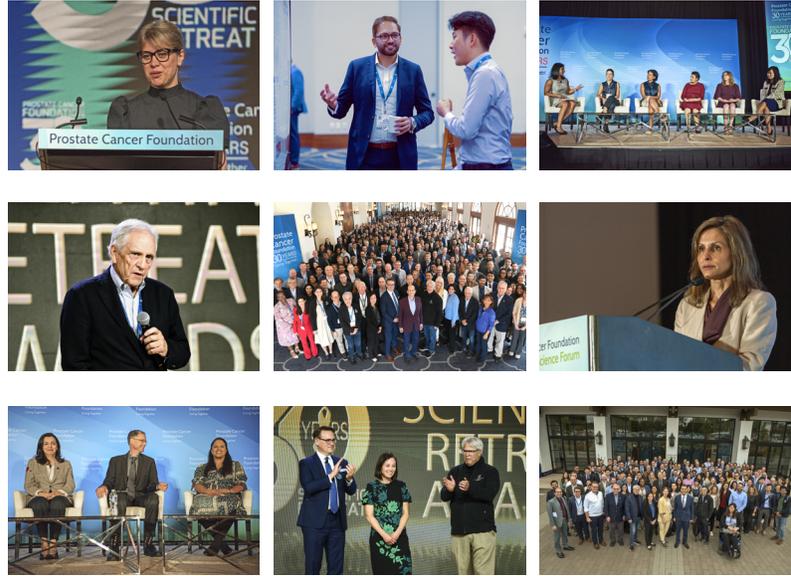


STATE *of the* SCIENCE REPORT



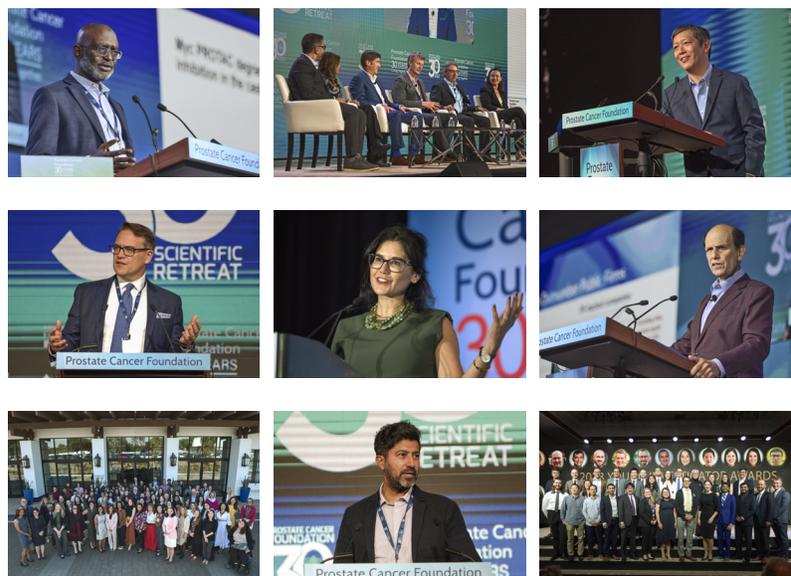
PROSTATE CANCER
FOUNDATION

30
YEARS
SCIENTIFIC
RETREAT

Highlights from
the 30th Annual
PCF Scientific Retreat
October 26-28, 2023

Provided compliments of the
Prostate Cancer Foundation

Prostate Cancer
Foundation
30 YEARS
Curing Together.



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Table of Contents

Introduction	3
Session 1: Cancer Stem Cells and Prostate Cancer Lineage Plasticity	5
Session 2: Treatment Resistance and Plasticity 2023	11
Session 3: The Future of AI in Diagnostic Medicine	16
Special Lecture: DEI Strategies for Advancing Cancer Care Equity	20
Session 4: Analytical Approaches and Computational Biology for Cancer Research	23
Special Lecture: Of Nerves and Cancer	27
Session 5: The Biology of Prostate Cancer Bone Metastases	29
Special Lecture: Transitioning from “Drug to Therapy Development Strategies” in Prostate Cancer	33
Special Lecture: Implementation Science and How It Can Improve Prostate Cancer Outcomes: The PCF-ADEPT Program	35
Special Lecture: The Global Public Square of Prostate Cancer	37
Session 6: The Contribution of Ancestry and Genomics to Prostate Cancer Disparities	38
Panel Discussion: State of Clinical Therapy for Advanced Prostate Cancer	44
Special Lecture: Pathways to Entrepreneurship	46
Session 7: Progress in New Targets and Treatments for Prostate Cancer	49
Session 8: Prostate Cancer 3D Genomics	53
Session 9: Biology and Translational Applications of Tumor Extracellular Vesicles	56
Keynote Address	58
Session 10: Updates from PCF TACTICAL Awards Teams	59
Session 11: Molecular Glues & Binding Inhibitors: Novel Small Molecule Cell Therapy Platforms ...	67
APPENDIX I: PCF Women in Science Forum Agenda	72
APPENDIX II: PCF Young Investigator Forum Agenda	73
APPENDIX III: 30th Annual PCF Scientific Retreat Program Agenda	74

Introduction

The 30th Annual Prostate Cancer Foundation (PCF) Scientific Retreat was held on October 26 – 28, 2023 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. This event enables attendees to present their latest research findings, exchange ideas, and explore emerging directions in the field. Attendees encompass prostate cancer researchers from academia, industry, and government, alongside patient advocates and representatives from non-profit organizations.

Spanning two and a half days, the Retreat features scientific lectures, panel discussions, poster sessions, and other interactive events. For the second year in a row, the Retreat was a hybrid event, enabling remote participants to engage in live presentations and discussions, and present virtual posters on their latest research. Recognized as a premier event in prostate cancer research, the PCF Annual Scientific Retreat has played a pivotal role in advancing scientific understanding and expediting the development of novel treatments for prostate cancer.

The 30th Annual PCF Scientific Retreat featured the following:

- 53 presentations and panels in the Plenary Session.
- 185 poster presentations.
- 33 different scientific disciplines related to prostate cancer research presented and discussed.
- 34% of speakers presented at a PCF Scientific Retreat for the first time.
- 934 individuals from 25 countries registered for the Retreat (651 in-person attendees + 283 virtual registrants), including 377 PhD, ScD, or DSc, 259 MD, MBBS, or DO, 123 MD/PhD, 2 JD, 28 PharmD, 2 DDS or DMD, 1 DVM/PhD, 1 DVM, 1 PhD/MBA, 1 PhD/PharmD, 1 MD/MBA, 2 MD/MBA/MS, 5 MD/MS, 1 MD/PhD/MBA, 2 PharmD/MBA, 1 PhD/RN, 24 MBA, 39 MS, and 1 RN.
- Retreat registrants included 621 academic researchers or health care professionals, 285 biopharmaceutical industry professionals, 10 patients, survivors, caregivers, advocates or other interested members of the general public, and 16 undergraduate and high school students.
- 145 academic institutions, 59 biopharmaceutical companies, and 10 medical research foundations.
- NIH, NCI, Dept. of Defense, and Veterans Affairs research leaders from over 10 organizations.
- Attendance by 231 PCF Young Investigators.
- Attendance by 18 PCF Board of Director members and major donors.
- The 8th Annual PCF Women in Science Forum was held with over 195 attendees.

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

2,250 research projects at 245 leading cancer centers, with a global footprint spanning 28 countries. Since PCF's inception, and through its efforts, patients around the world are living longer, suffering fewer complications, and enjoying better quality of life. PCF is committed to 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, Bayer, Amgen, Bristol-Meyers Squibb, Daiichi Sankyo, Lantheus, Lilly, Novartis, Pfizer, Regeneron, AstraZeneca, Foundation Medicine, Sun Pharma / SPARC, Royalty Pharma, Artera, Astellas, Exelixis, Merck, Fusion Pharmaceuticals, Arvinas, AdvanCell, Ambryx, Dendreon, Flare Therapeutics, Genentech, Illumina, Convergent Therapeutics, ESSA Pharmaceuticals, Telix, Harpoon Therapeutics, BostonGene, MacroGenics, Sumitomo Pharma, and Oncternal Therapeutics.

The 2023 State of Science Report distills the scientific insights presented at the Retreat into an accessible format for the general public. We hope that global dissemination of this knowledge will enhance understandings of current prostate cancer research, foster discussions, facilitate the exchange of ideas and information, ignite inspiration for new research initiatives, and cultivate heightened 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 30th Annual PCF Scientific Retreat, the 8th Annual PCF Women in Science Forum, and the PCF Young Investigator Forum, can be viewed here: <https://www.pcf.org/true/30th-annual-scientific-retreat-video-replays/>.

Yours sincerely,



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

Charles J. Ryan, MD
Chief Executive Officer



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

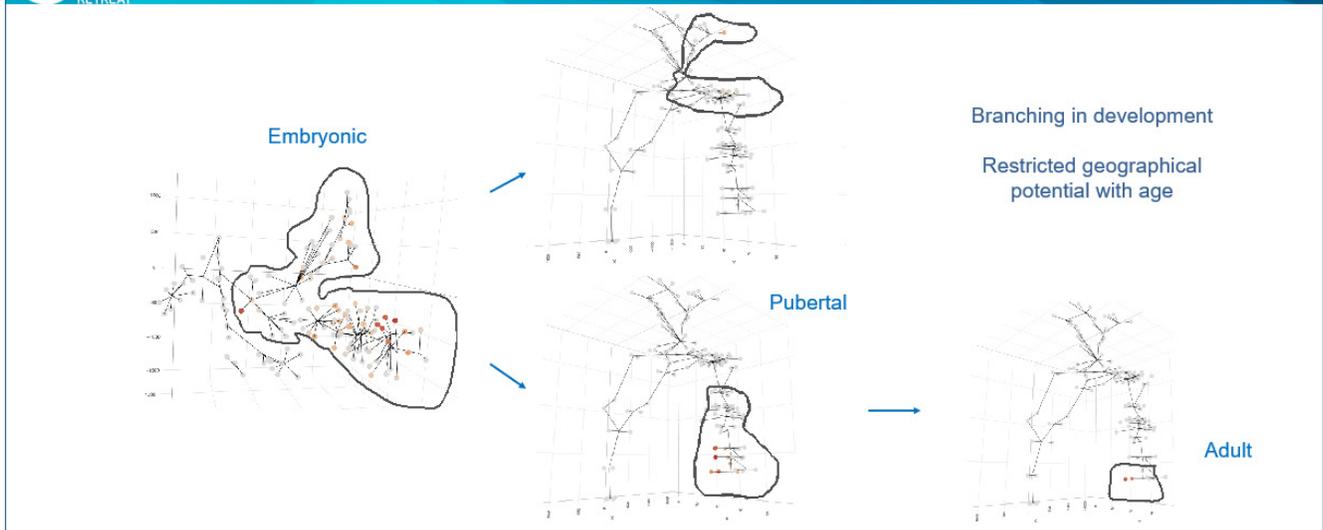
Session 1: Cancer Stem Cells and Prostate Cancer Lineage Plasticity

Development, Maturation, and Maintenance of Human Prostate

Rakesh Heer, MBBS, PhD
Newcastle University, UK

- Approximately 30% of patients with prostate cancer are diagnosed with advanced stage disease, which is no longer curable. Earlier detection of prostate cancers with metastatic potential is critical.
- Stem cells are specialized cells that act to replace aging cells and maintain tissues in the body. However, stem cells can accumulate mutations throughout life, which are passed to daughter cells, and increase chances for developing cancer.
- Dr. Rakesh Heer discussed genetically engineered mouse studies on lineage tracing of prostate stem cells, to understand how the prostate gland is formed and maintained, and which cells are the origins of prostate cancer. However, human studies were needed.
- Dr. Heer's studies of human prostate tissues found that mutations accumulate with age. These DNA mutations can be detected and traced over time and can be used as a "molecular clock". This provides an approach for lineage tracing of stem cells in human prostate.
- To infer the chronology and lineage of gained mutations, whole prostate tissues were micro-dissected, each micro-tissue section was genomically sequenced, and genomic alterations were then spatially mapped back to the whole prostate in 3D.
- In a prostate from a 59-year-old patient, 1,500 mutations were identified. The time when these mutations were gained could be estimated and mapped back to embryogenesis, puberty, and adulthood.
- Mutations gained during embryogenesis were dispersed in cells throughout the entire prostate, mutations gained during puberty were found regionally, and mutations gained in adulthood were more spatially restricted (**Figure**).
- A prostate cancer driver mutation was identified, *FOXA1*. This mutation was estimated to occur in puberty. The mutation conferred a selection advantage, allowing expansion of premalignant cells with this mutation over a larger area of the prostate.
- These findings enable new understandings of how the prostate and prostate cancer develop, and when and where cancer driver mutations emerge, which has implications for how to improve cancer screening strategies and focal treatment approaches.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-1-cancer-stem-cells-and-prostate-cancer-lineage-plasticity/>**

Nested clone mapping



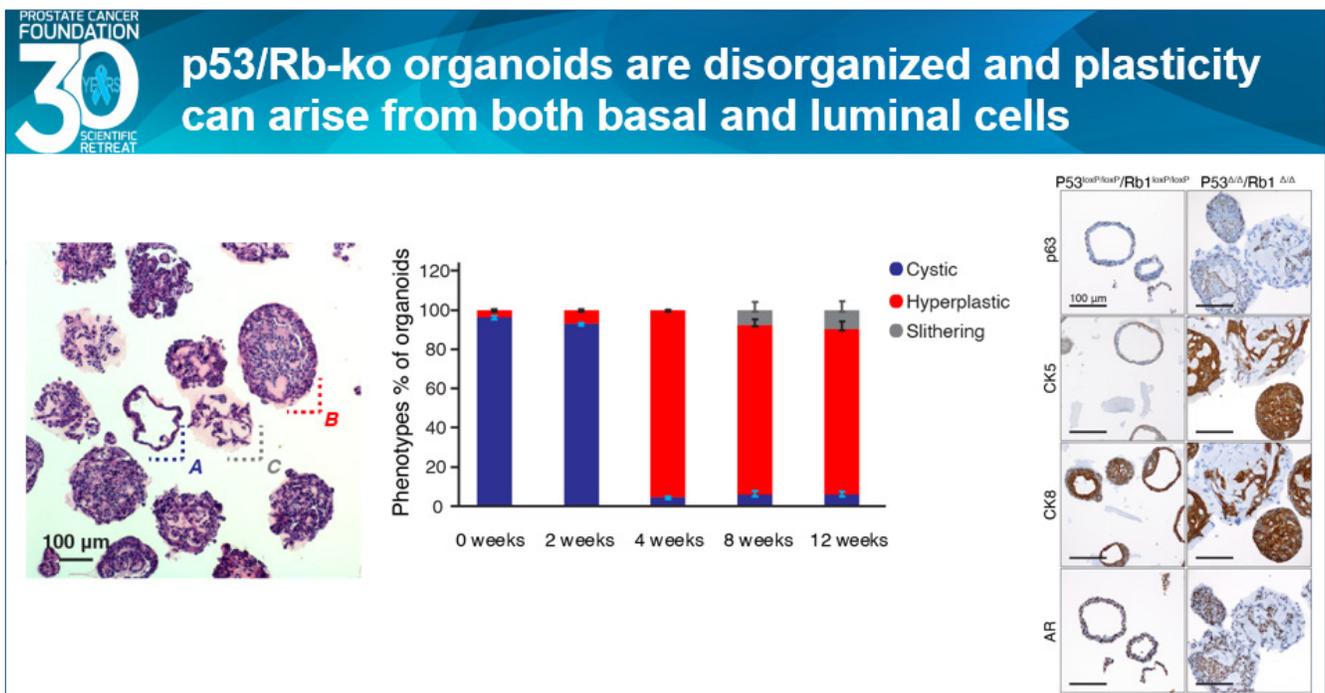
Targeting Lineage Plasticity in Prostate Cancer

Wouter Karthaus, PhD

Swiss Institute for Experimental Cancer Research, École Polytechnique Fédérale De Lausanne, Switzerland

- Prostate cancer is driven by the androgen receptor (AR), and thus AR is the primary therapeutic target for patients with advanced disease. However, resistance to AR-targeted therapies inevitably develops, and cancer progresses to a disease state called “castration-resistant prostate cancer” (CRPC).
- Multiple mechanisms can drive the development of CRPC. Tumor alterations that increase the activity of the AR pathway result in AR-driven CRPC. Alterations that enable prostate cancer cells to no longer need the AR pathway for survival result in AR-independent CRPC.
- A common feature of CRPC is lineage plasticity, in which cells lose prostate features and gain features of alternative cell types. The onset of lineage plasticity is associated with loss of both P53 and RB.
- Recently lineage-plastic CRPC has been divided in several subcategories. A well-known subtype being CRPC with neuroendocrine differentiation, but also other subtypes including CRPC-stem cell like (CRPC-SCL) and WNT signaling active CRPC (CRPC-WNT) have been recognized. What drives the choice of resistance mechanisms in CRPC remains unclear.
- Organoids are special laboratory models, in which prostate cancer cells grown in a 3D environment form miniature prostate tumors. While organoids do not fully recapitulate tumor biology, they are better models of cancer biology and treatment resistance than 2D cancer cell cultures and can be transplanted into mouse models to study whole-body tumor biology. Importantly organoid models do not include cells that make up the tumor microenvironment, such as stromal cells, immune cells, nerves, and endothelial cells.

- Dr. Karthaus discussed studies to determine whether organoids can model complex processes like lineage plasticity.
- Normal mouse prostate cells grown in organoid conditions develop into round structures without tumorigenic activities. To generate a minimal model of plasticity, the tumor suppressor genes P53 and RB1 were deleted in organoids and these were cultured over time. Upon loss of these tumor suppressors, the cells developed into disorganized mini-tumor structures that exhibited metastatic activities such as de-differentiation and invasive slithering, indicating lineage plasticity (**Figure**).
- When these tumor organoids were transplanted into mice and given anti-AR therapy, they developed features of neuroendocrine prostate cancer. Neuroendocrine features could not be observed if organoids were treated with anti-AR therapy in culture conditions however, indicating that something present in the whole body is missing in the organoid culture system that drives conversion to a neuroendocrine subtype.
- Single cell RNA sequencing of organoid cells revealed that multiple cancer cell states were present, including various basal and luminal states. Deletion of P53 and RB1 resulted in increased expression of lineage plasticity genes and JAK-STAT pathway genes. Treatment of organoid cultures with enzalutamide resulted in loss of defined basal and luminal populations and an increase of cancer cells in a lineage mixed state. Overall, these organoids resembled CRPC of the SCL-subtype.
- Treatment of organoid cultures with JAK-STAT inhibitors reverted lineage plasticity phenotypes and re-sensitized prostate cancer cells to treatment with enzalutamide, both in mouse models and patient-derived CRPC models of the SCL-subtype. JAK-STAT signaling was also implied as a driver of lineage plasticity in a mouse model of lineage plasticity.
- JAK-STAT and FGR signaling were also seen in a subset of patient biopsy samples of CRPC.
- Together, these studies suggest a minimal model of tumor plasticity, in which some features of plasticity are tumor intrinsic, while other features are driven by tumor microenvironment activities.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-1-cancer-stem-cells-and-prostate-cancer-lineage-plasticity/>**



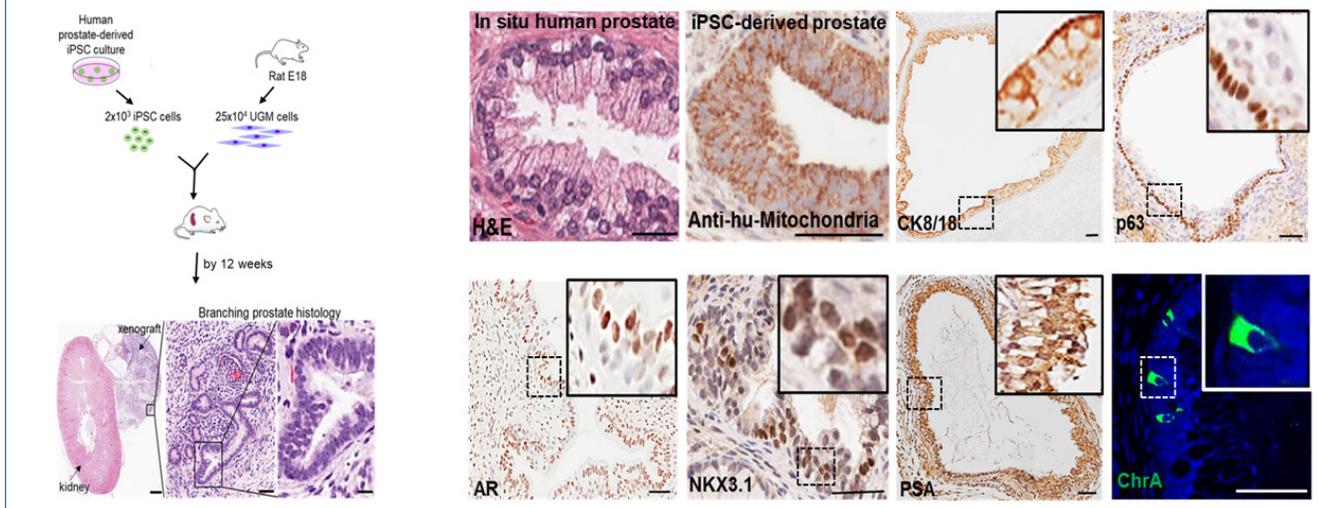
Engineering Prostate Cancer – Designer Organoids

Adriana Buskin, PhD
Newcastle University, UK

Anastasia Hepburn, PhD
Newcastle University, UK

- Organoids are cells grown in 3D laboratory culture systems that resemble miniature organs of the tissues they are derived from. Organoids can be established from adult or pluripotent stem cells, which have the capability to form the three different cell types that make up tissue layers (endoderm, mesoderm and ectoderm).
- Induced pluripotent stem cells (iPSCs) offer the most flexibility and fewest challenges for organoid development. iPSCs are created by genetically engineering cells to express certain stem cell genes.
- Dr. Anastasia Hepburn and Dr. Adriana Buskin discussed the development of prostate iPSCs.
- The team previously demonstrated that human prostate cells can be successfully engineered into prostate iPSCs. When engrafted into mice, these prostate iPSCs formed human prostate gland tissues. iPSCs also developed into miniature prostate glands when grown in 3D organoid conditions.
- This system is now being used to develop patient prostate cancer avatars, by inserting genes for patient-specific tumor mutations into prostate iPSCs, for purposes including personalized drug screening and disease modeling.
- For instance, iPSC-prostate cancer avatars with *TP53*-loss/*PTEN*-loss/*AR*-high mutations or with *TP53*-loss/*PTEN*-loss/*MYC*-high mutations were created. These mutations are commonly observed in metastatic CRPC. These mutations did not affect the pluripotent capability of the iPSCs, but enhanced the formation and growth of 3D tumor organoids.
- Of note, this experimental iPSC system required rat mesenchymal cells to be included in organoid cultures, which may impact tumor biology. The team have now developed a new method to generate prostate organoids from iPSCs without any animal-derived components to increase translatability and reduce drug attrition in clinical trials.
- Prostate iPSCs formed prostate organoids with typical prostate gene expression, such as PSA and AR. Compared with normal prostate iPSC organoids, *TP53*-loss/*PTEN*-loss/*AR*-high and *TP53*-loss/*PTEN*-loss/*MYC*-high iPSC organoids exhibited increased cell proliferation and loss of typical prostate glandular arrangements, being more disorganized.
- AR-overexpressing prostate iPSCs were developed and found to have higher proliferation rates, and enhanced budding and branching frequencies.
- Together, these studies demonstrate the ability to develop prostate iPSCs from human prostate tissues that can be genetically modified to express tumor-driving mutations and can be grown as organoids or in mice. Efforts are underway to introduce tumor microenvironment features, including vascularization, immune cells, and extracellular matrix into these systems to better understand and model prostate cancer.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-1-cancer-stem-cells-and-prostate-cancer-lineage-plasticity/>**

Generation of human prostate tissue from iPSCs



Organwide Spatial Analysis of Prostate and its Tumors

Joakim Lundeberg, PhD

KTH Royal Institute of Technology, Science for Life Laboratory, Solna, Sweden

- Tumors are highly heterogenous in biology and clinical response. They vary between patients as well as within different metastatic sites in the same patient, in biology, morphology, and the cell types they are composed of. Understanding tumors on the spatial level is critical to understanding the complexity of tumor heterogeneity and tumor biology.
- In addition, patients diagnosed with prostate cancer often have multiple co-occurring tumors in their prostate. Understanding which tumor lineages have metastatic potential and the evolutionary relationship between lineages, will improve diagnostic and prognostic tools.
- Dr. Joakim Lundeberg discussed the use of spatial analysis technologies to simultaneously evaluate spatial features of prostate tumors, including morphology and gene expression.
- Spatial transcriptomics is a research technology that first takes images of tissues on slides, and then captures mRNA from thousands of subdivided regions of the tissue, which are sequenced to determine gene expression and identify gene mutations, and mapped back to tissue regional locations.
- For instance, gene expression can be mapped to cell types that are in different tissue regions, such as benign areas, tumor stroma, cancer cells, pre-neoplastic glands, and immune cells.
- Spatial whole organ analyses can also be done by making cross-sectional slices of the entire organ and subjecting each to spatial transcriptomics.
- Spatial transcriptomics was performed on prostatectomy samples to identify the tumor lineages in the prostate and their evolutionary relationship to one another (**Figure**).
- In one example, a lineage hierarchy could be determined, which identified lineages that remained benign and that became malignant, and identified the genomic alterations that drove development

of malignant disease. These lineages and mutations were then mapped spatially to the tumor image, to identify regions of the tumor that are benign vs. malignant and study the tumor microenvironment.

- 3D modeling and machine learning/artificial intelligence are now being applied to these data, to better understand whole tumor biology.
- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-1-cancer-stem-cells-and-prostate-cancer-lineage-plasticity/>

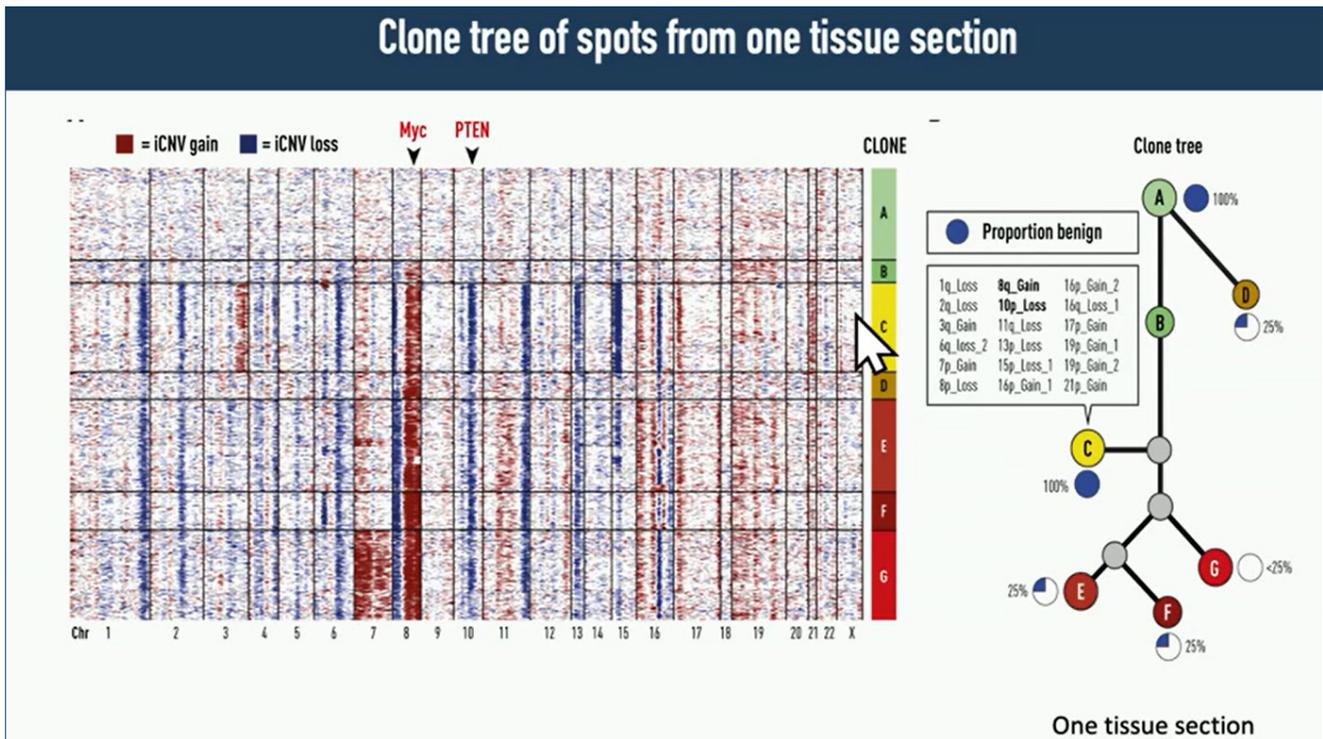


Figure: reproduced from Erickson et al, Nature. 2022 Aug;608(7922):360-367. doi: 10.1038/s41586-022-05023-2. Epub 2022 Aug 10. PMID: 35948708. <http://creativecommons.org/licenses/by/4.0/>.

