

# STATE OF THE SCIENCE REPORT

Highlights from  
the 24<sup>th</sup> Annual PCF  
Scientific Retreat  
October 2017



Provided with the compliments of  
the Prostate Cancer Foundation



Prostate Cancer  
Foundation  
Curing Together.



# Table of Contents

---

<b>Introduction</b> .....	<b>4</b>
<b>Session 1</b> Cell Cycle Dysregulation: Implications for Progression, Plasticity, and Management .....	<b>6</b>
<b>Session 2</b> Precision Medicine and Targeted Therapies .....	<b>12</b>
<b>Session 3</b> 3D Genomics: The Interface of Genomics, Epigenetics, and Cancer Biology.....	<b>16</b>
<b>Session 4</b> Making Immunotherapy Work in Prostate Cancer .....	<b>22</b>
<b>Session 5</b> DNA Damage Repair .....	<b>32</b>
<b>Session 6</b> PSMA Imaging and Radioligand Therapy.....	<b>39</b>
<b>Session 7</b> Meeting Reports.....	<b>47</b>
<b>Session 8</b> Potential Applications of Artificial Intelligence in Prostate Cancer .....	<b>59</b>
<b>Session 9</b> Recent Advances in Genetically Engineered Mouse Models (GEMMs) of Lethal Prostate Cancer .....	<b>67</b>
<b>Session 10</b> New Platforms to Attack Undruggable Targets.....	<b>71</b>
<b>APPENDIX:</b> 24 <sup>th</sup> ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT PLENARY PROGRAM AGENDA .....	<b>82</b>



## Introduction

---

The 24th Annual Prostate Cancer Foundation (PCF) Scientific Retreat was held from October 5-7, 2017, at the Omni Shoreham Hotel in Washington, DC. The PCF Retreat is the foremost scientific conference in the world focusing on research advances in prostate cancer biology and treatment. Attendees comprise the world's leaders in basic, translational, and clinical research in prostate cancer and other biomedical fields, as well as world leaders in industry, technology, government, and business.

The Retreat is PCF's penultimate prostate cancer global knowledge exchange event held to bring together the brightest minds in science to discuss exciting new areas of research that have significant promise for advancing new treatments for prostate cancer. The historical impact of the Retreat is immeasurable as not only are attendees exposed to cutting-edge research, but also use the event to network and brainstorm new projects and partnerships. Retreat attendees have been involved in the development of almost every treatment advancement for prostate cancer since the Foundation's inception, and many of them trace critical origins of their work to attendance at a PCF Retreat.

The 24th Annual Scientific Retreat featured the following:

- 50 presentations in the Plenary Session including a panel discussion on the potential applications of artificial intelligence in prostate cancer
- 124 poster presentations
- 25 different scientific disciplines related to prostate cancer research presented and discussed
- 51% of speakers presented first-in-field, unpublished data at a PCF Scientific Retreat for the first time
- Attendance by 563 participants from 17 countries, including 226 PhDs, 199 MDs, 98 MD PhDs, 5 PharmDs, 1 DMD, 1 DO, and 1 DVM PhD.
- 110 academic institutions, 46 biopharmaceutical companies, 8 medical research foundations, and 7 other for-profit companies
- NIH, NCI, Dept. of Defense, and Veterans Affairs research leaders
- Attendance by 155 PCF Young Investigators
- Attendance by 12 PCF Board of Director members and major donors, and 15 special guests including 1 Cabinet Secretary

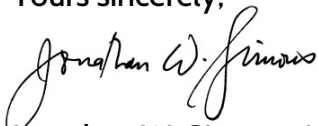
The PCF "Global Research Enterprise" currently extends to 19 countries and funds a robust research portfolio. Since 1993, PCF has awarded more than \$460 million in innovative

prostate cancer research projects, led by over 2,000 prostate cancer researchers. This includes \$46 million awarded to 226 PCF Young Investigators since 2007 and nearly \$174 million to PCF Challenge Award teams since 2008.

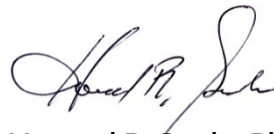
We thank the sponsors of the Retreat for their generous support: Sanofi Genzyme, Janssen Oncology, Bayer, Clovis Oncology, Amgen, Pfizer Oncology, Astellas, Bristol-Myers Squibb, Dendreon, Genentech, AstraZeneca, and Bavarian Nordic.

The 2017 State of Science Report was prepared by the Prostate Cancer Foundation to summarize the scientific presentations given at the Retreat for consumption by the scientific community, the public, and other interested stakeholders throughout the global community. We hope that this Report improves understanding of the current state of prostate cancer research, encourages discourse and the exchange of new ideas and information, inspires new patient-centric research, and stimulates increased support for scientific research. Please contact Dr. Andrea Miyahira at [amiyahira@pcf.org](mailto:amiyahira@pcf.org) if you have any questions about this Report.

