer Theranostics and Combination Therapies

Immunomodulation of Tumor Microenvironment with Molecular Targeted Radiotherapy to Facilitate Response to Combination Therapies

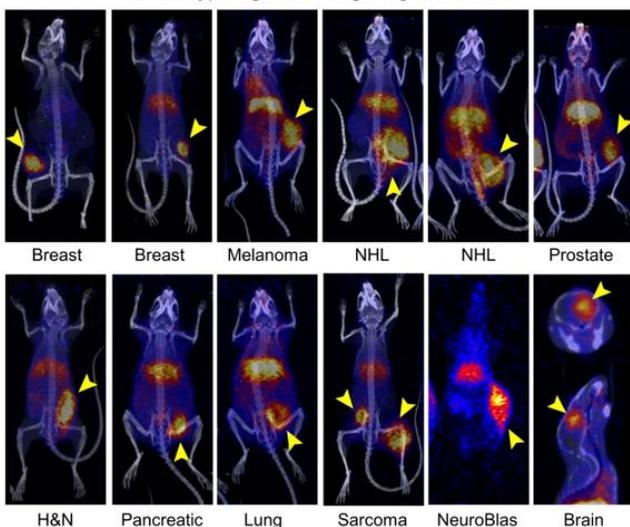
Zachary Morris, MD, PhD
University of Wisconsin

- Radiation therapy can directly kill tumor cells by damaging their DNA, and can also promote anti-tumor immune responses. These effects suggest that radiation therapy and immunotherapy may be synergistic.
- Dr. Zachary Morris discussed studies on combining a novel tumor-targeted radiation therapy with immunotherapy.
- NM600 is an alkylphosphocholine analog that selectively targets the membranes of most tumor cells. NM600 can be conjugated to radioactive isotopes, such as ^{90}Y , and thus has promise as a radionuclide therapy – an injectable treatment that targets radiation to tumors throughout the body.
- Preclinical studies in mouse tumor models found that NM600 can target a broad range of tumor types, including prostate cancer, and has other desirable pharmacokinetic and theranostic properties (**Figure**).
- Studies in mouse tumor models found that low-dose ^{90}Y -NM600 had limited anti-tumor activity alone, but was strongly synergistic with checkpoint immunotherapy.
- The combination of low-dose ^{90}Y -NM600 + checkpoint immunotherapy was found to promote expression of inflammatory genes in tumors and enhance tumor infiltration by T cells. Thus, this treatment combination effectively turned immunologically “cold” tumors “hot.” These tumor-infiltrating T cells were found to be clonal, suggesting that they are targeting tumor cells.
- The efficacy of this treatment combination was found to depend on the STING/type I interferon response pathway. The treatment combination had decreased anti-tumor activity in mice genetically lacking STING.
- There are various radioisotopes that can be used in radionuclide therapy, which differ in type of decay (emission of alpha vs beta particles), half-life, range in tissues, and linear energy transfer. Ongoing studies are evaluating how these properties may influence the immuno-biologic effects of a radionuclide therapy in the tumor microenvironment.
- Preclinical studies are now comparing the anti-tumor efficacy of immune checkpoint blockade when combined with NM600 attached to different radioisotopes, to identify optimal treatment strategies for prostate and other cancer types.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-7-next-generation-prostate-cancer-theranostics-and-combination-therapies/>**

Tumor targeting by NM600 is broad



Tumor-type agnostic targeting of NM600



Desirable features for immunoradiobiology

- Limited albumin binding
- Membrane uptake – radionuclide trapping
- Hepatic excretion
- Theranostic for dosimetry/patient selection
- Cross-species uptake enables clinical translation
- No known sanctuary sites in the body
- Comparative and mixed radionuclide studies
- Pan-tumor applications mirrors immunotherapy

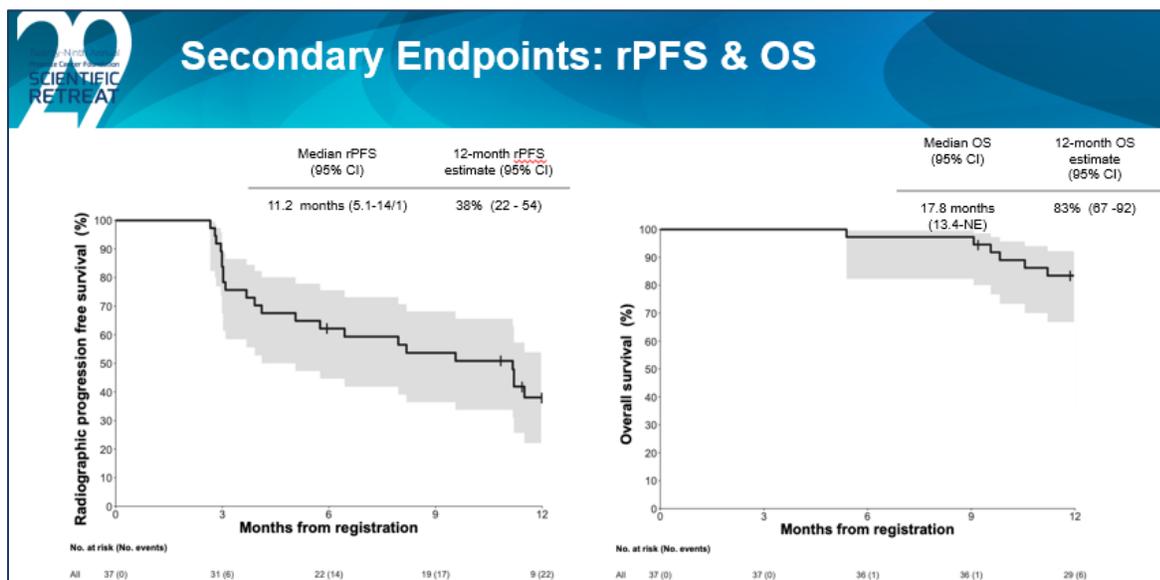
Grudzinski et al., JNM, 2019

Combination of PSMA-targeted Radiopharmaceutical Therapy and Immunotherapy for mCRPC

Shahneen Sandhu, MBBS
Peter MacCallum Cancer Centre, Australia

- ^{177}Lu -PSMA-617 (LuPSMA) is a systemically delivered form of targeted radiation that significantly improves radiographic progression free survival (rPFS) and overall survival (OS) in patients with metastatic castration-resistant prostate cancer (mCRPC), and was recently FDA-approved for mCRPC. However, patients treated with LuPSMA eventually progress and further optimization remains needed.
- Radiation therapies are thought to cause cancer cells to die in a way that alerts the immune system, and thus may synergize with immunotherapy.
- Dr. Sandhu and team led the phase 1b/2 PRINCE trial, to test the combination of LuPSMA (6 cycles, every 6 weeks) with the immunotherapy pembrolizumab (up to 35 cycles, every 3 weeks) in 37 patients with mCRPC.
- Overall, rPFS and OS rates at 12 months were 38% and 83%, respectively.
- The PSA response rate was 76%
- Some patients have had deep and durable responses. For instance, one case was presented in which an 81-year-old man experienced a complete response lasting over 60 weeks.
- Toxicities were consistent with those of single agent LuPSMA and pembrolizumab.
- Biomarker analysis is ongoing to understand the biological effects of the combination and define predictors of response and resistance.

- Additional trials at Peter MacCallum Cancer Centre are testing LuPSMA in combination with other agents or in different clinical spaces.
- EVOLUTION is a phase II study of LuPSMA vs LuPSMA + ipilimumab and nivolumab in patients with mCRPC (ANZUP 2001).
- LumOnate is a Phase Ib trial of LuPSMA + olaparib and pembrolizumab in patients with mCRPC.
- LuTectomy is a prospective Phase I/II study of LuPSMA given prior to surgery. This study has been completed and results will be reported soon.
- The team also hopes to undertake a trial testing LuPSMA + an ATR-inhibitor + anti-PD-1/PDL-1 immunotherapy.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-7-next-generation-prostate-cancer-theranostics-and-combination-therapies/>**

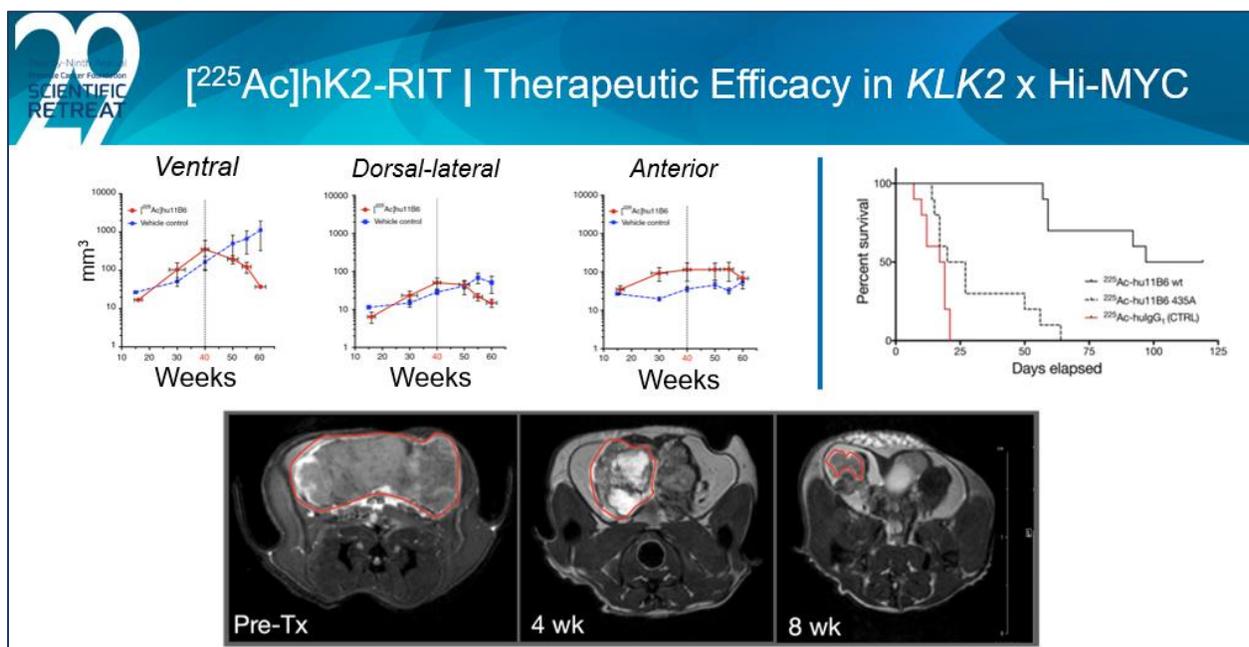


hK2 Targeted Radioimmunotheranostics for Prostate Cancer

David Ulmert, MD, PhD
University of California, Los Angeles

- hK2 (Human Kallikrein Related Peptidase 2) is a protein that is highly similar to PSA: they are 80% identical, and the expression of both is controlled by the androgen receptor (AR). They are specifically and highly expressed in the prostate and prostate cancer but not in other normal tissues. Thus hK2 may be a promising target for prostate cancer imaging and therapy.
- Dr. David Ulmert discussed studies on the development of hK2-targeting theranostics for prostate cancer.
- An antibody that specifically binds to the active form of hK2 was developed. hK2 is active in prostate tissues and becomes rapidly inactivated upon entering the bloodstream. Thus, this antibody can only target hK2 in prostate tissues.