Session 2: Treatment Resistance and Plasticity 2023

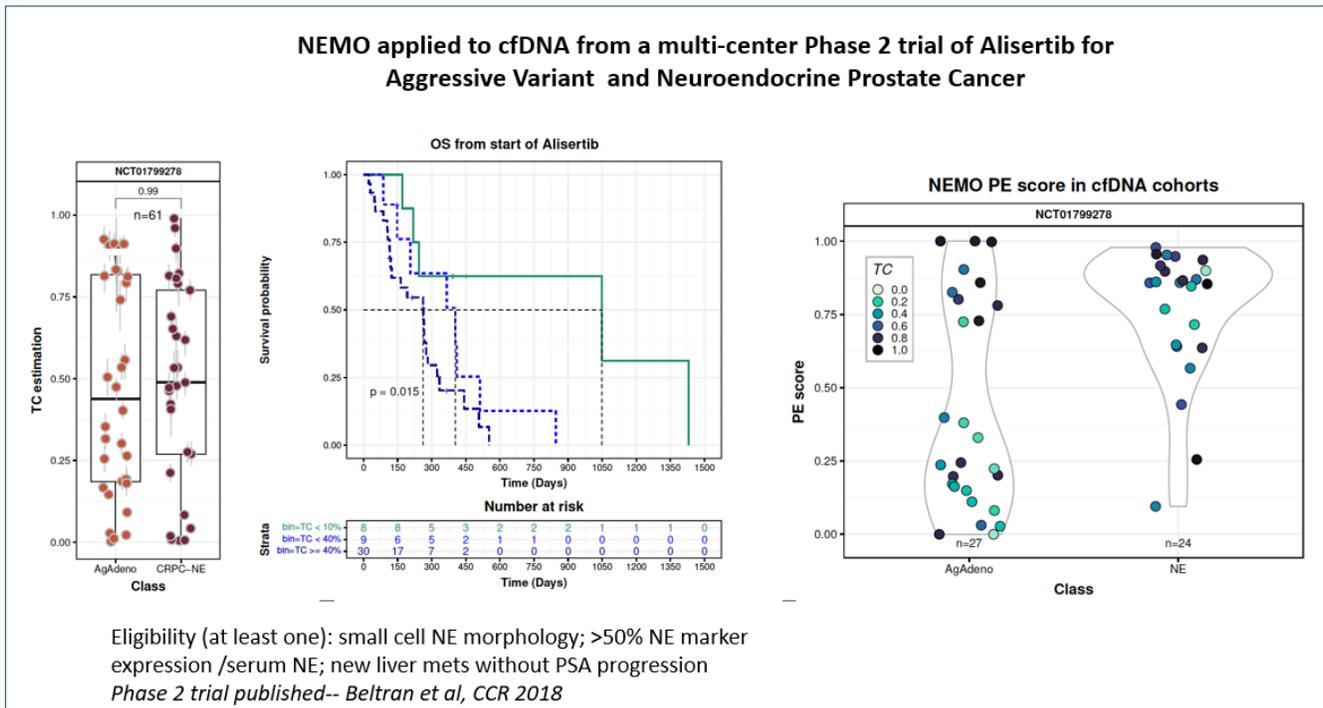
DNA Methylation as a Biomarker and Target in Neuroendocrine Prostate Cancer

Himisha Beltran, MD
Dana-Farber Cancer Institute

- Epigenetics is a key mechanism of regulating gene expression, in which chemical groups are added to or removed from DNA to control the 3D structure and accessibility of genes in that region. This form of control allows for the body to have many different types of cells, despite all sharing the same genome.
- However, cancer also uses epigenetics to alter gene expression and cancer phenotypes. For instance, neuroendocrine prostate cancer (NEPC), an advanced, aggressive form of castration-resistant prostate cancer (CRPC) is largely driven by epigenetic alterations.
- Dr. Himisha Beltran discussed how DNA methylation drives NEPC, and its potential as a biomarker and therapeutic target. DNA methylation is a form of epigenetic regulation that turns off gene expression.
- DNA methylation changes have been shown to distinguish NEPC from typical adenocarcinoma CRPC. These changes can be detected using tumor tissues as well as from circulating tumor DNA (ctDNA) released into the bloodstream of patients.
- A comparison of DNA methylation patterns across different states of prostate cancer found the greatest differences between benign prostate tissue and primary prostate adenocarcinoma, and between prostate adenocarcinoma and NEPC.
- NEMO (NEuroendocrine MOnitoring) is a test developed by Beltran and colleagues to noninvasively determine tumor burden and the extent of prostate adenocarcinoma vs. NEPC in patients, based on DNA methylation patterns in ctDNA from blood draws.
- Evaluation of different phenotypic subtypes of CRPC using NEMO found that DNA methylation patterns of AR-low/neuroendocrine-low cancers resembled those found in NEPC, while amphicrine prostate cancers were similar to adenocarcinoma. Other subtypes, such as WNT-driven CRPC, had an intermediate DNA methylation pattern. Overall, a spectrum or continuum of DNA methylation changes could be observed across all subtypes evaluated.
- The performance of NEMO was evaluated in a phase 2 trial, in which patients with NEPC or aggressive variant CRPC (diagnosed by pathologist evaluation of metastatic tumor biopsies) received alisertib, an inhibitor of the NEPC-driver Arora Kinase. Nearly all patients with NEPC in this trial had high NEMO scores, while both NEMO-high and NEMO-low subgroups were seen among patients with aggressive variant CRPC (**Figure**). Similar results were seen when NEMO was tested on samples from a phase 2 trial testing carboplatin + docetaxel in patients with anaplastic or aggressive variant CRPC.
- Overall, NEMO has demonstrated 93-97% accuracy in identifying patients with histology-confirmed NEPC, based on over 150 patients evaluated.
- NEMO was also able to identify patients with small cell lung cancer (SCLC), another type of cancer with neuroendocrine features.
- DNA methylation patterns in ctDNA can also be used as a proxy for gene expression. For instance, hypermethylation of the *EZH2* gene is a strong marker of low *EZH2* expression. *EZH2* is a driver of

NEPC and its expression is prognostic for worse survival. Thus, *EZH2* methylation levels may have potential for identifying patients who may benefit from EZH2-inhibitors.

- Ongoing studies are evaluating the timing and frequency of the emergence of neuroendocrine features after AR-targeted therapy, the impact of methylation features on responses to standard therapies, genomic features associated with predisposition to NEPC, and new biomarkers and therapeutic targets for NEPC.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/30th-annual/session-2-treatment-resistance-and-plasticity-2023/>



Targeting Prostate Cancer Plasticity in the Clinic

David Goodrich, PhD

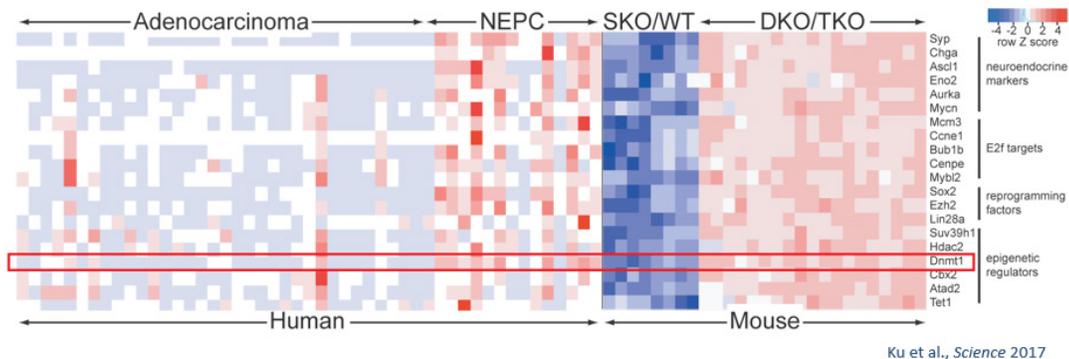
Roswell Park Comprehensive Cancer Center

- Androgen receptor signaling inhibitors (ARSI) are standard treatments for advanced prostate cancer; these include abiraterone, enzalutamide, apalutamide and darolutamide. While ARSI treatment is usually effective initially, these treatments are not curative and most patients eventually develop recurrence with castration-resistant prostate cancer (CRPC).
- Various biological mechanisms allow prostate cancer cells to adapt to ARSI and progress to CRPC. These include alterations that reactivate the androgen receptor (AR) pathway, and “AR-indifferent” alterations that allow prostate cancer cells to no longer rely on the AR pathway to survive and grow.
- Dr. David Goodrich discussed lineage plasticity, an AR-indifferent mechanism of CRPC, in which prostate cancer cells lose prostate cells features (and hence reliance on AR) and gain features of other cell types, most commonly neuroendocrine cells.

- Prostate cancer lineage plasticity is driven in part by epigenetic alterations, in which the chemical modifications that govern 3D structure and gene accessibility of DNA are altered.
- Dr. Goodrich and team found neuroendocrine prostate cancer (NEPC; the most common form of lineage-plastic CRPC) had increases in methylation of DNA at the control regions (“super-enhancers”) of cellular differentiation genes.
- NEPC and other lineage-plastic CRPC models exhibited increased expression of epigenetic regulators, including DNMT, an enzyme that adds methyl chemical groups to DNA (**Figure**).
- Treatment of enzalutamide-resistant prostate cancer cells with a DNMT-inhibitor re-sensitized the cells to enzalutamide, suggesting that DNMT may be a promising therapeutic target.
- The team initiated a phase 1b/2 clinical trial to test the oral DNMT-inhibitor decitabine/cedazuridine in combination with enzalutamide in patients with CRPC. The safety portion of this trial has been completed, finding the expected safety profile based on prior clinical trials with decitabine. The next phase of the trial will test preliminary efficacy of this combination in an expanded cohort of patients with CRPC containing genomic alterations in *RB1*, *TP53*, and *PTEN*, which are commonly mutated in lineage-plastic CRPC. Correlative studies to evaluate mechanisms of action will also be performed.
- A potential alternative approach for targeting lineage plasticity is to increase metabolism of acetylated polyamines, as this metabolism competes for resources with epigenetic regulatory enzymes.
- In preclinical studies, treatment with drugs that increase acetylated polyamine metabolism caused decreases in DNA methylation of super-enhancers involved in lineage plasticity. Furthermore, combining polyamine therapy with the DNMT-inhibitor synergistically increased death of prostate cancer cells. The impact of this treatment in mouse models of CRPC is being investigated.
- Bipolar androgen therapy (BAT) is an experimental treatment that alters extremely high and extremely low doses of androgens, which destabilizes prostate cancer cells and causes them to be sensitive to each switch. Clinical trials have found BAT is generally safe, improves quality of life in patients with CRPC, and can re-sensitize tumors in some patients to enzalutamide. Whether BAT impacts prostate cancer lineage plasticity is unclear.
- Preliminary preclinical studies by Dr. Goodrich and team found that BAT can suppress growth of CRPC models and suppress development of NEPC in mice. These studies suggest that BAT may revert lineage-plastic prostate cancer to a more typical prostate cancer phenotype. A BAT trial is being planned to evaluate this hypothesis.
- BCL2 is a protein that was found to be increased in AR-low CRPC models and was required for their growth. These data suggest BCL2 may be a therapeutic target in lineage-plastic CRPC.
- A clinical trial has recently been initiated to test the efficacy of the BCL2-inhibitor venetoclax in combination with enzalutamide in patients with CRPC. Ten patients have been accrued thus far and one exceptional responder remains alive. However, pharmacokinetic analyses suggest that there is an unfavorable drug interaction that results in suboptimal levels of venetoclax. Further studies are underway.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-2-treatment-resistance-and-plasticity-2023/>**

Epigenetic therapy: DNMT as a therapeutic target

- DNMT expression is elevated in prostate cancer lineage variants



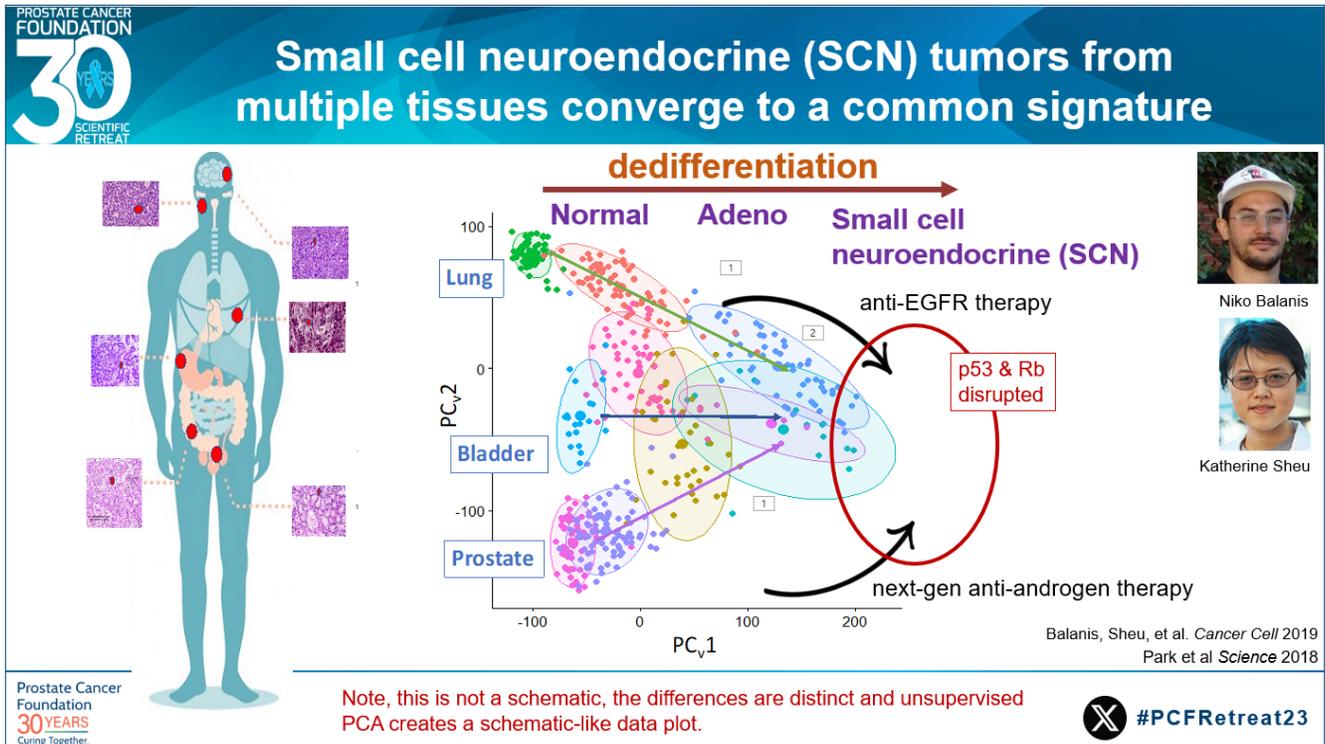
Temporal Evolution Reveals Bifurcated Lineages in Aggressive Neuroendocrine Small Cell Prostate Cancer Trans-Differentiation

Chia-Chun (Olga) Chen
University of California, Los Angeles

Thomas Graeber, PhD
University of California, Los Angeles

- The androgen receptor (AR) is the primary driver of prostate cancer growth and survival, and therefore the primary therapeutic target in patients with advanced or aggressive disease. Unfortunately, most patients eventually develop resistance to AR-targeted therapies and progress to castration-resistant prostate cancer (CRPC).
- While most CRPC cases develop via alterations that reactivate the AR signaling pathway, a growing percentage of CRPC are AR-independent. Neuroendocrine prostate cancer (NEPC) is a form of AR-independent CRPC that develop via lineage plasticity, in which prostate cell features are lost and small cell/neuroendocrine cell features are gained.
- Chia-Chun (Olga) Chen and Dr. Thomas Graeber discussed studies into how prostate cancers convert from a typical prostate adenocarcinoma state to an NEPC state.
- Other cancer types can also convert to a small cell/neuroendocrine form, including lung cancer and bladder cancer. A comparison of normal prostate, lung and bladder tissues, typical adenocarcinomas from these tissues, and small cell/neuroendocrine cancer forms, found that as these different tissues progressed from normal to small cell/neuroendocrine, their gene expression patterns converged (**Figure**).
- A similar pattern of convergence on this gene expression pattern was also observed during disease progression in a preclinical model of NEPC called PARCB. In this model, cellular gene expression programs shifted from inflammatory, to stress responsive, to reprogramming and stem-like, to neuronal/neural/neuroendocrine programs, during the transition from early tumors to NEPC.

- Two separate pathways for prostate cancer cells to transition to NEPC were identified in the PARCB model. One pathway was characterized by ASCL1 expression, and the other by ASCL2 expression. The mutually exclusive expression patterns of ASCL1 and ASCL2 were validated in clinical NEPC samples.
- Much of these data have recently been published: Chen et al., *Cancer Cell*, 2023, <https://doi.org/10.1016/j.ccell.2023.10.009>.
- A web-portal for exploring the data is available through the PARCB Time Course Multiomics Explorer at <https://systems.crump.ucla.edu/transdiff/>.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-2-treatment-resistance-and-plasticity-2023/>**



Session 3: The Future of AI in Diagnostic Medicine

Utility of Pathology Deep Learning Algorithms for Prostate Cancer

Tamara Lotan, MD
Johns Hopkins University

- Dr. Tamara Lotan discussed the development of deep learning algorithms for prostate cancer grading and clinical outcome predictions based on pathology slides.
- Several AI-pathology algorithms have been developed to diagnose and grade prostate cancer. The “ground truth” for validation of such studies has usually been in comparison to pathologists’ grading of slides, while few studies have been benchmarked by association with clinical outcomes.
- AIRAProstate is a deep learning tumor identification and grading algorithm under development that uses pathology slide images from biopsy and prostatectomy samples.
- The algorithm was trained using 7150 whole slide images from prostate biopsies, and validated on a dataset of 680 whole slide images. Testing of this algorithm on independent prostate whole slide image datasets demonstrated 92-98% accuracy in detecting the presence of cancer and 93-96% accuracy for determining the tumors’ grade group (**Figure**).
- The AIRAProstate algorithm also outperformed 5 other top-ranked public AI algorithms from the PANDA challenge and the commercial AI-based Paige Gleason grading algorithm.
- AIRAProstate is being tested for accuracy of predicting subsequent grade reclassification in Active surveillance cohorts, and for predicting biochemical recurrence or risk of metastasis after radical prostatectomy, compared to a consensus of 2-3 blinded uropathologists. The team is including the race cohort, which has ~50% Black patients, as one validation dataset, to ensure this algorithm will perform optimally in underrepresented minority populations.
- Deep learning algorithms to directly predict clinical outcomes are also under development, and are being compared to the performance of genomic classifiers such as Decipher and Prolaris.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-3-the-future-of-ai-in-diagnostic-medicine/>**

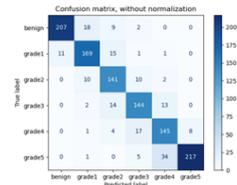
Training, validation and testing: Needle biopsies

Training and validation

Training	Validation
Cases from: US, Europe and India Scanned on: Aperio and Hamamatsu scanners	Cases from: US, Europe and India Scanned on: Aperio and Hamamatsu scanners
# of whole slide images: 7150	# of whole slide images: 680

Testing

Data source	Scanner	# of WSI	Tumor identification AUC	QWK
Radboud University Medical Center (PANDA Challenge)	3DHistech	1201	0.96	0.96
Karolinska Institute (PANDA Challenge)	Hamamatsu and Aperio	1303	0.92	0.93
Private Laboratory Network in US	Aperio	3518	0.98	0.94

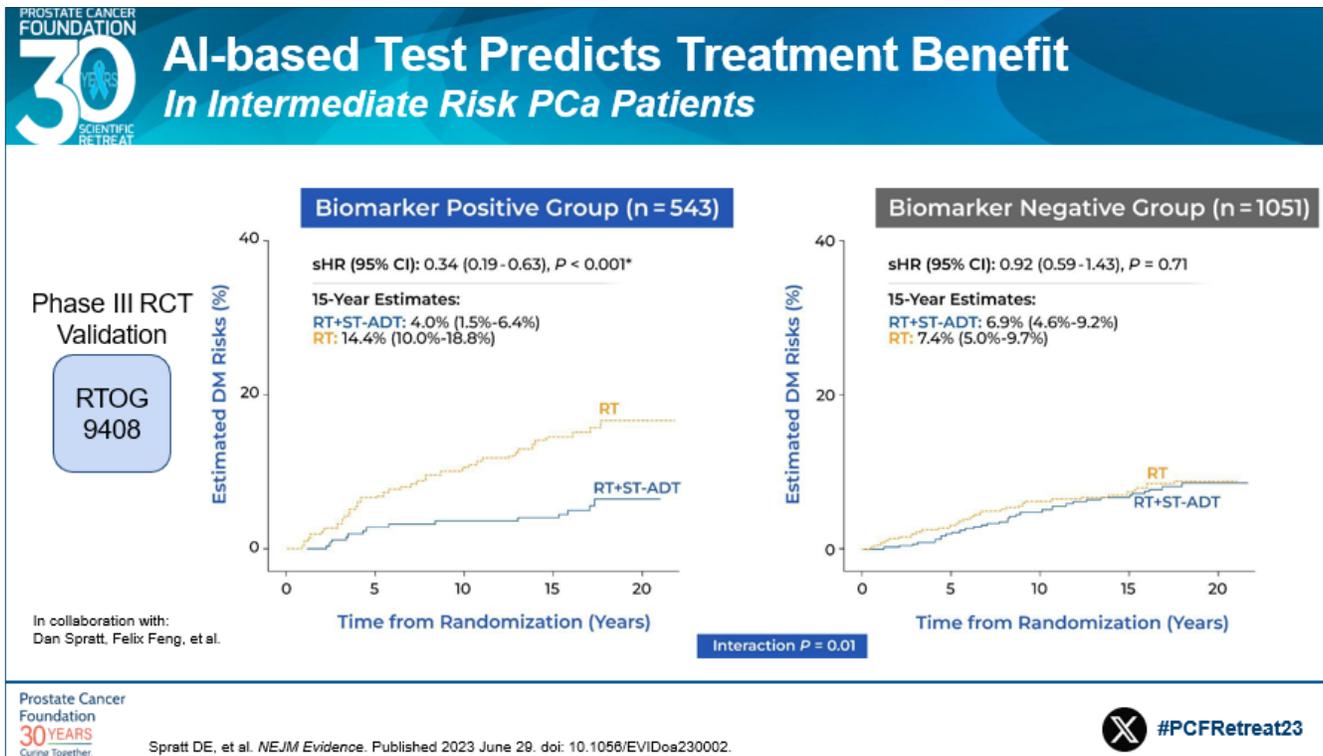


AI-Enabled Therapy Personalization

Andre Esteva, PhD ArteraAI

- Dr. Andre Esteva discussed ArteraAI and the multimodal artificial intelligence (MMAI) tests they have developed to help personalize therapy decisions for patients with prostate cancer.
- This MMAI model combines clinical data and digital image data from tumor pathology slides to prognosticate a patient's risk of developing metastasis or dying of cancer, or predicting treatment benefit to aid personalized treatment decisions.
- Prognostic and predictive MMAI models were trained and validated on clinical and pathology image data from thousands of patients with localized prostate cancer.
- The prognostic MMAI model used clinical and pathology image data from five phase 3 randomized prostate cancer clinical trials with long-term follow-up (10-20 years) to estimate distant metastasis (DM), biochemical recurrence (BCR), prostate cancer specific survival (PCaSS) and overall survival (OS), at 5- and 10-year timepoints. The clinical data included were Gleason grade, age, T-stage and PSA level at diagnosis. In hold-out validation studies, the performance accuracy of the prognostic MMAI model for each of these endpoints ranged from 65-84%, and all outperformed the current standard of care for risk prognostication (NCCN risk grouping).
- Additionally, this MMAI prognostic model was externally validated using data from the phase 3 SPARTAN and STAMPEDE clinical trials, in patients with non-metastatic castration-resistant prostate cancer (nmCRPC) and high-risk localized/metastatic prostate cancer, respectively. In nmCRPC, the MMAI prognostic model was able to identify patients who derived the greatest benefit from apalutamide. In patients with advanced prostate cancer, the MMAI prognostic model was able to identify those who were at highest risk for disease progression and death from prostate cancer.

- A predictive MMAI model was also developed to identify patients with intermediate-risk prostate cancer who may vs. may not benefit from the addition of short-term androgen deprivation therapy (ADT) to radiation therapy (RT) (**Figure**).
- Similarly, another predictive MMAI model was developed for patients with high-risk localized prostate cancer, to identify those who may vs. may not benefit from long-term ADT rather than short-term ADT, in addition to RT.
- An evaluation of the pathology features that the AI algorithm uses to make its outcomes predictions, reveals human-interpretable features including benign glands, enlarged cribriform glands, scattered individual tumor cells, scattered tumor cell clusters, clusters of individual tumor glands, and smooth muscle and blood vessels. These features have been identified by the MMAI algorithm as important features without any input from pathologists.
- This AI platform is highly scalable because it can be embedded into clinical workflows and uses standard clinical information and pathology slide images.
- The ArteraAI Prostate Test, which consists of both the prognostic biomarker and the ST-ADT predictive biomarker, is available to order in the U.S. It will soon be available in Australia, and countries in Asia and Europe.
- The ArteraAI Prostate Test, which has level 1 evidence, was added to NCCN guidelines as a risk stratification tool for prostate cancer in January 2023. To the knowledge of Dr. Esteva, this is the first AI tool added to any national medical guidelines.
- Predictive and prognostic MMAI tools are now being developed for other prostate cancer settings as well as additional cancer types.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-3-the-future-of-ai-in-diagnostic-medicine/>**

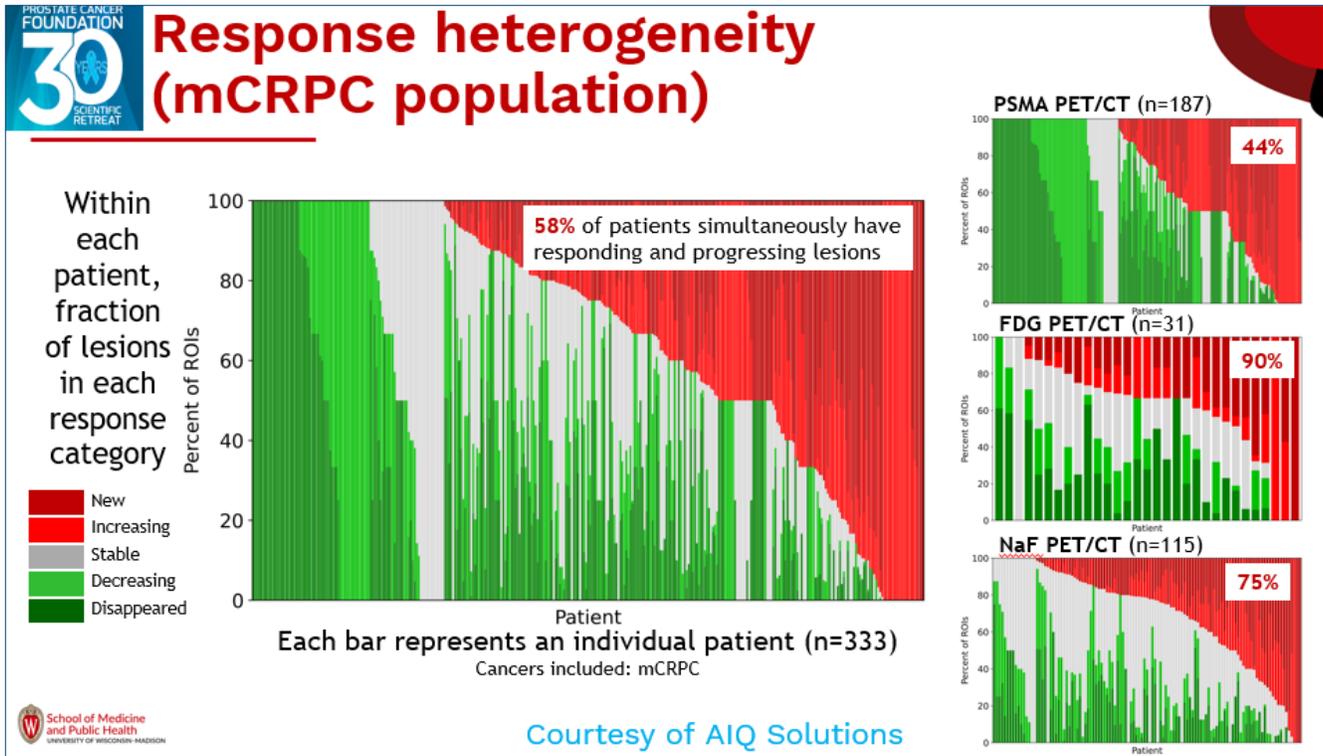


AI-Based Quantitative Imaging Biomarkers

Robert Jeraj, PhD

University of Wisconsin; AIQ Solutions

- Prostate cancer is a highly heterogeneous disease, even within patients. For instance, in patients with metastatic prostate cancer receiving a treatment, some metastases can shrink while others remain unchanged or grow, due to differences in tumor biology and location in the body.
- Dr. Robert Jeraj discussed an AI-based imaging biomarker that can quantitate changes in different metastatic lesions, to better understand treatment responses and resistance.
- In a study using molecular imaging of 1,100 patients with different types of metastatic cancer receiving treatment, it was observed that 61% had a heterogeneous response, in which some metastases shrank while others grew. 43% of patients in this study had limited resistance, and all or nearly all sites of metastasis shrank.
- Studies have also demonstrated that it is the resistant lesions, rather than responding lesions, that ultimately determine the patient's outcome. Thus, identifying these lesions is critical for optimizing treatment selection.
- AI-supported algorithms were developed to assess changes in size of all sites of metastases in a patient over time from molecular images such as CT and PET scans, and to predict patient outcomes.
- Among patients with metastatic castration-resistant prostate cancer (mCRPC), 58% were found to have simultaneously responding and progressing lesions. This fraction varied depending on the type of molecular imaging modality used: 44% had heterogeneous responses on PSMA PET, 75% had heterogeneous responses on NaF PET, and 90% had heterogeneous responses on FDG PET (**Figure**). Over time, such imaging analyses can be used to observe the evolution of response vs. resistance of individual tumor metastases.
- The use of imaging techniques that evaluate different features of tumor biology can be used to select optimal treatments. For instance, whether a targeted therapy can be used alone vs. a combination approach is needed, or whether a treatment should be continued, changed, or de-escalated.
- The AI models are also able to simulate how clinical outcomes might change if certain metastatic lesions were targeted with radiation. A study to prospectively test this hypothesis is underway.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-3-the-future-of-ai-in-diagnostic-medicine/>**



SPECIAL LECTURE: DEI Strategies for Advancing Cancer Care Equity

Tawana Thomas Johnson
American Cancer Society

- Tawana Thomas Johnson, Senior Vice President and Chief Diversity Officer at the American Cancer Society (ACS) discussed diversity, equity, and inclusion (DEI) strategies to advance cancer care equity.
- ACS is composed of three pillars: discovery, advocacy, and patient support. The discovery pillar funds cancer research programs. The advocacy pillar (ASC CAN) advocates at federal, state, and local levels across the U.S. for equitable access to cancer prevention, detection, treatment, and survivorship advances. The patient support pillar provides support and education to patients, caregivers, and clinicians.
- The U.S. is an increasingly diverse country, with a diverse cancer patient population.
- DEI strategies to advance cancer care equity include education, research, and community engagement.
- Health care organizations that acknowledge, accept, and uphold the cultural values of their patients and research participants are more likely to develop supportive and trusting relationships, which improve research and health care outcomes.
- The U.S. population is 13% Black and 18% Hispanic, while the oncology workforce is only 3% Black and 4.7% Hispanic. Research has shown that a more diverse oncology workforce, who have shared or similar lived experiences with the patients they serve, will lead to more equitable cancer care, and improve communication and adherence to medical advice.