Yours sincerely,



Jonathan W. Simons, MD  
President & CEO



Howard R. Soule, PhD  
Executive Vice President  
Chief Science Officer



# Session 1: Cell Cycle Dysregulation: Implications for Progression, Plasticity, and Management

---

## *Linking RB/p53 Dysfunction to Prostate Cancer Plasticity and Anti-Androgen Resistance*

David Goodrich, PhD  
Roswell Park Cancer Institute

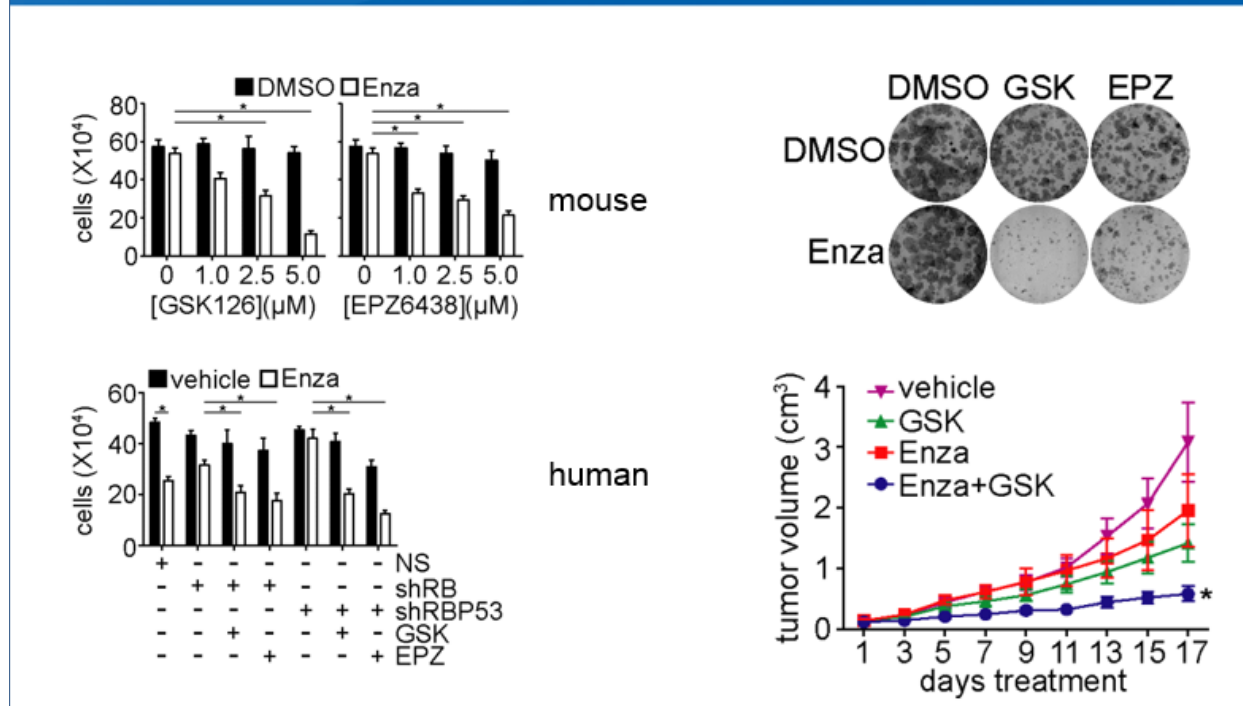
- Androgen deprivation therapy (ADT) is the primary treatment for high-risk, recurrent, or metastatic prostate cancer. ADT acts by dampening the synthesis of androgens, which activate the androgen receptor (AR), the primary regulator of growth and survival for prostate cancer cells.
- When tumors develop resistance to ADT and progress, they are referred to as castrate-resistant prostate cancer (CRPC). CRPC is often still driven by AR activity and might be sensitive to treatment with next generation AR-targeted therapies such as enzalutamide and abiraterone acetate.
- Other forms of CRPC are AR-independent, and instead arise through hijacking signaling systems that substitute for AR, or by taking on characteristics of cell types that do not rely on AR for survival and growth.
- Dr. David Goodrich discussed investigations concerning the development of androgen indifferent prostate cancer (AIPC), a form of CRPC that does not express or rely on AR and exhibits a neuroendocrine or small cell carcinoma phenotype.
- AIPC can be characterized by specific mutations including deletion or mutation of the RB and p53 tumor suppressor genes, and gain of additional copies of the MYC-N and AURKA oncogenes.
- Loss of the RB gene occurs very rarely in primary prostate cancer (1%), more frequently in metastatic prostate cancer (8-28%), and very frequently in AIPC (40-90%). This suggests that RB-loss is a minor contributor in the development of primary prostate cancer, but may drive the development of resistance to AR-targeted therapy and the development of AIPC.
- Dr. Goodrich and team developed genetically engineered mouse models to investigate the role of RB-loss in the development and progression of prostate cancer.
- Deletion of the PTEN tumor suppressor gene is a common mutation that occurs in prostate cancer during disease progression.
- Dr. Goodrich compared animal models of prostate cancer with PTEN-loss alone versus PTEN-loss and RB-loss. Loss of PTEN alone led to the development of invasive prostate cancer which rarely metastasized. However, when RB was also deleted, resulting prostatic tumors were aggressive, the animals developed metastatic disease, and death from disease was accelerated.



- Prostate cancer with PTEN-loss alone expressed AR and markers of luminal prostate cells. When RB was also deleted, tumors lost expression of AR and began expressing synaptophysin, a marker of neuroendocrine cells, suggesting they had de-differentiated into an alternate cell type.
- RB-loss also accelerated the development of CRPC following treatment with ADT.
- Progression of prostate tumors with both PTEN and RB-loss to CRPC coincided with spontaneous loss or mutation of the tumor suppressor gene p53. Like RB-loss, p53-alterations are primarily observed in advanced prostate cancer and rarely in earlier stages of disease. These data suggest that p53-loss cooperates with loss of PTEN and RB to drive resistance to ADT and the development of CRPC.
- To confirm a role for p53 mutations in driving ADT-resistance, animal models of prostate cancer with PTEN-loss + RB-loss + p53-loss were engineered. These tumors were resistant to ADT.
- When PTEN/RB/p53-deleted tumors were removed from the animals and grown in specialized laboratory conditions that enable cells to grow in tumor-like arrangements (a system referred to as tumor organoids or tumoroids), the cellular phenotype reverted to that of prostate-like cells, with expression of AR but not synaptophysin. If the organoids were transplanted back into mice, the tumors regained a neuroendocrine phenotype.
- Together these studies demonstrate that RB-loss in PTEN-deficient tumors drives prostate cancer metastasis and facilitates differentiation into alternate cell types, and that loss of PTEN, RB and p53 cooperate to drive AIPC.
- These experiments highlight the plastic nature of these tumors and suggest that the AIPC phenotype is driven by mutations, as well as by epigenetic factors. Epigenetic factors regulate the structure of DNA to control which genes a cell can express and are a primary mechanism governing what identity a cell can take on.
- Consistent with this hypothesis, epigenetic regulators, cellular reprogramming factors, and neuroendocrine genes were found to be highly upregulated in human AIPC samples and mouse AIPC tumor models compared with non-AIPC tumors. These genes included the epigenetic regulator EZH2, and the stem cell regulator SOX2.
- SOX2 levels were also increased in clinical samples with p53 and RB mutations, and in human prostate cancer cell lines in which RB and p53 were deleted.
- These studies suggest that AIPC transformation may be reversed by targeting epigenetic regulators. Indeed, targeting the epigenetic regulator EZH2 in PTEN/RB/p53-loss prostate cancer models reversed the AIPC phenotype and restored sensitivity to AR-targeted therapy.
- Collectively, these studies identify multiple critical drivers and potential therapeutic targets for AIPC, one of the most aggressive forms of lethal prostate cancer.



## EZH2 inhibition reverses antiandrogen resistance



**Figure:** Treatment of PTEN/RB/p53-loss prostate cancer models with EZH2-inhibitors (GSK126, EPZ6438) restored sensitivity to enzalutamide (Enza). Source: Ku et al., *Science*, 2017 Jan 6, 355(6320):78-83.