- The hK2-antibody was developed into a PET imaging probe by attaching it to ^{89}Zr , and could image prostate tumors in various mouse models and non-human primates.
- A fluorescent probe is being developed from the hK2-antibody, as a tool for imaging prostate cancer during surgery.
- In addition, an hK2-targeting radioligand therapy is being developed using this antibody. In studies in mice, this agent targeted sites of prostate cancer and had therapeutic efficacy (**Figure**). Studies are being done to evaluate mechanisms of resistance to this therapy.
- A first-in-human phase 0/1 trial has been initiated to evaluate the performance of a ^{111}In -hK2-SPECT imaging agent developed using this hK2-targeted antibody, compared with PSMA PET. In preliminary results, hK2 SPECT was able to image known metastases in all patients, with no evidence of abnormal organ accumulation.
- A phase I dose-escalating study evaluating ^{225}Ac -labeled hK2-targeted alpha therapy is ongoing in parallel with the SPECT imaging trial.
- Together, these studies demonstrate promise for hK2-targeted theranostics for prostate cancer imaging and treatment. Additional studies are warranted.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-7-next-generation-prostate-cancer-theranostics-and-combination-therapies/>**



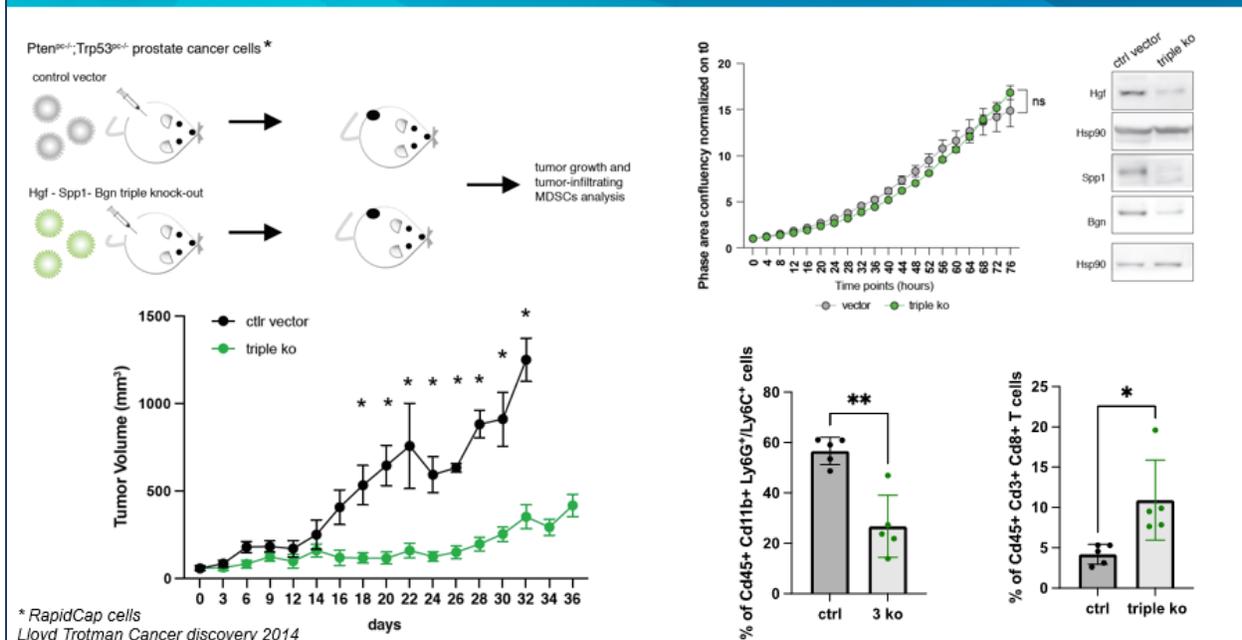
Session 8: Investigating the Path from PI3K to Protein Synthesis to Tailor Prostate Cancer Therapy

Therapeutic Targeting of the Translational Machinery Blocks MDSCs and Enhances Anti-Tumor Immunity in Prostate Cancer

Daniela Brina, PhD
Institute of Oncology Research, Switzerland

- Myeloid-derived suppressor cells (MDSCs) are a type of immune cell that suppresses anti-tumor immune responses and promotes tumor growth. In prostate cancer, MDSCs are often the main type of immune cells found in tumors, and their numbers tend to increase with tumor aggressiveness and correlate with poor prognosis.
- Dr. Daniela Brina discussed the therapeutic potential and strategies for targeting MDSCs in prostate cancer.
- CXCR2 is a protein on MDSCs that enables them to be recruited into tumors. Inhibition of CXCR2 reduced MDSC recruitment into tumors in prostate cancer mouse models.
- A study was done to identify proteins involved in interactions between prostate cancer cells and MDSCs.
- Interestingly, prostate cancer cell proteins that had higher translation efficiency (a higher number of proteins produced per mRNA) were largely involved in immune cell recruitment. This suggests that influencing immune cell recruitment to tumors is a “priority” for tumor cells.
- Several interaction-partners identified between tumors and MDSCs were found to promote MDSC migration and enhance their ability to suppress T cells.
- Deletion of three of these MDSC-interaction genes (*Bgn*, *Spp1* and *Hgf*) in prostate cancer cell mouse models resulted in reduced MDSC recruitment and tumor growth (**Figure**). Levels of these genes correlated with MDSC levels in tumors from patients.
- Initiation of protein translation was found to be the major rate-limiting step for the production of these three MDSC-recruitment proteins.
- Treatments that block translation initiation decreased levels of MDSC-recruitment proteins without affecting levels of proteins that did not have high translation efficiency. Additionally, this treatment reduced tumor growth and recruitment of MDSCs, and increased anti-tumor immune responses.
- The efficacy of combining treatments that block translation initiation with other treatments such as immunotherapy, is under investigation.
- Overall, these studies demonstrate that the protein translation machinery is a promising treatment target in prostate cancer. Targeting this machinery preferentially reduces the expression of genes that recruit immune-suppressive MDSCs into tumors, which may enhance the efficacy of immunotherapy in prostate cancer.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-8-investigating-the-path-from-pi3k-to-protein-synthesis-to-tailor-prostate-cancer-therapy/>**

Combined deletion of Bgn, Spp1 and Hgf dampen MDSCs recruitment and tumor growth



Defining the Therapeutic Selective Dependencies for Distinct Subtypes of PI3K Pathway- Altered Prostate Cancers

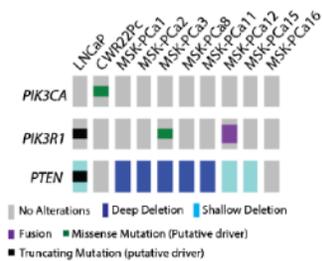
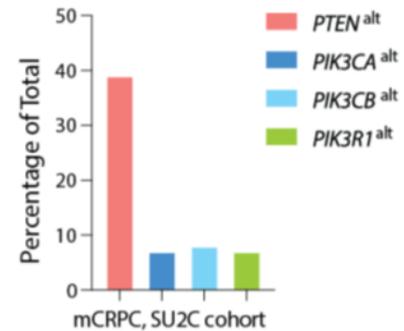
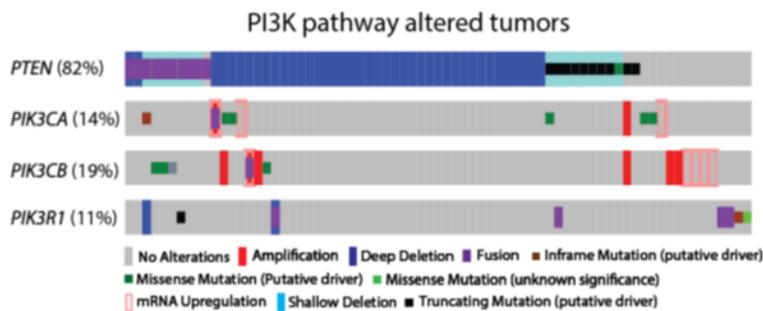
Brett Carver, MD
Memorial Sloan Kettering Cancer Center

- The PTEN/PI3K pathway is an important cellular pathway that regulates many aspects of cell growth, proliferation, and cell death. This pathway is commonly mutated in cancer, including in ~40-50% of metastatic castration-resistant prostate cancer (mCRPC) cases, and is a promising therapeutic target.
- Dr. Brett Carver discussed the biology and therapeutic targeting of PTEN/PI3K pathway alterations in mCRPC.
- Treatments that target various proteins in the PTEN/PI3K pathway have been developed, but single-agent treatments alone have had limited therapeutic success in prostate cancer clinical trials. This is because inhibition of the PI3K pathway results in activation of the androgen receptor (AR) pathway, and vice-versa. Treatment combinations that inhibit both pathways are being investigated.
- Recently, a phase 3 trial tested abiraterone combined with the PI3K pathway-inhibitor ipatasertib vs. placebo in patients with mCRPC with broadly-defined PTEN alterations. A 2.0-month improvement in median radiographic progression free survival was observed with ipatasertib. However, a subgroup analysis in patients with certain genomic alterations in the PTEN/PI3K pathway found a 4.9-month improvement in median radiographic progression free survival with ipatasertib. This suggests that biomarkers are needed to better select patients likely to benefit from this treatment combination.

- The most common mutations in mCRPC that result in activation of the PI3K pathway include *PTEN*-loss (82%), and mutations in *PIK3CA* (14%), *PIK3CB* (19%), and *PIK3R1* (11%) (**Figure**). These mutations can co-occur in some patients, though how these mutations interact and impact oncogenic signaling pathways and treatment responses is unclear.
- A prostate cancer model with a *PIK3CA*-mutation and normal *PTEN* status was highly sensitive to treatment with a P110-alpha-inhibitor combined with an AR-inhibitor, but was not responsive to an inhibitor of AKT (the downstream effector of the PI3K pathway).
- In a prostate cancer model with a *PIK3CA*-mutation and *PTEN*-loss, treatment with a P110-alpha-inhibitor was ineffective, though a pan-PI3K-inhibitor and an AKT-inhibitor (ipatasertib) had efficacy.
- Some prostate cancer models with *PTEN*-loss were found to be dependent on P110-alpha and others on P110-beta; the mechanisms that drive these different dependencies remain unknown. In these models, pan-PI3K-inhibitors or AKT-inhibitors may be needed.
- Pathways that activate the PI3K pathway can also modulate tumor biology and the efficacy of different PI3K pathway inhibitors. For instance, prostate cancer models with activation of the IGF1R pathway were resistant to PI3K inhibition but sensitive to AKT inhibition.
- In several models, acquired resistance to AKT-inhibitors was driven by restored mTOR signaling. The addition of mTOR inhibitors restored sensitivity to AKT-inhibitors in these models.
- Ongoing studies are investigating the mechanisms of response and resistance to various types of PI3K and AKT-inhibitors.
- Collectively, these studies demonstrate that different treatment strategies are needed for tumors with different types of PTEN/PI3K alterations. Developing biomarkers to match patients with optimal treatments strategies remains needed.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-8-investigating-the-path-from-pi3k-to-protein-synthesis-to-tailor-prostate-cancer-therapy/>**

Defining the therapeutic selective dependencies for distinct subtypes of PI3K pathway-altered prostate cancers

Ninghui Mao^{1,10}, Zeda Zhang^{1,2,10}, Young Sun Lee¹, Danielle Choi¹, Aura Agudelo Rivera¹, Dan Li¹, Cindy Lee¹, Samuel Haywood^{3,4}, Xiaoping Chen⁵, Qing Chang⁵, Guotai Xu¹, Hsuan-An Chen², Elisa de Stanchina⁵, Charles Sawyers^{1,6}, Neal Rosen⁷, Andrew C. Hsieh⁸, Yu Chen^{1,9} & Brett S. Carver^{1,3,4}✉



The Androgen Receptor Regulates a Druggable Translational Regulon in Advanced Prostate Cancer

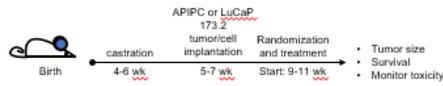
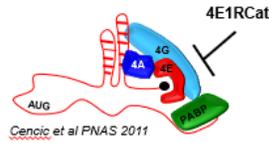
Andrew Hsieh, MD
Fred Hutchison Cancer Center

- A hallmark of cancer is rapid cell growth, requiring high levels of protein production.
- Translation of mRNA to protein is a complex process that requires coordination between various types of RNA (tRNA, rRNA, mRNA) and proteins (eIFs, eEFs, RPs).
- The androgen receptor (AR) is the primary driver of prostate cancer cell growth and proliferation. However, AR activity is lost in advanced forms of castration-resistant prostate cancer (CRPC).
- Dr. Andrew Hsieh discussed how alterations in mRNA translation contribute to prostate cancer progression and to the development of aggressive AR-low/independent CRPC.
- In a genetic mouse model of prostate cancer, androgen deprivation resulted in increased tumor cell proliferation and loss of AR expression, mimicking what can happen in AR-low prostate cancer or neuroendocrine prostate cancer.
- In this model, AR-low prostate tumors exhibited a significant increase in protein synthesis.
- The associated mechanism was found to be loss of 4EBP1, a protein that negatively regulates protein synthesis. Loss of 4EBP1 was also observed in human AR-low prostate

cancer cases. Expression of 4EBP1 was found to be directly regulated by AR, and could be restored in AR-low models by treatment with androgens.