- Of cancer clinical trial participants, only 4-6% are Black and 3-6% are Hispanic, yet of all patients with cancer, 15% are Black and 13% are Hispanic. Significant work is needed for clinical trial participants to reflect the diversity of the U.S. population.
- Strategies to improve diverse representation in cancer clinical trials include broadening clinical trial eligibility, education of communities and patients, and educating health care providers and holding them accountable to offering clinical trials to diverse patients.
- Community engagement is a key best practice to addressing health inequities. Bi-directional partnerships must be sought with key stakeholders, community members, and patients to create programs that reduce cancer risk, increase access to care, increase participation in cancer research, and increase trust.
- ACS programs to improve cancer care equity include the IMPACT (Improving Mortality from Prostate Cancer Together) initiative, which was launched in January 2023. Partners in this program include advocacy organizations, national African American organizations, members of congress, and pharmaceutical companies. This initiative will develop a new cohort of 100,000 Black men to study the social-contextual factors of prostate cancer outcomes and provide grants to research teams focused on reducing prostate cancer disparities.
- The patient support pillar aims to increase access to innovations in early detection, conduct patient and caregiver education campaigns to improve healthy living and active lifestyle behaviors, facilitate access to timely care, expand access to innovations in care, and enhance cancer therapy outcomes.
- Partnerships with national African American organizations are key to developing impactful DEI initiatives. For instance, in response to the murder of George Floyd, the ACS executive team convened meetings with several national Black organizations collectively representing 12.5 million African American, to discuss better ways to support the Black community. Education was identified as a key need, as there was a lack of information in the Black community around cancer prevention, early detection, and treatment. This led ACS to launch the Health Equity Ambassador program, which has trained over 2,100 volunteer health equity ambassadors from local communities, to educate communities on cancer prevention, early detection, treatment, and the importance of participating in clinical trials.
- ACS CAN is a 501(c)(4) organization, which can advocate for legislation that addresses health equities. For instance, ACS CAN has reintroduced the “PSA Screening for HIM” Act in the U.S. House to increase access to PSA screenings for men who are at high-risk for prostate cancer, and is advocating for state laws to eliminate co-pays for prostate cancer screening and reduce financial toxicity associated with a cancer diagnosis.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/special-lecture-dei-initiatives-in-biomedical-research-institutions/>**

DEI Strategies for Advancing Cancer Care Equity



Education

- Increase cultural competence of healthcare providers and researchers
- Create an oncology workforce that better reflects the diversity of the population



Research

- Ensure that clinical trials more accurately reflect the patient population
- Assess and mitigate barriers to patient screening and participation



Community Engagement

- Establish trusted and credible relationships with patients and community-based organizations serving diverse communities
- Cultivate strong partnerships between communities and researchers to develop culturally appropriate interventions to reduce cancer disparities
- Collaborate with community partners to address socio-economic needs and other barriers to quality care

Session 4: Analytical Approaches and Computational Biology for Cancer Research

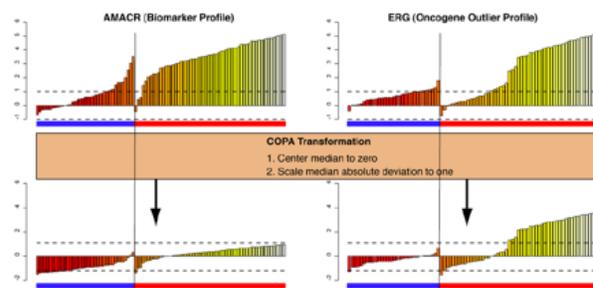
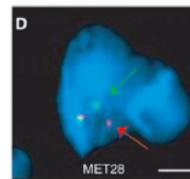
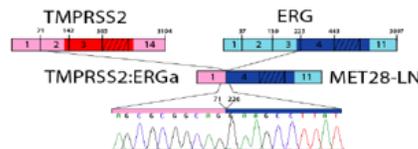
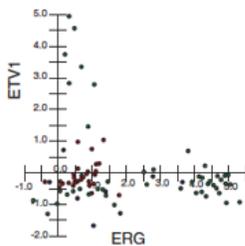
Introduction

Francesca Demichelis, PhD
University of Trento, Italy

- Bioinformatics is the application of computer science principles to understand and make sense of the vast life science data available.
- Computational biology is the development of new mathematical and computational methods to address knowledge gaps in biology. Computational biology is now a part of most scientific research papers.
- Artificial intelligence (AI) refers to the science and engineering of making intelligent machines. Machine learning is an AI method in which computer agents improve perception, knowledge, thinking, or actions based on experience or data. Both AI and machine learning are methods used in computational biology.
- Recently, AI has greatly increased in use due to the compilation of vast amounts of data and establishment of common language between computer scientists and researchers/clinicians.
- Simple and smart ways to look at existing data may lead to exceptional results. One such example is the 2005 discovery of recurrent *TMPRSS2-ETS* fusions in prostate cancer, where a data transformation pointed to the importance of *ETS* genes genomics (**Figure**).
- It is important to remember that these analytical and computational approaches need to be hypothesis-driven analyses with clear definition of the hypothesis space and the data boundaries. Large (multi-layer and multi-variable) datasets can be queried to provide a high-level overview but like any experiment, computational experiments require positive/negative controls.
- Inter-disciplinary common language is needed for bi-directional content-driven interactions between collaborating researchers.
- Researchers entering this field must learn what a good collaborative project looks like, when to say no to a project, how to understand the key experimental features (timing, complexity, amounts, etc.), and should identify one main area of expertise to build a track record around.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-4-analytical-approaches-and-computational-biology-for-cancer-research/>**

Recurrent Fusion of *TMPRSS2* and ETS Transcription Factor Genes in Prostate Cancer

Scott A. Tomlins,¹ Daniel R. Rhodes,^{1,2} Sven Perner,^{7,9}
Saravana M. Dhanasekaran,¹ Rohit Mehra,¹ Xiao-Wei Sun,⁷
Sooryanarayana Varambally,^{1,6} Xuhong Cao,¹ Joelle Tchinda,⁷
Rainer Kuefer,¹⁰ Charles Lee,⁷ James E. Montie,^{3,5,6}
Rajal B. Shah,^{1,3,5,6} Kenneth J. Pienta,^{3,4,5,6} Mark A. Rubin,^{7,8}
Arul M. Chinnaiyan^{1,2,3,5,6,9}

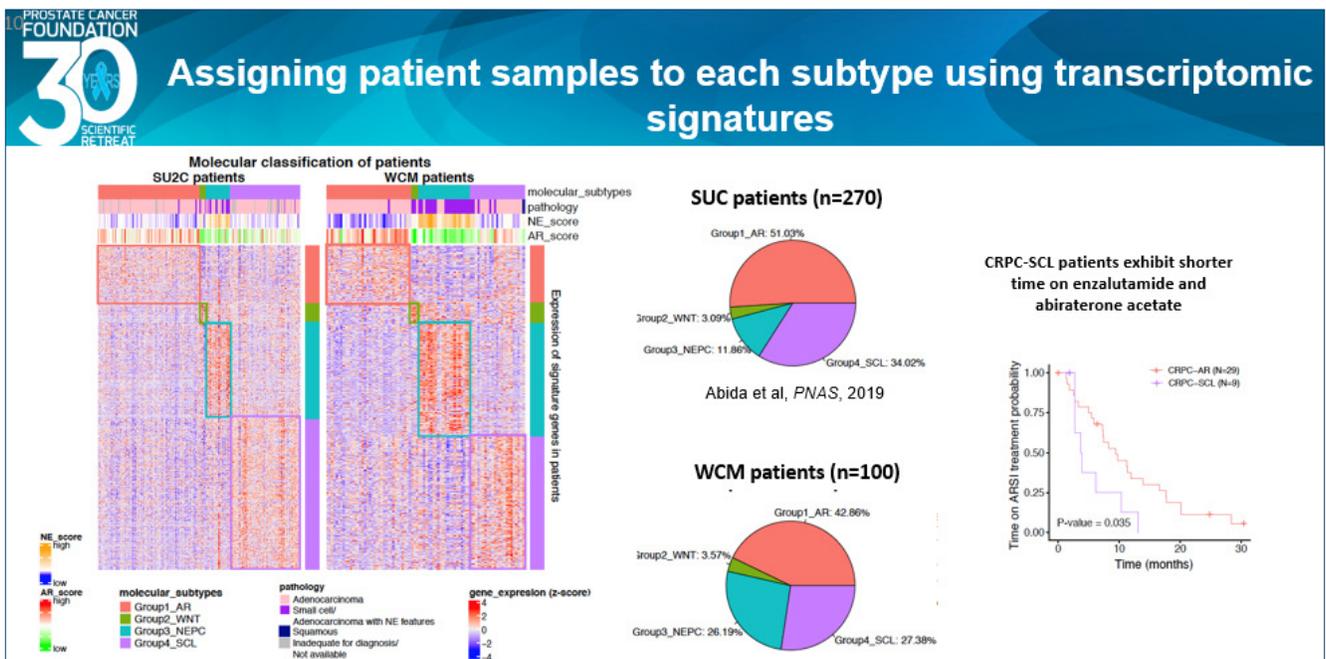


Non-Neuroendocrine Lineage Plasticity in Prostate Cancer

Ekta Khurana, PhD
Weill Cornell Medicine

- Cancer is an evolutionary process driven by the acquisition of genomic and epigenomic alterations that enable cells to continue growing, metastasizing, and developing resistance to treatments. Identifying the alterations that drive initial tumor growth and treatment resistance is key, however at least 25% of patients do not show mutations in known protein-coding drivers.
- Dr. Ekta Khurana discussed computational approaches developed to study the role of non-protein-coding genomic regions, such as alterations in genomic loops and 3D structural changes, in cancer development.
- Tumor organoids are mini-tumor models that can be grown and studied in the lab. Organoid models have been developed from patient tumor samples, which enable study of human prostate cancer.
- ATAC-seq is a genomic sequencing method that identifies “open” genomic regions that can be accessed by transcription factors (proteins that turn gene expression on or off).
- ATAC-seq data combined with gene expression data from 40 models (organoids, patient-derived xenografts, and cell lines) of metastatic castration-resistant prostate cancer (mCRPC) identified four mCRPC subtypes. These were primarily characterized by: androgen receptor (AR), WNT, neuroendocrine prostate cancer (NEPC), or stem cell-like activity. The stem cell-like subgroup also exhibited high expression of inflammatory genes and other pathways. The WNT and stem cell-like subgroups appear to overlap with “double-negative” subgroups identified by other research teams; this group lacks expression of both AR and NEPC genes.

- A computational method was developed to identify regulatory networks (genes and the transcription factors that regulate them) from ATAC-seq and gene expression data. This method was used to identify key transcription factors that drive each mCRPC subgroup.
- Key transcription factors included AR and FOXA1 for the AR subgroup, ASCL1 and NEUROD1 for the NEPC subgroup, TCF/LEF for the WNT subgroup, and AP1 for the stem cell-like subgroup.
- AP1 is known to cooperate with TEAD and YAP/TAZ transcription factors to drive tumor growth in other cancer types. These transcription factors were also found to cooperate in driving the growth of stem cell-like mCRPC tumors.
- Using a new gene expression-based computational approach, clinical mCRPC patient samples could be classified as one of these four subtypes. Overall, 43-51% of patients with mCRPC had the AR subtype, 27-34% had the stem cell-like subtype, 12-26% had the NEPC subtype, and 3-4% had the WNT subtype (**Figure**). Patients with the stem cell-like subtype had significantly worse clinical outcomes on AR signaling inhibitors than patients with the AR subtype (**Figure**).
- Ongoing studies are evaluating the potential of these transcription factors as therapeutic targets for the treatment of these tumor subtypes, and developing non-invasive methods for identifying which subtype of mCRPC a patient has.
- There are also large team efforts underway to use multi-omic data to reconstruct gene regulatory networks for different types of normal tissues and cell lines.
- Because 3D and CHIP-seq assays are highly infeasible for patient biopsies, new scalable machine learning methods are being developed to use only ATAC-seq and gene expression data to identify regulatory networks that are active in individual patient tumors.
- For example, *ESR1* enhancers in breast cancer were found to explain 93% of high *ESR1* expression in ER-positive breast cancer, while mutations that increase the number of *ESR1* gene copies only explained 1% of high *ESR1* expression.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-4-analytical-approaches-and-computational-biology-for-cancer-research/>**

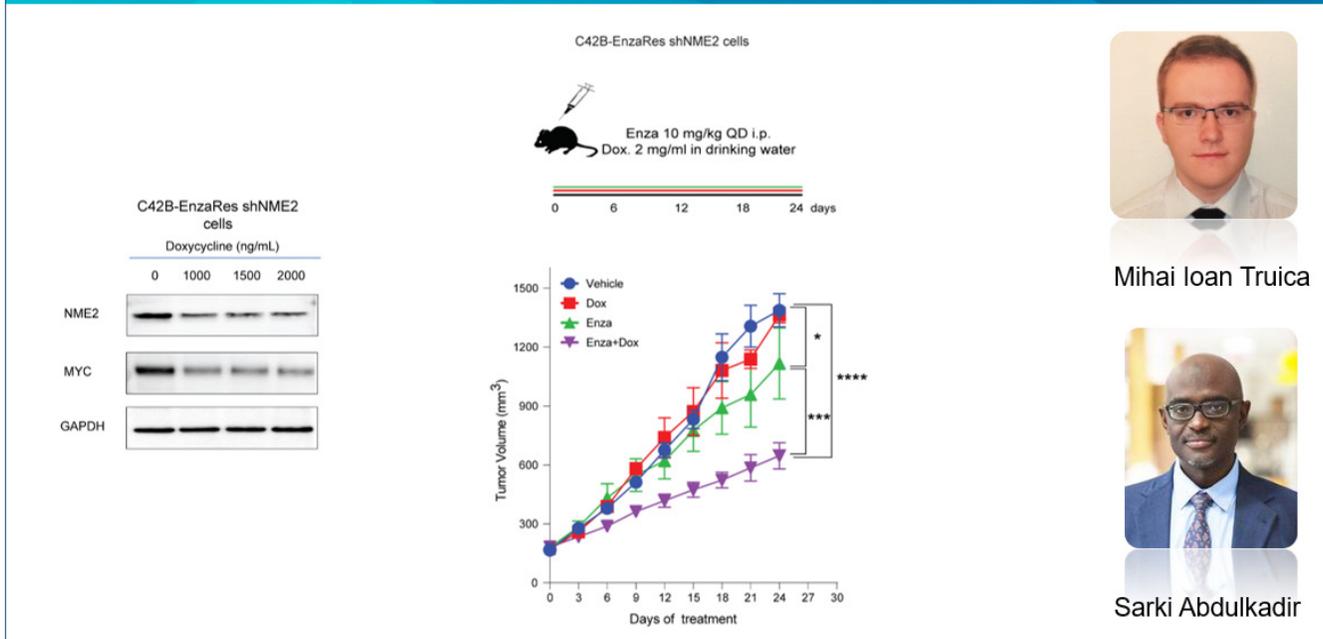


Mechanism-Centric Markers of Therapeutic Resistance in Oncology

Antonina Mitrofanova, PhD
Rutgers University

- MYC is a tumor-driving oncogene that is involved in over 70% of all types of cancers, including a significant portion of prostate cancer.
- In prostate cancer, high MYC levels have been associated with poorer responses to enzalutamide but may not impact responses to abiraterone. Understanding the role of MYC in mCRPC and treatment resistance is important.
- Dr. Antonina Mitrofanova discussed computational biology studies to better understand the role and mechanisms of MYC in enzalutamide resistance and whether this information may provide insights into new therapeutic strategies.
- New computational algorithms were developed to model regulatory signaling networks (that connect molecular pathways to their upstream transcriptional regulatory programs) in metastatic castration resistant prostate cancer (mCRPC). These networks were constructed using gene expression data from mCRPC biopsy samples. Networks that were different between untreated and enzalutamide-sensitive samples vs. enzalutamide-resistant samples, were identified; the MYC pathway was one of these.
- A computational model was developed to identify and prioritize upstream transcriptional regulators of MYC. NME2 was identified as having the largest effect on the MYC pathway, and its activity highly correlated with that of MYC and with response to enzalutamide. High levels of MYC and NME2 were associated with poorer responses to enzalutamide and worse clinical outcomes.
- In preclinical models, knockdown of NME2 reduced MYC levels. Targeting the NEM2 and MYC axis re-sensitized tumor cells to enzalutamide (**Figure**).
- These studies suggest that mCRPC patients that failed enzalutamide and have increased levels of NME2/MYC activity could benefit from combined therapeutic targeting along NME2/MYC and AR. Further studies are evaluating this hypothesis.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-4-analytical-approaches-and-computational-biology-for-cancer-research/>**

Targeting MYC/NME2 axes re-sensitizes Enzalutamide resistant tumors to Enzalutamide



Mihai Ioan Truica



Sarki Abdulkadir

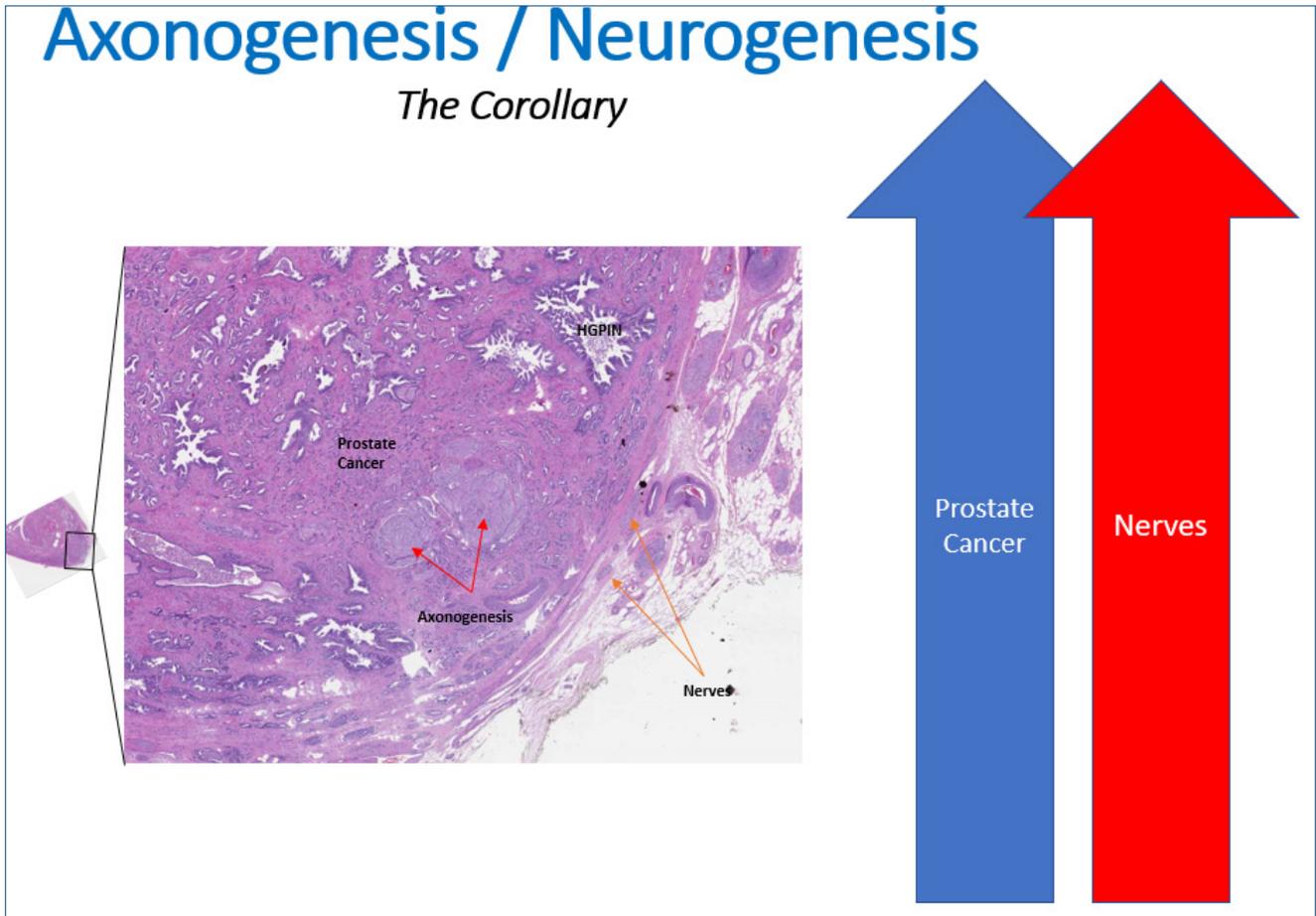
SPECIAL LECTURE: Of Nerves and Cancer

Gustavo Ayala, MD

The University of Texas Health Science Center at Houston

- Dr. Gustavo Ayala discussed the role of nerves in prostate cancer growth and progression.
- Nerves are required for biological processes such as the growth of new epithelium in wound healing processes. In animal models, inhibition of nerves perturbed wound healing processes and caused epithelial cells to become metabolically inefficient, becoming dependent on synthesis of glucose from non-carbohydrate sources rather than using existing glucose. Thus, nerves appear fundamental for the energetic homeostasis of normal epithelium.
- Nerves are also important for tumor growth and can be found in and surrounding tumor sites (**Figure**).
- Preclinical studies have found that cancer cells promote nerve cells to develop axons, and that neural cells from the brain migrate to sites of cancer to form new neuronal systems. Nerve inhibition also blocked tumor growth in mouse models of prostate, breast, and gastric cancer.
- Specific inhibition of the neurotransmitter protein neuropeptide Y (NPY) also blocked growth of tumor cells and altered metabolism.
- Based on these data, Dr. Ayala and colleagues initiated a proof-of-concept phase 1 clinical trial to study the effect of Botox on prostate cancer. In this trial, patients with primary prostate cancer were given an injection of Botox on one side of their prostate and a shot of saline on the other side; patients underwent prostatectomy four weeks later. The effects of Botox vs saline on tumor biology were then compared in surgical samples.

- Neuroendocrine prostate cancer (NEPC) is a form of advanced prostate cancer in which prostate cancer cells lose prostate features and gain neuronal features to evade anti-androgen therapy. NEPC cells do not completely convert into neurons, but do express neural genes including dendrite and axon genes and can transmit potential between cells.
- Overall, these studies demonstrate that nerves are critical for prostate cancer energetic metabolism and growth. However, some prostate cancers can evolve into NEPC, an autonomous tumor form that generates its own nerve signals for growth.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/special-lecture-of-nerves-and-cancer/>**



Session 5: The Biology of Prostate Cancer Bone Metastases

Building on Insights from Murine Models and Clinical Studies of Prostate Cancer Bone Metastases

Estefania Labanca, PhD

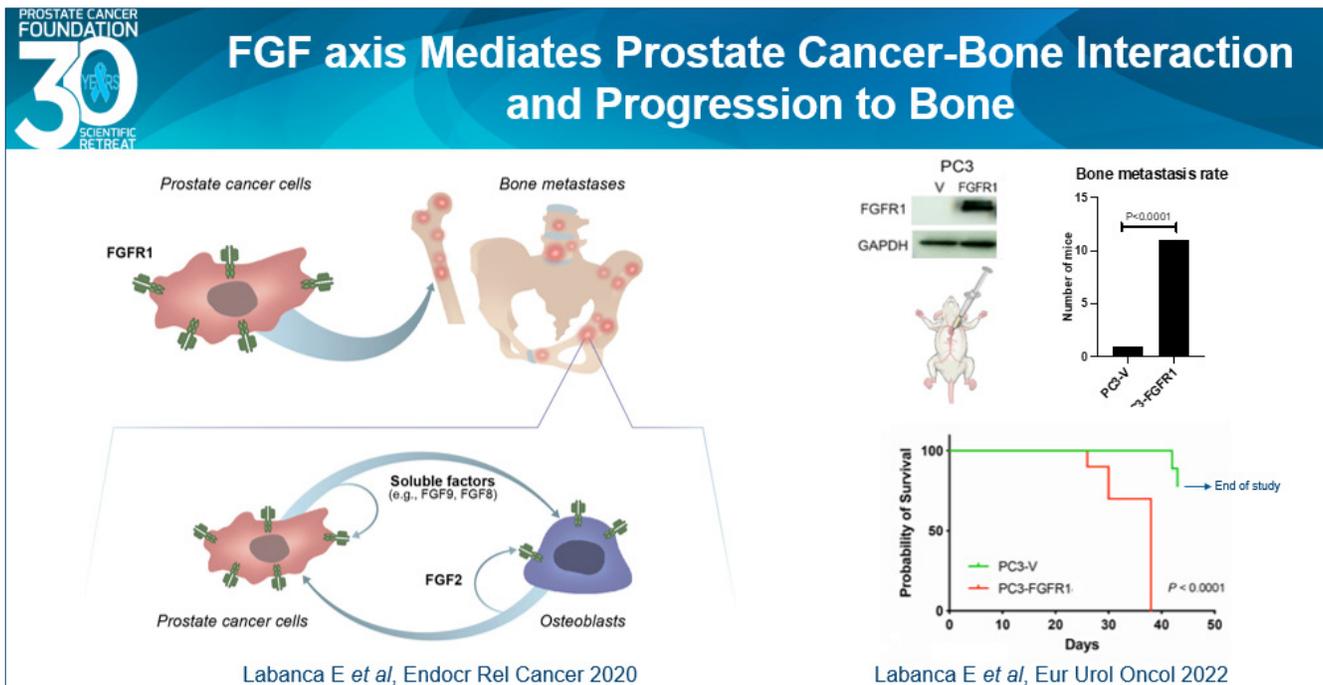
The University of Texas MD Anderson Cancer Center

Nora Navone, MD, PhD

The University of Texas MD Anderson Cancer Center

- Bone is the primary site of prostate cancer metastasis, and nearly all patients with metastatic prostate cancer will experience bone metastases which contribute to lethality.
- On behalf of Dr. Nora Navone, Dr. Estefania Labanca presented studies on preclinical models of prostate cancer bone metastases.
- Dr. Navone and team have established over 150 prostate cancer patient-derived xenograft (PDX) models. These models of human prostate cancer are grown in mice and several studies have established their therapeutic relevance. Organoid models, in which mini prostate tumors can be grown in the lab, have also been developed from these PDX. These preclinical models represent a range of prostate cancer subtypes and clinical states and were derived from tumor samples taken from primary prostate cancer and various metastatic sites including bone. These models are being comprehensively characterized.
- The bone growth factor FGF9 was found to be highly expressed in a model that manifests a robust bone formation reaction. Treatment of mice with an FGF9-inhibitor limited development of bone metastases.
- Extracellular vesicles (EVs) are small particles released from cells that transfer bioactive molecules including DNA, RNA and proteins, to other cells. FGF9 transcripts were detected in EVs from the bone metastatic prostate cancer murine model and from patients with bone metastases.
- After being released from cells, FGF9 binds to FGF-Receptor-1 (FGFR1) to trigger growth pathways. FGFR1 was found to be highly expressed on prostate cancer cells, and was associated with higher rates of bone metastases and shorter survival in mouse models (**Figure**).
- In a prior clinical trial, some patients with metastatic prostate cancer who were treated with the non-specific FGFR-inhibitor dovitinib exhibited improvements in bone scans and a decrease in bone alkaline phosphatase, but no improvement in PSA levels.
- The specific FGFR-inhibitor Erdafitinib was evaluated in prostate cancer mouse models and showed reduction in bone metastasis formation. A clinical trial testing Erdafitinib in patients with bone metastatic prostate cancer was initiated. Similar to the dovitinib trial, some patients experienced improvements in bone scans and a decrease in bone alkaline phosphatase, but no PSA reductions occurred.
- Radium-223 is an FDA-approved treatment for bone metastatic prostate cancer that targets the bone microenvironment as it is a calcium-mimetic. The impact of Radium-223 on FGF signaling and bone biology is being investigated in prostate cancer mouse models and patients. Whether patient outcomes can be improved by therapy combinations with FGF-targeting treatment remains under investigation.

- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-5-the-biology-of-prostate-cancer-bone-metastases/>

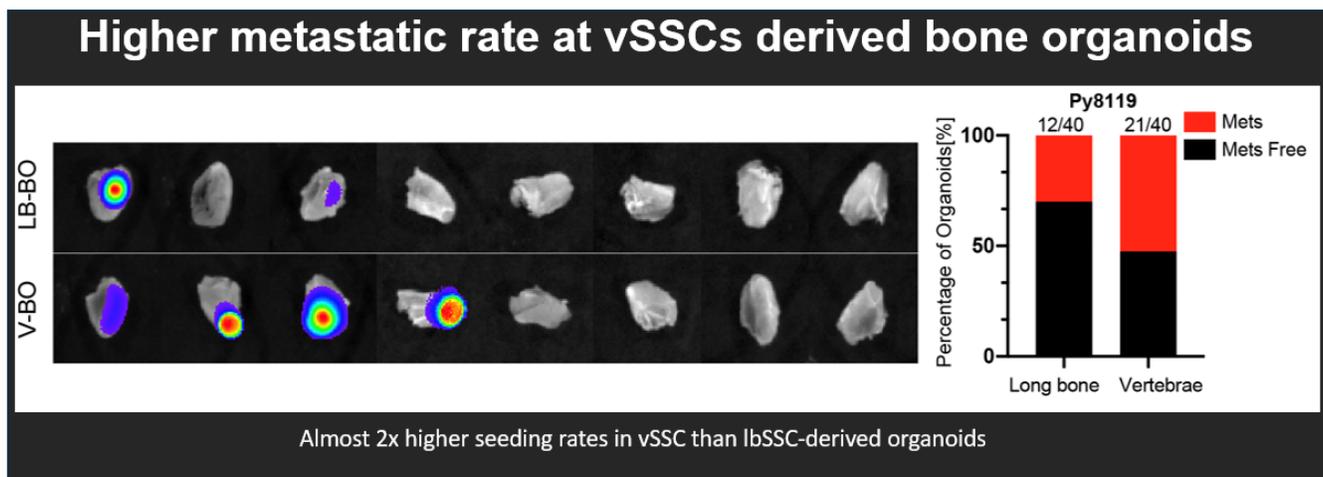


A Skeletal Stem Cell Directing Prostate Cancer Spine Metastases

Matthew Greenblatt, MD, PhD
Weill Cornell Medicine

- The vast majority of patients with metastatic prostate cancer experience bone metastases, while distant lymph node and liver metastases are less common. Bone metastases are a major source of pain and disability and are associated with reduced overall survival.
- The spine is the most common site of bone metastases; however only a small portion of blood flow enters the vertebrae, so it is unclear what is unique about the vertebrate skeleton that allows for this.
- Dr. Matthew Greenblatt discussed studies on the biology of prostate cancer spine metastases.
- Different regions of bone are formed by distinct sets of stem cells. Vertebral bone has a distinct evolutionary and developmental origin from long bone, suggesting it may also develop from a unique group of stem cells.
- Vertebral cells that express known markers of other types of bone stem cells were identified in vertebral endplate cartilage in mice and humans. These putative stem cells expressed other proteins that were distinct from long bone stem cells, such as *Zic1*. Further studies confirmed that these cells fulfill stem cell criteria including the ability to continually make daughter vertebral cells, and thus are likely vertebral stem cells.
- Mice genetically engineered to lack *Zic1*-expressing vertebral stem cells don't form dorsal spine, have low bone mass in the vertebrae, and develop paraplegia and severe spine instability.

- In mouse breast cancer models, enhanced early metastasis was observed in vertebral bone compared to long bone.
- Whether vertebrae metastasis is driven by vertebral stem cells was investigated by transplanting vertebral vs. long bone stem cells in muscle of mice. Over time, these stem cells formed miniature bones (“organoids”) in the muscle. When these mice were injected with breast cancer cells, twice as many metastatic tumors formed in vertebral bone organoids vs. long bone organoids (**Figure**). Prostate cancer is now being investigated in this model.
- The secreted bone-regulating protein MFGE8 was found to be a molecular mediator driving vertebral metastasis. Mice genetically engineered to lack MFGE8 developed fewer bone metastases. In cell culture studies, MFGE8 was required for bone stem cells to attract tumor cells to them.
- Overall, these studies demonstrate that vertebral stem cells play a major role in driving the development of breast and prostate cancer bone metastases by secreting MFGE8 to attract tumor cells to the bone. Additional studies on mechanisms and treatment opportunities are underway.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-5-the-biology-of-prostate-cancer-bone-metastases/>**



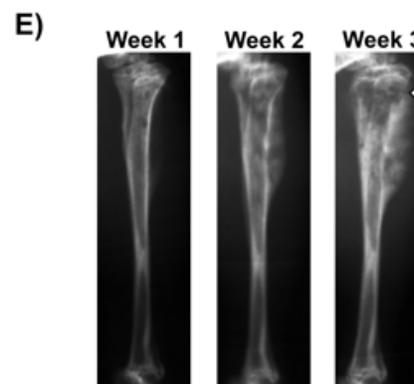
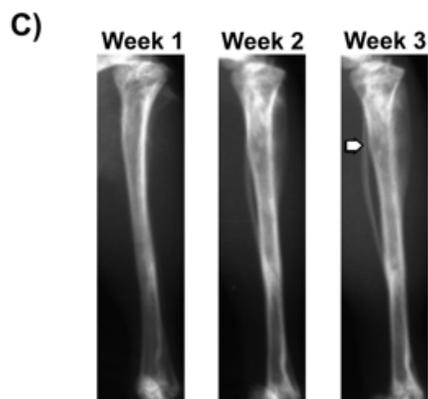
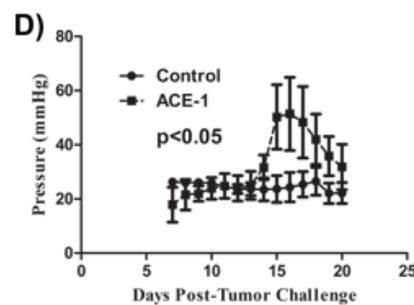
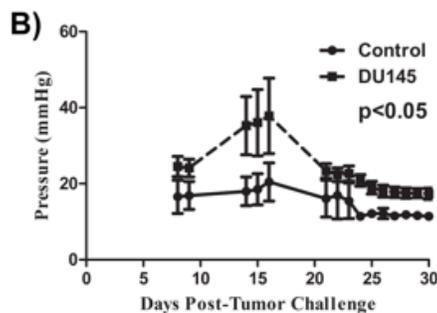
Role of Osteocytes in Prostate Cancer Bone Metastasis

Evan T. Keller, DVM, PhD
University of Michigan

- The bone is the primary site of prostate cancer metastases, contributing significantly to patients' morbidity and mortality. The factors that drive prostate cancer bone metastases are important to study in order to develop new treatment strategies.
- Dr. Evan T. Keller discussed the role of osteoblasts in prostate cancer bone metastasis.
- There are several types of cells that form bone, including osteocytes, osteoblasts, and osteoclasts. Osteocytes are the most abundant bone cell type, and play a key role in sensing physical forces and damage in the bone and coordinating bone remodeling responses.
- Whether prostate cancer bone metastases generate physical forces in the bone that impact disease progression was investigated.

- A pressure monitor was transplanted into bone marrow of mice with prostate cancer. As tumors grew in bone, pressure increases were observed over time, with intermittent bone fractures that released pressure (**Figure**).
- An experimental system was developed that could induce pressure on cells. Pressure increases caused osteocytes to release factors that increased migratory and invasive activity of tumor cells. These released factors include CCL5, a protein that can attract migration of cancer cells, and MMP9, a protein that degrades extracellular matrixes to allow tissue remodeling. Thus, as tumors grow in bone and exert pressure on surrounding bone cells, osteocytes are triggered to produce factors that further break down bone and allow tumor cell invasion.
- Further laboratory studies identified crosstalk between prostate cancer cells and osteocytes, in which factors produced by prostate cancer cells caused osteocytes to release factors that then promote growth and invasive activities of prostate cancer cells.
- GDF15 was identified as one factor that osteocytes produced which promoted prostate cancer growth. Inhibition of GDF15 decreased prostate tumor growth and bone damage in mice. The mechanisms by which GDF15 promotes prostate cancer activities are being investigated.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-5-the-biology-of-prostate-cancer-bone-metastases/>**

Tumor growth induces intratibial pressure



Sottnik et al, Can Res 2151-8, 2015

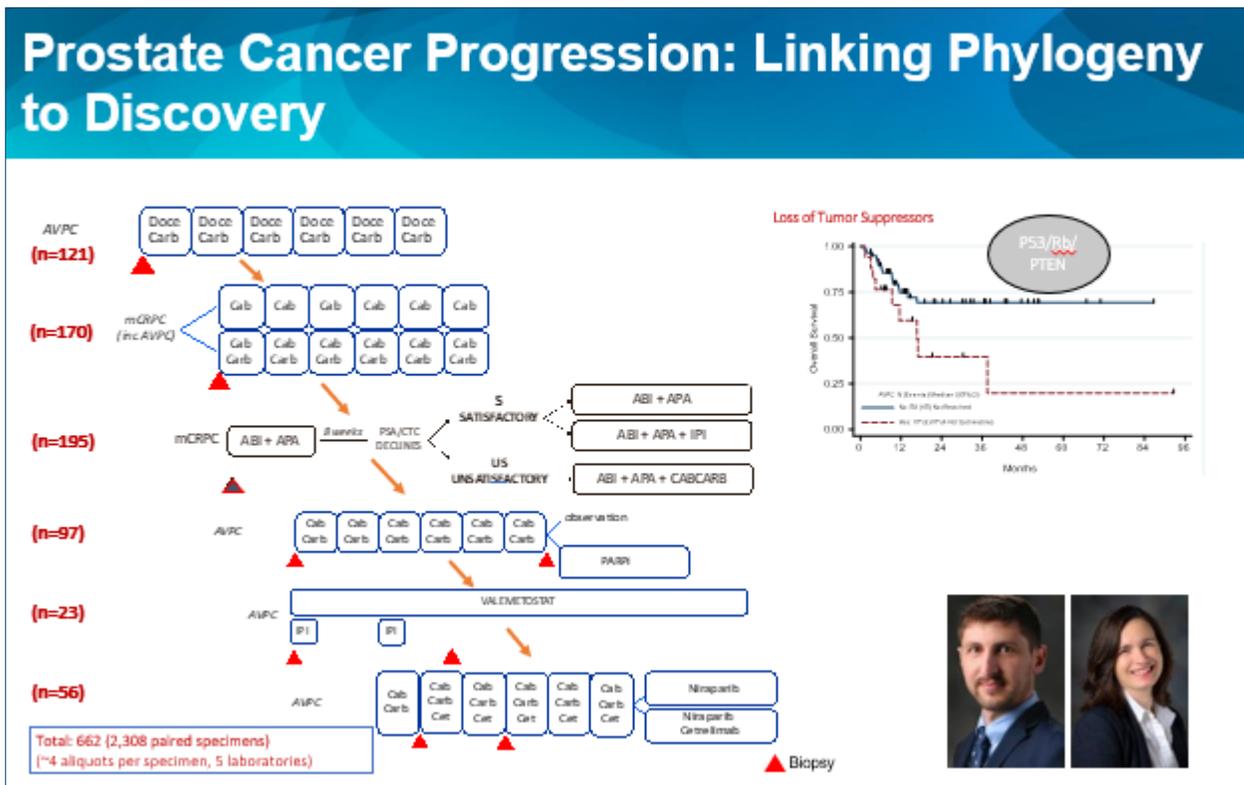
SPECIAL LECTURE: Transitioning from “Drug to Therapy Development Strategies” in Prostate Cancer

Christopher Logothetis, MD

The University of Texas MD Anderson Cancer Center

- Drug development strategies focus on optimizing drugs against a specific target. Treatment development strategies in contrast, focus on the patient as a whole, to include considerations of the complex environment patients live in and the heterogeneity of patients and tumors.
- Dr. Christopher Logothetis discussed approaches to improve selection of treatments for patients by considering the complex biology of tumors and patients.
- Cancers can evolve through different pathways. Some tumors are highly clonal, with little genomic/molecular heterogeneity that develops late in disease history, some develop genomic/molecular heterogeneity early in disease history, and some gain aggressive disease attributes through interactions with cells and factors in the surrounding microenvironment.
- Clinical trials testing three months of androgen deprivation therapy (ADT) alone vs. with the addition of abiraterone prior to prostatectomy in patients with high-risk localized prostate cancer have found that patients that experience significant disease regression of the primary tumor also do significantly better long-term, while those with primary resistance do poorly.
- A trial testing 8 months of ADT alone vs. with abiraterone demonstrated that the addition of abiraterone significantly extended progression-free survival in ~25% of patients.
- These trial results suggest that responses seen in the primary tumor for patients treated with androgen signaling inhibition may be biomarkers of treatment response and could guide treatment selection for patients. The finding with androgen signaling inhibition in the pre-operative setting may not have similar predictive outcomes in cancers treated with alternative therapies.
- Patients with genetically unstable advanced prostate cancer such as aggressive variant prostate cancer (AVPC), may benefit from more intense treatments. This was demonstrated in a trial that found patients with AVPC had better outcomes when treated with cabazitaxel plus carboplatin compared with cabazitaxel alone.
- A series of trials was initiated to test six different treatment approaches in over 660 patients with AVPC and evaluate biological responses in addition to clinical outcomes (**Figure**).
- For example, one trial is testing cabazitaxel plus carboplatin followed by a PARP-inhibitor vs observation. Studies on samples from this trial found that alterations in DNA repair genes were associated with benefit from PARP-inhibitors.
- Ongoing studies will determine whether and how to identify patients who don't have DNA repair gene alterations but benefit from PARP-inhibitors, as well as how to identify such patients early in disease history.
- In one study, increases in DNA damage could be observed in some primary tumors without DNA repair mutations after treatment with hormonal therapy, suggesting these patients could benefit from additional early treatment. A trial is underway to evaluate whether patients with high-risk localized disease who show unfavorable responses to ADT + apalutamide, will benefit from subsequent immunotherapy.
- PET scans are now being developed to monitor PARP activity in patients undergoing treatment.
- Prostate cancer bone metastases cause remodeling of the bone microenvironment that contributes to disease progression and lethality. This biology underlies the efficacy of the radioactive calcium-mimetic treatment Radium-223, which targets bone remodeling.

- Interactions between bone and prostate cancer cells also cause suppression of anti-tumor immune responses, which can be reversed by treatments that block these cell-cell interactions.
- Bone-related genes that have increased expression in patients with bone metastases have been identified; higher expression of these genes is associated with poorer responses to Radium-223. Immunotherapy may be able to overcome treatment resistance in the bone metastatic niche.
- Four agents have been shown to significantly increase patient survival in epidemiologic studies but not in clinical trials: beta blockers, statins, metformin, and aspirin. This is thought to be due to the “overlap syndrome” in which many patients in the real world have multiple comorbidities including cardiovascular, cognitive, and bone health issues, that benefit from these treatments, while these comorbidities are minimal in the optimized patient population that are usually included in clinical trials. Understanding the molecular basis of benefit with these treatments will be useful in identifying patients who should receive these.
- Collecting rich molecular and clinical data from patients is critical for developing strategies to predict benefit and toxicities and guide optimal treatment decisions for individual patients.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/special-lecture-transitioning-from-drug-to-therapy-development-strategies-in-prostate-cancer/>**



SPECIAL LECTURE: Implementation Science and How It Can Improve Prostate Cancer Outcomes: The PCF-ADEPT Program

William K. Oh, MD

Chief Medical Officer, Prostate Cancer Foundation

- Dr. William Oh discussed the PCF-ADEPT (Assessing and Delivering Excellent Prostate cancer Treatment) Program, which is developing new implementation science initiatives.
- Implementation science is a subset of health services research that focuses on dissemination and implementation of research and health advances into policy and practice.
- Prostate cancer remains the leading type of cancer diagnosed in men, and the second-leading cause of prostate cancer deaths in male patients. In 2023, an estimated 288,300 new cases of prostate cancer and 34,700 deaths from prostate cancer will occur.
- Despite the many new life-extending treatment combinations for metastatic hormone-sensitive prostate cancer (mHSPC) that have become available over the past decade, studies have found that only 9-38% of patients receive the current standard of care (**Figure**).
- This demonstrates there are gaps in practice implementation, between established best practices and their delivery. Identifying these gaps and clear action plans for different stakeholders, including clinicians, government, industry, researchers, payors, and patients, is critical for reducing barriers to delivery of standard of care and novel therapies to patients with prostate cancer.
- Dr. Oh discussed several PCF-ADEPT programs that focus on reducing disparities and enhancing care for patients with metastatic prostate cancer.
- There are significant prostate cancer racial disparities experienced by Black patients. These include significantly higher incidence and mortality rates compared with White patients, and a higher likelihood of being diagnosed at a younger age and/or with more advanced disease. Black patients are also underrepresented in clinical trials and research.
- Recent studies have found that the incidence of metastatic prostate cancer has been rising in the past few years; this effect is even more profound in Black patients compared with other races/ethnicities. This increase is due largely to changes in prostate cancer screening guidelines. Risk-stratified screening guidelines are needed.
- To address this issue, PCF-ADEPT created PCF screening guidelines for prostate cancer in Black patients in the U.S. A panel of experts representing a range of clinical disciplines and patient advocates, led by Dr. Isla Garraway and Dr. Sigrid Carlsson, was convened to create these guidelines and messaging for patients. These guidelines are now under review for publication.
- Factors influencing prostate cancer outcomes in Black patients include cultural mistrust of the health care system, physician-patient communication, knowledge of prostate cancer in the Black community, treatment access for Black patients, geographic access to care, socioeconomic factors and affordability, and Black patient enrollment on clinical trials.
- A recent study found that in Atlanta, Black patients with “low-risk” prostate cancer have a 5-fold higher risk of dying from the disease compared with White patients. This is the largest disparity across 17 regions in the U.S., according to data from the SEER registry.
- The PCF Implementation Consortium is an initiative to partner with local community leaders and academic hospitals to create programs focused on implementation goals that are achievable quickly and have the greatest ability to change outcomes. For instance, one focus will be the implementation of the PCF screening guidelines for Black patients. The initiative will also track outcomes at baseline and thereafter in that community and will include a PCF Implementation Advisory Board to establish a blueprint for best practices.

- Most patients with advanced prostate cancer do not receive the current standard of care and are undertreated. Patients more likely to receive standard of care are younger, White, live in urban areas, receive care at academic medical institutions, and have fewer co-morbidities. Oncologists are also more likely to prescribe current standard of care than urologists.
- To improve the delivery of standard of care therapies for metastatic prostate cancer, PCF-ADEPT held a PCF Clinician-Industry Roundtable on Metastatic Prostate Cancer. This new partnership between PCF, non-profit cancer research and patient advocacy organizations, and academic and industry partners focused on leveraging shared resources, publicly available data, and PCF-affiliated expertise to identify and implement solutions to the known underutilization of optimal treatment of metastatic prostate cancer, starting with mHSPC.
- Major components of the partnership include an ongoing core and extended team discussion forum, disease-focused, brand-agnostic proposals intended to improve care for all patients, and cross-industry and cross-organization collaboration including patient advocacy groups.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/special-lecture-implementation-science-and-how-it-can-improve-prostate-cancer-outcomes-the-pcf-adept-program/>**

Does Research from Clinical Trials in mHSPC Translate into Access to Treatments for Patients in the “Real World”?

- 13 papers: 6 full-text articles and 7 abstracts for a total of 166,876 patients
- Treatment intensification with docetaxel or ARSI: **9.3% to 38.1%**
- More likely to receive:
 - Younger, White, Urban, Fewer Co-morbidities, Academia
- Oncologists > Urologists

Dodkins et al. Jun 2023 Eur Urol Oncol

30 YEARS
Curing Together.

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/30th-annual/special-lecture-the-global-public-square-of-prostate-cancer/>

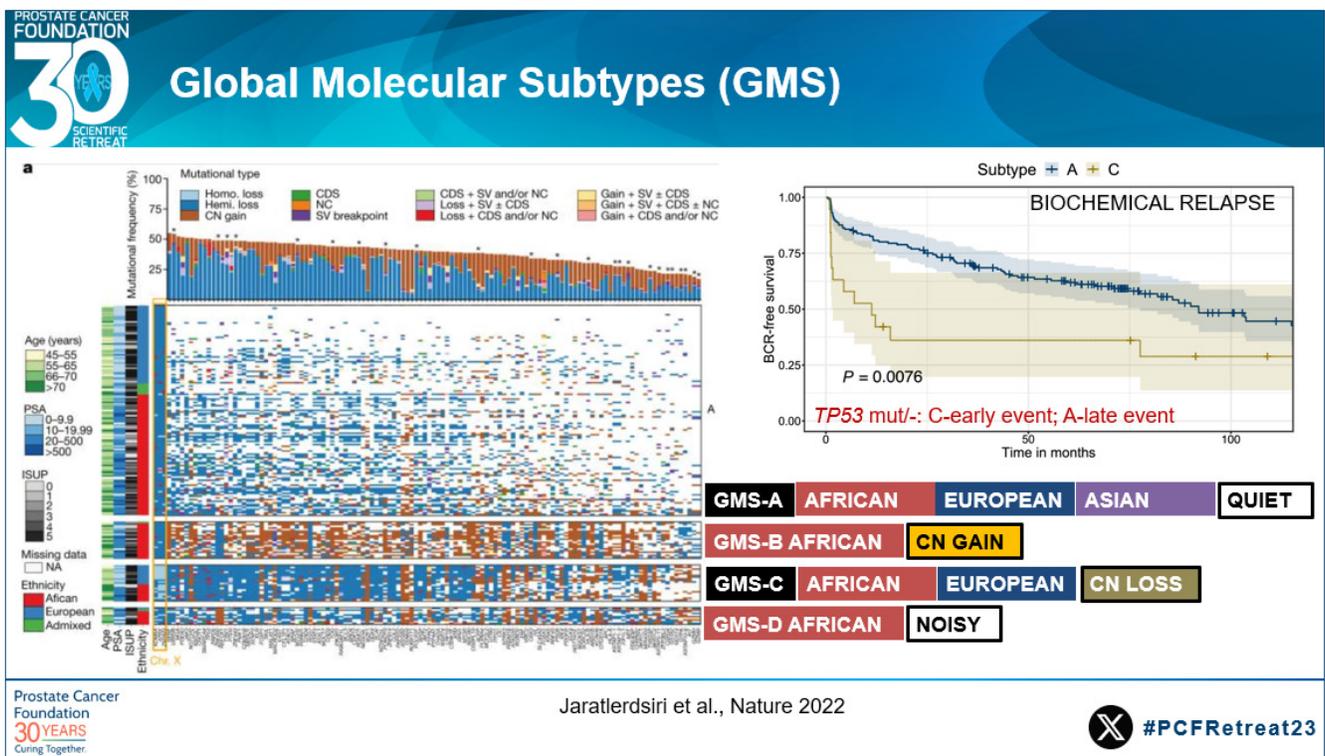
Session 6: The Contribution of Ancestry and Genomics to Prostate Cancer Disparities

African-Specific Molecular Taxonomy of Prostate Cancer

Vanessa Hayes, PhD
The University of Sydney, Australia

- Dr. Vanessa Hayes discussed studies on prostate cancer health disparities in Africa.
- Studies have found that prostate cancer mortality rates are 2.5-fold higher in Sub-Saharan Africa compared to the U.S.
- Patients in South Africa have a 2.1-fold greater risk of presenting with a high-grade prostate cancer compared to African American patients and have significantly higher PSA levels at diagnosis.
- The first African genome was sequenced in 2010. Today, only 2% of all sequenced genomes come from people of African ancestry.
- The PCAWG consortium, which is the largest prostate cancer genome sequencing resource, currently contains no genomes from patients on the African continent.
- Over 1.5 billion people live in Africa today. The ancestral diversity in Africa is significant, with over 2,000 languages spoken across 54 countries.
- Dr. Hayes and colleagues sequenced the whole genomes of 183 prostate cancers from patients in Africa, Brazil, and Australia; this included 113 patients of African ancestry and 61 patients of European ancestry.
- African ancestry patients had over ~1 million more single nucleotide variants in their genomes than European-Australian ancestry patients. Current cancer genomic tests only included ~5.6% of the prostate cancer risk single nucleotide variants found in African ancestry patients.
- Some genetic prostate cancer risk variants such as in *HOXB13* and *CHEK2* found in West African populations were absent in South Africa populations.
- Tumor mutational burden is a measure of mutational load in cancers. Tumor mutational burden and the number of copy number alterations were significantly greater in African vs European ancestry patients.
- Ancestry-specific differences in driver gene mutations in prostate cancer were identified. While there were no ancestral differences in the total number of structural mutations (chromosome rearrangements) observed, copy number alterations, gene duplications, hyper-SV genomes, hyper-deletions, and hyper-translocations were more common in African ancestral prostate cancer.
- Overall, four prostate cancer molecular subtypes were identified in a cohort of African, European and Asian ancestry patients, which corresponded strongly with ancestry (**Figure**). Subtype-A was mutationally quiet and found in all ancestries. Subtype-B was characterized by copy number gains and was found almost exclusively in African ancestry patients. Subtype-C was characterized by copy number losses and was found in African and European ancestry patients. Subtype-D was mutationally “noisy” and found almost exclusively in African ancestry patients. Subtype-A was associated with significantly better clinical outcomes than Subtype-C.
- Of note were the more than 650 genes contributing to epigenetic regulation found to be significantly impacted in African vs. European derived tumors.

- Only one significant prostate cancer mutational signature was identified in European ancestry patients, while 10 mutational signatures were identified in African ancestry patients, all of unknown origin.
- Overall, these data demonstrate a higher mutation burden, a greater number of unknown mutational signatures, and a greater tumor genomic heterogeneity in African vs. European ancestry patients.
- Interestingly, a small number of White South African patients also had African-specific tumor molecular subtypes. This suggests there may be an environmental carcinogen that is contributing, at least in part, to aggressive prostate cancer in Southern African patients. The role of ancestral vs. geographical effects are being studied.
- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-6-the-contribution-of-ancestry-and-genomics-to-prostate-cancer-disparities/>



Biomarker Benchmarking across Ancestral Populations

Elio Adib, MD

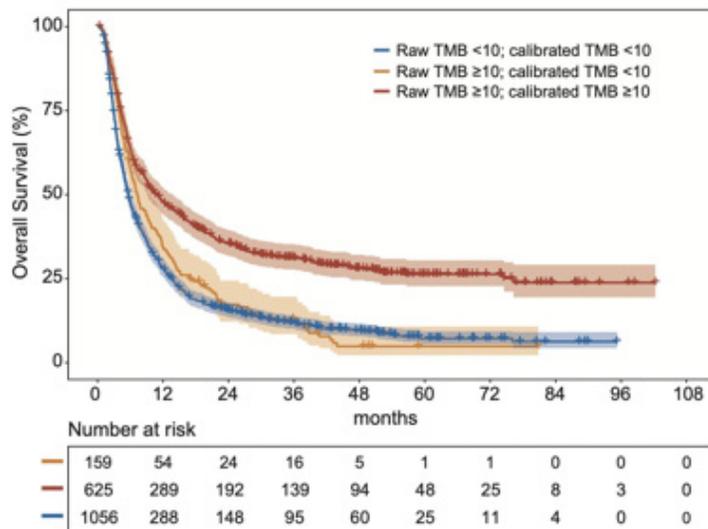
Brigham and Women's Hospital; Massachusetts General Hospital

Amin H. Nassar, MD

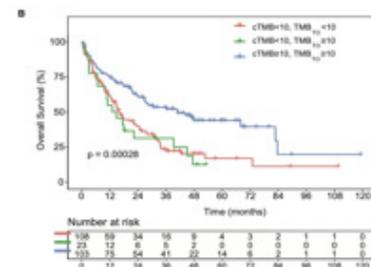
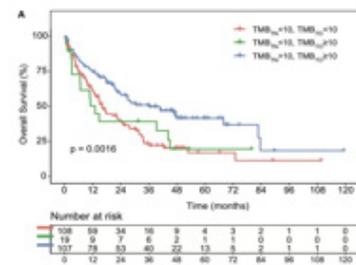
Yale New Haven Hospital

- Drs. Amin Nassar and Elio Adib discussed studies to benchmark genomic biomarker studies in non-White populations, which are vastly underrepresented in genomics research and clinical trials.
- For instance, in the Genome Aggregation Database (gnomAD), individuals of European descent comprise 78% of genomes, a number 6-fold higher than individuals of African descent.
- Some new cancer treatments are prescribed based on a patient's genomics rather than the tumor type. For instance, pembrolizumab immunotherapy is approved for patients with advanced solid tumors who have mismatch repair deficiency or tumor mutational burden-high (TMB-H) tumors. This is because the immune system is more likely to be activated by immunotherapy treatments when tumors have many mutations and thus look "foreign" to the immune system. However, in the trials that led to these approvals, 80% of clinical trial participants were White and 13% were Asian, while the numbers of Black participants were unknown.
- Importantly, identification of genomic "mutations" or "variants" requires knowledge of what is normal – this knowledge is vastly lacking in non-White populations. This has resulted in disparately high numbers of false germline variants being called in non-White individuals when tumor-only sequencing is done, which impedes accurate predictions of whether immunotherapy will be of benefit in these patients.
- Drs. Nassar and Adib conducted a study to provide ancestry-calibrated tumor mutational burden estimates to predict clinical benefit with cancer immunotherapy.
- Three cohorts representing over 13,000 patients with various cancer types were used to identify TMB based on continental ancestry. When tumor genomic data were benchmarked by tumor-normal data and adjusted by cancer type and ancestry, false TMB-high classifications were found to be significantly higher among patients of African (40%) and Asian (37%) ancestry compared to European (21%) ancestry.
- False TMB-high classifications were associated with significantly worse patient outcomes when treated with immunotherapy (**Figure**); these patients did not benefit from immunotherapy treatment as much as their true TMB-high counterparts.
- In a small study, ancestry-calibrated TMB-high classification did not predict for immunotherapy benefit in some non-White patient cohorts, suggesting it may not be a universal marker of clinical outcomes across ancestral populations. More definitive studies are needed.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-6-the-contribution-of-ancestry-and-genomics-to-prostate-cancer-disparities/>**

False TMB-high tumors are associated with worse outcomes



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Lessons from Genomics and Health Disparities in Breast Cancer

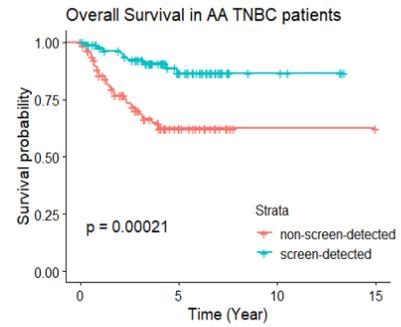
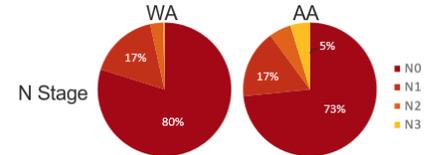
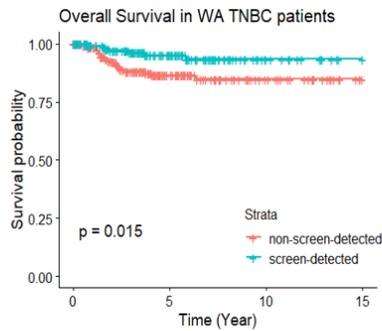
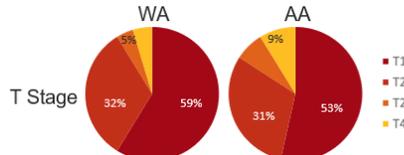
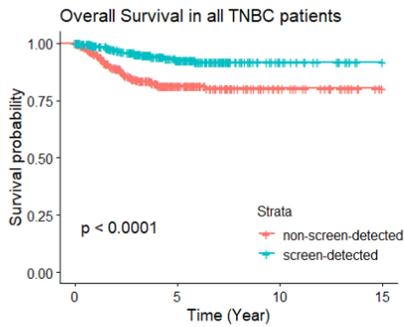
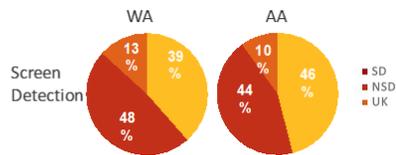
Melissa Davis, PhD
Morehouse School of Medicine

- Dr. Melissa Davis discussed factors that contribute to racial disparities in breast cancer outcomes. Like prostate cancer, breast cancer has significantly higher incidence and mortality rates in Black individuals compared with White individuals. Breast cancer mortality rates are over 40% higher in African American patients than Caucasian American patients.
- Social determinants of health, including access to healthcare and access to technologies are major drivers of health disparities. New technologies and new treatments often exacerbate disparities as they are not made equitably available to underserved populations.
- Worse breast cancer mortality rates have been observed in Black vs. White patients regardless of poverty levels, suggesting that socioeconomic status is not a major driver of breast cancer racial disparities. In fact, racial disparities in breast cancer mortality were not seen prior to 1990, when targeted endocrine therapy became available. This suggests that racial disparities arose due to inequities in access to targeted endocrine therapy and/or differences in breast cancer biology between White and Black patients.
- Prognosis and treatments for breast cancer are determined based on tumor expression of the hormone receptors HER2, ER and PR. Triple negative breast cancer (TNBC) is a diagnosis of exclusion, in which HER2, ER and PR are not expressed.
- African American patients have a two-fold higher rate of TNBC, which has the worst prognosis due to being a more aggressive subtype with a lack of targeted therapies available.