### CDK4/6 Inhibitors: Learning from Experiences in Breast Cancer, Other Solid Tumors, and Hematologic Malignancies

Geoffrey Shapiro, MD, PhD  
Harvard: Dana-Farber Cancer Institute

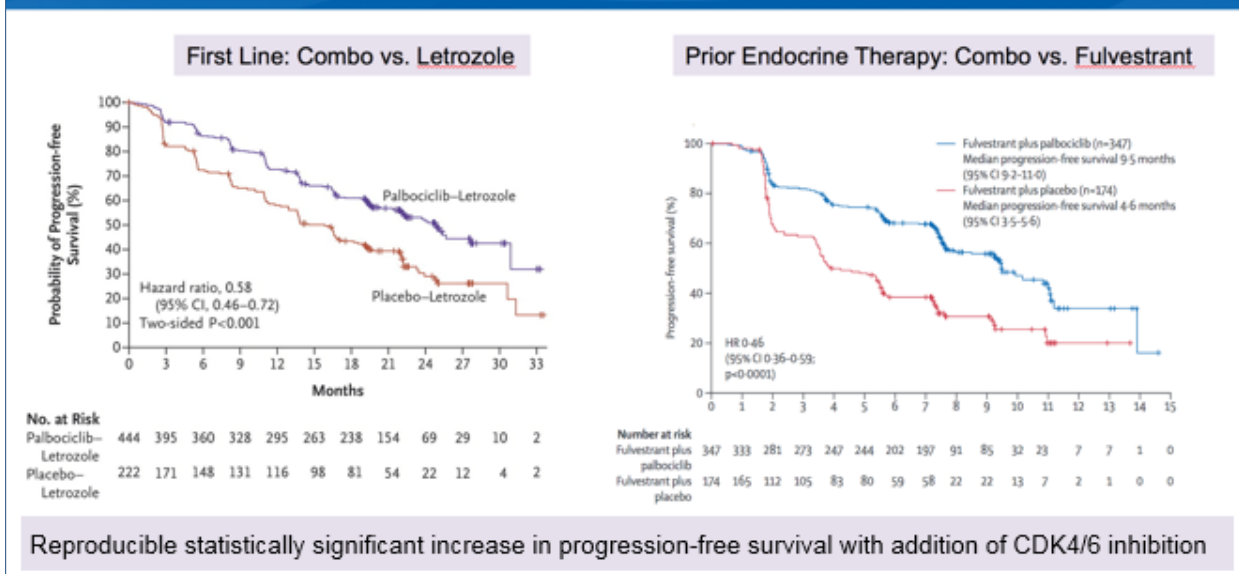
- CDK4 and CDK6 are proteins involved in promoting cell growth by forcing cell cycle progression. CDK4/6 act by reducing the activity of RB, a protein that suppresses cell division and is a critical tumor suppressor gene. Dysregulation of the CDK4/6 pathway drives cancer cell growth.
- Three CDK4/6-inhibitors have been FDA-approved for the treatment of hormone receptor-positive breast cancer: palbociclib, ribociclib, and abemaciclib. These treatments have similar mechanisms of action but differ in side effect profiles.
- CDK4/6-inhibitors are being tested in clinical trials for the treatment of other cancer types including prostate cancer.
- Dr. Geoffrey Shapiro discussed lessons learned from using CDK4/6-inhibitors to treat breast cancer, other solid tumors, and hematologic malignancies.

- Treatment with CDK4/6-inhibitors can result in either cancer cell death or senescence, a state in which cells do not divide or have much metabolic activity. CDK4/6-inhibitors also have effects on immune cell activity.
- In most cancer cells, CDK4/6-inhibitors cause a temporary state of cell cycle “arrest” where cells temporarily do not divide. Only a subset of cells within a tumor will enter a state of “deep senescence,” a more permanent state of inactivity.
- Whether cancer cells treated with CDK4/6-inhibitors enter transient arrest versus deep senescence was found to depend on the activity of the MDM2 protein. MDM2 degrades senescence-activating proteins, while CDK4/6-inhibitors cause degradation of MDM2 to drive cells into deep senescence. However, in some cells, MDM2 evades degradation caused by CDK4/6-inhibitors, limiting their efficacy.
- Benefit from palbociclib treatment of patients with liposarcoma correlated with a subsequent reduction in levels of MDM2. Biomarkers that inform of a reduction in MDM2 will help to more precisely select patients for treatment with CDK4/6-inhibitors.
- CDK4/6-inhibitors are also effective against certain leukemias in preclinical models, including T cell acute lymphoblastic leukemia (T-ALL).
- In leukemia cells, CDK6 drives the production of antioxidants, while CDK6-inhibitors reduce antioxidant levels and increase levels of toxic reactive oxygen molecules that cause cell death.
- CDK4/6-inhibitors may also favorably affect anti-tumor immune cell activities. Tumor cells treated with CDK4/6-inhibitors upregulate expression of endogenous viral genes that are encoded in the human genome, triggering anti-viral immune responses that target the tumor.
- CDK4/6-inhibitors also reduce the number of negative regulatory T cells, which block the activity of tumor-killing T cells.
- In animal models of breast cancer, CDK4/6-inhibitors have demonstrated synergy with immune checkpoint blockade which is leading to clinical trials testing these combinations in patients.
- CDK4/6 inhibitors are being tested in clinical trials in combination with various other treatments.
- In breast cancer, estrogen signaling is tightly linked to CDK4/6 activity, which has led to clinical trials testing hormonal therapy (letrozole or fulvestrant) combined with CDK4/6-inhibitors.
- Trials testing letrozole +/- palbociclib as a first line therapy and fulvestrant +/- palbociclib in patients with prior endocrine therapy found that the addition of palbociclib resulted in a significant increase in progression-free survival (Figure). Similar data are available for ribociclib and abemaciclib.
- Based on these trials, hormonal therapy + CDK4/6-inhibitor combinations are now standard of care for the treatment of ER-positive breast cancer.
- After initial treatment with palbociclib and letrozole, an ongoing trial is testing fulvestrant alone vs. fulvestrant + palbociclib vs. fulvestrant + palbociclib + avelumab (an immune

checkpoint inhibitor). This trial will help determine whether continuing palbociclib with second-line hormonal treatment is useful and will also address whether combining palbociclib with an immune checkpoint inhibitor is beneficial.

- Because mutations that hyper-activate the tumor-promoting PI3K pathway are common in breast cancer, ongoing trials are testing the combination of hormonal treatment (letrozole or fulvestrant), palbociclib, and PI3K-inhibitors.
- In addition, CDK4/6-inhibitors are also being tested in combination with MEK inhibitors in tumors with RAS pathway mutations. Promising results have been seen for these combinations in clinical trials in RAS-mutant melanoma and non-small cell lung cancer.
- As CDK4/6-inhibitors become more widely used, it will be critical to identify patients who will respond as well as understand mechanisms of treatment resistance.
- Identification of biomarkers that can predict who will benefit from CDK4/6 treatment is critical.
- Trials have found that CCND1 gene amplification and CDKN2A gene loss were not predictive of breast cancer patients who benefited from treatment with palbociclib.
- Because CDK4/6-inhibitors work by releasing repression of the tumor suppressor gene RB, loss of RB may be a biomarker of resistance to CDK4/6-inhibitors.
- Cells can also develop resistance to CDK4/6-inhibitors by activating an alternate pathway of cell growth through mutations that activate or amplify the CDK2 or CCNE1 (cyclin E) genes.
- CDK6 gene amplification can also occur as a mechanism of resistance to CDK4/6-inhibitors.
- Biomarkers are being developed to examine CDK4/6 activity in blood from patients as a way to monitor effects of treatment with CDK4/6-inhibitors.
- Overall, these studies highlight mechanisms by which CDK4/6-inhibitors exert their effects in breast and other cancers, promising treatment combinations, and mechanisms of treatment resistance. These understandings will help to accelerate the effective use of these treatments in prostate cancer.