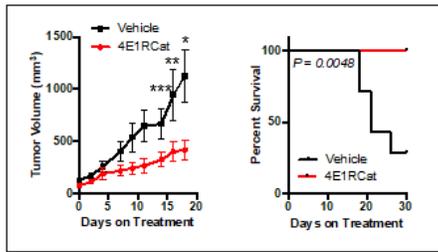
- These studies demonstrated that AR regulates protein synthesis directly through 4EBP1, and that loss of AR results in loss of 4EBP1 which increases mRNA translation.
- The proteins that were increased in AR-low prostate cancer were found to have a “guanine-rich translational element” in their mRNA sequences; these included cell proliferation proteins.
- Through further modeling, it was found that the translation initiation complex was required for the increased tumor growth rate in AR-low prostate cancer.
- In mouse models, the growth of AR-low/independent prostate cancer subtypes were blocked by an experimental treatment that inhibits the translation initiation complex. The treatment had no effect in AR-proficient models (**Figure**).
- The team is now working to develop clinical-grade translation inhibitors.
- Alterations in mRNA may also impact mRNA translation and influence prostate cancer progression.
- The 5' untranslated region (UTR) of mRNA is critical for determining how many copies of proteins can be made.
- Sequencing of mRNA from 226 prostate cancer cases identified over 2,200 point-mutations in 5' UTRs. 259 genes were found to have recurrent mutations. Approximately 1/3 of the 5' UTR mutations were found to impact mRNA translation or transcription.
- For example, a mutation in the 5' UTR of the *FGF7* gene was found to create a binding site for the oncogenic driver MYC, resulting in higher levels of FGF7 mRNA.
- In another example, a mutation in the 5' UTR of the *CKS2* gene created a new translation start site, which resulted in high levels of a longer, mutant form of CKS2.
- 5' UTR mutations in the MAPK pathway were found to be enriched in prostate cancer and were associated a 2-fold increased risk for metastatic prostate cancer at diagnosis.
- Ongoing studies are evaluating the landscape and impacts of mutations in the 3' UTR of mRNA in prostate cancer.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-8-investigating-the-path-from-pi3k-to-protein-synthesis-to-tailor-prostate-cancer-therapy/>**

AR low prostate cancer is more sensitive to eIF4E/eIF4G disruption than AR proficient prostate cancer

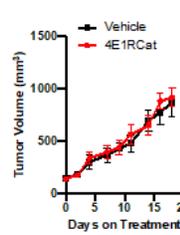


Next step: Developing new 4E inhibitors through AI-assisted approaches

AR-null
 APIPC
 Xenograft

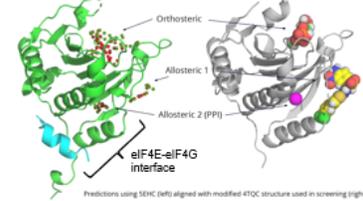


AR+ parental
 Xenograft



CYCLICA

Pocket selection



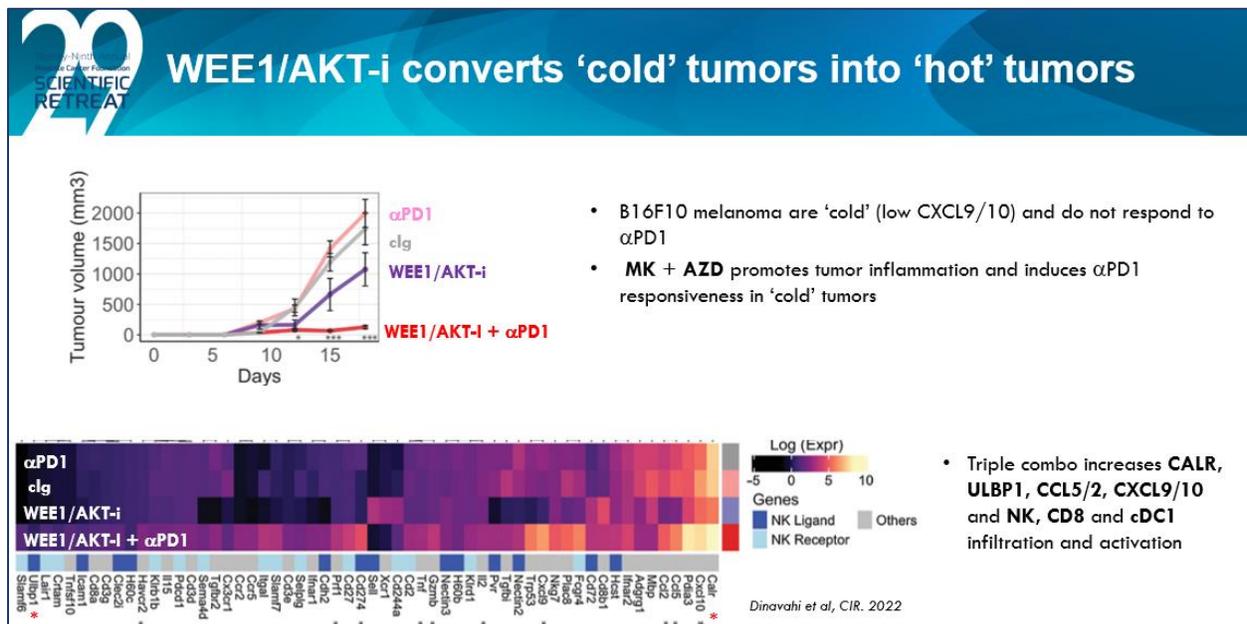
Session 9: Combining Immunomodulatory Treatments for Prostate Cancer

Targeting P53 to Induce ICB Response in Cold Tumors

Nicholas Huntington, PhD
Monash University, Australia

- Immunotherapy strategies for cancer have largely focused on activating T cells, a type of immune cell with the ability to recognize target cells that express specific antigens and potently kill them.
- T cell-based immunotherapies include checkpoint immunotherapy (anti-PD1, anti-PDL1, anti-CTLA4), CAR T cells, and bispecific T cell engagers.
- However, many tumor types, including prostate cancer, do not respond well to these classes of immunotherapies.
- The efficacy of T cell immunotherapies typically requires tumors to have high numbers of protein mutations, which become the antigens the T cells can recognize. The T cells must also be able to easily enter and function within tumors. Most prostate cancers do not have many protein mutations and have highly immunosuppressive tumor microenvironments, which prevents the efficacy of T cell immunotherapies.
- Dr. Nicholas Huntington discussed alternative strategies focused on using Natural Killer (NK) cells for cancer immunotherapy.
- NK cells recognize target cells in a different way than T cells, but have a similar capacity to kill them. Rather than recognizing antigens, NK cells recognize and target cells that express certain stress signals or are missing certain “self” antigens.
- Preclinical studies have found that NK cells are required for optimal control of solid tumors and for CD8 T cell responses to checkpoint immunotherapy. This is likely due to the production of immune-activating signals by NK cells.
- Tumor cell death via p53 causes upregulation of stress signals (MICA, MICB, and CALR) recognized by the NK receptors NKG2D and NKp46. Mechanisms to increase p53 activity in tumor cells may increase NK cell recognition of tumor cells.
- Dr. Huntington and team found that combining treatments that target the AKT and WEE1 pathways (which block p53), upregulated p53 levels in tumor cells and increased expression of stress ligands recognized by NKG2D and NKp46.
- A combination treatment with an AKT-inhibitor + WEE1-inhibitor + anti-PD1 was highly effective in mouse melanoma models (**Figure**). This combination increased expression of NK ligands, immune-activation molecules, and tumor infiltration with NK cells, T cells, and other anti-tumor immune cells (**Figure**). The efficacy of this combination required NK cells, T cells, and p53.
- IL-15 is a critical immunostimulatory protein that activates T cells and NK cells. IL-15 levels in patients are highly correlated with overall survival.
- IL-15 activity was found to be negatively regulated by the CISH protein. Deletion of the *CISH* gene in NK cells and CD8 T cells significantly enhanced their activation by IL-15 and increased their ability to block tumor growth in preclinical models.

- Together, these studies identify several promising NK cell-based immunotherapy strategies, including combination treatment with AKT-inhibitor + WEE1-inhibitor + anti-PD1, and treatments to increase IL-15 activity. Additional studies are warranted.
- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-9-combining-immunomodulatory-treatments-for-prostate-cancer/>

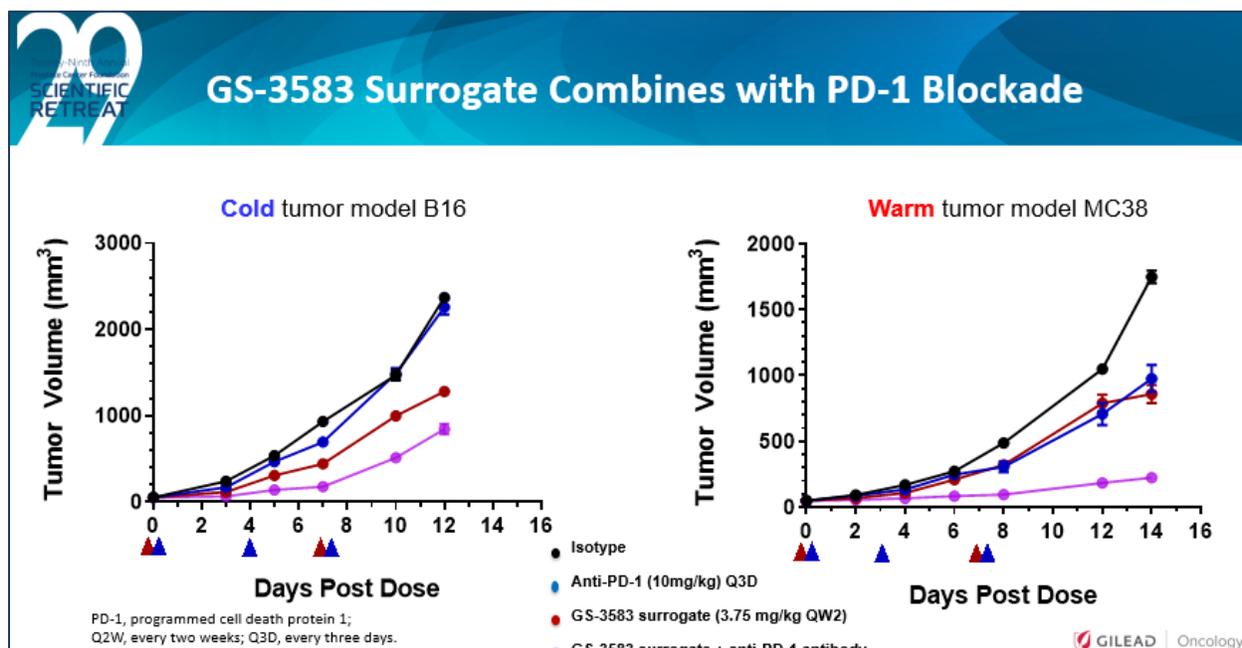


Engaging FLT3 to Promote Dendritic Cell Expansion & Drive the Adaptive Anti-Tumor Immune Response

Michelle Kuhne, PhD
Gilead Sciences

- Dendritic cells (DCs) are a type of immune cell that play a primary role in alerting and activating T cells against pathogens and cancer, and are required for the efficacy of certain cancer immunotherapies, such as anti-PD1 or anti-PDL1.
- Dendritic cell proliferation and activation can be driven by FLT3-ligand. As such, FLT3-ligand based treatments are being developed and tested for patients with cancer and infectious diseases.
- Dr. Michelle Kuhne discussed the development of FLT3-ligand based treatments for cancer.
- A FLT3-agonist, GS-3583, was developed with comparable activity to manufactured FLT3-ligand, however with improved pharmacokinetic properties extending the half-life of FLT3-ligand.
- GS-3583 exhibited anti-tumor efficacy in mouse tumor models, increased the numbers of dendritic cells in blood and tumors, and increased the numbers of CD8 T cells in tumors.
- GS-3583 had synergistic anti-tumor activity when combined with anti-PD1 in several tumor models, including a model that was non-responsive to anti-PD1 alone (**Figure**).