- A study that evaluated whether screening differences contributed to racial disparities in TNBC outcomes found no significant differences in rates of screen-detected or tumor stages of TNBC between White and Black patients (**Figure**). Overall survival was significantly worse in patients whose TNBC was not screen-detected as these cancers are typically found later. However, survival was significantly worse for Black patients compared with White patients with non-screen detected TNBC, suggesting treatments for TNBC may not work as well in Black patients.
- A reanalysis of breast cancer data in The Cancer Genome Atlas (TCGA) to identify race-group differences in TNBC biology, found that 81% of TNBC from Black patients lacked expression of the androgen receptor (AR) compared with 56% of TNBC from White patients. TNBC tended to be an earlier onset disease in Black patients. Significant racial differences were also found in epigenetic signatures, including differences in the MYC oncogene pathway.
- A study in Africa found regional differences in TNBC rates, with the highest rates in West Africa and Sub-Saharan Africa. Globally, TNBC rates are highest in individuals of West African descent, which is the region of Africa that was targeted for slave trade to the Americas.
- A study was done to identify ancestry-associated gene expression patterns in TNBC. African ancestry was associated with higher levels of naïve immune cell infiltration into tumors.
- In prior cancer studies, higher levels of immune cells have been associated with improved survival; this supposed benefit was not seen in African-ancestry patients with TNBC.
- The immune system is highly complex. African ancestry populations have evolved different types of immune responses compared with European ancestry populations, due to the differences in pathogens in those global regions.
- The Duffy-null gene allele is common among in individuals of African descent and rare in other ancestral populations. The Duffy-null allele confers immunity to malaria, but also loss of regulation over aspects of systemic inflammation.
- In TNBC, the Duffy-null allele was associated with higher levels of tumor inflammation. How Duffy-null is associated with worse outcomes in African descent individuals with TNBC is under study.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-6-the-contribution-of-ancestry-and-genomics-to-prostate-cancer-disparities/>**

Survival Differences in Screen-Detected vs Non-Screen-Detected TNBC

What is the difference?



PANEL DISCUSSION: State of Clinical Therapy for Advanced Prostate Cancer

Moderator: Charles J. Ryan, MD
Prostate Cancer Foundation

Panelists:

Alok Tewari, MD, PhD (Dana-Farber Cancer Institute)

Ana Aparicio, MD (The University of Texas MD Anderson Cancer Center)

Angelo De Marzo, MD, PhD (The Johns Hopkins University School of Medicine)

Thomas Hope, MD (University of California, San Francisco)

David Jarrard, MD (University of Wisconsin)

Neha Vapiwala, MD (University of Pennsylvania)

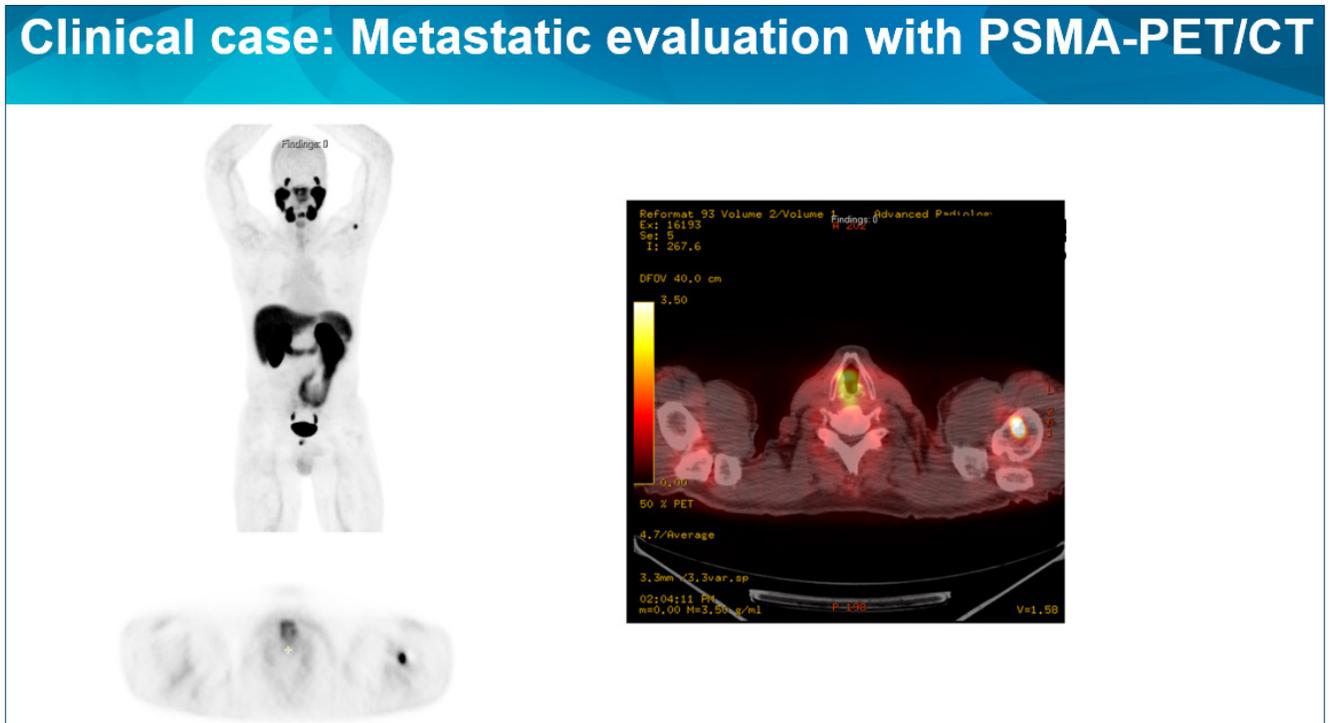
- Dr. Charles Ryan moderated a multi-disciplinary tumor board panel to discuss a complex prostate cancer clinical case. The panelists were Drs. Alok Tewari (medical oncology), Ana Aparicio (medical oncology), Angelo De Marzo (pathology), Thomas Hope (nuclear medicine and radiology), David Jarrard (urology), and Neha Vapiwala (radiation oncology).
- The case discussed was a 63-year-old male patient with a history of non-muscle-invasive bladder cancer. In 2022, the patient had a PSA level of ~6ng/ml, from 3ng/ml previously. An MRI of the prostate identified a 1.6 x 1 cm PI-RADS 5 lesion in the left peripheral zone, and subsequent biopsy revealed a Gleason 9 prostate adenocarcinoma.
- As a relatively healthy patient with high-risk prostate cancer, no comorbidities but with lower urinary symptoms, the patient could be a candidate for surgery or radiation, but more information would aid in this decision.
- Because of the tumor's high grade and hence risk for metastatic disease, PSMA PET/CT imaging was performed, which revealed a focal region of avidity in the prostate corresponding to the prior MRI finding, and single PSMA-positive lesion in the humerus (**Figure**).
- PSMA PET/CT imaging is currently recommended for patients with a biopsy-based diagnosis of unfavorable-intermediate-risk or high-risk prostate cancer. Technetium bone scans are less sensitive at this PSA level.
- One relative weakness of PSMA PET/CT is in the false positive detection of solitary bone lesions as potential metastatic lesions. Solitary rib lesions are almost always benign. Benign spinal lesions such as hemangiomas can be PSMA-avid. It is a little less likely that a humerus lesion is a benign finding. Features like SUVmax should not be used solely to assess likelihood of a metastasis, but rather interpreted in the context of the overall pre-test probability of the presence of metastasis.
- Additional imaging modalities such as MRI (not bone scan) can help to confirm whether a PSMA-positive lesion is a tumor metastasis or not. Although the patient could undergo biopsy of the metastatic site to further confirm it is tumor, as single metastatic lesions are rare, the patient underwent an MRI of the humerus, which, combined with the PET scan results, strongly suggested the lesion was a tumor metastasis.
- The panel discussed treatment options for this patient, who has newly diagnosed "oligometastatic" (often defined as <3-5 metastases on conventional imaging) prostate cancer.
- Guidelines-based treatment options supported by Phase 3 trials including STAMPEDE and HORRAD recommend the combination of ADT and radiation to the primary prostate as an option. Other options discussed include androgen deprivation therapy (ADT) combined with stereotactic

body radiation therapy (SBRT/SABR) to the metastatic lesion in combination with management of the primary lesion. Randomized phase 2 clinical trials have demonstrated a benefit for SABR directed to sites of metastasis in patients with oligometastatic disease.

- It remains unclear from clinical trial results whether treatment of the primary tumor in this setting is beneficial in all patients with low metastatic burden, and whether radiation or surgery is the better option, particularly when considering toxicities. Trials typically evaluate short-term high-grade toxicities, but not long-term lower grade toxicities that may significantly impact quality of life. These should be weighed against the known long-term systemic effects of indefinite androgen deprivation. Trials such as SWOG1802 and g-RAMPP are ongoing in patients with oligometastatic prostate cancer to evaluate ADT +/- surgery or radiation of the primary tumor, and the patient could be considered for such trials.
- Whether or not the patient's goals include avoiding or deferring ADT would also help to decide the up-front treatment strategy. Other neoadjuvant treatments could be considered and are being evaluated in clinical trials.
- Of note, as prior prostate cancer clinical trials that included "oligometastatic" disease used conventional imaging to identify and select patients, the role of PSMA-PET to define patient management in the oligometastatic setting is unknown.
- After multidisciplinary discussion and shared decision making, the patient began ADT, followed one month later by prostatectomy and pelvic lymph node dissection, followed two months later by SBRT to the humerus lesion. This is not a standard approach, as neoadjuvant trials typically evaluate 3-6 months of ADT preceding prostatectomy.
- Pathological evaluation of the primary tumor found high volume disease and a positive surgical margin. Two microscopic lymph node metastases were also found, which were not seen with the PSMA PET.
- The ability of PSMA PET to detect lesions depends both on PSMA levels and lesion size. This interplay impacts the use of PSMA PET to follow patients undergoing ADT, as lesions may upregulate PSMA expression but decrease in size.
- Salvage radiation refers to radiation to the prostate/pelvic region after prostatectomy when there is detectable/rising PSA or radiographic evidence of local recurrence (i.e biochemical or clinical recurrence). Adjuvant radiation is post-prostatectomy radiation for suspected remnant disease, such as in patients with advanced T stage, high Gleason score, positive surgical margins, or lymph node metastases. The use and timing of radiation depends on various factors, including the presence of positive lymph nodes.
- Germline genetic testing to evaluate for hereditary prostate cancer risk genes is now recommended for all patients with high-risk and metastatic prostate cancer. Patients may also undergo somatic (tumor) genomic sequencing to evaluate for tumor mutations that can indicate treatment options and help to better understand tumor biology. Germline genetic testing was performed and did not find evidence for pathogenic variants in DNA repair pathway genes.
- This patient underwent somatic genomic sequencing of the primary tumor, which identified a *TMPRSS2-ERG* gene rearrangement, a mutation in the *PTEN* tumor suppressor gene, and several variants of unknown significance. These mutations did not indicate changes to the treatment plan.
- After the initial treatment plan of neoadjuvant ADT, surgery, and SBRT to the humerus lesion, the patient had a PSA of 0.026 ng/ml and no additional metastases found on bone scan. The patient underwent adjuvant radiotherapy to the prostatic bed and pelvis and is now undergoing abiraterone + prednisone for two years.
- Whether this plan is optimal is unclear. The patient has oligometastatic prostate cancer, which is seen by some as incurable. In this setting, SBRT to lesions can be of benefit. However, withholding definitive-intent treatment due to a single lesion seen only on PET in a patient who is otherwise cM0 by conventional imaging may compromise long-term disease control. Post-prostatectomy radiation to the pelvis can exacerbate existing risk of post-operative urinary incontinence, so this

should always be considered. Furthermore, a two-year course of abiraterone + prednisone is a standard of care in patients with intact primary tumors but has not yet been evaluated in patients who have undergone primary tumor removal.

- This panel discussion can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/panel-state-of-clinical-therapy-for-advanced-prostate-cancer/>



SPECIAL LECTURE: Pathways to Entrepreneurship

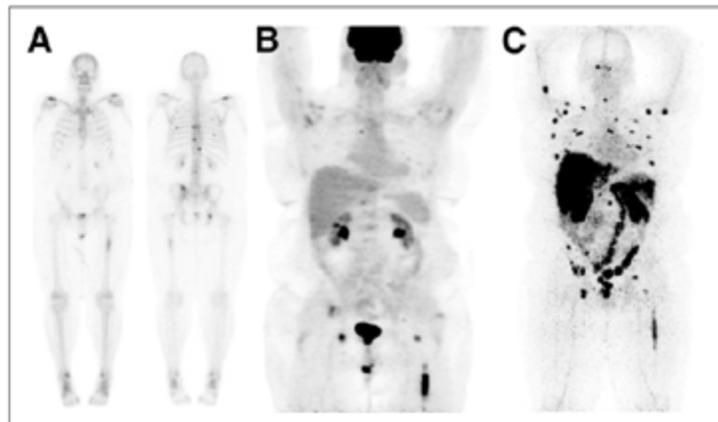
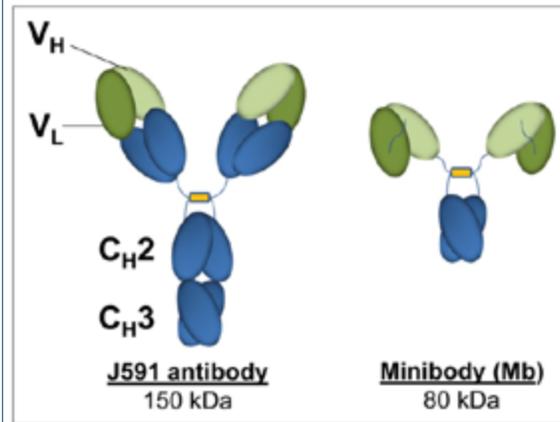
Robert Reiter, MD
University of California, Los Angeles

- Dr. Robert Reiter is a urologist at UCLA who has founded several biotech start-ups, and discussed pathways to entrepreneurship and lessons learned.
- In the 1990s, Dr. Reiter was an Instructor in the Owen Witte laboratory at UCLA, after completion of fellowship at NCI. His research goal was to identify prostate cancer cell surface targets for antibody-based therapy. This idea was based on the successful pharmaceutical development of the HER2-targeting antibody Herceptin as a treatment for breast cancer.
- Several prostate cancer cell lines were developed as models for studying treatment-resistant prostate cancer. Using this system, PSCA (prostate stem cell antigen) was discovered as a prostate cancer specific cell surface protein. Antibodies were developed to target PSCA and demonstrated to inhibit prostate tumor growth in mouse models.
- Agensys was a startup founded out of UCLA by Dr. Arie Belldegrun, Dr. Reiter, and others, to commercialize gene therapy work done in the Belldegrun lab. Subsequently, the company decided to focus on developing antibodies against novel cell surface targets in prostate cancer, and Dr. Reiter's anti-PSCA antibody was licensed for development.

- Seed money was obtained, a CEO was hired, and lab space was leased in Santa Monica, CA. As co-founder, Dr. Reiter served on the scientific advisory and spent half a day a week at the company. Agensys was sold in 2007 to Astellas in a deal for >\$350 million.
- The PSCA-antibody was tested in clinical trials in prostate cancer and pancreatic cancer. A phase 2 trial in metastatic pancreatic cancer demonstrated a significant improvement in overall survival in patients with PSCA-positive tumors. Despite this promising activity, Astellas did not continue development of this antibody.
- Successes of Agensys included the cloning of the prostate cancer cell surface proteins STEAP 1, STEAP 2, and NECTIN-4. A NECTIN-4 antibody was developed with SeaGen to become ENFORTUMAB, which is now a standard of care first line treatment with pembrolizumab for metastatic urothelial cancer.
- A different project in Dr. Reiter's lab focused on developing prostate cancer molecular imaging agents. In collaboration with Dr. Anna Wu, PSCA-targeted antibody fragments ("minibodies") were developed into PET imaging agents.
- ImaginAb was a startup founded to develop the PSCA minibody and other engineered antibody-based imaging agents for clinical use. A PSMA-targeted antibody developed by Dr. Neil Bander was also licensed to re-engineer as minibody for prostate cancer staging.
- Seed funding, a CEO, and lab space were obtained. Dr. Reiter and Dr. Wu were founders and served as chief medical officer, scientific advisors, and as early board members.
- The first clinical trial of the PSMA-minibody imaging agent demonstrated promising sensitive detection of prostate cancer in patients (**Figure**).
- ImaginAb is also developing imaging agents to visualize components of the immune system. A CD8-targeted PET imaging agent was developed for imaging CD8 T cells that infiltrate tumors. This agent showed promise for imaging T cells in melanoma tumors following treatment with immunotherapy in clinical trials, and was associated with response to immunotherapy. This is now being studied as a treatment response biomarker for patients receiving immunotherapy.
- Overall, entrepreneurship is challenging, but also fun and a way to turn academic work into a reality. Challenges include difficulties in balancing time between academic/clinical responsibilities with needs of the company, or making a decision about whether to join the company full-time. A good team is essential, and the right people may change as the company evolves. Ultimately, the Board controls the company, and founders have diminishing influence over company decisions as the company grows and evolves.
- The UCLA Innovation Fund is a venture capital fund established in 2016 to provide seed funding for therapeutics and medical technology startups, and to mentor biotech entrepreneurs. 50 projects have been funded thus far, 13 of which have exited (a 26% success rate).
- Currently, there are 177 active startup companies founded out of UCLA.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/special-lecture-pathways-to-entrepreneurship/>**

First-in-Human Imaging with ^{89}Zr -Df-IAB2M Anti-PSMA Minibody in Patients with Metastatic Prostate Cancer: Pharmacokinetics, Biodistribution, Dosimetry, and Lesion Uptake

Neeta Pandit-Taskar^{1,2}, Joseph A. O'Donoghue³, Shutian Ruan¹, Serge K. Lyashchenko⁴, Jorge A. Carrasquillo^{1,2}, Glenn Heller⁵, Danny F. Martinez⁶, Sarah M. Cheal⁷, Jason S. Lewis^{1,2,4,7}, Martin Fleisher⁸, Jennifer S. Keppler⁹, Robert E. Reiter⁹, Anna M. Wu⁹, Wolfgang A. Weber^{1,2}, Howard I. Scher^{6,10}, Steven M. Larson^{1,2,7}, and Michael J. Morris^{6,10}



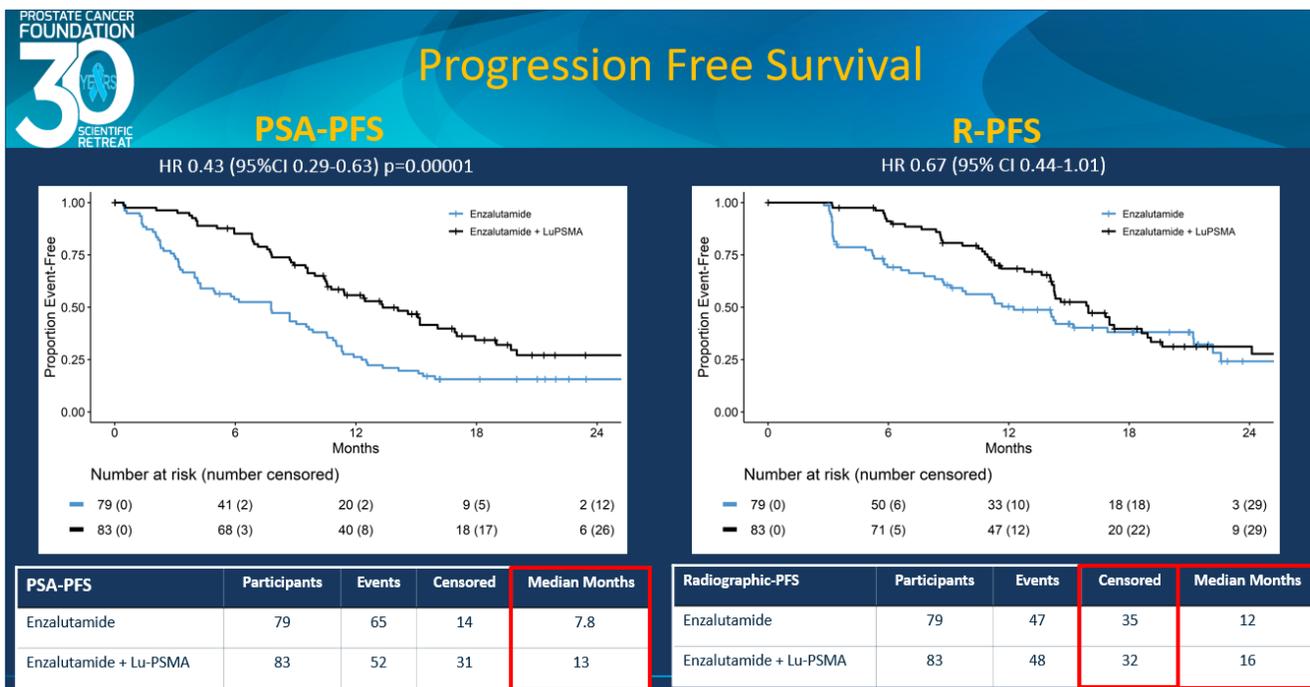
Session 7: Progress in New Targets and Treatments for Prostate Cancer

ENZA-p: A Randomised Phase II Trial using PSMA as a Therapeutic Agent and Imaging Biomarker in Men with Metastatic Castration-Resistant Prostate Cancer Treated with Enzalutamide (ANZUP 1901)

Louise Emmett, MD
St Vincent's Hospital Sydney, Australia

- Enzalutamide is an androgen receptor (AR)-targeted therapy that is approved for several indications in advanced prostate cancer. However, some patients have early failure with enzalutamide, suggesting additional strategies to improve treatment efficacy are needed.
- LuPSMA (177-Lutetium-PSMA-617; Pluvicto®) is a PSMA-targeted radioligand therapy approved for patients with metastatic castration-resistant prostate cancer (mCRPC) who have previously progressed on AR-targeted therapy and taxane chemotherapy and have positive PSMA PET scans.
- Dr. Louise Emmett discussed preliminary results from the randomized phase 2 ENZA-p clinical trial, which tested enzalutamide alone vs. enzalutamide + adaptive dosing (2 or 4 doses) of LuPSMA, in patients with mCRPC who have not previously received chemotherapy for mCRPC and have positive PSMA PET scans.
- The rationale for this trial includes data that blocking AR results in upregulation of PSMA, suggesting that PSMA-targeted therapy may synergize with AR-targeted therapy. PSMA PET scans have been used to visualize an increase in PSMA levels on prostate tumors shortly after initiation of enzalutamide treatment.
- In the trial, patients on the adaptive LuPSMA arm undergo a PSMA PET scan at baseline, and on day 15 of enzalutamide treatment before the first dose of LuPSMA, to evaluate if PSMA expression was increased by enzalutamide. After the first 2 doses of LuPSMA, patients undergo another PSMA PET scan; only patients whose tumors remain PSMA PET-positive receive another 2 doses of LuPSMA. All patients received a PSMA PET and FDG PET scan at the time of progression.
- At the time of this presentation, 220 patients had been screened, 162 had been randomized, and PSA progression free survival (PSA PFS; time from enrollment until PSA levels rise) data was available for 117 patients.
- PSA PFS was significantly improved in patients who received LuPSMA + enzalutamide vs. patients who received enzalutamide alone (median of 13 months vs. 7.8 months) (**Figure**). Radiographic PFS (time from enrollment until tumors grew on conventional scans) was also improved with the addition of LuPSMA vs. enzalutamide alone (median of 16 months vs. 12 months) (**Figure**).
- 93% of patients who received LuPSMA + enzalutamide experienced PSA decreases $\geq 50\%$ compared with 68% of patients who received enzalutamide alone. 78% of patients who received LuPSMA + enzalutamide experienced PSA decreases $\geq 90\%$ compared with 37% of patients who received enzalutamide alone.
- The frequency of adverse events was similar between the two arms. Serious adverse events were observed in 35% of patients who received enzalutamide alone vs 33% who received enzalutamide + Lu-PSMA. Grade 4-5 adverse events were observed in 4% of patients who received enzalutamide alone vs 6% who received enzalutamide + Lu-PSMA.