# Combinatorial Approaches: Hormonal Combinations in ER+ Breast Cancer



**Figure:** Breast cancer trials testing letrozole +/- palbociclib as a first line therapy (left) and fulvestrant +/- palbociclib (right) in patients with prior endocrine therapy both found that progression-free survival was nearly doubled with addition of CDK4/6-inhibitors. These treatments are now standard of care in ER-positive breast cancer. Sources: Finn et al., *New Engl J Med*, 2016 Nov 17, 375(20):1925-1936; Turner et al. *New Engl J Med*, 2015; 373:209-219.

## Session 2: Precision Medicine and Targeted Therapies

---

### *Special Lecture: Defining the Actionable Genome*

David Solit, MD

Memorial Sloan Kettering Cancer Center

- Precision medicine is a relatively new approach in oncology in which treatments are selected on an individualized basis based on the unique genomic alterations discovered in a patient's tumor.
- Identifying the genomic alterations that drive development and progression of cancer is critical for facilitating precision medicine advancements.
- Several precision therapies are indicated for prostate cancer.
- Two to five percent of patients with advanced prostate cancer have tumors with microsatellite instability (MSI) or mutations in MMR genes, which make them candidates for treatment with the checkpoint immunotherapy pembrolizumab. The FDA recently approved pembrolizumab for the treatment of all malignancies possessing MSI/MMR alterations.
- 25-30% of metastatic prostate cancers have mutations in DNA damage repair (DDR) gene mutations such as BRCA1/2, and such tumors are more likely sensitive to treatment with PARP-inhibitors or platinum chemotherapy. Multiple PARP inhibitors are being tested in registrational clinical trials for various clinical states of prostate cancer.
- MMR, DDR and other tumor mutations may have been inherited by the patient which necessitates not only assessment of patient tumors for these mutations, but also the patient's normal/germline DNA. Identification of these mutations in the germline would indicate the need to consider genetic screening in family members.
- Because of these findings, Dr. Solit's group and others now recommended that all patients with advanced prostate cancer be screened for tumor and germline mutations in MMR and DDR genes.
- Until recently, sequencing of tumors to identify mutations had been viewed as standard care for select solid tumors, including lung, colorectal, melanoma, and gastrointestinal stromal tumors, but not prostate cancer.
- Dr. Solit discussed the Molecular Oncology Profiling Initiative at Memorial Sloan Kettering Cancer Center (MSKCC). This program aims to define the molecular driver mutation in every patient and identify germline mutations that increase heritable risk for cancer, in order to accelerate the development and validation of new precision medicine cancer treatments.
- The program uses MSK-IMPACT, a recently FDA-authorized test that sequences DNA from tumors for mutations in 468 cancer-related genes. Patients can also consent to have their whole genomes, exomes, or transcriptomes sequenced for discovery studies.
- Patients enrolled in this program can opt-in to be informed if they carry pathogenic germline mutations in 88 genes.

- To date, mutations in tumors from over 23,000 patients have been assessed by MSK-IMPACT including over 1,300 advanced prostate cancer patients.
- All of this data is being made available to the research community through the AACR GENIE program.
- The MSK-IMPACT program is coupled to a number of precision medicine clinical trials which patients may be enrolled into if they carry mutations that predict response to the experimental treatment.
- “Basket” trials, which select patients based on biomarkers such as particular genomic mutations instead of anatomical tumor type, can be more efficient than conducting separate trials testing the treatment in individual malignancies. MSK-IMPACT has accelerated patient enrollment into basket trials that otherwise may not have accrued enough patients to be completed.
- One basket trial is testing the efficacy of the HER2/3-inhibitor neratinib in solid tumors with HER2 or HER3 mutations. HER2/3 mutations are found in many types of cancer, but typically in fewer than 5% of patients. Some breast cancer patients are classified as HER2-normal based on standard-of-care HER2 tests that examine protein levels of gene amplification, but actually have HER2 mutations which affect the protein’s activity. An example of such a patient was presented who had a complete response to neratinib. This example highlights how prospective molecular characterization of tumors can accelerate the testing of new targeted drugs in a defined molecular genotype. Such patients often have no other effective treatment options.
- Mutations in the ERCC2 gene in bladder cancer have been found to predict for sensitivity to neoadjuvant chemotherapy. A clinical trial will test bladder-sparing surgery versus radical cystectomy after neoadjuvant chemotherapy in bladder cancer patients with ERCC2 mutations.
- MSK-IMPACT is being expanded and improved on by the addition of more genes and non-coding regions, viral probes to identify tumors driven by virus infections (such as EBV and HPV), and to improve our ability to identify tumor features such as microsatellite instability (MSI) and whether both copies of a gene are mutated or lost.
- Mutations in MMR genes result in a very high level of tumor mutations and microsatellite instability (MSI). Tumors with MMR gene mutations and MSI are more likely to respond to treatment with checkpoint immunotherapy.
- A patient with metastatic CRPC found to have MSI was enrolled in a clinical trial testing the checkpoint inhibitor atezolizumab plus the investigational agent GDC-0919. This patient had a complete and durable response (Figure).
- MSI is detected by sequencing genomic regions that are unstable when the cell has MMR mutations. Typical MSI tests assess 5-7 hotspots which may result in missing patients with MSI in other regions. MSKCC uses an algorithm called MSI-Sensor which examines 1,000 MSI regions to better identify patients with MSI. Integration of these test results with genomic sequencing data from MSK-IMPACT can further refine identification of patients with MSI and MMR mutations.
- “Clonal hematopoiesis” is a common phenomenon in older individuals in which a large fraction of normal immune cells acquire mutations that are common in patients with