- A phase 1a trial tested the safety and pharmacokinetics of GS-3583 in healthy volunteers. This trial validated that GS-3583 can increase the numbers of dendritic cells in humans, and was used to establish an optimal dosing regimen.
- Altogether, these studies suggest that activation of FLT3 with GS-3583 will increase dendritic cell numbers, and may increase the efficacy of checkpoint immunotherapy in patients with cancer, including in patients with immunologically “cold” tumors, such as prostate cancer. Further studies are warranted.
- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-9-combining-immunomodulatory-treatments-for-prostate-cancer/>

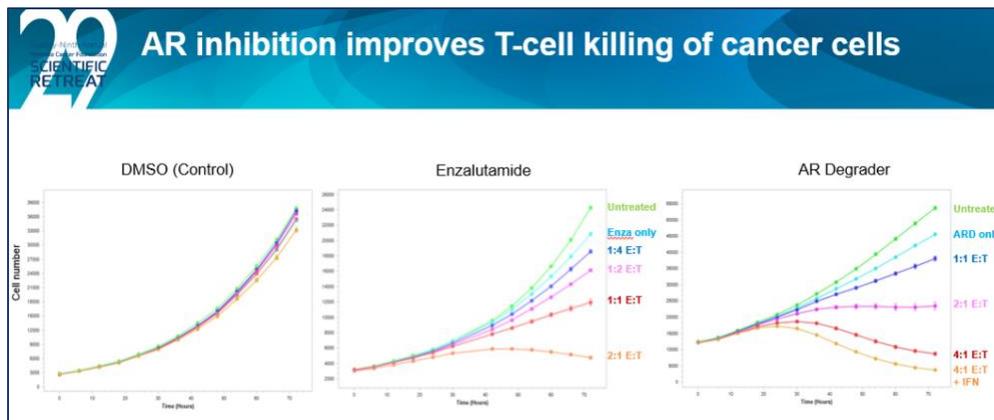


Leveraging an Interplay Between Hormone Receptor Signaling and Immune Recognition to Enhance Immunotherapy in Prostate Cancer

Lisa Chesner, PhD
University of California, San Francisco

- Immune checkpoint blockade has had limited efficacy in metastatic castration-resistant prostate cancer (mCRPC). Pembrolizumab is indicated for patients with mismatch repair (MMR) mutations, which are present in 3-5% of patients. There is a great need to better understand the mechanisms that control anti-tumor immune responses, to improve immunotherapy.
- CD8 T cells are a primary tumor-killing immune cell type. CD8 T cells are activated by recognizing small protein fragments called antigens, which cancer cells present within a protein complex called MHC Class I.
- Dr. Lisa Chesner discussed studies on MHC Class I in prostate cancer.

- Prostate cancer was found to have low levels of MHC Class I. This indicates that increasing MHC expression on prostate cancer cells may increase antigen presentation and improve the efficacy of checkpoint inhibitors.
- Using a whole-genome CRISPR screen, the androgen receptor (AR) was found to be associated with low MHC levels. AR-inhibition resulted in increased MHC expression and improved T cell killing of cancer cells (**Figure**).
- Evaluation of patient samples from a pembrolizumab clinical trial found that patients with mCRPC who responded to pembrolizumab had low AR activity and high MHC Class I levels.
- Together, these data demonstrate that a critical immune-activating pathway is inhibited by AR and increased by AR-inhibition in prostate cancer.
- These data suggest strategies for combining immunotherapy with AR-inhibitors, and may lead to the development of biomarkers to identify patients most likely to respond to immunotherapy.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-9-combining-immunomodulatory-treatments-for-prostate-cancer/>

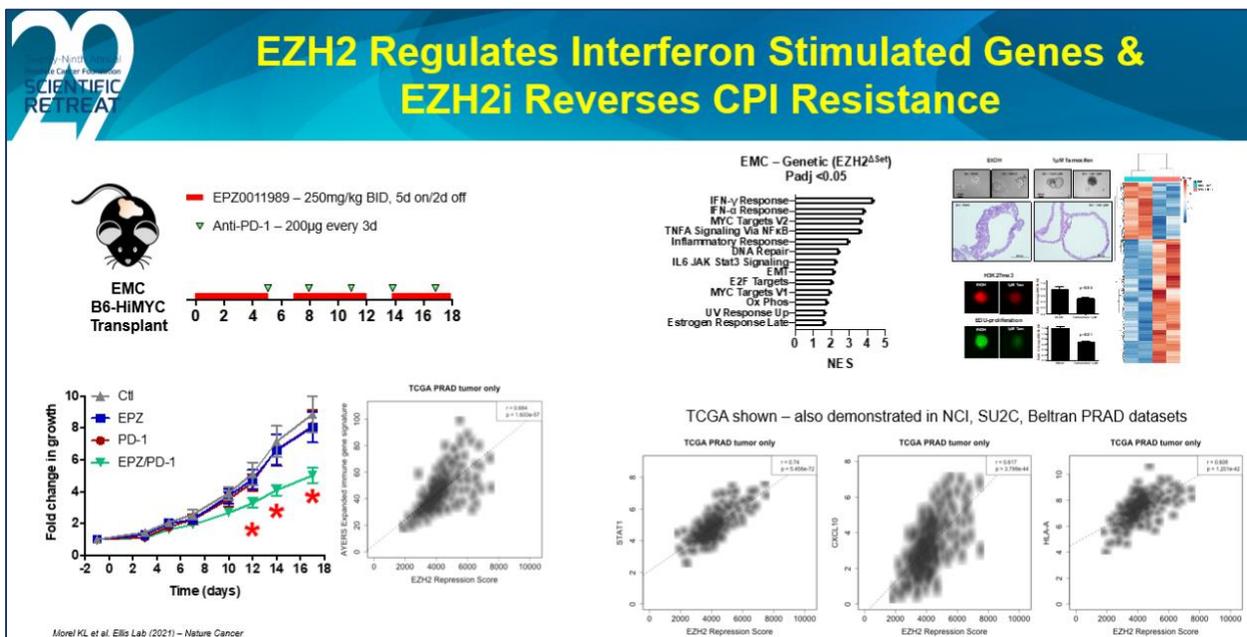


EZH2 Inhibition Reprograms the Tumor Microenvironment to Potentiate Response to Checkpoint Inhibition

Leigh Ellis, PhD
Cedars Sinai Medical Center

- Epigenomics are chemical modifications on DNA that alter its 3D structure to regulate gene expression. Epigenomics are the major regulatory mechanism that ensures different cell types have different phenotypes and functions despite having the same genome, for instance, prostate cells vs. brain cells.
- Epigenomic alterations also drive cancer cell progression and the development of resistance to treatments, and can impact immune responses to tumors.
- Dr. Leigh Ellis discussed the role of epigenomic alterations in immune responses to prostate cancer.
- EZH2 is an epigenetic regulator that is commonly altered in prostate cancer.

- EZH2 activity was found to be negatively associated with immune activation signatures in prostate cancer samples.
- An EZH2-inhibitor was synergistic with anti-PD1 immunotherapy in a prostate cancer mouse model. Tumors treated with this combination or with the EZH2-inhibitor alone had significantly higher levels of T cell infiltration, but lower levels of immune-suppressive macrophages.
- The EZH2-inhibitor was found to promote expression of genes that are usually activated in response to viral infections, which alert the immune system. This “viral mimicry” was found to be due to reactivation of endogenous retrovirus gene expression by EZH2-inhibition.
- Activation of immune responses following EZH2-inhibition required the STING pathway, a major driver of anti-viral immune responses.
- These data suggest that EZH2-inhibition in combination with anti-PD1 immunotherapy may have promise for the treatment of prostate cancer.
- In ongoing studies, surgical samples from prostate cancer patients being treated with an EZH2-inhibitor prior to prostatectomy are being evaluated for the impact of the treatment on anti-tumor immune responses.
- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-9-combining-immunomodulatory-treatments-for-prostate-cancer/>



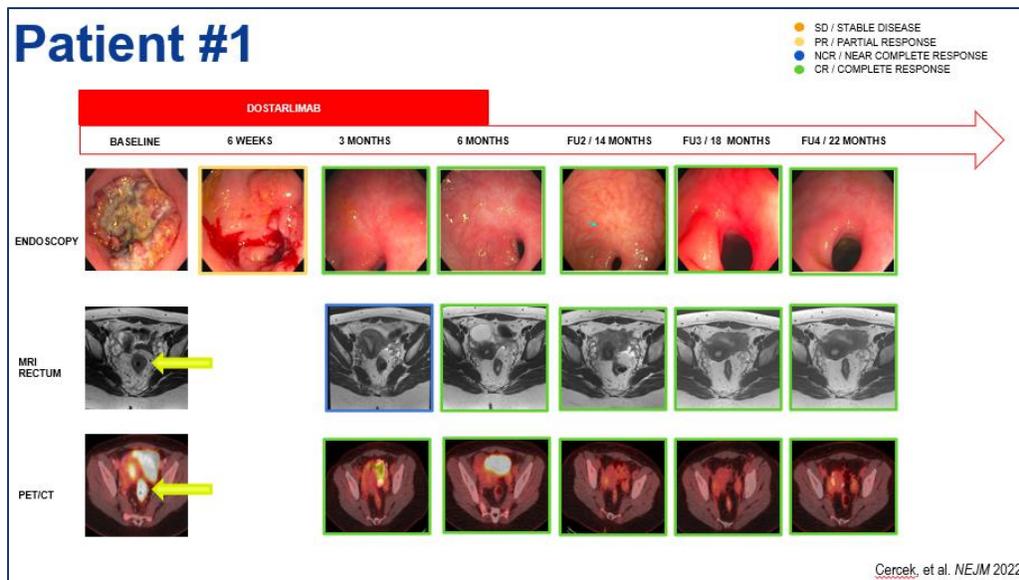
Session 10: Lessons from Other Cancers

MMR and Immunoablative Therapy

Luis Diaz, MD

Memorial Sloan Kettering Cancer Center

- Mismatch repair deficiency (MRD) is caused by alterations in DNA mismatch repair (MMR) genes and results in exceptionally high levels of mutations and microsatellite instability (MSI), and is a major driver of cancer. MMR alterations can be inherited (Lynch syndrome) or can be acquired during tumor development. MRD/MSI is most common in colorectal cancer, but can occur in many tumor types, including ~3-5% of prostate cancer cases.
- Tumor mutations can be recognized and targeted by the immune system, thus MRD/MSI tumors are typically highly infiltrated with immune cells and are often sensitive to treatment with checkpoint immunotherapy.
- The checkpoint immunotherapy pembrolizumab has been FDA-approved for the treatment of advanced solid tumors with MRD or with a high tumor mutation burden. However, whether checkpoint immunotherapy is effective in early-stage cancers was unknown.
- Dr. Luis Diaz discussed a clinical trial that tested the PD1-inhibitor dostarlimab in patients with newly diagnosed rectal cancer with MRD.
- Of 14 consecutive patients enrolled, all achieved a clinical complete response. No disease recurrence had been observed during the follow-up period, at the time of this presentation (example of one patient in **Figure 1**).
- No grade 3 or 4 adverse events were observed. No patients required chemotherapy, radiation, or surgery.
- Additional patients have been enrolled and are being followed.
- Patients with highest mutational burden, such as those with MRD and *POLE1* mutations, appear to be most sensitive to checkpoint immunotherapy, and can achieve deep and durable responses that may be cures.
- Combination treatment with the chemotherapy agents temozolamide + cisplatin has been found to induce a high mutational burden similar to MRD, and activates anti-tumor immune responses. Combining these with anti-PD1 led to complete responses in mouse tumor models. These data suggest that recapitulation of the MRD genotype may be a strategy to make cold tumors immunogenic, and could improve responses to checkpoint immunotherapy.
- A proof-of-concept clinical trial testing temozolamide + cisplatin + nivolumab in patients with MMR-proficient colorectal cancer is underway.
- These studies pave the way for neoadjuvant therapy to be curative and replace the need for surgery, chemotherapy, and radiation in patients with tumors that have MRD genotypes.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-10-lessons-from-other-cancers/>**