- This trial included a significant number of biomarker analyses, including serial PET and SPECT scans, tissue biopsies taken at baseline and progression, and serial blood draws.
- PET scans are being used to evaluate the potential of PSMA PET/CT to identify sites of AR-therapy resistance in patients being treated with enzalutamide, explore the significance of early PSMA PET imaging changes in patients commencing enzalutamide, and determine whether clinically worse outcomes identified are mitigated with the addition of LuPSMA.
- PSMA SPECT imaging, which is done following treatment with LuPSMA to visualize LuPSMA in the body, is being evaluated for its potential as an early response biomarker for LuPSMA therapy.
- Blood draws (liquid biopsies) are being used to study circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) over time, to identify mechanisms of response and resistance to the treatments.
- This is the first trial to use adaptive dosing of LuPSMA based on an interim PSMA PET, which may help to reduce toxicity by avoiding treatment of patients unlikely to benefit from additional doses.
- Overall, this trial provides strong evidence that combining LuPSMA with enzalutamide delays disease progression in patients with mCRPC. Whether additional doses of LuPSMA (beyond 4) may further improve outcomes deserves study. The trial is ongoing, with planned follow-up of progression free survival and overall survival in 2024.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-7-progress-in-new-targets-and-treatments-for-prostate-cancer/>**

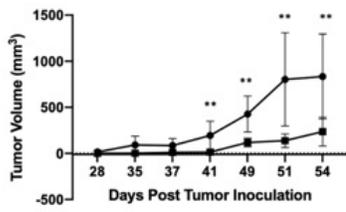


GPC3 as a Novel Therapeutic Target of Prostate Cancer

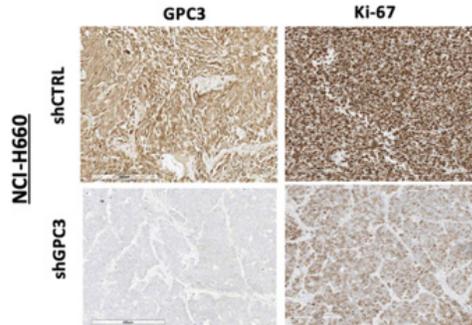
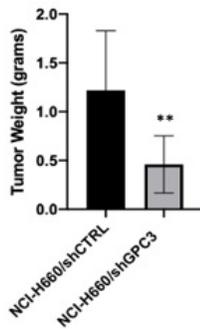
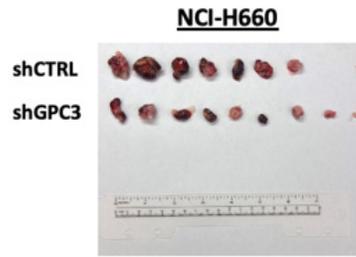
Jiaoti Huang, MD, PhD
Duke University

- Neuroendocrine prostate cancer (NEPC) is a highly aggressive form of advanced prostate cancer for which there are currently no effective therapies.
- Dr. Jiaoti Huang discussed studies to identify new therapeutic targets for NEPC.
- Dr. Huang and team previously identified CXCR2 as a protein expressed on NEPC cells. However, therapeutic targeting of CXCR2 results in neutropenia toxicities.
- Novel NEPC-specific targets that are highly expressed specifically on NEPC, are critical to the survival of NEPC cells, and which do not result in unacceptable toxicities when targeted, are needed.
- To discover new NEPC targets, gene expression analyses and metabolic profiling were performed on CXCR2-expressing NEPC cells from prostate cancer patients and cell lines.
- Expression of the cell surface protein Glypican-3 (GPC3) was found to be up-regulated in NEPC cell lines. GPC3 was also found to be expressed on human NEPC samples but not in adenocarcinoma forms of prostate cancer.
- GPC3 is expressed ubiquitously in embryonic development but is not expressed in normal, healthy tissue. GPC3 is also highly expressed on other cancer types, including hepatocellular carcinoma (HCC), yolk sac tumors, esophageal squamous cell carcinoma, melanoma, and some sarcomas. GPC3-targeted therapy is being tested for HCC patients with minimal toxicity in clinical trials.
- Together, these data suggest GPC3 may be a promising therapeutic target for NEPC.
- Studies in prostate cancer cell lines found that GPC3 levels increased after treatment with enzalutamide.
- In NEPC models, deletion of GPC3 reduced cell proliferation and cell survival rates. Prostate tumors lacking GPC3 had reduced growth rates in mice (**Figure**).
- In ongoing studies, new agents targeting GPC3 are being developed and studied.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-7-progress-in-new-targets-and-treatments-for-prostate-cancer/>**

Knockdown of GPC3 causes decreased tumor growth rate in NCI-H660 xenograft model system



● NCI-H660/shCTRL
 ■ NCI-H660/shGPC3



Butler...Huang, J. Pathol, 2023

Session 8: Prostate Cancer 3D Genomics

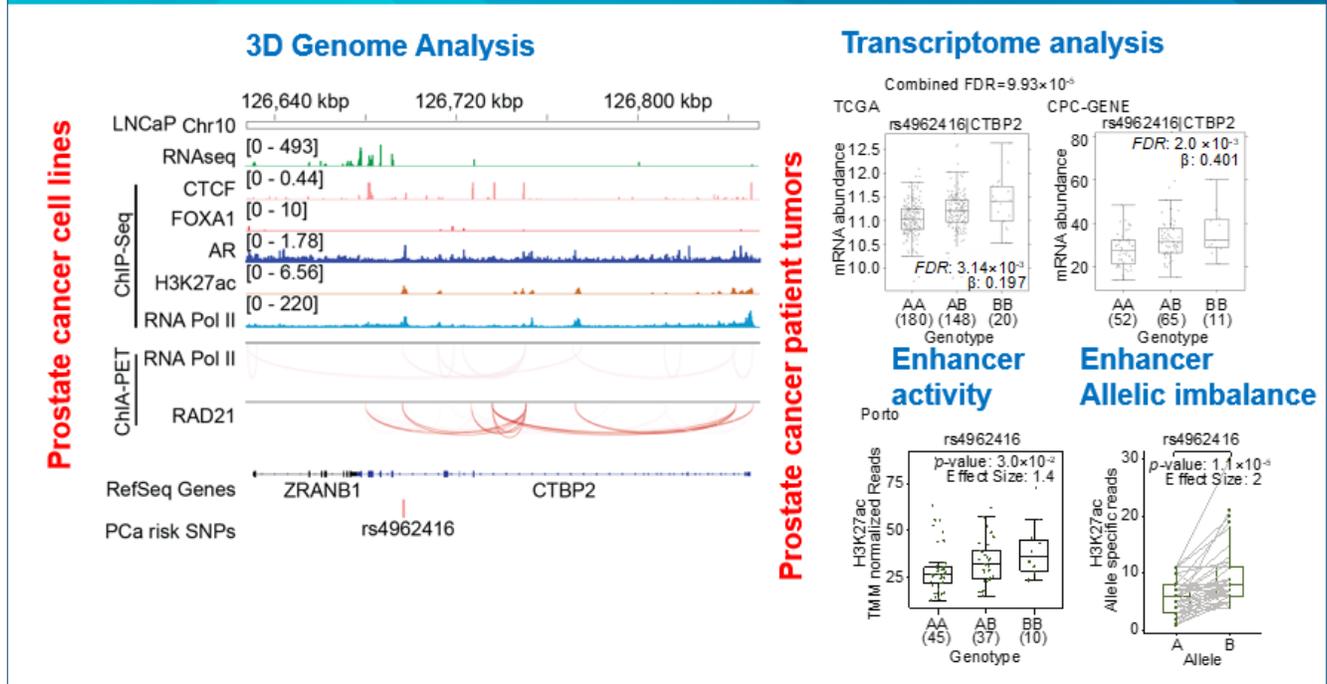
Prostate Cancer Transcriptomic Regulation by the Interplay of Germline Risk Alleles, Somatic Mutations and 3D-Genomic Architecture

Ram Mani, PhD
UT Southwestern Medical Center

- Dr. Ram Mani discussed studies on altered 3D genomic organization in prostate cancer.
- The 3D organization of chromosomes determines which genes are expressed vs. silenced and is regulated by a hierarchy of control mechanisms. This allows many different cell types to exist using a single genome.
- Enhancers are genomic regions that act as switches to turn genes on or off, and interact in 3D with the gene(s) they control to coordinate gene expression. Those that are far away must form 3D loops to interact with genes. Enhancers attract various transcriptional regulators, including transcriptional activators and repressors, to regulate gene expression.
- Specialized genomic sequencing techniques can be used to map 3D genomic loops and the location of transcription factor binding sites to determine the activity of enhancers and genes.
- Prostate cancer is one of the most heritable human cancers. Genome-wide association studies (GWAS) have identified several hundred prostate cancer germline risk alleles, many of which are in noncoding regions and have not yet been linked to specific genes.
- Dr. Mani performed a study to determine if prostate cancer germline risk alleles regulate enhancer activity or control gene-expression via long-range 3D genomic interactions.
- Genomic data from prostate cancer cohorts on gene expression, transcription factor binding sites, enhancer sites, and 3D genome structure maps were combined with data on prostate cancer germline risk alleles.
- Some prostate cancer risk alleles that impacted enhancer activity and regulated expression of one or more genes were identified. Examples of several findings were presented.
- The prostate cancer risk allele rs4962416 is located within the *CTBP2* gene and was found to increase activity of the *CTBP2* enhancer and increase expression of *CTBP2* (**Figure**). Androgen activity further increased *CTBP2* expression, especially in prostate cancer models with the rs4962416 allele. Loss of critical tumor suppressor genes *PTEN* and *RB1* were also found to impact the activity of the rs4962416 allele.
- The prostate cancer risk allele rs684232 was found to reduce the expression levels of the *VPS53*, *FAM57* and *GEMIN4* genes by downregulating the activity of their enhancers.
- The prostate cancer risk allele rs8102476 was found to create looping interactions with two genes, *PPP1R14A* and *SPINT2*. However, rs8102476 reduced expression of *PPP1R14A* in smooth muscle cells but increased expression of *SPINT2* in epithelial cells.
- The relationships between prostate cancer risk alleles and gene expression can also have impacts in other cell types.
- These studies highlight the importance of studying the impacts of 3D genomic alterations in prostate cancer.
- In ongoing studies, machine learning algorithms are being applied to large multi-omic prostate cancer datasets to predict 3D genome organization and its clinical implications.

- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-8-prostate-cancer-3d-genomics/>

Prostate Cancer Risk SNP rs4962416 and CTBP2 transcript abundance



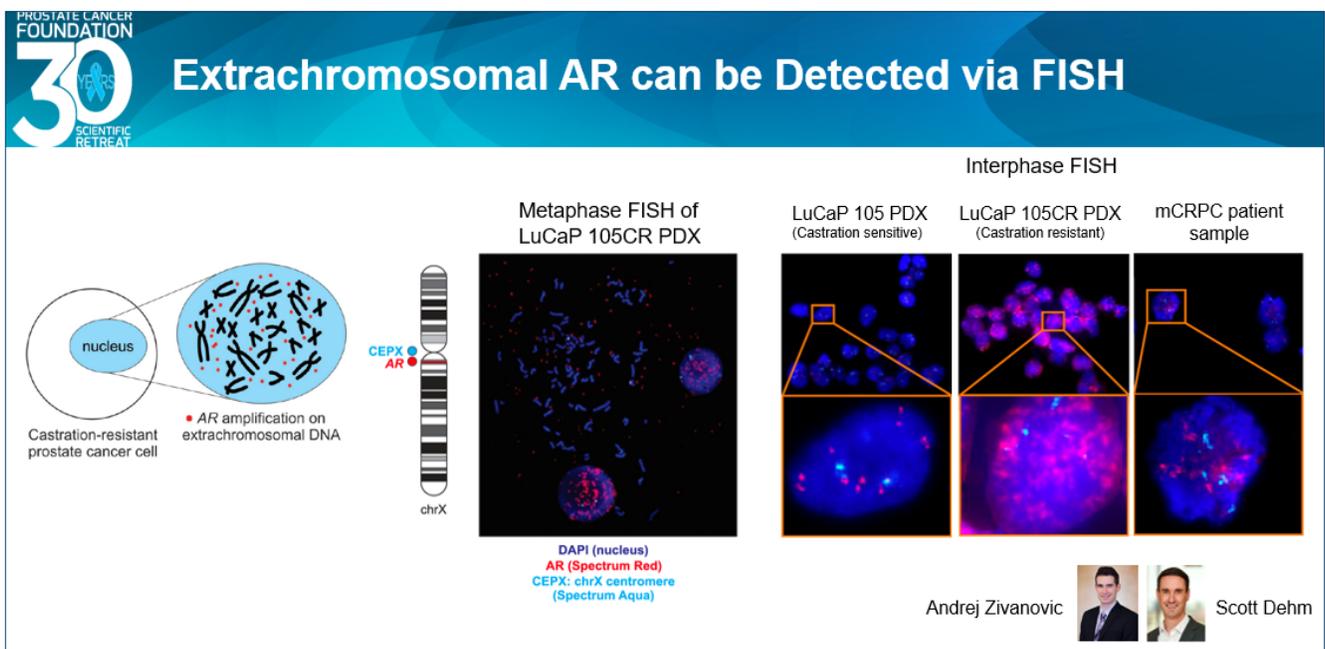
New Insights on the Three-Dimensional Genome of Metastatic Prostate Cancer

Felix Feng, MD
University of California, San Francisco

- Dr. Felix Feng discussed studies on the 3D genome of metastatic prostate cancer.
- The PCF West Coast Prostate Cancer Dream Team has undertaken an effort to characterize the genomic and epigenomic landscape of metastatic castration-resistant prostate cancer (mCRPC).
- Multi-omics sequencing was performed on metastatic biopsies from over 100 patients with mCRPC. These included whole genome sequencing (to evaluate genomic alterations), RNA sequencing (to evaluate gene expression), whole-genome bisulfite sequencing (WGBS) and 5-hydroxymethylcytosine (5hmC) sequencing (to evaluate DNA methylation), ATAC-sequencing (to evaluate chromatin accessibility) and Hi-C sequencing (to evaluate 3D genome structure). These data have been made available to the scientific community.
- Gene expression is regulated at many levels, including at the 3D genomic level, in which interactions between different regions of DNA enable or repress gene expression.
- Hi-C sequencing is a method to map genome-wide 3D chromosomal interactions and structural features, including the locations of enhancers and topologically associating domains (TADs). Enhancers are nearby or faraway DNA regions that regulate gene expression, often through 3D

interactions. TADs are localized chromosomal regions that have high degrees of interactions within that region.

- Analyses of Hi-C data found that mCRPC could be grouped into two subtypes: those with fewer broad TADs, and those with many narrow TADs. mCRPC with fewer broad TADs had worse outcomes and higher levels of oncogene activity such as MYC. This is the first study demonstrating a cancer can be subtyped based on 3D genomics that are associated with clinical outcomes.
- Hi-C analyses also found two different types of 3D interactions occurred around the androgen receptor (*AR*) gene: normal/high levels of 3D interactions (~70% of samples) and very little 3D interactions (~30% of samples). Further studies found that in the latter subtype, the *AR* gene was amplified on small extra-chromosomal circular DNAs (eccDNA); these findings corroborate similar findings by Dr. Scott Dehm and team (**Figure**). Patients with *AR* eccDNA tended not to respond to treatment with anti-androgen therapies.
- In approximately half of mCRPC cases, *AR* or other oncogenes including *MYC*, were found on eccDNA. eccDNAs could also include multiple genes.
- Together, these data suggest that *AR* and other oncogenes on eccDNA may represent an adaptive mechanism for accelerated treatment resistance and tumor evolution.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-8-prostate-cancer-3d-genomics/>**



Session 9: Biology and Translational Applications of Tumor Extracellular Vesicles

Prostate Cancer-Derived Extracellular Vesicles as Biomarkers

Johan Skog, PhD

ExosomeDx, a Bio-Techne Brand

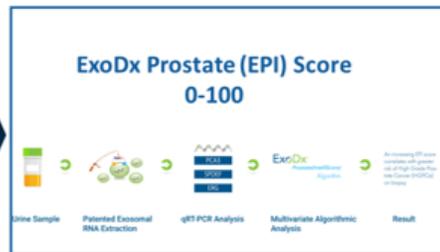
- Extracellular vesicles (EVs) are small vesicles secreted from cells that contain a subset of the cell's proteins, metabolites, RNA and DNA. EVs contribute to cell-cell communication and other biological roles. EVs can be found in biofluids such as blood, urine, and saliva. In cancer patients, cancer cell EVs can be studied as surrogates of tumor biology.
- Dr. Johan Skog discussed the performance and utility of existing urine EV based biomarkers for prostate cancer as well as future directions and opportunities.
- Platforms have been developed to isolate EVs from biofluid samples and obtain EV DNA, RNA and proteins, and at the same time obtain cell-free tumor DNA (ctDNA), which is tumor DNA that has been released into the circulation or into urine.
- ExoDX Prostate (EPI) is a urine EV-based biomarker test that evaluates the presence of three prostate cancer-related genes, *ERG*, *PCA* and *SPDEF*, and predicts the likelihood of high-grade prostate cancer on initial or repeat biopsy in patients who are 50-years and older, with a PSA of 2-10ng/mL (**Figure**). This test uses a urine collection system that can be mailed, enabling either in-clinic or at-home sample collection.
- A prospective multi-center utility trial with a blinded control arm with over 1,000 patients enrolled compared a standard of care decision making process vs. the use of the EPI test to guide a shared decision-making process for treatment/management selection. EPI was found to identify an additional 30% of high-grade prostate cancer cases that were not identified by standard of care risk stratification methods and reduced the need for biopsies in patients with low-grade prostate cancer.
- EV RNA has been shown to mirror the diversity of tissue RNA and can be used to study tumor biology more broadly.
- A multi-omic biofluid discovery platform has been developed, which includes genomic sequencing of ctDNA, and RNA sequencing and proteomic studies using EVs.
- A multi-omic analysis of biofluid samples from patients with colorectal cancer (CRC) identified genomic alterations and genes important in CRC biology. These multi-omic signatures were used to create a biomarker with 99% accuracy in distinguishing healthy patients from those with CRC.
- A multi-omic urine test to identify patients with clinically relevant prostate cancer based on sequencing of EV RNA and ctDNA is being developed.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/30th-annual/session-9-biology-and-translational-applications-of-tumor-extracellular-vesicles/>

EXODX PROSTATE (EPI)

The EPI risk score is used to risk stratify likelihood of high grade (GG ≥ 2) prostate cancer on initial or repeat biopsy in men 50-years and older, with a PSA 2-10ng/mL.



At-home urine collection kit or "in-office"



EPI performance across 1730 Patients



- Urine sample collection (done "in-office" or with "at-home collection kit")
- Completely independent molecular information
- Does not include SOC information for the performance

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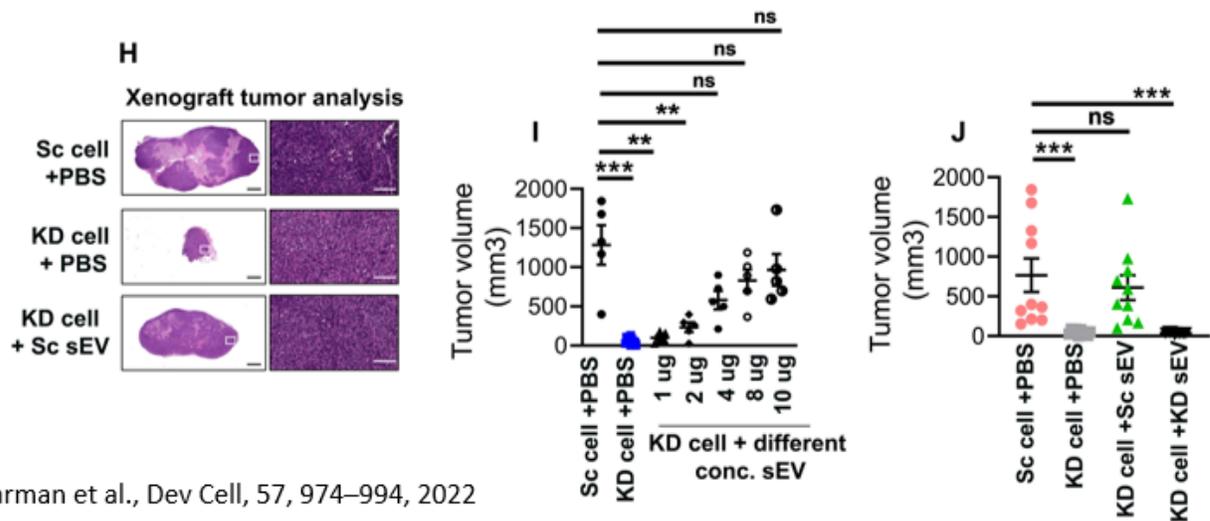
The Role of Tumor Extracellular Vesicles in Promoting Aggressive Cancer Behaviors

Alissa Weaver, MD, PhD
Vanderbilt University School of Medicine

- Extracellular vesicles (EVs) are small vesicles secreted from cells into the circulation, that contain cellular proteins, metabolites, RNA, and DNA, and are important for cell-cell communication. Cancer cells secrete high numbers of EVs, which can be easily collected from biofluids and used to study tumor biology.
- Dr. Alissa Weaver discussed studies on the functions of EVs and their cargo in cancer.
- It has remained unclear how RNA and other molecules are selected and put into EVs.
- The endoplasmic reticulum (ER) is a cellular organelle that plays a major role in protein synthesis, interacts with many RNA-processing components, and makes contacts with many cellular organelles including multivesicular bodies which form EVs.
- The ER can be prevented from interacting with multivesicular bodies by inhibiting the activity of the VAP-A protein. Inhibition of VAP-A significantly reduced the numbers of EVs and the amount of RNA in EVs.
- RNA was found to be primarily in a subset of "dense" EVs. The function of EVs carrying RNA was investigated. When tumors were prevented from making EVs, they grew slower in animal models (**Figure**). When EVs were administered in these models, tumor growth accelerated (**Figure**).
- These studies demonstrate that VAP-A enables the genesis of RNA-containing EVs by regulating the contact between the ER and multivesicular bodies in the cell, that the VAP-A controlled EVs drive tumor growth.

- In models of head and neck squamous cell carcinoma (HNSCC), EVs were found to promote the formation of tumor blood vessels by transporting proteins important to this process, including EphB2. Blocking EphB2 also blocked this process. Direct cell-cell contact was not required.
- These studies suggest that cancer cells can communicate long-distance using EVs, to promote development of tumor blood vessels and drive tumor growth.
- Overall, EVs are an important part of the tumor microenvironment that drive various processes. Further studies are needed.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-9-biology-and-translational-applications-of-tumor-extracellular-vesicles/>**

The EV population controlled by VAP-A mediates miR-100 transfer and tumor growth



KEYNOTE ADDRESS

Michael Milken
 Founder and Chairman
 Prostate Cancer Foundation

This presentation can be viewed in full at:

<https://www.pcf.org/scientific-retreat/30th-annual/keynote-address-michael-milken/>

Session 10: Updates from PCF TACTICAL Awards Teams

Developing Engineered Cell Therapies for Metastatic Castrate-Resistant Prostate Cancer to Increase Efficacy and Decrease Toxicity

Carl June, MD
University of Pennsylvania

Saul Priceman, PhD
City of Hope

- Drs. Carl June and Saul Priceman discussed their PCF-TACTICAL Award program to advance the development of CAR T cells for prostate cancer.
- CAR (chimeric antigen receptor) T cells are an engineered cellular therapy in which a patient's own T cells are uploaded with a gene for an engineered chimeric protein composed of a tumor-targeting antibody component linked to a T cell activating component. This allows the T cell to identify and kill cancer cells.
- The goals of this PCF-TACTICAL program are to identify new CAR T cell targets in prostate cancer, characterize tumor resistance mechanisms to CAR T cells, optimize intrinsic CAR T cell functions, identify methods to reduce toxicities, and use this knowledge to develop more effective and safe new CAR T cells that are effective in racially diverse prostate cancer models (**Figure**). These will then be tested in clinical trials.
- The team includes investigators at the Veteran Administration (VA), who are providing samples from Black patients with prostate cancer, to increase the racial diversity of samples that are studied.
- This team is conducting four prostate cancer CAR T cell clinical trials, including different CAR T cells targeting the prostate cancer proteins PSCA and PSMA. A fifth trial with a STEAP2-targeted CAR T cell will be opened in 2024. Samples from these trials will be used to identify mechanisms of resistance vs. response to CAR T cells.
- Resistance to CAR T cells include insufficient levels of active T cells in patients that can be used to generate CAR T cells (due to the older age of patients with prostate cancer), the typically immunosuppressive microenvironment of prostate cancer, short CAR T cell lifespans, and loss/heterogeneity of the CAR T cell target protein by tumor cells.
- The team is investigating ways to increase T cell levels, activity, and lifespan. They have found that high levels of FOXO1 in CAR T cells increases anti-tumor potency and T cell lifespan. However, FOXO1 levels decrease with patient age. Methods and effects of increasing FOXO1 levels in CAR T cells are being studied.
- Dr. June and colleagues previously developed a PSMA dnTGFR β II CAR T cell. This CAR T cell targets PSMA, and carries a dominant-negative TGFR β II gene, which helps to block immunosuppressive signals from the tumor microenvironment. In a phase 1 clinical trial, promising activity was seen, but some patients experienced significant immune-related toxicities. The team is investigating inflammatory pathways that are associated with these toxicities and methods to reduce toxicities.
- Dr. Priceman and colleagues previously developed a PSCA-targeting CAR T cell and tested this in a phase 1 trial. Promising activity was observed, including some patients experiencing PSA declines and reduction in tumor burden on scans.

- Next generation approaches are being used to identify novel prostate cancer targets for CAR T cells, including in Black patients.
- The team is also developing strategies to overcome issues caused by heterogeneity of tumor antigen expression and immunosuppression in the tumor microenvironment, and to increase the ability of CAR T cells to penetrate prostate cancer bone metastases. These include engineering the CAR T cells to also produce T cell activation proteins and antibodies that block immunosuppressive signals.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/30th-annual/session-10-updates-from-pcf-tactical-awards-teams/>

30

PROSTATE CANCER FOUNDATION
SCIENTIFIC RETREAT

CAR T TACTICAL Team: Overview of Program

Aim 1: Optimize T cell intrinsic functions
ID3 / TET2 / Foxo1
htert / senescence

Aim 2: Optimize T cell extrinsic functions in the TIME
target discovery
IL12 / IL18
TIME / Bone mets

Aim 3: CAR T trials in mCRPC
PSMA / PSCA / KLK2
TIME / Bone mets
racially diverse

Table 1. CAR T trials at COH and PENN for mCRPC.

NCT Number	Title	Status
NCT03873805	PSCA-CAR T Cells in Treating Patients With PSCA+ Metastatic Castration Resistant Prostate Cancer	Recruiting, COH
NCT05022849	A Study of JNJ-75229414 for Metastatic Castration-resistant Prostate Cancer Participants	Recruiting, COH, PENN
NCT04249947	P-PSMA-101 CAR-T Cells in the Treatment of Subjects With Metastatic Castration-Resistant Prostate Cancer (mCRPC) and Advanced Salivary Gland Cancers (SGC)	Recruiting, COH
NCT03089203	CAR-PSMA-TGFBRDN Cells for Castrate-Resistant Prostate Cancer	Recruiting, PENN

CLINICAL CANCER RESEARCH

REVIEWS | OCTOBER 21 2021

Novel Redirected T-Cell Immunotherapies for Advanced Prostate Cancer

Tanya B. Dorff¹, Vivek Narayan², Stephen J. Forman³, Peter D. Zang⁴, Joseph A. Fraietta⁵, Carl H. June⁵, Naomi B. Haas², and Saul J. Priceman³

UNIVERSITY OF PENNSYLVANIA
 Abramson Cancer Center

City of Hope
 RESEARCH · TREATMENT · CURES

NIH NATIONAL CANCER INSTITUTE

Keck School of Medicine of USC

Children's Hospital of Philadelphia

VA

U.S. Department of Veterans Affairs
 Veterans Health Administration
 Corporal Michael J. Crescenzo VA Medical Center

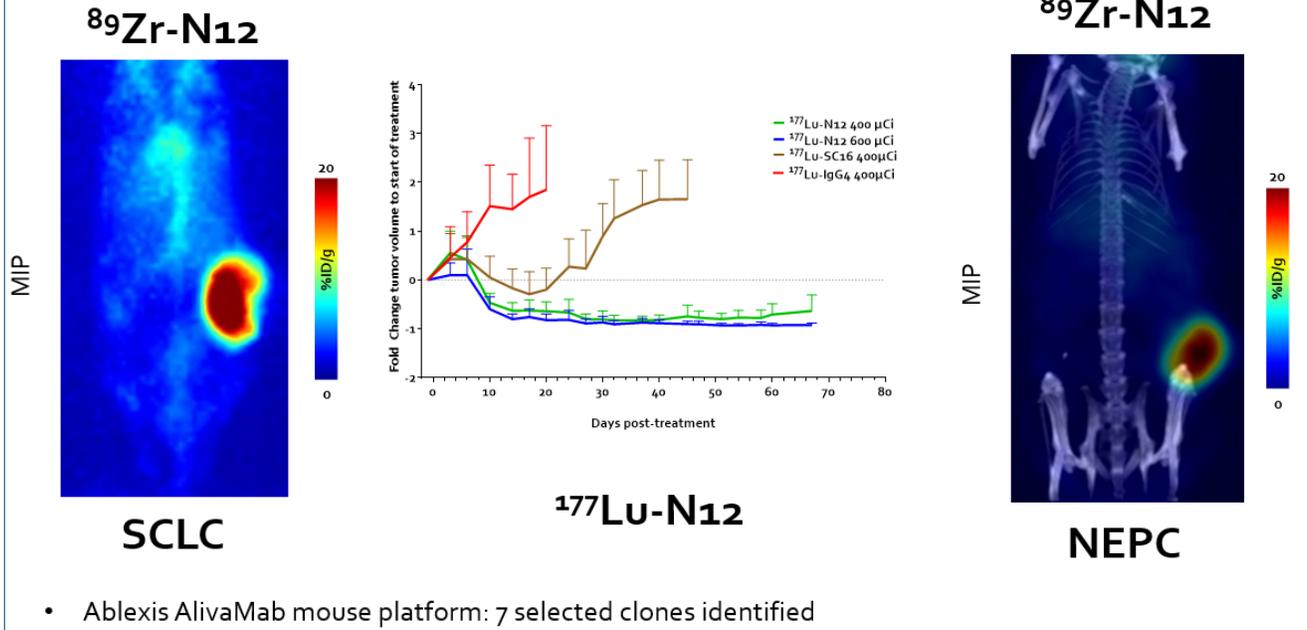
Novel Theranostic Agents for Neuroendocrine Prostate Cancer

Jason Lewis, PhD
 Memorial Sloan Kettering Cancer Center

- Radiotheranostics is an oncology paradigm of “see what you treat and treat what you see,” in which the same tumor target is used for both imaging and treatment. This approach first uses PET or SPECT imaging to determine whether a patient’s tumor expresses sufficient levels of the tumor target, and if so, the patient can receive a radioligand therapy against that target. PET or SPECT imaging can also be used after treatment, to evaluate the levels of the treatment that reach the tumor or to monitor clinical responses.
- For instance, PSMA radiotheranostics, which have recently been FDA-approved for advanced metastatic castration-resistant prostate cancer (mCRPC), use PSMA PET imaging to determine whether a patient is eligible to receive PSMA-targeted radioligand therapy (Pluvicto).