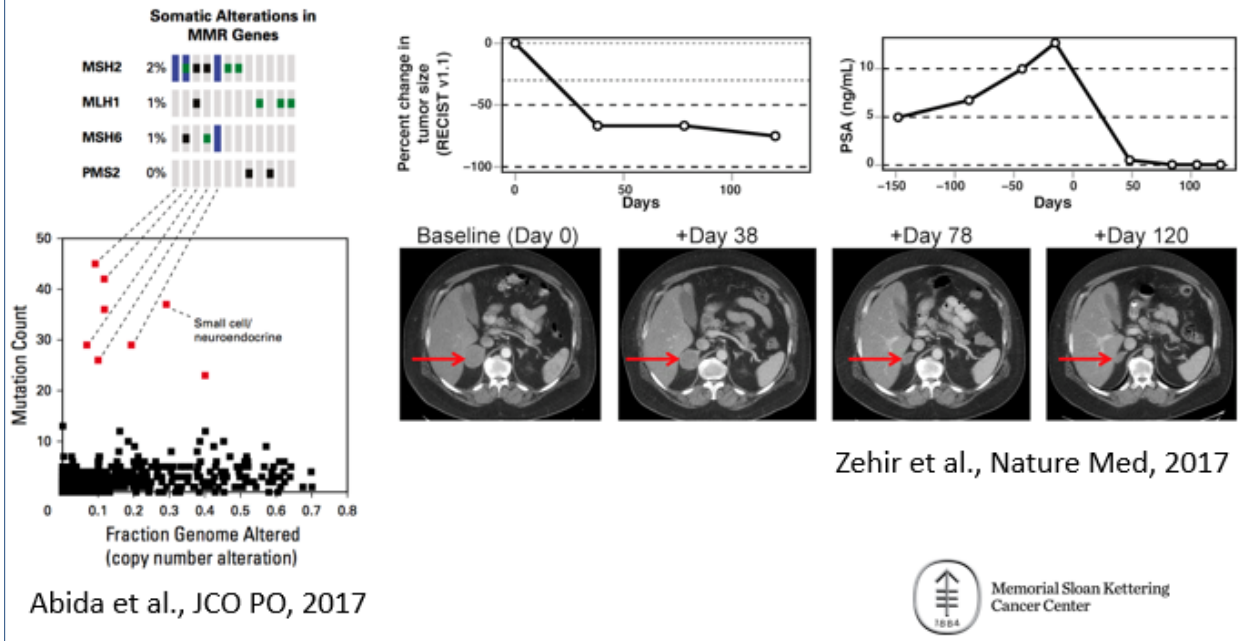
leukemia. If not accounted for as “normal,” these mutations could be confused with tumor cell mutations because immune cells are present in tumor and blood samples used for precision medicine tests. MSK-IMPACT is being enhanced to improve identification of “normal” versus tumor cell mutations.

- As part of the MSK-IMPACT program, patient germline DNA is being assessed for inherited cancer-causing mutations. Thus far, 16% of 3,400 assessed cancer patients have been found to carry mutations in the germline DNA that are associated with increased heritable cancer risk.
- MSK-IMPACT studies discovered that 27% of advanced prostate cancer patients had tumors with mutations in DDR genes. BRCA1/2 mutations were found to occur early in tumor development and were associated with higher grade and more aggressive disease.
- 19% of advanced prostate cancer patient tumors possessed germline DDR mutations. Half of these patients did not have a family history that would have triggered testing for inherited tumor mutations based upon current clinical criteria.
- In a subset of patients with no tumor mutations in the 468 gene MSK-IMPACT panel, whole exome sequencing is performed to identify new cancer drivers.
- Other specialized sequencing tests can be performed if MSK-IMPACT and whole exome sequencing do not identify cancer driver mutations. For instance, a gene-fusion assay was used to identify an ETV6-NTRK3 gene fusion in a patient with widely metastatic melanoma. This patient was enrolled into a basket clinical trial for the TRK-inhibitor LOXO-101, and experienced a complete response.
- Circulating tumor DNA (ctDNA) is DNA released from dying tumor cells into the bloodstream. ctDNA can be collected from a blood draw and used for tumor mutational profiling. MSK is working to optimize the use of ctDNA for precision medicine so that future patients may avoid undergoing invasive tissue biopsies.
- MSKCC is also creating programs to make the MSK-IMPACT test available to patients outside of MSKCC. The IMPACTED study has a goal of helping to end racial disparities and is offering free MSK-IMPACT testing to patients at Queens County Hospital (Queens, NY), Kings County Hospital (Brooklyn, NY) and the Ralph Lauren Center in Harlem, NY. The Make-an-IMPACT study offers free MSK-IMPACT testing to patients anywhere in the world with certain rare cancer types. These patients can then be offered precision treatments for their cancer.
- Overall, the MSK-IMPACT program has demonstrated that finding actionable tumor mutations can directly alter a patient’s treatment by identifying standard and investigational agents most likely to be effective based upon the patient’s individual tumor and germline genetic profiles.
- Given the increasing number of tumor types including prostate cancer in which tumor genetic testing is now being used to guide treatment selection, it is predicted that tumor genomic sequencing will be a standard care for all cancer patients in the near future.



# Benefit to immunotherapy in prostate cancer

Patient treated with GDC-0919 and atezolizumab (anti-PD-L1)



**Figure:** Genomic sequencing was used to identify prostate cancers with mutations in MMR genes (MSH2, MLH1, MSH6, PMS2), which result in a very high level of mutations (left top and bottom panels). Right panels: A patient with advanced metastatic CRPC found to have MMR mutations using the MSK-IMPACT test was enrolled in a clinical trial testing the checkpoint inhibitor atezolizumab plus GDC-0919. The patient went on to have a complete and durable response. Sources: Abida et al., *JCO Precis Oncol*, 2017 Jul; Zehir et al., *Nature Med*, 2017 Jun, 23(6):703-713.