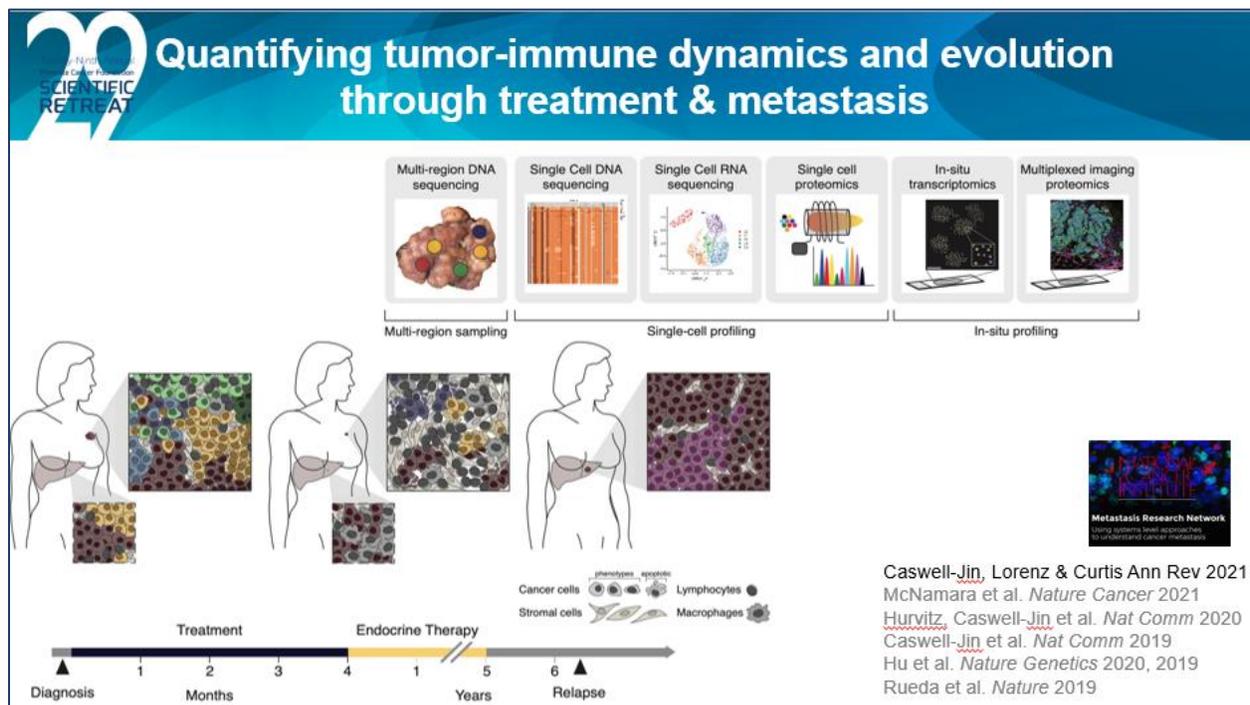


Spatial and Single Cell Profiling of Breast Cancer through Neoadjuvant Therapy

Christina Curtis, PhD, MSc
Stanford University

- Understanding how tumor cells and the tumor microenvironment evolve over the disease course and with treatment is critical, and will help to inform biomarkers to guide treatment selection and the identification of new treatment opportunities.
- Dr. Christina Curtis discussed studies to profile breast cancer evolution during neoadjuvant treatment, using single cell and spatial technologies.
- Trastuzumab is a standard treatment for HER2+ breast cancer. However, a subset of patients experience recurrence. New biomarkers that help to select the most optimal next treatment for these patients are needed.
- The phase 2 TRIO-US-B07 trial tested neoadjuvant trastuzumab and/or lapatinib, followed by docetaxel and carboplatin with trastuzumab and/or lapatinib, and then surgery, in patients with HER2+ breast cancer.
- Tumor samples collected before, during, and after treatment (at the time of surgery) from these patients, were molecularly profiled to identify changes in gene expression.
- Overall, HER2 signaling and proliferation signatures decreased while stromal and immune signatures increased over the course of therapy.
- Spatial proteomic profiling (a technology that can evaluate gene expression in different microscopic tumor regions) of these samples found that baseline (pre-treatment) levels of HER2 and immune cells did not predict response to treatment.
- However, decreases in HER2 signaling and increases in immune signaling over time, were highly associated with achieving pathological responses.
- An AI algorithm was developed that could predict pathological responses from spatial proteomic profiling data; the most relevant of these data were immune markers including CD45, a marker of all immune cells. CD45 data alone could also robustly predict pathological responses.

- Dynamic changes over time were observed in immune markers in the tumor microenvironment, which correlated with the response to treatment.
- These data may help to determine an optimal time for patients to receive immunotherapy. Studies are also being done to identify biomarkers that can inform when treatment de-escalation can be done, for instance, forgoing chemotherapy.
- Additional multi-omic single cell technologies were used to profile genomic alterations, gene expression and epigenetic patterns in tumor samples from a subset of 21 patients (**Figure**). These data could be used to identify and study molecular patterns in different cell types including tumor cells and various immune and stromal populations, to determine if specific cell types were informative biomarkers, and different cell states over time.
- Overall, these studies demonstrate the impact of using multi-omic single cell and spatial molecular profiling technologies to study the behavior of different types of cells in the tumor microenvironment. These types of studies will help to inform new biomarkers and identify new treatment opportunities.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-10-lessons-from-other-cancers/>



Drivers of Merkel Cell Carcinoma Provide Insight into Neuroendocrine Prostate Cancer

James DeCaprio, MD
Dana-Farber Cancer Institute

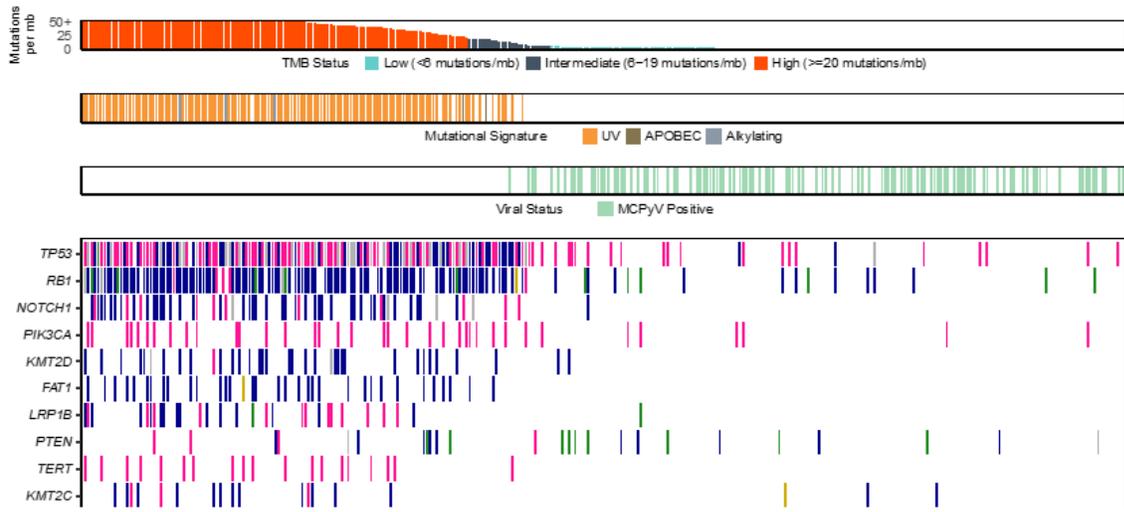
- Merkel cell carcinoma (MCC) is a high-grade neuroendocrine carcinoma of the skin. MCC is relatively rare, with ~3,000 new cases per year in the U.S., and a 40% mortality rate. In

comparison, there are ~77,000 new cases of invasive melanoma per year in the U.S., with a 13% mortality rate.

- Risk and presentation factors for MCC include asymptomatic/lack of tenderness at the site, that is expanding rapidly, immune suppression, older than 50 years of age, ultraviolet-exposure, and fair skin.
- Treatments for MCC include surgery with or without adjuvant radiation therapy for patients with localized disease, and checkpoint immunotherapy (pembrolizumab or avelumab) for patients with advanced or recurrent disease.
- 80% of MCC cases are caused by the Merkel cell polyomavirus, a ubiquitous skin virus that is present on nearly everyone, but which only rarely integrates its viral sequences into the skin cell genome and causes transformation. Virus-positive MCC are characterized by very few genomic alterations.
- 20% of MCC cases are driven by UV damage from sunlight exposure. This polyoma virus-negative subtype of MCC has many mutations and genomic alterations.
- A study on 317 MCC cases, found that virus-negative MCC has frequent mutations or loss in *p53* and *RB* (**Figure**). PTEN and PI3K pathway alterations are also common in both forms of MCC (**Figure**).
- In virus-positive MCC, viral T antigens can inhibit RB and p53, which can drive tumor development and progression in the absence of genomic mutations in these genes.
- Several other oncogenic pathways were mutated in virus-negative MCC but altered by virus genes in virus-positive MCC. Thus, virus-positive MCC often enacts similar alterations in oncogenic cellular pathways as virus-negative MCC.
- Studies are ongoing to better understand the biology, drivers, and possible treatment targets in virus-positive and virus-negative MCC.
- Because MCC is a neuroendocrine cancer, it has some shared features with neuroendocrine prostate cancer (NEPC). Studies on MCC may provide insights into the biology and treatment strategies for NEPC.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-10-lessons-from-other-cancers/>**

MCCN has frequent loss or mutation of p53 and RB

317 MCC



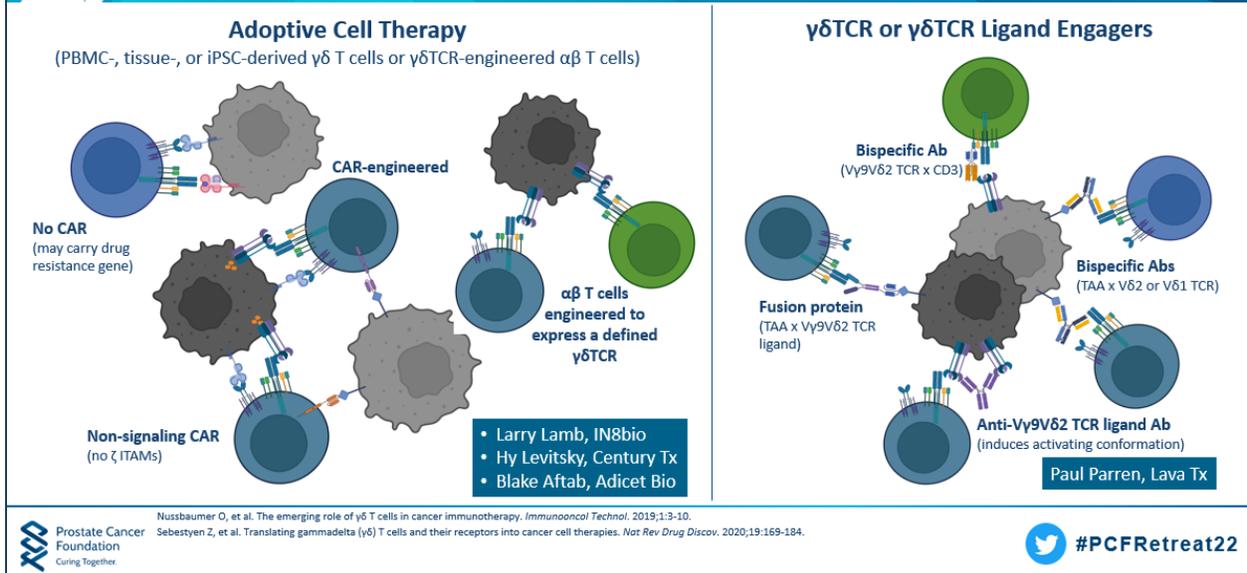
Knepper et al.
Clinical Cancer Research. 2019

Session 11: Novel Gamma Delta T Cell Therapy Platforms for Oncology

Primer on the Biology of $\gamma\delta$ T cells and their Use in Cancer Cell Therapy

Sandy Hayes, PhD
Janssen

- Dr. Sandy Hayes gave an overview on the biology of $\gamma\delta$ T cells, their role in anti-tumor immune responses, and their potential as effectors of cancer immunotherapies.
- $\gamma\delta$ T cells are a distinct class of immune cells that function and recognize antigens differently from typical CD4 and CD8 T cells. $\gamma\delta$ T cells play an important role in immune surveillance and can recognize and kill stressed, infected, or malignant cells.
- A study evaluating immune infiltration across 25 types of cancer found that $\gamma\delta$ T cells are the most significant, favorable, and prognostic immune cell population. Studies in multiple cancer types have found that higher numbers of tumor-infiltrating $\gamma\delta$ T cells correlate with better overall survival.
- In prostate cancer, higher numbers of tumor-infiltrating $\gamma\delta$ T cells correlate with lower rates of biochemical recurrence.
- These studies suggest that $\gamma\delta$ T cells are attractive candidates for cancer immunotherapy approaches. Multiple therapeutic approaches to harness and engage $\gamma\delta$ T cells are under study (**Figure**), including adoptive cell therapy approaches (in which $\gamma\delta$ T cells can be engineered to target tumor cells), and $\gamma\delta$ TCR or $\gamma\delta$ TCR ligand engagers (in which bi-specific antibodies, fusion proteins, or other strategies are used to bring $\gamma\delta$ T cells into contact with tumor cells).
- Several of these approaches were discussed by other presenters in this session.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-11-novel-gamma-delta-t-cell-therapy-platforms-for-oncology/>**