- Neuroendocrine prostate cancer (NEPC) is a highly aggressive form of advanced prostate cancer for which there are no effective therapies. New therapies are urgently needed.
- Dr. Jason Lewis discussed his team's PCF TACTICAL Award project, which aims to develop a novel radiotheranostic for NEPC.
- NEPC often highly expresses the protein DLL3. Other cancers with small cell/neuroendocrine features, such as small cell lung cancer (SCLC), also express DLL3. DLL3 is a promising radiotheranostic target for NEPC and SCLC.
- Rova-T is an experimental antibody-drug conjugate targeting DLL3 that was previously tested in clinical trials. Rova-T exhibited promising clinical activity but also significant toxicity, which halted further clinical development.
- The toxicity of Rova-T was hypothesized to be due to the poor chemistry of the antibody-drug conjugate, allowing the chemotherapy toxin to easily fall off in circulation and damage other tissues.
- The DLL3-targeting antibody (SC16) from Rova-T is being repurposed for testing as a radiotheranostic by Dr. Lewis and team. A DLL3-targeting PET imaging agent and a radioligand therapy using SC16 were developed.
- The DLL3-PET agent has been tested in clinical trials in patients with SCLC. In one patient presented, DLL3-PET imaging was able to visualize SCLC metastases in the brain, liver, and skeleton. Biopsies of selected sites confirmed they were DLL3-expressing tumor metastases.
- The DLL3-PET agent was able to view tumors in NEPC mouse models, and was then tested in clinical trials in patients with NEPC.
- Of importance, patients with NEPC often have non-NEPC prostate metastases (adenocarcinoma) at the same time. Imaging of the entire tumor burden likely requires several types of imaging, as DLL3-PET cannot detect adenocarcinoma lesions, while PSMA PET often cannot detect NEPC lesions. FDG-PET, which detects rapidly growing tumor lesions, also does not overlap entirely with detection of DLL3 or PSMA expressing lesions.
- For instance, in one patient presented, DLL3-PET imaging detected two lesions, while FDG-PET imaging detected many more. In another patient, DLL3-PET and PSMA-PET detected different subsets/areas of metastatic lesions.
- How to best image and treat patients with heterogeneous metastatic prostate cancer remains a challenge and area of intense research.
- A 177-Lutetium-DLL3-targeted radioligand therapy, ¹⁷⁷Lu-SC16, was developed. 177-Lutetium is the same radioactive warhead used in Pluvicto. In preclinical mouse SCLC and NEPC tumor models, treatment with ¹⁷⁷Lu-SC16 resulted in complete and durable tumor regressions.
- A clinical trial testing ¹⁷⁷Lu-SC16 in patients with NEPC and SCLC is planned.
- However, SC16 is a proprietary technology, and the company that owns it is not pursuing further development as a theranostic.
- The team has developed a novel DLL3-targeted antibody, N12, that is superior to SC16 for NEPC imaging and radioligand therapy in preclinical studies (**Figure**). Studies to prepare these agents for clinical trials are ongoing.
- The team is also investigating NEPC biology to identify new theranostic targets and develop additional new radiotheranostic agents.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-10-updates-from-pcf-tactical-awards-teams/>**

SCLC and NEPC -- Imaging, Biodistribution, and Therapeutic studies N12

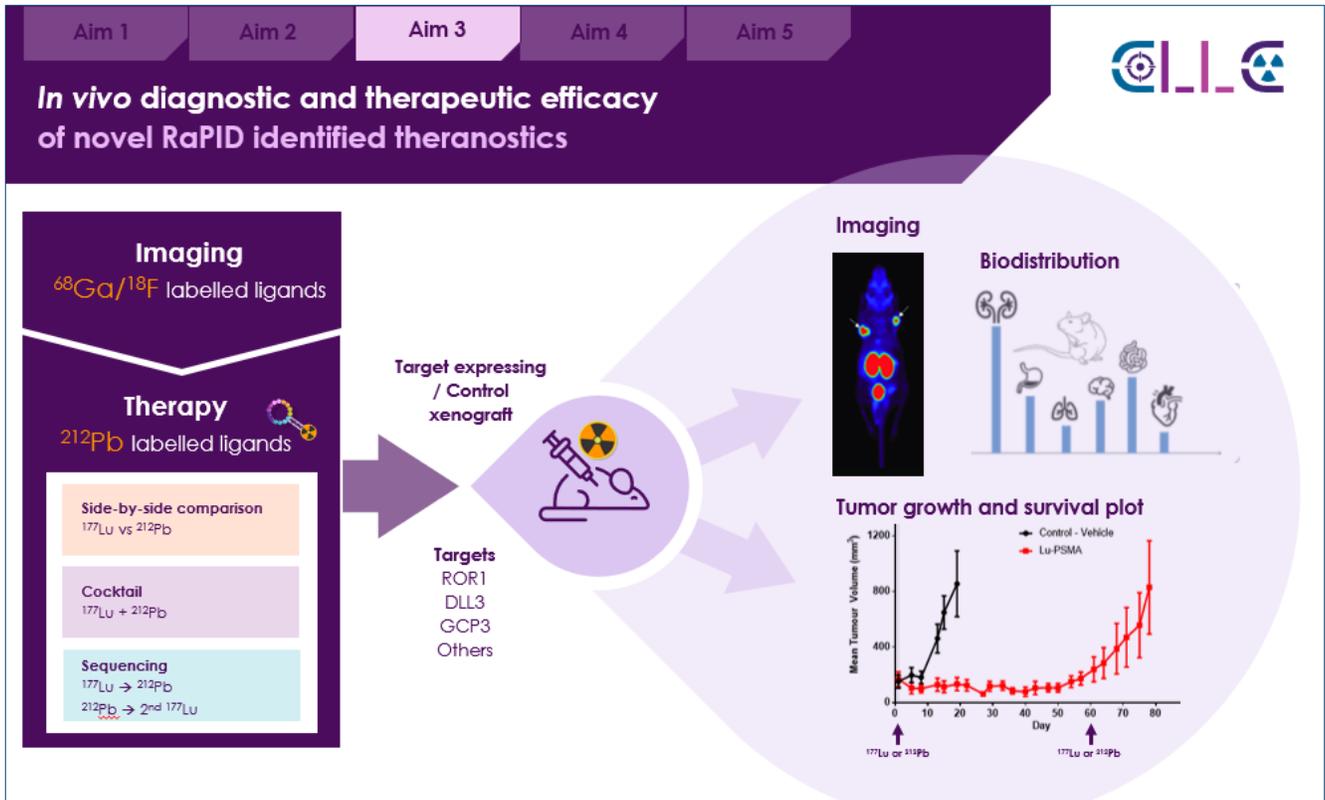


An Accelerated Platform using Lead-212 Targeted α -Particle Therapy to Radically Improve Cancer Lethality of Prostate Cancer Theranostics using Novel Targets and Better Understanding of Resistance: The Cancer Lethality Lead Collaboration

Michael Hofman, MBBS
Peter MacCallum Cancer Centre, Australia

- Dr. Michael Hofman discussed his team's PCF TACTICAL Award project, which aims to develop new first-in-class radioligand therapies (RLT) and PET (positron emission tomography) imaging agents for prostate cancer. The team will also develop new biomarkers to help select patients for treatment, and identify mechanisms of resistance to RLTs and methods to overcome treatment resistance (**Figure**).
- This PCF TACTICAL Award is led by Peter MacCallum Cancer Centre, in collaboration with UCSF, UCLA and Essen in Germany.
- RLTs are a class of cancer treatments that consist of tumor-targeting molecules attached to radioactive isotopes that kill cancer cells.
- Pluvicto® (LuPSMA; $^{177}\text{-Lutetium-PSMA-617}$) is a PSMA-targeted radioligand therapy that emits radioactive beta particles and was FDA-approved for treatment of metastatic castration-resistant prostate cancer (mCRPC) in 2022. While Pluvicto was shown to extend patient survival and could produce striking, deep responses, not all patients responded and nearly all patients eventually develop resistance and progress.
- The TACTICAL team is using next generation chemistry technologies to create a library of 10-trillion cyclic peptides and screen these for high affinity binding to prostate cancer proteins.

- The prostate cancer proteins targeted include PSMA, ROR1, DLL3, GPC3, FAP, and others.
- Promising prostate cancer-targeted cyclic peptides will be made into RLTs by attaching them to the alpha-emitting radioisotope 212-Lead, and into PET imaging agents by attaching them to positron-emitting radioisotopes.
- Thus far, the team has identified 3 promising ROR1-targeted peptides. These are being developed into RLTs and PET imaging agents for testing in preclinical models and clinical trials.
- The team is focusing on developing alpha-emitting radioisotopes because they deliver much higher energy and are more potent than beta-emitters. Alpha-emitters also have a shorter range than beta-emitters and thus may be more effective in micro-metastases, while beta-emitters may be more effective in larger tumors.
- 225-Actinium is an alpha-emitter that has previously been tested in PSMA-targeted RLTs. This experimental agent elicited potent and long-term responses in patients with advanced prostate cancer, but also caused significant toxicities to salivary and lacrimal glands.
- 212-Lead is hypothesized to be a safer alternative to 225-Actinium, with more ideal decay properties and an ideal half-life for small molecule-based RLTs. 212-Lead can also be sustainably and scalably produced using a tabletop generator, while 225-Actinium production is limited.
- A first-in-human trial using 212-Lead-labeled octreotate demonstrated safety and complete responses in neuroendocrine tumors.
- Team members in Germany are focusing on FAP (fibroblast activation protein), a protein expressed on stromal cells in many cancer types, including prostate cancer. Stromal cells are non-tumor cells that support the growth of tumors and may be promising therapeutic targets.
- Thus far, beta-emitting FAP-targeted RLT agents that have been tested in patients appear less ideal for prostate cancer compared to PSMA-targeted RLTs. However, 212-Lead-based FAP RLTs may be more effective.
- Prostate cancer typically has an immunosuppressive microenvironment, limiting the efficacy of immunotherapy treatments. Radiation-based therapies may synergize with immunotherapy.
- The TACTICAL team is investigating ways to combine RLT with immunotherapy to achieve therapeutic synergy.
- STING is an immune signaling protein that activates immune responses when DNA fragments are detected inside cells, an indicator of viral infections. Studies in prostate cancer mouse models found that STING-activating agents can have therapeutic synergy with PSMA-targeted RLT.
- The team is also developing new biomarkers using tumor tissue and blood, for patient prognosis, monitoring disease burden, and predicting treatment responses and treatment resistance.
- A rapid autopsy program has been established at Peter MacCallum Cancer Center. This allows researchers to attain samples of dozens of metastases from patients who died from lethal prostate cancer. These samples will be used to study tumor biology, identify new prostate cancer therapeutic targets and molecular biomarkers, and determine heterogeneity of tumor expression of therapeutic targets to direct improved therapeutic combinations.
- The team is also highly engaged in knowledge sharing through educational webinars, podcasts, and conferences, for patients, researchers and clinicians, as well as other forms of communication, training and education efforts.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-10-updates-from-pcf-tactical-awards-teams/>**



SPECIAL LECTURE: Novel Target Identification as a Bottleneck in Biotech Innovation: Implications for Academic Entrepreneurs

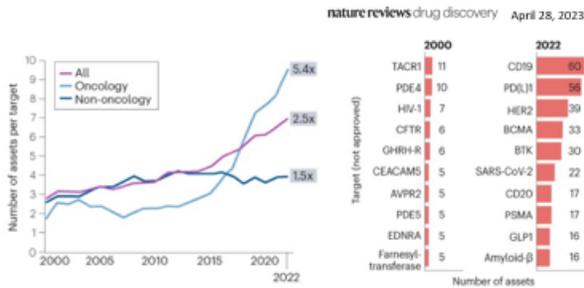
Ahmed Alkhateeb, PhD
Sanofi

- Dr. Ahmed Alkhateeb discussed a pharmaceutical business development perspective on oncology drug target identification and current trends in biotech.
- A recent review article published in *Nature Reviews Drug Discovery* demonstrated that the biotech sector is experiencing a shortage of novel therapeutic targets. Over the past ~10 years, the number of clinical oncology assets per drug target has increased by 5.4-fold.
- For instance, in 2000, TACR1 was the target with the most assets, at 11, which is considered a healthy number. In 2022, CD19 was the target with the most assets, at 60.
- In 2022, 17 assets targeted the prostate cancer protein PSMA, though this is likely okay, as there is significant diversity in the modality of PSMA-targeted agents under development.
- Concentrating investments on specific targets dilutes the clinical impact, as significant resources become focused on fewer targets.
- Potential causes of this shift include increased investment in 'platform' biotech technologies, a focus on achieving best-in-class profiles for validated targets, and the need to decrease reliance on competitor backbone therapies.

- In another recent analysis published in *Biocentury*, 75% of pharma deals between July 2022 to July 2023 involved in first-in-class assets, which are products against targets for which there are no therapies of the same modality on the market or are at least two stages ahead in the clinic for the same disease. However, over 50% of these recent deals involved conventional modalities (small molecules or antibodies), suggesting the target is the novel component of these assets.
- Together, these analyses suggest that novel oncology targets have high value, but there is a shortage of them.
- Academia is the source of over 90% of oncology drug targets. The number of papers published by academia increases every year, with over 1.8 million biomedical papers published in 2022 alone. There are over 136,000 papers published on prostate cancer, of which 41,000 (30%) were published in the last 5 years. Thus, academic output is not the issue contributing to the dearth of novel targets in biotech/pharma.
- Academia contributions to the drug development process include target identification and validation and providing other insights. Biotech, pharma, and venture capital efforts focus on replication, preclinical and clinical drug development, and regulatory approvals.
- Overall, there is a 5-10% success rate across the drug development process, resulting in an average R&D cost of \$2.3 Billion per approved drug.
- Phase 2 clinical trial failures represent the largest hurdle in the drug development process. Over 50% of phase 2 failures are due to a lack of efficacy, despite demonstrations of sufficient safety and target engagement. Target-disease mismatch may contribute to these failures.
- Another major bottleneck in the translation from academic insights into therapies, is poor reproducibility of scientific studies. For instance, a study by Amgen in 2012 found that target validation studies from only 6 of 53 (11%) high-impact papers could be replicated. The Reproducibility Project confirmed difficulty in replication, finding only 18-40% (based on effect size) of published target validation studies could be replicated.
- A natural language processing analysis of over 3,000 papers found if at least 2 independent papers (with non-overlapping authors) made similar findings, these were 2.3-times more likely to be replicable than results from a single paper. Thus, there is high value in independent academic groups studying the same oncology targets.
- Efforts to improve the transfer of academic innovation to biotech/pharma include increasing efforts on target validation, expansion of initial validation work in various cellular and molecular contexts, and publication of results, including negative replication results, in a way that increases visibility and discoverability by biotech, pharma, and venture capital.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/special-lecture-novel-target-identification-as-a-bottleneck-in-biotech-innovations/>**

The biotech sector is experiencing a shortage of novel oncology targets

Avg. number of clinical assets per target has increased 5.4x in oncology (2000-2020)



Fougnier et al (2023) Nature Reviews Drug Discovery

- Pharma and biotech companies are experiencing pipeline “herding”
- Concentrating investments on specific targets dilutes clinical impact
- Potential causes:
 - Increased investment in ‘platform’ biotech technologies
 - The focus on achieving best-in-class profile for validated targets
 - The need to decrease reliance on competitor’s backbone therapies

Session 11: Molecular Glues & Binding Inhibitors: Novel Small Molecule Cell Therapy Platforms

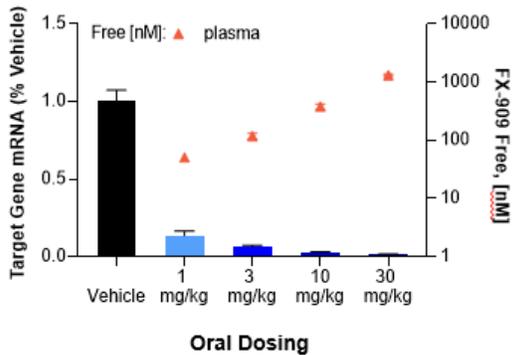
A New Paradigm in Drugging Transcription Factors

Robert Sims, PhD

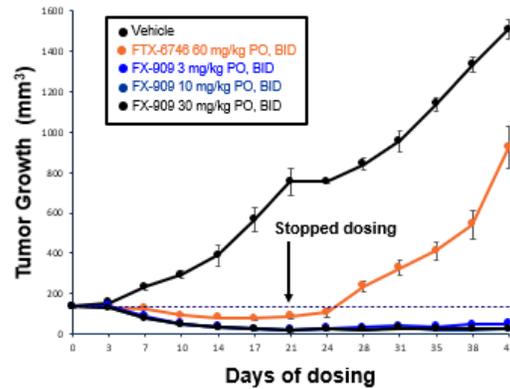
FLARE

- Transcription factors are proteins that bind to DNA and regulate gene expression. Altered transcription factors are common drivers in cancer, and targeting these are important cancer drug development goals. However, transcription factors are often dynamic and transiently structured, which have made drug development efforts challenging.
- For instance, prostate cancer-driving transcription factors include the androgen receptor (AR), HOXB13, ERG, and FOXA1, but only AR has been successfully targeted by treatments. Across all cancer types, only AR (prostate cancer), ER (breast cancer), and HIF2A (kidney cancer) have effective treatments against them.
- Dr. Robert Sims discussed a novel drug development platform to target cancer-driving transcription factors. This platform focuses on finding and targeting ligandable pockets (“switch sites”) that influence transcription factor function through conformation, or using ligands to target drugs to the transcription factors.
- Certain transcription factors are critical for cell identity, including in cancer. For instance, AR is necessary for prostate tissues to survive and for prostate cancer to maintain prostate features. Targeting these transcription factors is a clinically validated therapeutic strategy.
- Such transcription factors are commonly mutated in cancer, to remain in active conformations. Drugs that block the active conformations may be more effective than other methods of inhibiting the transcription factor.
- PPARG is a critical transcription factor in urothelial cancer. A PPARG-targeted treatment, FX-909, was developed that blocks the active conformation of PPARG and was highly effective in preclinical models, even apparently able to cure mice with urothelial cancer without continued treatment (**Figure**).
- A phase 1 clinical trial testing FX-909 in patients with advanced solid tumors, including urothelial cancer, has been initiated.
- Unique chemistry methods are being used to identify and specifically target transcription factors that may have promise as therapeutic targets in different cancer types, including novel strategies to target transcription factors in prostate cancer.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-11-molecular-glues-binding-inhibitors-novel-small-molecule-cell-therapy-platforms/>**

PPARG Target Gene Suppression



Durable Tumor Regression



Hold and Kill: RIPTAC™ Therapeutics Present a Novel Mechanism to Conquer Prostate Cancer

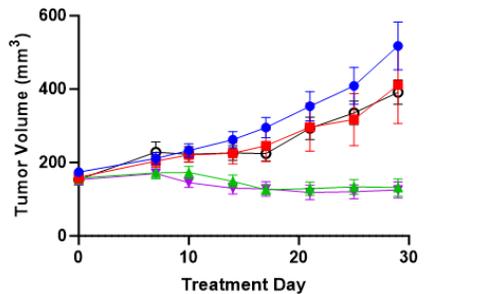
Kat Kayser-Bricker, PhD
Halda Therapeutics

- Dr. Kat Kayser-Bricker discussed the development of a novel class of bifunctional small molecule tumor-targeting therapeutics called RIPTACs™ (Regulated Induced Proximity Targeting Chimera).
- RIPTACs are dual-targeted small molecules that simultaneously bind a tumor-specific protein and a protein essential for cell survival, creating a stable complex that inactivates the essential protein and results in tumor cell death.
- A novel drug development platform is used that includes a pairing algorithm to identify complementary tumor-specific protein and essential protein pairs, and designs small molecules to target these. Candidate small molecules are then evaluated for pharmacodynamics and efficacy in a platform of preclinical tests.
- An orally available RIPTAC “H001,” has been developed that targets the androgen receptor (AR) and an essential protein, for the treatment of prostate cancer.
- H001 demonstrated promising anti-tumor activity in preclinical AR-positive prostate cancer models, and weak activity in AR-negative/low prostate cancer models.
- H001 demonstrated superior efficacy compared to enzalutamide in models with low enzalutamide sensitivity (**Figure**) and was effective in enzalutamide-resistant models.
- A phase 1 clinical trial testing an AR-RIPTAC in patients with prostate cancer is planned in 2025.
- RIPTACs for the treatment of other cancer types are also under development.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/30th-annual/session-11-molecular-glues-binding-inhibitors-novel-small-molecule-cell-therapy-platforms/>

Orally Bioavailable H001 Demonstrates Superior Efficacy to SoC

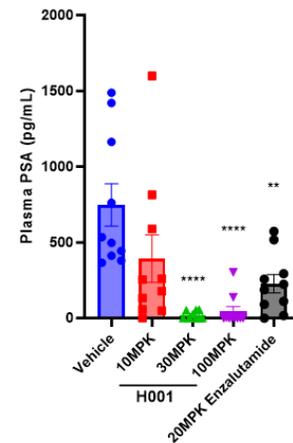
Dose-dependent oral activity

Robust Efficacy in Castrated VCaP Model, Superior to Enzalutamide (VCaP = AR^{amp}, V7⁺, Low Enza sensitivity)



No drug-related changes in bodyweight (n= 10 / group)

Plasma PSA Declines at Efficacious Doses (Day 25)



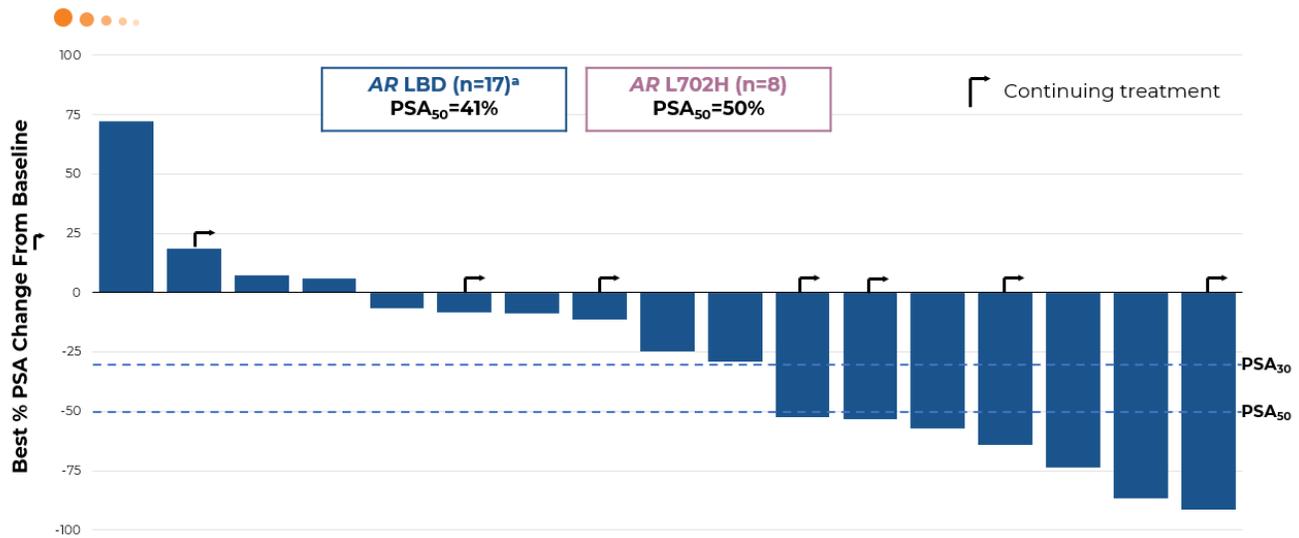
Development of PROTAC® AR Degraders in Advanced Prostate Cancer

Ron Peck, MD Arvinas

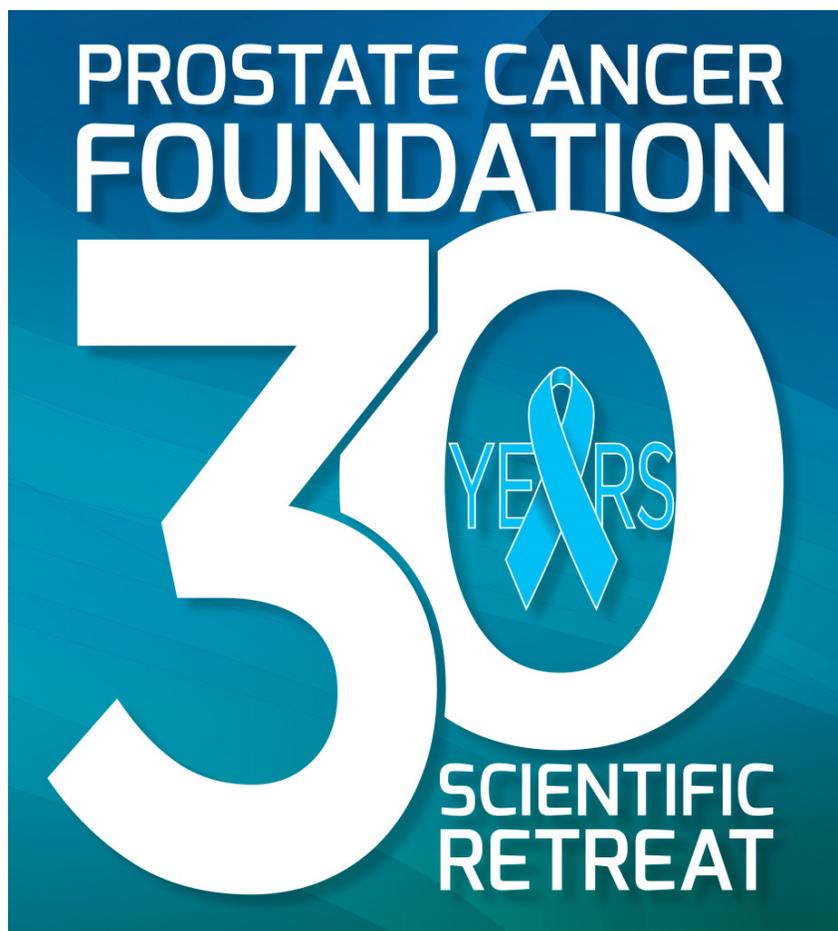
- PROTACs are chimeric molecules that bind to disease-causing proteins and tag them for degradation by the proteasome, the cell's machinery to degrade and recycle proteins.
- PROTACs have the benefits of both small molecule inhibitors and gene-based knockdown technologies.
- Dr. Ron Peck discussed Arvinas' development of PROTACs for the treatment of prostate cancer.
- Two PROTACs for prostate cancer, ARV-110 (Bavdegalutamide) and ARV-766, are currently in clinical trials.
- PROTACs for breast cancer are now in phase 3 clinical trials. Several other PROTACs are under development.
- ARV-110 was the first androgen receptor (AR)-targeting PROTAC to be developed. ARV-110 binds normal AR as well as AR mutants commonly seen in advanced prostate cancer, except for the AR L702H mutant. ARV-110 demonstrated promising activity in AR-positive prostate cancer models.
- In a phase 1 dose-escalation clinical trial in patients with metastatic castration resistant prostate cancer (mCRPC), ARV-110 was demonstrated to cause AR degradation in tumor tissues, and had promising preliminary anti-tumor efficacy. Overall, two of 12 patients treated with ARV-110 had confirmed PSA declines of ≥50%, one of whom also had tumor shrinkage on scans. The two patients who responded had tumors with mutations in the AR ligand-binding-domain (LBD), which causes AR to be constantly active.

- In a phase 2 trial, ARV-110 was tested in two groups of patients with mCRPC: a subgroup defined by AR alterations (3 mutation classes), and a subgroup defined by clinical characteristics. PSA declines of $\geq 50\%$ were seen in all subgroups.
- Across all 28 patients in the phase 1 + 2 trials who had tumors with AR T878X/H875Y mutations, 46% had PSA declines of $\geq 50\%$. If patients with L702H mutations were excluded, 54% had PSA declines of $\geq 50\%$, while among patients with L702H mutations only 9% had PSA declines of $\geq 50\%$. This confirms that AR L702H mutations are not targeted by ARV-110.
- Of all 44 patients with AR LBD mutations (excluding L702H mutations alone), 36% had PSA declines of $\geq 50\%$.
- Median radiographic progression free survival (rPFS; the time from trial enrollment to growth of tumors on scans) was 8.2 months for patients with AR LBD mutations (excluding L702H mutations alone) and 11.1 months for patients with AR T878X/H875Y mutations (without L702H mutations). Real-world data from patients with AR T878X/H875Y mutations suggests poor outcomes with current therapies.
- ARV-110 demonstrated a manageable safety profile. The most common adverse effects included nausea, fatigue, and vomiting. No grade 4 adverse effects occurred. 17 patients (11%) had an adverse effect leading to dose reduction and 19 (12%) had an adverse effect leading to treatment discontinuation.
- ARV-766 is a second-generation AR degrader that can also degrade AR L702H mutants. Promising preclinical activity was observed with ARV-766 in prostate cancer models.
- In a phase 1/2 clinical trial, ARV-766 demonstrated an improved tolerability profile compared to ARV-110. In preliminary results, PSA declines of $\geq 50\%$ were seen in 41% of all patients with AR LBD mutations and 50% of patients with AR L702H mutations (**Figure**). This trial is ongoing.
- Because of its broader activity and superior safety, ARV-766 is being prioritized for registration development in patients with mCRPC who were previously treated with AR-targeted therapy. A phase 1b trial to test ARV-766 in patients not yet treated with AR-targeted therapy is planned to open soon.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/30th-annual/session-11-molecular-glues-binding-inhibitors-novel-small-molecule-cell-therapy-platforms/>**

PSA Declines of $\geq 50\%$ Were Seen in 41% of AR LBD Patients and 50% in the AR L702H Subgroup, treated with ARV-766



^aIncludes biomarker-evaluable patients with ≥ 4 weeks of PSA follow-up. Data cutoff date: August 23, 2023.
AR=androgen receptor, LBD=ligand-binding domain, PSA=prostate-specific antigen, PSA₃₀=best PSA declines $\geq 30\%$, PSA₅₀=best PSA declines $\geq 50\%$



APPENDIX I:

30th ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT



Prostate Cancer Foundation
Women in Science Forum

OCTOBER 26, 2023

PROGRAM AGENDA



Prostate Cancer Foundation Women in Science Forum

The 8th Annual PCF Women in Science Forum

Thursday, October 26, 2023

*All times in U.S. PDT

*Omni La Costa Resort
Carlsbad, California*

Location: Costa De La Luna 4

Organizers: **Sarah Amend, PhD** (Johns Hopkins University), **Claire Fletcher, PhD** (Imperial College London), **Veda N. Giri, MD** (Yale University and Yale Cancer Center), **Emily Grist, MBBS** (University College London Cancer Institute), **Susan Halabi, PhD** (Duke University), **Salma Kaochar, PhD** (Baylor College of Medicine), **Fatima Karzai, MD** (National Cancer Institute), **Andrea Miyahira, PhD** (Prostate Cancer Foundation), **Eileen Parkes, MD, PhD** (University of Oxford), **Ayesha Shafi, PhD** (Center for Prostate Disease Research (CPDR); USU Walter Reed Surgery), and **Amina Zoubeidi, PhD** (Vancouver Prostate Centre)

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

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

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

Welcome, Introductions and Vision

8:00 AM – 8:05 AM

Claire Fletcher, PhD (Imperial College London)
Fatima Karzai, MD (National Cancer Institute)

Session 1: Keynote: Excellence through Equity: Promoting Representation and Access for All

8:05 AM – 8:50 AM

8:05 AM - 8:35 AM

Neha Vapiwala, MD, FACR, FASTRO, FASCO

Professor and Vice Chair of Education, Department of Radiation Oncology; Dean of Admissions, Perelman School of Medicine
University of Pennsylvania

Introduced by Susan Halabi, PhD

*N/A post-meeting for On Demand

8:35 AM - 8:50 AM

Questions

Session 2: Negotiation Strategies for Women in Research and Academic Medicine

8:50 AM - 9:35 AM

8:50 AM - 9:20 AM

Stacey Lee, JD

Professor of Practice, Johns Hopkins University

Introduced by Ayesha Shafi, PhD

9:20 AM - 9:35 AM

Questions

9:35 AM - 9:45 AM Break

Session 3: Conversation: Strategies for Amplifying the Voices of Women in Science

9:45 AM – 10:30 AM

Moderator: Veda N. Giri, MD

Yale University and Yale Cancer Center

Natasha Kyprianou, MBBS, PhD

Icahn School of Medicine at Mount Sinai

Todd Morgan, MD

University of Michigan

Session 4: Panel Discussion: How to Take Leadership while Maintaining Excellence in Science

10:30 AM – 11:30 AM

Introduction by Anima Zoubeidi, PhD

Moderator: Renu Eapen, MBBS, FRACS (Urology)

Peter MacCallum Cancer Center

Panelists:

Charlotte Bevan, PhD (Imperial College London)

Francesca Demichelis, PhD (University of Trento)

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

Shahneen Sandhu, MBBS (Peter MacCallum Cancer Center)

Jindan Yu, MD, PhD (Emory University)