## Session 3: 3D Genomics: The Interface of Genomics, Epigenetics, and Cancer Biology

---

### *3D Genome Organization & Transcription Regulation in Cancer Cells*

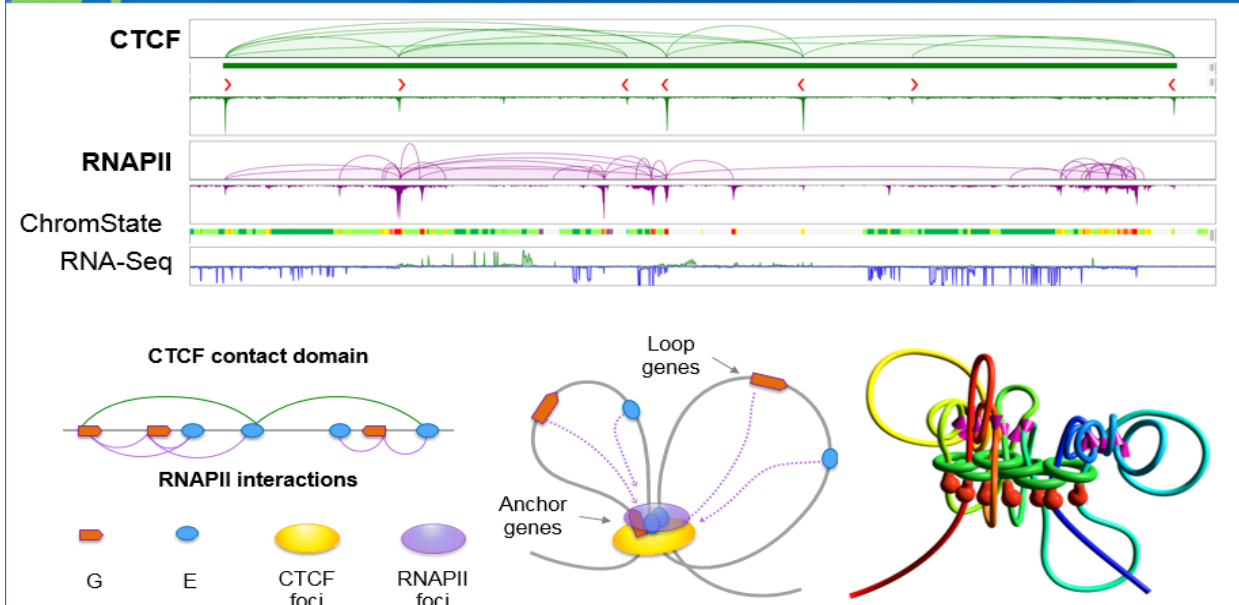
Yijun Ruan, PhD

The Jackson Laboratory for Genomic Medicine

- Large scale genomic alterations are hallmarks of cancer. Much of the mechanism is still unknown about how various mutations including large scale genomic rearrangements arise in cancer cells and their impact on cancer biology.
- Dr. Yijun Ruan discussed an emerging area of study in cancer biology – how 3D genome organization in cancer cells affects expression of genes and the development and progression of cancer.
- Alterations in genome organization have been associated with a number of pathologies including cancer, premature aging syndromes, and laminopathies.
- The relationship between alterations in the genome at the 3D level, alterations at the individual nucleotide level, and epigenetic alterations (which affect the genes that are expressed but not the DNA sequence), are also not yet understood.
- Various 3D genome visualization and mapping technologies have been developed. Older technologies are low-resolution and do not allow visualization of the genome at the individual gene level.
- In 2009, two methods were developed to map 3D genome organization: ChIA-PET and Hi-C.
- Hi-C creates a high-level view of the 3D organization of the genome.
- ChIA-PET maps areas of the genome that are brought into close 3D proximity by specific proteins of interest.
- Dr. Ruan discussed the use of ChIA-PET to map the 3D genome in normal and cancer cells.
- Chromatin is a basic level of 3D genome organization which enables DNA to be arranged in a highly organized configuration. In chromatin, DNA is wrapped around complexes of histone, architecture proteins, and transcription factors. These packages determine if a stretch of DNA is to be active or repressed for gene transcription.
- ChIA-PET maps were created to relate chromatin structure to which genes are being transcribed into RNA.
- To examine chromatin arrangement in 3D, the chromatin organization protein CTCF was used for ChIA-PET mapping (Figure). To examine the 3D genome in relationship to which genes are being transcribed into RNA, the main enzyme that transcribes DNA into RNA, RNA polymerase II (RNAPII) was used (Figure).

- When the two datasets were analyzed together, it became apparent that regions in the DNA bound by CTCF may function as docking sites for RNAPII (Figure).
- These 3D genome maps demonstrated that certain genes encoded in different regions of DNA are brought into close proximity during gene transcription. This likely enables cells to transcribe multiple genes together as part of a coordinated program.
- 3D maps can also be created to look at “enhancer-promoter” interactions. Enhancers are segments of DNA that may or may not be near a gene, but function to promote transcription of that gene. Promoters are the DNA sequences immediately in front of a gene that control gene transcription. Transcription factors are proteins that bind to promoter or enhancer regions of specific genes to regulate transcription.
- A major transcription factor that drives breast cancer is the estrogen receptor (ER). Enhancer-promoter interactions in breast cancer cells were examined by creating 3D genome maps using RNAPII and ER. These studies helped to reveal the areas of the genome that ER interacts with in order to drive breast cancer.
- Leukemia can be driven by mutations that fuse two transcription factors into a single protein.
- ChIA-PET was performed to gain insights into how the leukemia fusion gene PML-RARA alters the 3D genome of leukemia cells. PML-RARA fusions were found to cause the 3D genome structure in leukemia cells to collapse, contributing to a different program of genes being expressed.
- Overall, these studies demonstrate that the 3D structure of the genome plays a role in regulating which genes can be expressed by a cell. Changes in the 3D genome in cancer cells enable a different set of genes to be expressed, which likely plays a role in driving cancer growth and progression.
- These studies provide insight into how a normal genome becomes a cancer genome.

## Relate chromatin structure to transcription function



**Figure:** The relationship between chromatin structure and gene expression was assessed by performing ChIA-PET mapping using the chromatin organization protein CTCF (top), and RNAPII, the main enzyme that transcribes DNA into RNA (middle). Data was used to reconstruct 3D genome maps (bottom) depicting regions of DNA brought into close proximity by these proteins, which suggest that regions in the DNA bound by CTCF may function as docking sites for RNAPII. Source: Tang et al., *Cell*, 2015 Dec 17, 163(7):1611-27.

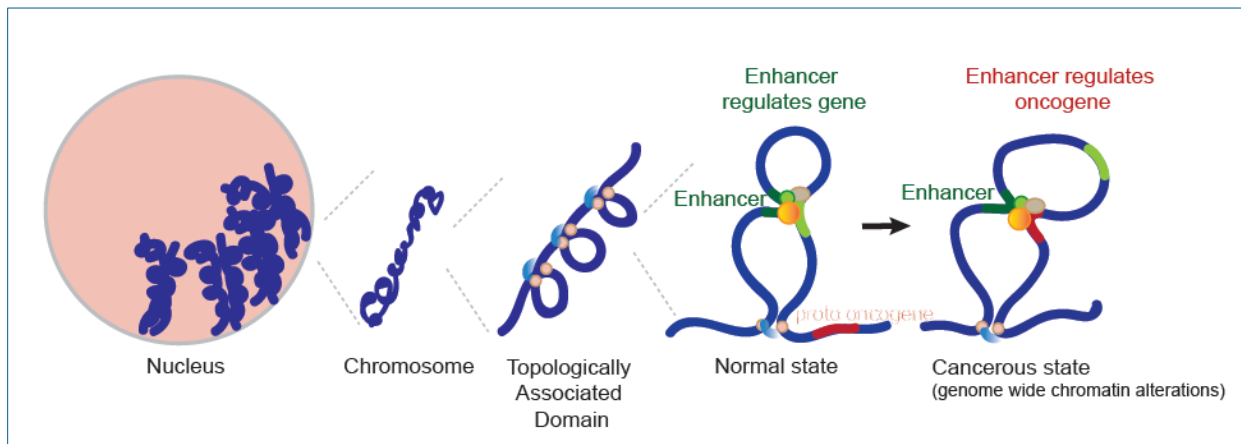
### *Enhancer Mediated Transcriptional Dysregulation in Prostate Cancer*

Ram Mani, PhD

The University of Texas Southwestern Medical Center

- It is increasingly clear that the 3D organization of the genome plays a large role in determining which genes are expressed and which are not. Understanding how changes in the 3D structure of the genome drives cancer may enable the identification of new treatment strategies.
- In recent years, new technologies have been developed to examine the 3D organization of the genome, including Chromatin Interaction Analysis by Paired-End Tag Sequencing (ChIA-PET) and Hi-C.
- ChIA-PET is a technique to map where a protein of interest interacts with the genome in 3D. Hi-C creates a high-level map of how the genome is arranged in 3D.