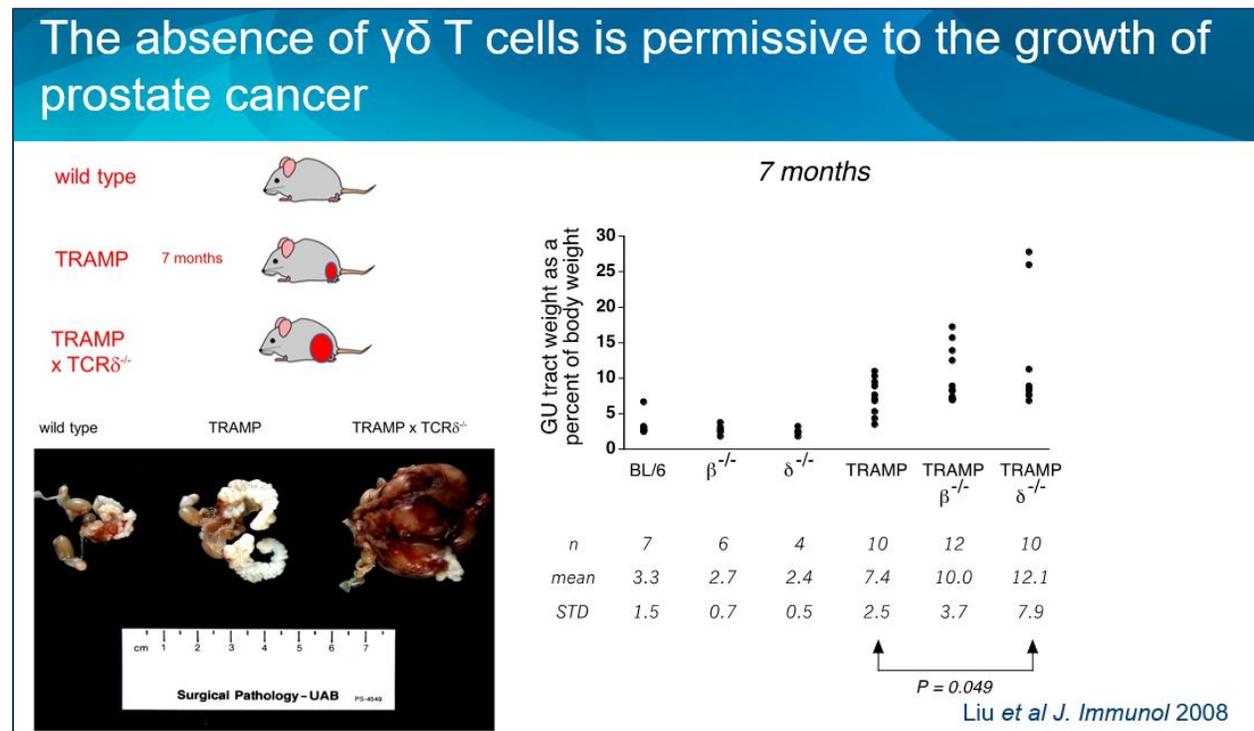


Novel $\gamma\delta$ T Cell Therapy Platform

Lawrence Lamb, Jr., PhD
IN8bio

- $\gamma\delta$ T cells are a type of immune cell that play an important role in anti-tumor immune responses and have potential for cancer immunotherapy approaches.
- Dr. Lawrence Lamb, Jr. discussed development of a novel platform to generate $\gamma\delta$ T cells as a cancer treatment.
- Cancer patients often have low levels of $\gamma\delta$ T cells, particularly patients with later stages of disease.
- Studies in mouse prostate cancer models found that tumors progressed and grew faster when mice lacked $\gamma\delta$ T cells (**Figure**). When $\gamma\delta$ T cells were replaced in these mice, tumor growth slowed.
- Treatment of prostate cancer patients with agents that activate $\gamma\delta$ T cell proliferation resulted in transient increases in numbers of $\gamma\delta$ T cells. Transient PSA decreases could be seen in some patients, that coincided with high $\gamma\delta$ T cell numbers.
- These studies suggest that sustained tumor remission may be obtained with consistently high $\gamma\delta$ T cell numbers.
- A platform was developed to manufacture clinical grade $\gamma\delta$ T cell treatments. In this method, blood cells drawn from patients are genetically reprogrammed into $\gamma\delta$ T cells. The cells can be created in large quantities in the laboratory, and delivered back to patients or stored. These genetically engineered $\gamma\delta$ T cells are highly functional and can kill tumor cells.
- Overall, these studies suggest that delivery of high numbers of $\gamma\delta$ T cells may be an effective therapy for patients with prostate and other cancers.

- Strategies to target $\gamma\delta$ T cells directly to cancer cells, for instance using CAR T or bispecific antibody approaches, may also have promise.
- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-11-novel-gamma-delta-t-cell-therapy-platforms-for-oncology/>



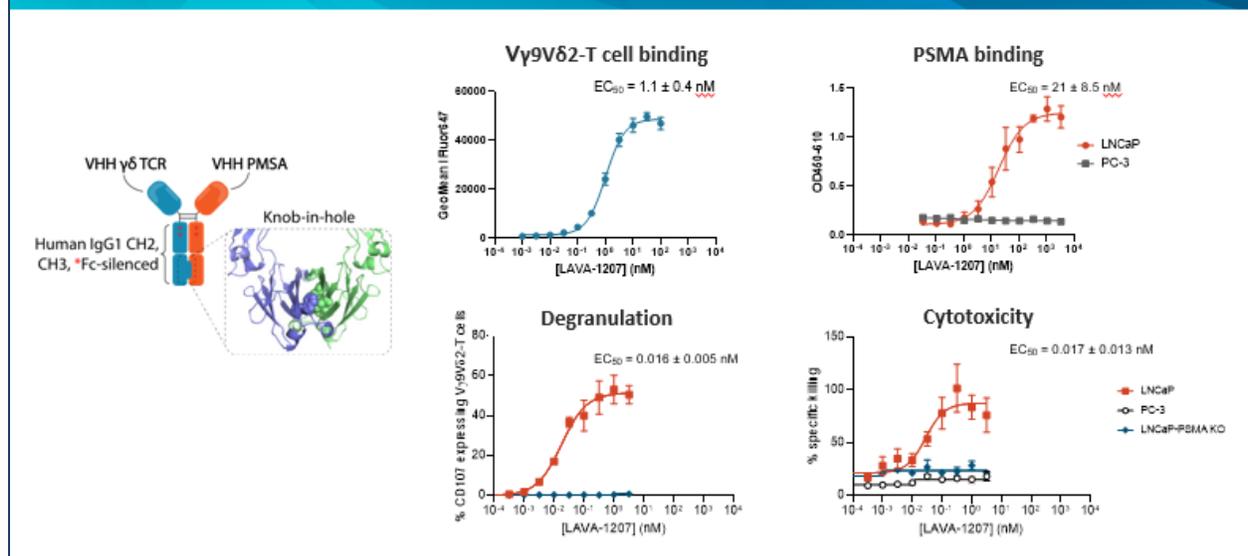
Bispecific $\gamma\delta$ T Cell Engagers for the Treatment of Prostate Cancer

Paul Parren, PhD
LAVA Therapeutics

- Bi-specific T cell engagers are antibody-based treatments that simultaneously bind to both a T cell receptor and tumor cell antigen. This brings T cells into contact with tumor cells to kill them. Four bi-specific T cell engagers have been FDA-approved, and over 80 are in clinical development.
- Bi-specific T cell engagers can have significant toxicities caused by activating the immune system. The “therapeutic window” (where doses have sufficient therapeutic effects with minimal toxic effects) is often very narrow.
- One strategy for widening the therapeutic window for bi-specific engagers, is to target alternative immune effector cells, rather than standard T cells.
- Dr. Paul Parren discussed the development of bi-specific T cell engagers that target $\gamma\delta$ T cells instead of standard T cells.
- $\gamma\delta$ T cells share some similarities with standard T cells, including the ability to kill target cells, but use different mechanisms to recognize their targets and become activated.

- $\gamma\delta$ T cells have a natural ability to recognize and kill tumor cells, and are present at high levels in prostate tumors.
- In patients with prostate cancer, higher numbers of $\gamma\delta$ T cells in tumors correlate with decreased rates of biochemical recurrence.
- A bispecific engager that targets $\gamma\delta$ T cells and the prostate cancer protein PSMA was developed (LAVA-1207) (**Figure**). In studies using tumor and blood samples from patients, LAVA-1207 activated $\gamma\delta$ T cells to kill prostate cancer cells from the same patient.
- LAVA-1207 did not cause immune cells from healthy donors to release high levels of IL-6, an inflammatory protein that is responsible for significant toxicities associated with other immunotherapies.
- In pharmacokinetics studies in non-human primates, LAVA-1207 exhibited a half-life similar to antibodies.
- Non-human primates do not express PSMA and cannot act as models for safety studies. Instead, a different bispecific $\gamma\delta$ T cell engager that targets EGFR was tested for safety in non-human primates. No changes in general health parameters, clinical chemistry, hematology, or histopathology were observed.
- A phase 1/2 clinical trial testing LAVA-1207 in patients with metastatic castration-resistant prostate cancer (mCRPC) has recently begun. This trial will evaluate safety, identify optimal doses, and be used to indicate preliminary anti-tumor efficacy.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/29th-annual/29th-annual-scientific-retreat-video-replays/session-11-novel-gamma-delta-t-cell-therapy-platforms-for-oncology/>**

PSMA-targeting Gammabody LAVA-1207 triggers degranulation and cytolytic activity of V γ 9V δ 2-T cells



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Prostate Cancer Foundation Women in Science Forum

PCF Women in Science Forum

October 27, 2022
***All times in U.S. PDT**

*Omni La Costa Resort
Carlsbad, California*

Location: Costa De La Luna 4

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

Overview: This is a half-day networking event for PCF women in conjunction with the October 2022 Scientific Retreat. This seventh annual event is open to all women and men attending the PCF Scientific Retreat, both junior and senior and across the disciplines of basic science, medicine, and population science. The goals are to create a network of PCF women, to team build through discussion and social events, to ensure a strong pipeline of female prostate cancer researchers and clinicians, and identify opportunities for further training, mentoring and synergy of a stellar network of female prostate cancer researchers and clinicians.

6:30 AM **Registration** Costa De La Luna Foyer

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

Welcome, Introductions and Vision

8:00 AM – 8:05 AM

Himisha Beltran, MD (Harvard: Dana-Farber Cancer Institute)
Susan Halabi, PhD (Duke University)
Eileen Parkes, MD, PhD (University of Oxford)

Session 1: Keynote: Lessons and Insights from a Career in Medicine and Health Equity
8:05 AM – 8:50 AM

8:05 AM - 8:35 AM **Alice Hm Chen, MD, MPH**
Chief Medical Officer, Covered California,
Health Equity and Quality Transformation Division;
Professor of Clinical Medicine, University of California, San Francisco

Introduced by Lorelei Mucci, ScD

8:35 AM - 8:50 AM Questions

Session 2: Introduction of New PCF Women in Science Networking Initiative
8:50 AM - 9:00 AM

8:50 AM - 8:55 AM **Fatima Karzai, MD**
National Cancer Institute

Introduced by Susan Halabi, PhD

8:55 AM - 9:00 AM Questions

Session 3: Panel Discussion: Non-Academic Paths to Success
9:00 AM – 10:30 AM

Moderators:

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

Panelists:

Alessandra Cesano, MD, PhD (ESSA Pharma)
Magda Grabowska, PhD (Caris Life Sciences)
Fatima Karzai, MD (National Cancer Institute)
Andrea Miyahira, PhD (Prostate Cancer Foundation)

Session 4: Introduction to Students, Networking Sessions and Closing Remarks
10:30 AM – 10:45 AM

Kathryn O'Connor (MedTech Academy, San Diego)
Ayesha Shafi, PhD (Center for Prostate Disease Research (CPDR); USU
Walter Reed Surgery)
Amina Zoubeidi, PhD (Vancouver Prostate Centre)

Session 5: Mini-Networking Session: Connecting Across Ages and Experiences

***In-person event only; Not available on the Virtual PCF Retreat Platform**

10:45 AM – 11:15 AM

Groups representing high school students and individuals from all levels of expertise will chat about STEM careers, questions, and advice.

Group Picture

11:15 AM – 11:30 AM

Session 6: Lunch/Networking

Costa De La Luna Lawn

***In-person event only; Not available on the Virtual PCF Retreat Platform**

11:30 AM – 12:30 PM

**** Meeting Adjourned ****

***The 29th Annual Prostate Cancer Foundation Scientific Retreat
begins promptly at 1:00 PM in the Costa Del Sol Ballroom***

***The 2022 PCF Women in Science Forum
is proudly sponsored by the Prostate Cancer Foundation***



**Prostate Cancer
Foundation**

Curing Together.