Session 5: Introduction to Students and Closing Remarks

11:30 AM – 11:35 AM

Kathryn O'Connor (MedTech Academy, San Diego)

Andrea Miyahira, PhD (Prostate Cancer Foundation)

Group Picture

11:35 AM – 11:45 AM

Session 6: Lunch/Networking

11:45 AM – 12:30 PM

Costa De La Luna Lawn

**** Meeting Adjourned ****

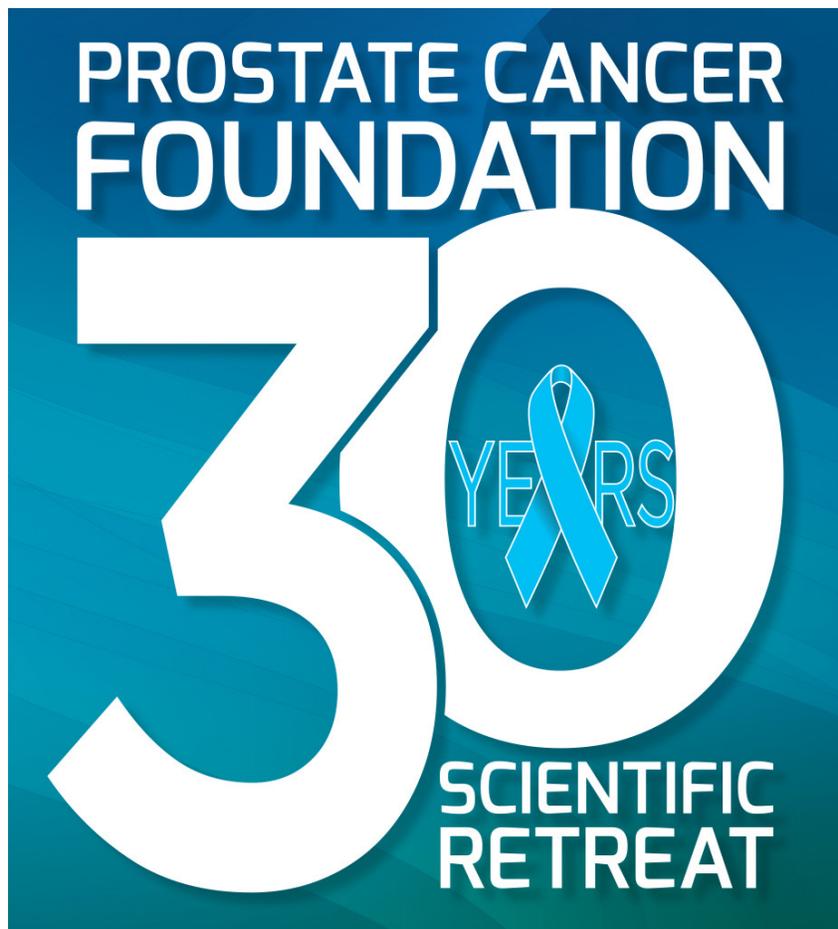
***The 30th Annual Prostate Cancer Foundation Scientific Retreat
begins promptly at 1:00 PM in the Costa Del Sol Ballroom***

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



Supported by





APPENDIX II:

30th ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT



Prostate Cancer Foundation
Young Investigator Forum

OCTOBER 25, 2023

PROGRAM AGENDA



Prostate Cancer Foundation
Young Investigator Forum

***30th Annual Prostate Cancer Foundation
Scientific Retreat***

PCF YOUNG INVESTIGATOR FORUM

Wednesday, October 25, 2023

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

AGENDA

YOUNG INVESTIGATOR FORUM

Wednesday, October 25, 2023

*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: Panel Discussion: Career Paths to Entrepreneurship

8:10 AM - 8:55 AM

8:10 AM - 8:40 AM **Moderator: Howard Soule, PhD** (Prostate Cancer Foundation)

Nicholas Reder, MD, MPH

Alpenglow Biosciences; University of Washington

Scott Tomlins, MD, PhD

Strata Oncology; University of Michigan

8:40 AM - 8:55 AM Discussion

Wednesday, October 25, 2023

Session 2: Panel Discussion: What about being a Public Servant? Careers in Government Science

8:55 AM - 9:40 AM

8:55 AM - 9:25 AM **Moderator: James Gully, MD, PhD** (National Cancer Institute)

Fatima Karzai, MD
National Cancer Institute

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

9:25 AM - 9:40 AM Discussion

Session 3: Panel Discussion: Negotiating your First Job: An MD and PhD Perspective

9:40 AM - 10:30 AM

9:40 AM - 10:10 AM **Moderator: Abhijit Parolia, PhD** (University of Michigan)

Ryan Park, MD
University of Texas MD Anderson Cancer Center

Elizabeth Wasmuth, PhD
UT Health Science Center at San Antonio

*N/A post-meeting for On Demand

10:10 AM - 10:30 AM Discussion

10:30 AM - 10:40 AM **Break**

Session 4: The Prostate Cancer Clinical Trials Consortium: Your Resource for Clinical Trial Development and Execution & Real World Data Project Opportunities

10:40 AM - 11:00 AM

10:40 AM - 10:55 AM **Jake Vinson**
Prostate Cancer Clinical Trials Consortium (PCCTC)

10:55 AM - 11:00 AM Discussion

Wednesday, October 25, 2023

Session 5: Panel Discussion: Industry-Academic Collaborations:
11:00 AM - 12:00 PM

11:00 AM - 11:45 AM **Moderator: Andrea Miyahira, PhD**
Prostate Cancer Foundation

Panelists:

Ricardo Attar, PhD (Janssen)

Himisha Beltran, MD (Dana-Farber Cancer Institute)

Rana McKay, MD (University of California, San Diego)

Margaret Yu, PhD (Janssen)

11:45 AM - 12:00 PM Discussion

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 6**

Location: Costa De La Luna 4

Wednesday, October 25, 2023

Session 6: Introduction to High Achieving 2022 PCF Young Investigators

1:30 PM - 2:30 PM

Moderator: Howard Soule, PhD

Prostate Cancer Foundation

1:30 PM - 1:40 PM

Lutetium PSMA in Localised Prostate Cancer and its Effects on the Tumour Microenvironment

Renu Eapen, MBBS, FRACS (Urology)

Peter MacCallum Cancer Centre

1:40 PM - 1:45 PM

Discussion

1:45 PM - 1:55 PM

Biomarkers of Aggressive Disease Biology in mCRPC: From Tissue to Liquid Biopsy

Marina Sharifi, MD, PhD

University of Wisconsin

*N/A post-meeting for On Demand

1:55 PM - 2:00 PM

Discussion

2:00 PM - 2:10 PM

STEAP1-Directed CAR T Cell Therapy for Prostate Cancer – Rational Combination Strategies to Overcome Therapy Resistance

Vipul Bhatia, PhD

University of California, Los Angeles

*N/A post-meeting for On Demand

2:10 PM - 2:15 PM

Discussion

2:15 PM - 2:25 PM

Developing a Precision-Based Approach to Predict Cardiovascular Toxicity from Androgen Deprivation Therapy Using a Randomized Controlled Trial

Sagar Patel, MD

Emory University

*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 7

Location: Costa De La Luna 1-3

Wednesday, October 25, 2023

Session 7: PCF Young Investigator Speed Networking 10.0

3:00 PM - 5:15 PM

Location: Costa De La Luna 1-3

Moderators: **Marina Sharifi, MD, PhD** (University of Wisconsin)
Renu Eapen, MBBS, FRACS (Urology) (Peter MacCallum Cancer Centre)
Alexandros Papachristodoulou, PhD (Columbia University)

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

3:00 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**

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)

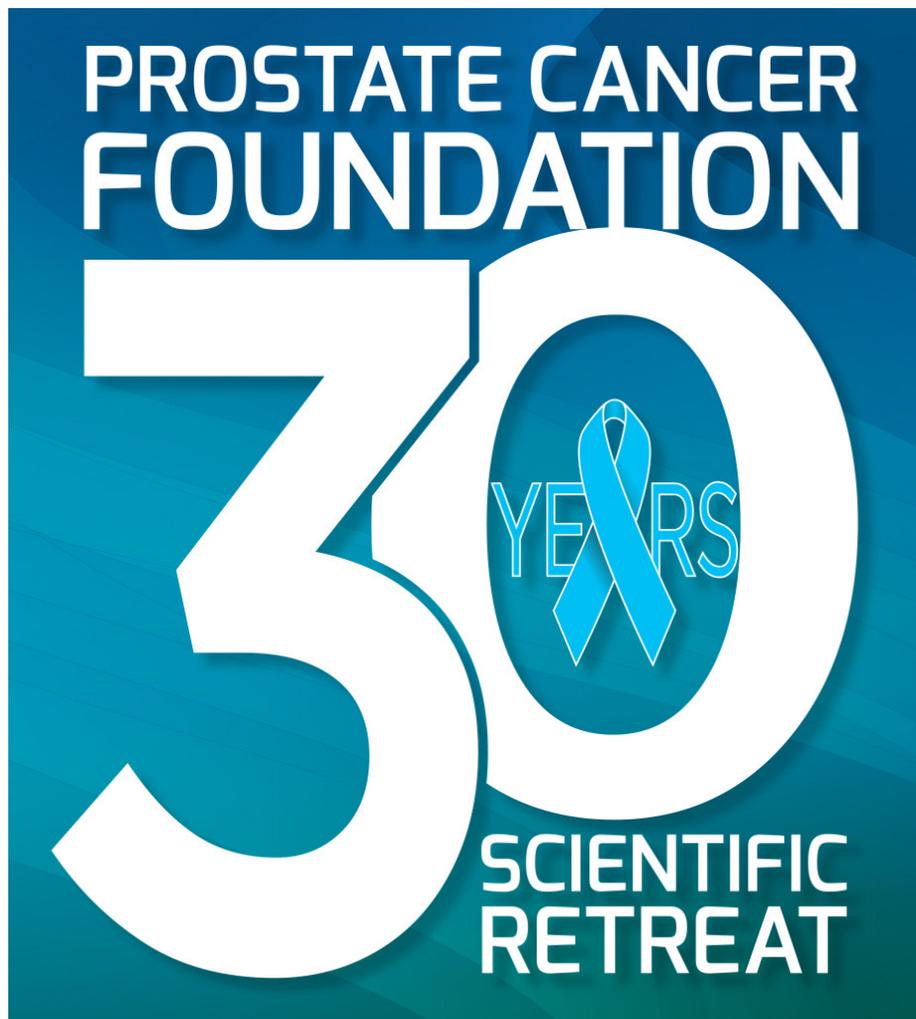
We deeply thank our supporters for providing funding for this educational initiative.



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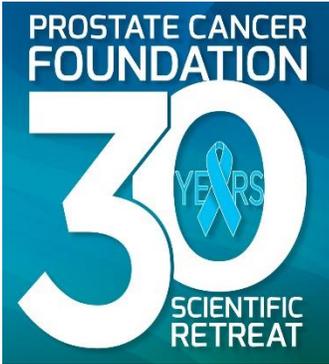
FOUNDATION
MEDICINE



APPENDIX III:

**30th ANNUAL PROSTATE CANCER FOUNDATION
SCIENTIFIC RETREAT
OCTOBER 26-28, 2023**

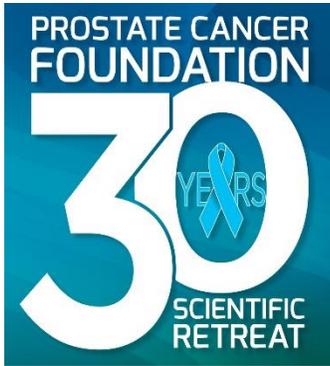
PROGRAM AGENDA



***30th Annual Prostate Cancer Foundation
Scientific Retreat***

October 26 - 28, 2023

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



AGENDA

Thursday, October 26, 2023

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: Cancer Stem Cells and Prostate Cancer Lineage Plasticity

1:05 PM - 2:25 PM

Moderator: Rakesh Heer, MBBS, PhD

Newcastle University, UK

1:05 PM - 1:20 PM

Development, Maturation, and Maintenance of Human Prostate

Rakesh Heer, MBBS, PhD

Newcastle University, UK

1:20 PM - 1:25 PM

Discussion

1:25 PM - 1:40 PM

Targeting Lineage Plasticity in Prostate Cancer

Wouter Karthaus, PhD

Swiss Institute for Experimental Cancer Research, École Polytechnique Fédérale De Lausanne, Switzerland

1:40 PM - 1:45 PM

Discussion

1:45 PM - 2:00 PM

Engineering Prostate Cancer – Designer Organoids

Adriana Buskin, PhD

Newcastle University, UK

Anastasia Hepburn, PhD

Newcastle University, UK

2:00 PM - 2:05 PM

Discussion

Thursday, October 26, 2023

- 2:05 PM - 2:20 PM ***Organwide Spatial Analysis of Prostate and its Tumors***
Joakim Lundeberg, PhD
KTH Royal Institute of Technology, Science for Life Laboratory, Solna, Sweden
- 2:20 PM - 2:25 PM **Discussion** (*N/A post-meeting for On Demand)

Session 2: Treatment Resistance and Plasticity 2023

2:25 PM - 3:45 PM

Moderator: David Goodrich, PhD
Roswell Park Comprehensive Cancer Center

2:25 PM - 2:40 PM ***The 4D Nucleome Underlying Neuroendocrine Transformation of Prostate Cancer***

Jindan Yu, MD, PhD
Emory University

2:40 PM - 2:45 PM **Discussion**

2:45 PM - 3:00 PM ***DNA Methylation as a Biomarker and Target in Neuroendocrine Prostate Cancer***

Himisha Beltran, MD
Dana-Farber Cancer Institute

3:00 PM - 3:05 PM **Discussion**

3:05 PM - 3:20 PM ***Targeting Prostate Cancer Plasticity in the Clinic***

David Goodrich, PhD
Roswell Park Comprehensive Cancer Center

3:20 PM - 3:25 PM **Discussion**

3:25 PM - 3:40 PM ***Temporal Evolution Reveals Bifurcated Lineages in Aggressive Neuroendocrine Small Cell Prostate Cancer Trans-Differentiation***

Chia-Chun (Olga) Chen
University of California, Los Angeles

Thomas Graeber, PhD
University of California, Los Angeles

3:40 PM - 3:45 PM **Discussion**

Thursday, October 26, 2023

Session 3: The Future of AI in Diagnostic Medicine

3:45 PM - 5:05 PM

Moderator: Thomas Fuchs, DSc

Icahn School of Medicine at Mount Sinai

3:45 PM - 4:00 PM

AI-Based Pathology Biomarkers for Predicting Cancer Outcomes

Thomas Fuchs, DSc

Icahn School of Medicine at Mount Sinai

4:00 PM - 4:05 PM

Discussion

4:05 PM - 4:20 PM

Utility of Pathology Deep Learning Algorithms for Prostate Cancer

Tamara Lotan, MD

Johns Hopkins University

4:20 PM - 4:25 PM

Discussion

4:25 PM - 4:40 PM

AI-Enabled Therapy Personalization

Andre Esteva, PhD

ArteraAI

4:40 PM - 4:45 PM

Discussion

4:45 PM - 5:00 PM

AI-Based Quantitative Imaging Biomarkers

Robert Jeraj, PhD

University of Wisconsin; AIQ Solutions

5:00 PM - 5:05 PM

Discussion

SPECIAL LECTURE

5:05 PM - 5:20 PM

Transforming the Clinical Trial Experience to Ensure Breakthroughs for All

Judy Swards

Pfizer

Introduced by Matthew Cotter, PhD

Pfizer

5:20 PM - 5:25 PM

Discussion

Thursday, October 26, 2023

SPECIAL LECTURE

5:25 PM - 5:45 PM

DEI Strategies for Advancing Cancer Care Equity

Tawana Thomas Johnson

American Cancer Society

Introduced by Brandon Mahal, MD

University of Miami

5:45 PM - 5:50 PM

Discussion

Dinner

6:30 PM - 7:30 PM

Dinner Location: Costa Del Sol Patio

Poster Session and Dessert

7:30 PM - 10:30 PM

Poster Session and Dessert Location: Costa De La Luna Ballroom

Friday, October 27, 2023

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 4: Analytical Approaches and Computational Biology for Cancer Research

7:00 AM - 7:45 AM

Moderator: Francesca Demichelis, PhD

University of Trento, Italy

7:00 AM - 7:05 AM

Introduction

Francesca Demichelis, PhD

University of Trento, Italy

7:05 AM - 7:20 AM

Non-Neuroendocrine Lineage Plasticity in Prostate Cancer

Ekta Khurana, PhD

Weill Cornell Medicine

7:20 AM - 7:25 AM

Discussion

7:25 AM - 7:40 AM

Mechanism-Centric Markers of Therapeutic Resistance in Oncology

Antonina Mitrofanova, PhD

Rutgers University

7:40 AM - 7:45 AM

Discussion

Friday, October 27, 2023

SPECIAL LECTURE

7:45 AM - 8:00 AM

Of Nerves and Cancer

Gustavo Ayala, MD

The University of Texas Health Science Center at Houston

*Introduced by Howard Soule, PhD
Prostate Cancer Foundation*

8:00 AM - 8:05 AM

Discussion

Session 5: The Biology of Prostate Cancer Bone Metastases

8:05 AM - 9:25 AM

Moderator:

Matt Greenblatt, MD, PhD

Weill Cornell Medicine

8:05 AM - 8:20 AM

Building on Insights from Murine Models and Clinical Studies of Prostate Cancer Bone Metastases

Estefania Labanca, PhD

The University of Texas MD Anderson Cancer Center

Nora Navone, MD, PhD

The University of Texas MD Anderson Cancer Center

8:20 AM - 8:25 AM

Discussion

8:25 AM - 8:40 AM

A Skeletal Stem Cell Directing Prostate Cancer Spine Metastases

Matt Greenblatt, MD, PhD

Weill Cornell Medicine

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

8:40 AM - 8:45 AM

Discussion

8:45 AM - 9:00 AM

Uncovering Opportunities for Immune Targeting of Prostate Cancer Bone Metastases

Belinda Parker, PhD

Peter MacCallum Cancer Centre, Australia

9:00 AM - 9:05 AM

Discussion

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

Friday, October 27, 2023

9:05 AM - 9:20 AM ***Role of Osteocytes in Prostate Cancer Bone Metastasis***
Evan T. Keller, DVM, PhD
University of Michigan (*N/A post-meeting for On Demand)

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

SPECIAL LECTURE

9:25 AM - 9:40 AM

Transitioning from "Drug to Therapy Development Strategies" in Prostate Cancer

Christopher Logothetis, MD

The University of Texas MD Anderson Cancer Center

Introduced by Ana Aparicio, MD

The University of Texas MD Anderson Cancer Center

9:40 AM - 9:45 AM

Discussion

Special Lecture

9:45 AM - 10:00 AM

**Implementation Science and How It Can Improve Prostate Cancer Outcomes:
The PCF-ADEPT Program**

William K. Oh, MD

Chief Medical Officer, Prostate Cancer Foundation

*Introduced by Charles J. Ryan, MD
Prostate Cancer Foundation*

10:00 AM - 10:05 AM

Discussion

Friday, October 27, 2023

SPECIAL LECTURE

10:05 AM - 10:35 AM

The Global Public Square of Prostate Cancer

Charles J. Ryan, MD

Prostate Cancer Foundation

Introduced by Howard Soule, PhD

Prostate Cancer Foundation

10:35 AM - 10:40 AM

Discussion

Session 6: The Contribution of Ancestry and Genomics to Prostate Cancer Disparities

10:40 AM - 11:40 AM

Moderator: Vanessa Hayes, PhD

The University of Sydney, Australia

10:40 AM - 10:55 AM ***African-Specific Molecular Taxonomy of Prostate Cancer***

Vanessa Hayes, PhD

The University of Sydney, Australia

10:55 AM - 11:00 AM **Discussion**

11:00 AM - 11:15 AM ***Biomarker Benchmarking across Ancestral Populations***

Elio Adib, MD

Brigham and Women's Hospital; Massachusetts General Hospital

Amin H. Nassar, MD

Yale New Haven Hospital

11:15 AM - 11:20 AM **Discussion**

11:20 AM - 11:35 AM ***Lessons from Genomics and Health Disparities in Breast Cancer***

Melissa Davis, PhD

Morehouse School of Medicine

11:35 AM - 11:40 AM **Discussion**

Friday, October 27, 2023

Group Photo

11:40 AM - 11:50 AM

Location: Costa Del Sol Foyer

Lunch

11:50 AM - 12:40 PM

Location: Costa Del Sol Patio

12:40 PM - 12:50 PM Move to Session

Location: Costa Del Sol Ballroom

PANEL: State of Clinical Therapy for Advanced Prostate Cancer

12:50 PM - 1:35 PM

Moderator: Charles J. Ryan, MD

Prostate Cancer Foundation

Panelists:

Alok Tewari, MD, PhD (Dana-Farber Cancer Institute)

Ana Aparicio, MD (The University of Texas MD Anderson Cancer Center)

Angelo De Marzo, MD, PhD (The Johns Hopkins University School of Medicine)

Thomas Hope, MD (University of California, San Francisco)

David Jarrard, MD (University of Wisconsin)

Neha Vapiwala, MD (University of Pennsylvania)

Friday, October 27, 2023

SPECIAL LECTURE

1:40 PM - 1:55 PM

Pathways to Entrepreneurship

Robert Reiter, MD

University of California, Los Angeles

Introduced by Howard Soule, PhD

Prostate Cancer Foundation

1:55 PM - 2:00 PM

Discussion

Session 7: Progress in New Targets and Treatments for Prostate Cancer

2:00 PM - 4:00 PM

Moderator: Howard Soule, PhD

Prostate Cancer Foundation

2:00 PM - 2:15 PM

ENZap: A Randomised Phase II Trial using PSMA as a Therapeutic Agent and Imaging Biomarker in Men with Metastatic Castration-Resistant Prostate Cancer Treated with Enzalutamide (ANZUP 1901)

Louise Emmett, MD

St Vincent's Hospital Sydney, Australia

2:15 PM - 2:20 PM

Discussion

2:20 PM - 2:35 PM

GPC3 as a Novel Therapeutic Target of Prostate Cancer

Jiaoti Huang, MD, PhD

Duke University

2:35 PM - 2:40 PM

Discussion

2:40 PM - 2:55 PM

Targeting CD40 to Stimulate Anti-Tumor Immunity in Prostate Cancer

Matthew Dallos, MD

Memorial Sloan Kettering Cancer Center

2:55 PM - 3:00 PM

Discussion

3:00 PM - 3:15 PM

PSMAfore: Phase III trial of PSMA-617 Lu-177 in Taxane-Naïve mCRPC Patients

A. Oliver Sartor, MD

Mayo Clinic

3:15 PM - 3:20 PM

Discussion

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

Friday, October 27, 2023

- 3:20 PM - 3:35 PM ***Insights from B7-H3 Trials***
Eugene Shenderov, MD, DPhil
Johns Hopkins University (*N/A post-meeting for On Demand)
- 3:35 PM - 3:40 PM **Discussion**
- 3:40 PM - 3:55 PM ***Threading the Needle Between Efficacy and Toxicity with PSMAxCD28 T Cell Bispecific***
Sumit Subudhi, MD, PhD
The University of Texas MD Anderson Cancer Center
- 3:55 PM - 4:00 PM **Discussion** (*N/A post-meeting for On Demand)

Session 8: Prostate Cancer 3D Genomics

4:00 PM - 5:00 PM

Moderator: Ram Mani, PhD
UT Southwestern Medical Center

- 4:00 PM - 4:15 PM ***Prostate Cancer Transcriptomic Regulation by the Interplay of Germline Rsk Alleles, Somatic Mutations and 3D-Genomic Architecture***

Ram Mani, PhD
UT Southwestern Medical Center

- 4:15 PM - 4:20 PM **Discussion**

- 4:20 PM - 4:35 PM ***New Insights on the Three-Dimensional Genome of Metastatic Prostate Cancer***

Felix Feng, MD
University of California, San Francisco

- 4:35 PM - 4:40 PM **Discussion**

- 4:40 PM - 4:55 PM ***3D Epigenomics: Non-Coding but Functional Regions Linked to Prostate Cancer***

Suhn Rhie, PhD
University of Southern California (*N/A post-meeting for On Demand)

- 4:55 PM - 5:00 PM **Discussion**

5:00 PM - 7:00 PM Break

Friday, October 27, 2023

Dinner, Awards Ceremony, and Special Lecture

7:00 PM - 10:00 PM

Location: Costa Del Sol Ballroom

PCF Awards Ceremony

7:45 PM - 10:00 PM

2023 PCF Young Investigator Awards

2022 PCF TACTICAL Awards

2023 PCF TACTICAL Award

2022 PCF Challenge Awards

2023 PCF Challenge Awards

Saturday, October 28, 2023

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: Biology and Translational Applications of Tumor Extracellular Vesicles

7:00 AM - 8:00 AM

Moderator: Dolores Di Vizio, MD, PhD

Cedars-Sinai Medical Center

7:00 AM - 7:15 AM ***The Biology of Prostate Cancer-Derived Extracellular Vesicles***

Dolores Di Vizio, MD, PhD

Cedars-Sinai Medical Center

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

7:20 AM - 7:35 AM ***Prostate Cancer-Derived Extracellular Vesicles as Biomarkers***

Johan Skog, PhD

ExosomeDx, a Bio-Techne Brand

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

7:40 AM - 7:55 AM ***The Role of Tumor Extracellular Vesicles in Promoting Aggressive Cancer Behaviors***

Alissa Weaver, MD, PhD

Vanderbilt University School of Medicine

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

KEYNOTE ADDRESS

8:00 AM - 9:00 AM

Michael Milken

Founder and Chairman

Prostate Cancer Foundation

Introduced by Stuart Holden, MD

Prostate Cancer Foundation

Saturday, October 28, 2023

Group Photo

9:00 AM - 9:15 AM

Location: Costa Del Sol Foyer

Session 10: Updates from PCF TACTICAL Awards Teams

9:15 AM - 10:35 AM

Moderator: Howard Soule, PhD
Prostate Cancer Foundation

9:15 AM - 9:30 AM

Developing Engineered Cell Therapies for Metastatic Castrate-Resistant Prostate Cancer to Increase Efficacy and Decrease Toxicity

Carl June, MD
University of Pennsylvania

Saul Priceman, PhD
City of Hope

9:30 AM - 9:35 AM

Discussion

9:35 AM - 9:50 AM

Novel Theranostic Agents for Neuroendocrine Prostate Cancer

Jason Lewis, PhD
Memorial Sloan Kettering Cancer Center

9:50 AM - 9:55 AM

Discussion

9:55 AM - 10:10 AM

An Accelerated Platform using Lead-212 Targeted α -Particle Therapy to Radically Improve Cancer Lethality of Prostate Cancer Theranostics using Novel Targets and Better Understanding of Resistance: The Cancer Lethality Lead Collaboration

Michael Hofman, MBBS
Peter MacCallum Cancer Centre, Australia

10:10 AM - 10:15 AM

Discussion

10:15 AM - 10:30 AM

Tactical Approaches to Repress Oncogenic Gene Expression in Prostatic Tumors (TARGET)

Sarki Abdulkadir, MD, PhD
Northwestern University

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

10:30 AM - 10:35 AM

Discussion

Saturday, October 28, 2023

SPECIAL LECTURE

10:35 AM - 10:50 AM

**Novel Target Identification as a Bottleneck in Biotech Innovation:
Implications for Academic Entrepreneurs**

Ahmed Alkhateeb, PhD

Sanofi

*Introduced by Howard Soule, PhD
Prostate Cancer Foundation*

10:50 AM - 10:55 AM Discussion

**Session 11: Molecular Glues & Binding Inhibitors: Novel Small Molecule Cell Therapy
Platforms**

10:55 AM - 12:20 PM

Moderator: Marco Gottardis, PhD

Gottardisbiotech LLC

10:55 AM - 11:00 AM Introduction

Marco Gottardis, PhD

Gottardisbiotech LLC

11:00 AM - 11:15 AM *Drugging the Chromatin Regulatory System*

Steven Bellon, PhD

FOGHORN

11:15 AM - 11:20 AM Discussion

11:20 AM - 11:35 AM *A New Paradigm in Drugging Transcription Factors*

Robert Sims, PhD

FLARE

11:35 AM - 11:40 AM Discussion

**11:40 AM - 11:55 AM *Hold and Kill: RIPTAC™ Therapeutics Present a Novel Mechanism to
Conquer Prostate Cancer***

Kat Kayser-Bricker, PhD

Halda Therapeutics

11:55 AM - 12:00 PM Discussion

Saturday, October 28, 2023

12:00 PM - 12:15 PM ***Development of PROTAC[®] AR Degraders in Advanced Prostate Cancer***

Ron Peck, MD

Arvinas

12:15 PM - 12:20 PM **Discussion**

Closing Remarks

12:20 PM - 12:25 PM

Howard Soule, PhD

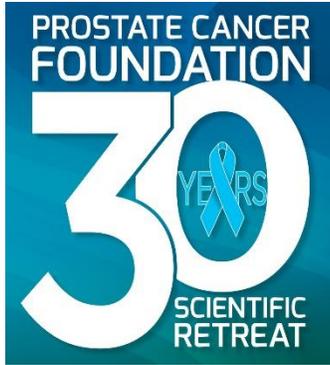
Prostate Cancer Foundation

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)

Francesca Demichelis, PhD (University of Trento, Italy)

Dolores Di Vizio, PhD (Cedars-Sinai Medical Center)

Thomas Fuchs, DSc (Icahn School of Medicine at Mount Sinai)

Marco Gottardis, PhD (Gottardisbiotech LLC)

David Goodrich, PhD (Roswell Park Comprehensive Cancer Center)

Matt Greenblatt, MD, PhD (Weill Cornell Medicine)

Vanessa Hayes, PhD (The University of Sydney, Australia)

Rakesh Heer, MBBS, PhD (Newcastle University, UK)

Salma Kaochar, PhD (Baylor College of Medicine)

Brandon Mahal, MD (University of Miami)

Ram Mani, PhD (UT Southwestern Medical Center)

Charles J. Ryan, MD (Prostate Cancer Foundation)

Alok Tewari, MD, PhD (Dana-Farber Cancer Institute)

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