- Dr. Ram Mani discussed integrating ChIA-PET with other types of genomic data to understand how the 3D genome of prostate cancer cells regulates which genes are expressed.
- ChIA-PET was performed to identify where RNA polymerase II (RNAPII, the main enzyme that transcribes DNA into RNA), binds and interacts in the genome. These data were overlaid with gene expression and Hi-C data.
- This study found that domains in the genome that are involved in many 3D interactions could be divided into regions of low gene expression vs. regions of high gene expression.
- These data were overlaid with data indicating the locations of gene regulatory regions including promoters and enhancers.
- Using these methods, Dr. Mani developed 3D maps of gene expression in prostate cancer cells. The regions of DNA involved in 3D interactions were found to vary significantly in different prostate cancer cell lines.
- MYC and EZH2 are genes that drive prostate cancer and many other cancer types. Examination of 3D genome maps from several prostate cancer cells lines revealed that expression of MYC and EZH2 were uniquely regulated in each cell line.
- Overall, these studies suggest that the genome is partitioned into different 3D “neighborhoods,” that regulate which genes are expressed, and how different genes are expressed coordinately (Figure).
- Alterations in the arrangement of these neighborhoods affect 3D interactions between gene regulatory regions and likely play an important role in cancer progression (Figure).
- These studies provide new insights into how gene expression in cancer cells is controlled by alterations in the 3D arrangement of the genome.



**Figure:** Proposed model for transcriptional regulation in Topologically Associated Domains (TADs). During cancer development, the architecture of TADs gets altered, resulting in up-regulation of oncogenes by tissue specific enhancers.

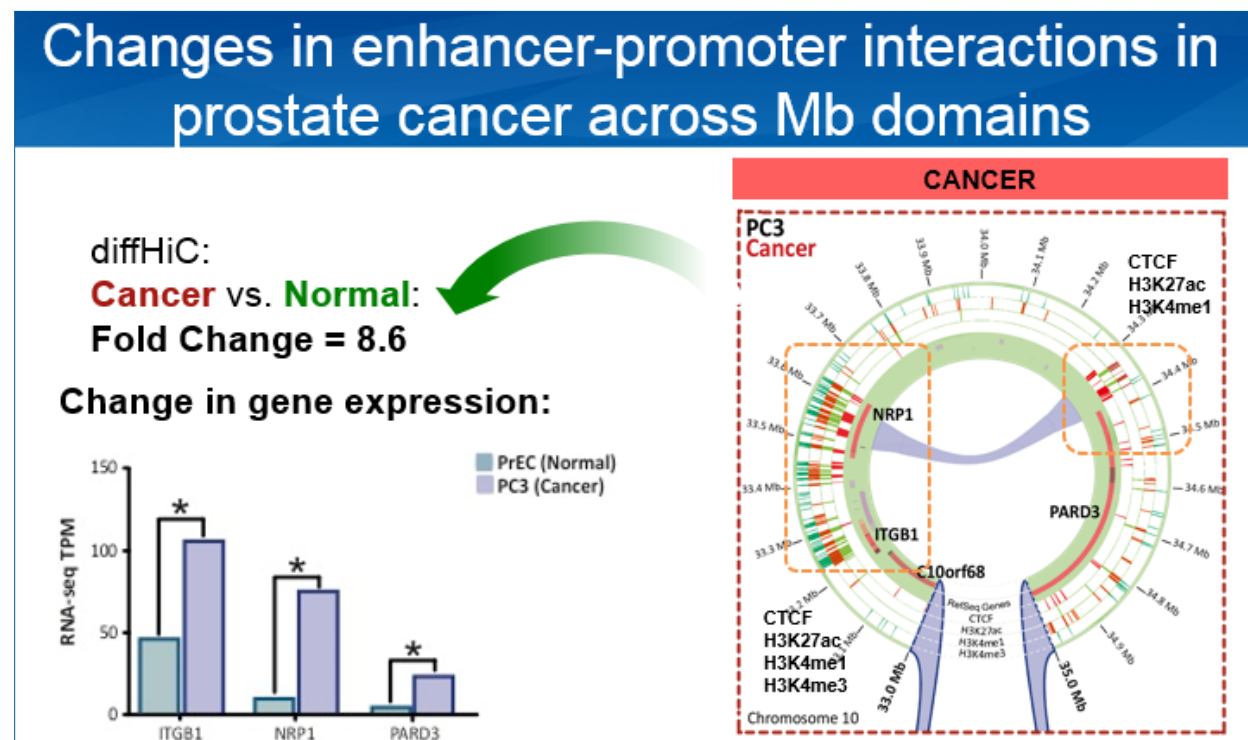
## *Three-Dimensional Genetic and Epigenetic Disorganization of the Prostate Cancer Genome*

Susan Clark, PhD

Garvan Institute of Medical Research, Australia

- Gene expression is a tightly regulated cellular script that is controlled at many levels including by the 3D organization of the genome.
- 3D genome organization in turn, is controlled by many factors. One of these is “epigenetic” regulation, in which chemical marks are attached to different areas of the genome to promote or prevent other regulators from interacting with DNA and activating gene expression.
- Understanding how epigenetic alterations affect 3D genome organization and impact cancer cells will improve our understanding of prostate cancer biology and lead to new treatment strategies.
- Dr. Susan Clark discussed epigenetic and 3D genome alterations in prostate cancer.
- Compared with normal cells, prostate cancer cells were found to have large genomic regions containing multiple genes that were abnormally turned on or off by epigenetic regulators.
- One of these regions includes the KLK locus, the genomic region which encodes the family of KLK genes. The KLK locus was found to be divided into abnormally activated and silenced regions in prostate cancer cells, compared with normal cells.
- PSA, a well-known biomarker of prostate cancer, is a KLK gene (KLK3), and was found to be in the active region of the KLK locus in prostate cancer cells.
- To determine whether the 3D genome and epigenome are altered in prostate cancer, experiments were performed to map gene expression, 3D genome structure, and the locations of epigenetic regulators in the genome.
- For a gene to be expressed, the genome must take on a 3D conformation that brings “enhancers,” which are important control regions of a gene that could be located anywhere in the genome, into close physical contact with “promoters,” which are the gene start sites that control the turning on of a gene.
- Over 3,000 alterations in promoter-enhancer interactions were identified in prostate cancer cells compared with normal cells. These interactions were highly associated with which genes were and were not expressed.
- A novel bioinformatics method was developed to identify new promoter-enhancer interactions occurring in prostate cancer cells. Several new promoter-enhancer interactions were identified that resulted in activation of the affected gene, as well as nearby genes (Figure). Prostate cancer cells were also found to have lost a number of normal promoter-enhancer interactions, which resulted in abnormal gene repression.

- The genome is segmented into large 3D “topological associated domains” (TADs) consisting of ~1 million DNA bases with definite boundaries maintained by architectural proteins. This organization is conserved across many cell types and plays a role in restricting interactions between faraway regions of the genome and improving control of gene expression. Whether TADs are altered in cancer cells is unclear.
- Compared with normal cells, prostate cancer cells were found to have new, smaller, and abnormal TADs. The locations of TAD boundaries were also altered but still depended on the same CTCF architectural protein as in normal cells.
- ~70% of altered TADs in prostate cancer cells were found to be driven by mutations that deleted or inserted large genomic regions.
- Dr. Clark’s studies also found that changes in the epigenome resulted in changes in the timing of cell replication events in prostate cancer cells. Such changes may cause cancer cell genomes to be less stable and more likely to acquire additional mutations.
- Overall, these studies demonstrate that the 3D structure of the genome plays a large role in regulating gene expression in cancer cells, and identifies some of the ways in which the 3D genome is regulated, as well as how dysregulation may drive cancer cell growth and the acquisition of new mutations.