Prostate Cancer Foundation Young Investigator Forum

Supported by



*29th Annual Prostate Cancer Foundation
Scientific Retreat*

PCF YOUNG INVESTIGATOR FORUM

Wednesday, October 26, 2022

*Omni La Costa Resort
Carlsbad, California*

AGENDA

YOUNG INVESTIGATOR FORUM

Wednesday, October 26, 2022

*All times in U.S. PDT

6:30 AM **Registration**

Location: Costa De La Luna Foyer

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

Location: Costa De La Luna Lawn

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

Location: Costa De La Luna 4

Welcome & Introduction

8:00 AM - 8:10 AM

Howard Soule, PhD
Prostate Cancer Foundation
Andrea Miyahira, PhD
Prostate Cancer Foundation

Session 1: Negotiating Start-Up Packages

8:10 AM - 8:55 AM

8:10 AM - 8:40 AM **Joshua Lang, MD**
University of Wisconsin
8:40 AM - 8:55 AM Discussion

Session 2: An Industry Career Perspective

8:55 AM - 9:40 AM

8:55 AM - 9:25 AM **Jennifer Bishop, PhD**
Janssen Pharma
9:25 AM - 9:40 AM Discussion

Wednesday, October 26, 2022

Session 3: Starting a Company Out of Academia

9:40 AM - 10:25 AM

9:40 AM - 10:10 AM **Felix Feng, MD**
University of California, San Francisco
10:10 AM - 10:25 AM Discussion

Session 4: Virtual Mentoring through PCF-ONE

10:25 AM - 10:50 AM

10:25 AM - 10:40 AM **Sarah Amend, PhD**
Johns Hopkins University
Ayesha Shafi, PhD
Center for Prostate Disease Research (CPDR); USU Walter Reed Surgery
10:40 AM - 10:50 AM Discussion

Session 5: The PCF Young Investigator Community: A Call for New Ideas

10:50 AM - 11:10 AM

10:50 AM - 11:00 AM **Andrea Miyahira, PhD**
Prostate Cancer Foundation
11:00 AM - 11:10 PM Discussion

11:10 AM - 11:15 AM Break

Session 6: Young Investigator Forum Fireside Chat: Sociology of Disparities in Higher Medical and Research Education

11:15 AM - 12:00 PM

11:15 AM - 11:45 AM **Moderator: Leanne Burnham, PhD**
Morehouse School of Medicine

Panelists:

Christina Cajigas-Du Ross, PhD (Cleveland Clinic)
Brandon Contreras (Whaley Middle School; Dominguez High School)
Christopher Sistrunk, PhD (City of Hope)
Mya Walker (City of Hope)

11:45 AM - 12:00 PM Discussion

Wednesday, October 26, 2022

Group Photo
12:00 PM - 12:15 PM

Lunch
12:15 PM - 1:15 PM

Lunch Location: Costa De La Luna Lawn

1:15 PM - 1:30 PM **Move to Session 7**

Location: Costa De La Luna 4

Session 7: Introduction to High Achieving PCF Young Investigators

1:30 PM - 2:30 PM

Moderator: Howard Soule, PhD
Prostate Cancer Foundation

1:30 PM - 1:40 PM *Discovery and Qualification of Multi-Modality Biomarkers for Men Starting Long-Term Androgen Deprivation Therapy in the STAMPEDE Clinical Trial*

Emily Grist, MBBS
University College London Cancer Institute, UK

1:40 PM - 1:45 PM Discussion

1:45 PM - 1:55 PM *Identifying and Targeting Immunogenic Prostate Cancer*

David Einstein, MD
Beth Israel Deaconess Medical Center

1:55 PM - 2:00 PM Discussion

2:00 PM - 2:10 PM *Biochemical, Structural and Molecular Dissection of Androgen Receptor Transcriptional Activity*

Elisabeth Wasmuth, PhD
University of Texas Health at San Antonio

2:10 PM - 2:15 PM Discussion

Wednesday, October 26, 2022

2:15 PM - 2:25 PM *Dissecting Tumor-Immune Dynamics and Radiotherapy Response in Advanced Prostate Cancer, and Understanding Current Challenges of Precision Oncology for Racial/Ethnic Minorities with Prostate Cancer*
Sophia Kamran, MD
Harvard: Massachusetts General Hospital *N/A post-meeting for On Demand

2:25 PM - 2:30 PM Discussion

2:30 PM - 2:45 PM **Break**

2:45 PM - 3:00 PM **Move to Session 8**

Location: Costa De La Luna 1-3

Session 8: PCF Young Investigator Speed Networking 5.0

*In-person event only; Not available on the Virtual PCF Retreat Platform

3:00 PM - 5:15 PM

Moderators: **Anuradha Jayaram, MBBS** (University College London)
Lucia Nappi, MD (University of British Columbia)
Alexandros Papachristodoulou, PhD (Columbia University)

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

3:00 PM - 3:20 PM **Introduction**

3:20 PM - 3:45 PM **Speed Networking Group 1**

3:45 PM - 4:10 PM **Speed Networking Group 2**

4:10 PM - 4:35 PM **Speed Networking Group 3**

4:35 PM - 5:00 PM **Speed Networking Group 4**

5:00 PM - 5:15 PM **Conclusion**

Wednesday, October 26, 2022

Young Investigator Reception

5:15 PM - 6:15 PM

Reception Location: Costa De La Luna Lawn

Young Investigator Dinner

6:15 PM - 8:00 PM

Dinner Location: Costa De La Luna Lawn

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



Program Committee:

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

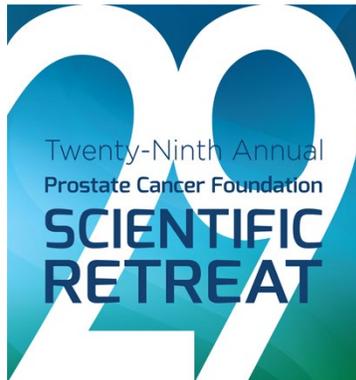
Sarah Amend, PhD (Johns Hopkins University)
Leanne Burnham, PhD (Morehouse School of Medicine)
Joshua Lang, MD (University of Wisconsin)
Anuradha Jayaram, MBBS (University College London)
Lucia Nappi, MD (University of British Columbia)
Alexandros Papachristodoulou, PhD (Columbia University)
Sethu Pichiaya, PhD (University of Michigan)
Ayesha Shafi, PhD (Center for Prostate Disease Research (CPDR); USU Walter Reed Surgery)

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



Supported by

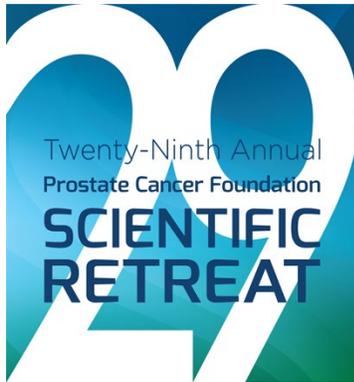




***29th Annual Prostate Cancer Foundation
Scientific Retreat***

October 27 - 29, 2022

***Omni La Costa Resort
Carlsbad, California***



AGENDA

Thursday, October 27, 2022

*All times in U.S. PDT

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, PhD
Prostate Cancer Foundation
Andrea Miyahira, PhD
Prostate Cancer Foundation

Session 1: Novel Clinical Trial Updates

1:05 PM - 2:25 PM

Moderator: Jake Vinson, MHA
The Prostate Cancer Clinical Trials Consortium

1:05 PM - 1:20 PM *Targeting a Tumor-Specific CD46 Epitope in Metastatic Castration Resistant Prostate Cancer*

Rahul Aggarwal, MD
University of California, San Francisco

1:20 PM - 1:25 PM Discussion

1:25 PM - 1:40 PM *Targeting Myeloid Chemotaxis via CXCR2 Blockade as a Therapeutic Strategy in Advanced Prostate Cancer*

Christina Guo, MD
Institute for Cancer Research; Royal Marsden Hospital, UK

1:40 PM - 1:45 PM Discussion

Thursday, October 27, 2022

- 1:45 PM - 2:00 PM *Biomarker Results from Targeting TROP2 with Sacituzumab Govitecan in mCRPC*
Joshua Lang, MD
University of Wisconsin
- 2:00 PM - 2:05 PM Discussion
- 2:05 PM - 2:20 PM *TRITON3: A Phase 3 Study of Rucaparib vs. Physician's Choice of Therapy in mCRPC associated with HRD*
Alan Bryce, MD
Mayo Clinic
- 2:20 PM - 2:25 PM Discussion

SPECIAL LECTURE

2:25 PM - 2:45 PM

The Magic of Mayonnaise

Kenneth Pienta, MD

Johns Hopkins University

Introduced by Howard Soule, PhD

Prostate Cancer Foundation

2:45 PM - 2:50 PM

Discussion

2:50 PM - 2:55 PM Break

PANEL: State of Science on Diet and Lifestyle in Lethal Prostate Cancer and Survivorship

2:55 PM - 3:55 PM

Moderator: Lorelei Mucci, ScD

Harvard TH Chan School of Public Health

Panelists:

William Aronson, MD (University of California, Los Angeles)

June Chan, ScD (University of California, San Francisco)

Christina Dieli-Conwright, PhD, MPH (Dana-Farber Cancer Institute)

Edward Giovannucci, MD, ScD (Harvard TH Chan School of Public Health)

Thursday, October 27, 2022

3:55 PM - 4:00 PM Break

KEYNOTE ADDRESS

4:00 PM - 5:00 PM

Michael Milken

Founder and Chairman
Prostate Cancer Foundation

*Introduced by Stuart Holden, MD
Prostate Cancer Foundation*

Group Photo

5:00 PM - 5:15 PM

Location: Costa Del Sol Foyer

5:15 PM - 7:00 PM Break

Thursday, October 27, 2022

Dinner and Awards Ceremony

7:00 PM - 10:00 PM

Location: Costa Del Sol Ballroom

PCF Awards Ceremony

8:00 PM - 9:00 PM

2020 PCF Young Investigator Awards

2021 PCF Young Investigator Awards

2022 PCF Young Investigator Awards

2022 PCF VALor Precision Oncology Center of Excellence Awards

2020 PCF Challenge Awards

2021 PCF Challenge Awards

2022 PCF Challenge Awards

Friday, October 28, 2022

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

PANEL: State of Clinical Therapy for Advanced Prostate Cancer

7:00 AM - 8:00 AM

Moderator: Charles J. Ryan, MD

Prostate Cancer Foundation

Panelists:

Jessica Hawley, MD, MS (University of Washington; Fred Hutchinson Cancer Center)

Renu Eapen, MBBS, FRACS (Urol) (Peter MacCallum Cancer Centre, Melbourne; University of Melbourne)

Felix Feng, MD (University of California, San Francisco)

Michael Haffner, MD, PhD (University of Washington; Fred Hutchinson Cancer Center)

Ana Kiess, MD, PhD (Johns Hopkins University)

Colin Pritchard, MD, PhD (University of Washington; Fred Hutchinson Cancer Center)

8:00 AM - 8:05 AM *Break*

Session 2: Impact of Molecular and Genomic Factors on Prostate Cancer Disease Etiology and Health Disparities

8:05 AM – 9:25 AM

Moderator: Salma Kaochar, PhD

Baylor College of Medicine

8:05 AM - 8:20 AM *Immunogenomic Landscape of African-American Prostate Cancer*

Tamara Lotan, MD

Johns Hopkins University

8:20 AM - 8:25 AM Discussion

Friday, October 28, 2022

- 8:25 AM - 8:40 AM *Alternative RNA Splicing in African American Prostate Cancer*
Steven Patierno, PhD
Duke University
- 8:40 AM - 8:45 AM Discussion
- 8:45 AM - 9:00 AM *Epidemiology: Are Biologic Impacts Due to Ancestry vs Socio-Economic impacts of Racism?*
Folakemi Odedina, PhD
Mayo Clinic
- 9:00 AM - 9:05 AM Discussion
- 9:05 AM - 9:20 AM *Reprogramming of AR in African American Prostate Cancer*
Salma Kaochar, PhD
Baylor College of Medicine
- 9:20 AM - 9:25 AM Discussion (*N/A post-meeting for On Demand)

Session 3: Neuroendocrine Prostate Cancer

9:25 AM - 10:25 AM

Moderator: Himisha Beltran, MD
Dana-Farber Cancer Institute

- 9:25 AM - 9:40 AM *Circular RNA in NEPC and CRPC*
Hansen He, PhD
Princess Margaret Cancer Centre, Canada
- 9:40 AM - 9:45 AM Discussion
- 9:45 AM - 10:00 AM *The Role of ASCL1 in NE Reprogramming of Prostate Cancer*
John Lee, MD, PhD
Fred Hutchinson Cancer Center
- 10:00 AM - 10:05 AM Discussion
- 10:05 AM - 10:20 AM *PSMA Heterogeneity in NEPC and CRPC*
Himisha Beltran, MD
Dana-Farber Cancer Institute
- 10:20 AM - 10:25 AM Discussion

Friday, October 28, 2022

Session 4: Single Cell Sequencing

10:25 AM – 11:25 AM

Moderator: Michael Shen, PhD
Columbia University

10:25 AM - 10:40 AM *Longitudinal Single-Cell Analysis of Metastases from Men with mHSPC Treated with ADT and Anti-PD-1*

Jessica Hawley, MD, MS
University of Washington; Fred Hutchinson Cancer Center

10:40 AM - 10:45 AM Discussion

10:45 AM - 11:00 AM *Harnessing Single Cell Analysis of the Tumor Microenvironment to Improve Immunotherapy Approaches in Prostate Cancer*

Amy Moran, PhD
Oregon Health Sciences University

11:00 AM - 11:05 AM Discussion

11:05 AM - 11:20 AM *Heterogeneity and Complexity of the Prostate Epithelium: New Findings from Single-Cell RNA Sequencing Studies*

Michael Shen, PhD
Columbia University (*N/A post-meeting for On Demand)

11:20 AM - 11:25 AM Discussion

SPECIAL LECTURE

11:25 AM - 12:00 PM

The Global Public Square of Prostate Cancer

Charles J. Ryan, MD
Prostate Cancer Foundation

Introduced by Howard Soule, PhD
Prostate Cancer Foundation

Friday, October 28, 2022

Lunch

12:00 PM - 12:50 PM

Location: Costa Del Sol Patio

12:50 PM - 1:00 PM Move to Session 5
Location: Costa Del Sol Ballroom

SPECIAL LECTURE

1:00 PM - 1:15 PM

**Rational Combinations with Androgen Receptor Inhibition
for Prostate Cancer Treatment**

Jeff Settleman, PhD

Chief Scientific Officer, Oncology R&D, Pfizer

(*N/A post-meeting for On Demand)

*Introduced by Howard Soule, PhD
Prostate Cancer Foundation*

1:15 PM - 1:20 PM

Discussion

Friday, October 28, 2022

Session 5: Lessons from Primary Prostate Cancer

1:20 PM - 2:40 PM

Moderator: Jiaoti Huang, PhD

Duke University

1:20 PM - 1:35 PM *Molecular Signatures to Risk-Stratify Intermediate-Risk Primary Prostate Cancer*

Jiaoti Huang, PhD

Duke University

1:35 PM - 1:40 PM Discussion

1:40 PM - 1:55 PM *Cellular Origins of Therapy Resistance / Biologic Features in Primary Prostate Cancer that may Inform Outcome or Therapy Response*

Mary-Ellen Taplin, MD

Dana-Farber Cancer Institute

1:55 PM - 2:00 PM Discussion

2:00 PM - 2:15 PM *Predicting Prostate Cancer Outcome and Molecular Subtype with Artificial Intelligence*

Tamara Lotan, MD

Johns Hopkins University

2:15 PM - 2:20 PM Discussion

2:20 PM - 2:35 PM *Lineage Plasticity in Cancers of the Lung and Prostate*

Charles Rudin, MD, PhD

Memorial Sloan Kettering Cancer Center

2:35 PM - 2:40 PM Discussion

Session 6: Genetic, Epigenetic, Epitranscriptomic and Post-Translational Mechanisms and Clinical Heterogeneity in Prostate Cancer

2:40 PM - 3:40 PM

Moderator: Nigel Mongan, PhD

The University of Nottingham, UK

2:40 PM - 2:55 PM *Genetic Determinants of Clinical Heterogeneity in Prostate Cancer*

Brian Robinson, MD

Weill Cornell Medicine

2:55 PM - 3:00 PM Discussion

Friday, October 28, 2022

- 3:00 PM - 3:15 PM *Epitranscriptomic and Epigenetic Determinants of Prostate Cancer*
Jennie Jeyapalan, PhD
The University of Nottingham, UK (*N/A post-meeting for On Demand)
- 3:15 PM - 3:20 PM Discussion
- 3:20 PM - 3:35 PM *Post-Transcriptional Regulation of Androgen Receptor During Prostate Cancer Progression*
Charlotte Bevan, PhD
Imperial College London, UK (*N/A post-meeting for On Demand)
- 3:35 PM - 3:40 PM Discussion

Session 7: Next Generation Prostate Cancer Theranostics and Combination Therapies

3:40 PM - 5:00 PM

Moderator: Ana Kiess, MD, PhD
Johns Hopkins University

- 3:40 PM - 3:55 PM *Immunomodulation of Tumor Microenvironment with Molecular Targeted Radiotherapy to Facilitate Response to Combination Therapies*
Zachary Morris, MD, PhD
University of Wisconsin
- 3:55 PM - 4:00 PM Discussion
- 4:00 PM - 4:15 PM *Combination of PSMA-targeted Radiopharmaceutical Therapy and Immunotherapy for mCRPC*
Shahneen Sandhu, MBBS
Peter MacCallum Cancer Centre, Australia
- 4:15 PM - 4:20 PM Discussion
- 4:20 PM - 4:35 PM *hK2 Targeted Radioimmunotheranostics for Prostate Cancer*
David Ulmert, MD, PhD
University of California, Los Angeles
- 4:35 PM - 4:40 PM Discussion
- 4:40 PM - 4:55 PM *Combinations of Radiopharmaceutical Therapies and SBRT for Oligometastatic Hormone-Sensitive Prostate Cancer*
Ana Kiess, MD, PhD
Johns Hopkins University (*N/A post-meeting for On Demand)
- 4:55 PM - 5:00 PM Discussion

Friday, October 28, 2022

Session 8: Investigating the Path from PI3K to Protein Synthesis to Tailor Prostate Cancer Therapy

5:00 PM - 6:00 PM

Moderator: Daniela Brina, PhD

Institute of Oncology Research, Switzerland

5:00 PM - 5:15 PM

Therapeutic Targeting of the Translational Machinery Blocks MDSCs and Enhances Anti-Tumor Immunity in Prostate Cancer

Daniela Brina, PhD

Institute of Oncology Research, Switzerland

5:15 PM - 5:20 PM

Discussion

5:20 PM - 5:35 PM

Defining the Therapeutic Selective Dependencies for Distinct Subtypes of PI3K Pathway-Altered Prostate Cancers

Brett Carver, MD

Memorial Sloan Kettering Cancer Center

5:35 PM - 5:40 PM

Discussion

5:40 PM - 5:55 PM

The Androgen Receptor Regulates a Druggable Translational Regulon in Advanced Prostate Cancer

Andrew Hsieh, MD

Fred Hutchison Cancer Center

5:55 PM - 6:00 PM

Discussion

Dinner

6:30 PM - 7:30 PM

Dinner Location: Costa Del Sol Patio

Poster Session and Dessert

7:30 PM - 10:30 PM

Poster Session and Dessert Location: Costa De La Luna Ballroom

Saturday, October 29, 2022

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 9: Combining Immunomodulatory Treatments for Prostate Cancer

7:00 AM - 8:40 AM

Moderator: Nicholas Huntington, PhD

Monash University, Australia

7:00 AM - 7:15 AM

Targeting P53 to Induce ICB Response in Cold Tumors

Nicholas Huntington, PhD

Monash University, Australia

7:15 AM - 7:20 AM

Discussion

7:20 AM - 7:35 AM

Engaging FLT3 to Promote Dendritic Cell Expansion & Drive the Adaptive Anti-Tumor Immune Response

Michelle Kuhne, PhD

Gilead Sciences

7:35 AM - 7:40 AM

Discussion

7:40 AM - 7:55 AM

Leveraging an Interplay Between Hormone Receptor Signaling and Immune Recognition to Enhance Immunotherapy in Prostate Cancer

Lisa Chesner, PhD

University of California, San Francisco

7:55 AM - 8:00 AM

Discussion

8:00 AM - 8:15 AM

EZH2 Inhibition Reprograms the Tumor Microenvironment to Potentiate Response to Checkpoint Inhibition

Leigh Ellis, PhD

Cedars Sinai Medical Center

8:15 AM - 8:20 AM

Discussion

8:20 AM - 8:35 AM

CoStimulatory Bispecifics for Prostate Cancer Immunotherapy

Israel Lowy, MD, PhD

Regeneron Pharmaceuticals Inc.

8:35 AM - 8:40 AM

Discussion

Saturday, October 29, 2022

Session 10: Lessons from Other Cancers

8:40 AM - 10:00 AM

Moderator: Peter Nelson, MD

Fred Hutchinson Cancer Center

8:40 AM - 8:55 AM

MMR and Immunoablative Therapy

Luis Diaz, MD

Memorial Sloan Kettering Cancer Center

8:55 AM - 9:00 AM

Discussion

9:00 AM - 9:15 AM

Spatial and Single Cell Profiling of Breast Cancer through Neoadjuvant Therapy

Christina Curtis, PhD, MSc

Stanford University

9:15 AM - 9:20 AM

Discussion

9:20 AM - 9:35 AM

Drivers of Merkel Cell Carcinoma Provide Insight into Neuroendocrine Prostate Cancer

James DeCaprio, MD

Dana-Farber Cancer Institute

9:35 AM - 9:40 AM

Discussion

9:40 AM - 9:55 AM

Collective Signaling Factors Driving Breast Cancer Metastasis and Therapy Resistance

Kevin Cheung, MD

Fred Hutchinson Cancer Center

(*N/A post-meeting for On Demand)

9:55 AM - 10:00 AM

Discussion

Session 11: Novel Gamma Delta T Cell Therapy Platforms for Oncology

10:00 AM - 11:45 AM

Moderator: Marco Gottardis, PhD

Janssen Research & Development, LLC

10:00 AM - 10:05 AM ***Introduction***

Marco Gottardis, PhD

Janssen Research & Development, LLC

10:05 AM - 10:20 AM

Primer on the Biology of $\gamma\delta$ T cells and their Use in Cancer Cell Therapy

Sandy Hayes, PhD

Janssen

10:20 AM - 10:25 AM

Discussion

Saturday, October 29, 2022

10:25 AM - 10:40 AM *Novel $\gamma\delta$ T Cell Therapy Platform*
Lawrence Lamb, Jr., PhD

IN8bio

10:40 AM - 10:45 AM Discussion

10:45 AM - 11:00 AM *Bispecific $\gamma\delta$ T Cell Engagers for the Treatment of Prostate Cancer*

Paul Parren, PhD

LAVA Therapeutics

11:00 AM - 11:05 AM Discussion

11:05 AM - 11:20 AM *Using iPSC-derived $\gamma\delta$ CAR-T cells to Overcome the TME barrier in Solid Tumors*

Hy Levitsky, MD

CENTURY TX

11:20 AM - 11:25 AM Discussion

11:25 AM - 11:40 AM *Progress with γ/δ T Cell Therapy in the Treatment of Cancer*
Blake Aftab, PhD

Adicet Bio, Inc.

(*N/A post-meeting for On Demand)

11:40 AM - 11:45 AM Discussion

Closing Remarks

11:45 AM - 12:00 PM

Howard Soule, PhD

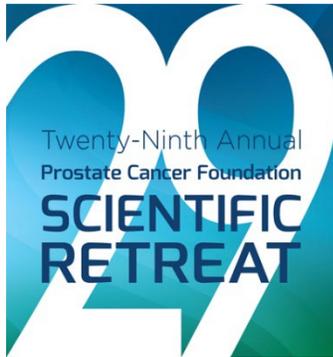
Prostate Cancer Foundation

Andrea Miyahira, PhD

Prostate Cancer Foundation

Meeting Adjourned

***** A boxed lunch will be provided *****



Program Committee:

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

Charles J. Ryan, MD (Prostate Cancer Foundation)
Himisha Beltran (Dana-Farber Cancer Institute)
Daniela Brina, PhD (Institute of Oncology Research, Switzerland)
Marco Gottardis, PhD (Janssen Research & Development, LLC)
Jessica Hawley, MD, MS (University of Washington; Fred Hutchinson Cancer Center)
Jiaoti Huang, PhD (Duke University)
Nicholas Huntington, PhD (Monash University, Australia)
Salma Kaochar, PhD (Baylor College of Medicine)
Anna Kiess, MD (Johns Hopkins University)
Nigel Mongan, PhD (The University of Nottingham)
Peter Nelson, MD (Fred Hutchinson Cancer Center)
Michael Shen, PhD (Columbia University)
Jake Vinson, MHA (The Prostate Cancer Clinical Trials Consortium)

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





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