**Figure:** 3D genome mapping in prostate cancer cells identified novel promoter-enhancer interactions between the PARD3 and NRP1 genes, resulting in upregulation of PARD3, NRP1, and nearby gene ITGB1 in prostate cancer cells (PC3) compared to normal cells (PrEC). Source: Taberlay\* and Achinger-Kawecka\* et al., *Genome Res*, 2016 Jun, 26(6):719-31.



## Session 4: Making Immunotherapy Work in Prostate Cancer

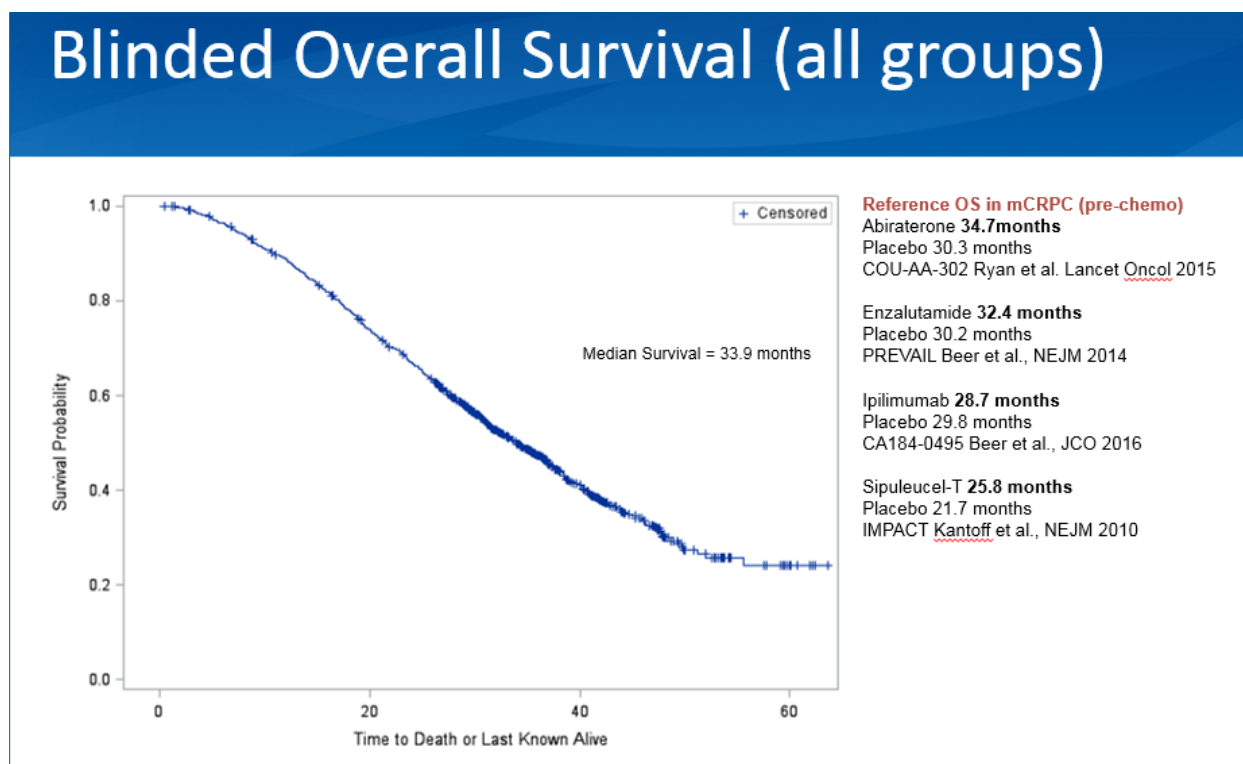
---

### *Introduction: Making Immunotherapy Work in Prostate Cancer*

James Gulley, MD, PhD  
National Cancer Institute

- Cancer immunotherapies are treatments that activate immune cells to target and kill tumor cells.
- Effective immunotherapy requires both generation of an anti-tumor immune response, and the ability of tumor-killing immune cells to function within the tumor.
- In people with certain types of cancer, often an anti-tumor immune response naturally develops but gets shut down by suppressive mechanisms within the tumor. In these individuals, checkpoint inhibitor immunotherapy, which reactivates anti-tumor immune cells by blocking suppressive signals, is highly effective and can result in long-term tumor regressions and even cures. However, in prostate cancer, checkpoint inhibitor immunotherapy has not yet been very effective.
- Checkpoint inhibitor immunotherapy is likely ineffective against most prostate cancers because natural anti-tumor immune responses are not present. In such patients, treatment with a cancer vaccine to activate an anti-tumor immune response, followed by an immune checkpoint inhibitor, might be more effective.
- ProstVac is a prostate cancer vaccine that was tested in the phase III PROSPECT clinical trial. 1,297 metastatic castrate-resistant prostate cancer (mCRPC) patients were randomized to one of three treatments: ProstVac, ProstVac + the immune activating molecule GM-CSF, and placebo. Patients were then followed for 5 years to document survival and other outcomes.
- Together, the 1,297 patients in the three treatment arms had a median overall survival of 34 months (Figure). This time was better than placebo arms in other clinical trials in similar groups of mCRPC patients. For instance, in the abiraterone COU-AA-302 trial, patients receiving placebo lived for 30.3 months on average, while patients who received abiraterone lived 34.7 months on average. This led to speculation that the PROSPECT trial would be positive and results were eagerly anticipated.
- However, Bavarian Nordic declared the PROSPECT trial negative and the trial was discontinued, indicating survival of patients receiving ProstVac was not better than patients receiving placebo.
- Reasons for failure of the ProstVac vaccine could be due to either a failure to induce an anti-tumor immune response, or an inability of the anti-tumor immune cells elicited by the vaccine to remain active in the tumor.
- Past studies have demonstrated that ProstVac can activate anti-tumor immune responses. Thus, it may be more likely that the tumor suppressed the activity of immune cells.

- If this hypothesis is true, then these patients may respond well to the addition of a checkpoint inhibitor immunotherapy after vaccination with ProstVac.
- Clinical trials have been initiated to test the activity of ProstVac combined with checkpoint inhibitor immunotherapy. Results from an NCI trial were discussed by Dr. Ravi Madan (below).



**Figure:** The median overall survival of 1,297 mCRPC patients in the phase III PROSPECT clinical trial was 34 months. Patients were randomized to one of three treatments: ProstVac, ProstVac + the immune activating molecule GM-CSF, and placebo. Overall survival from the placebo arm of several other mCRPC clinical trials is indicated on the right.

## *Promising Immune Checkpoint Inhibitor Combination Studies in Prostate Cancer*

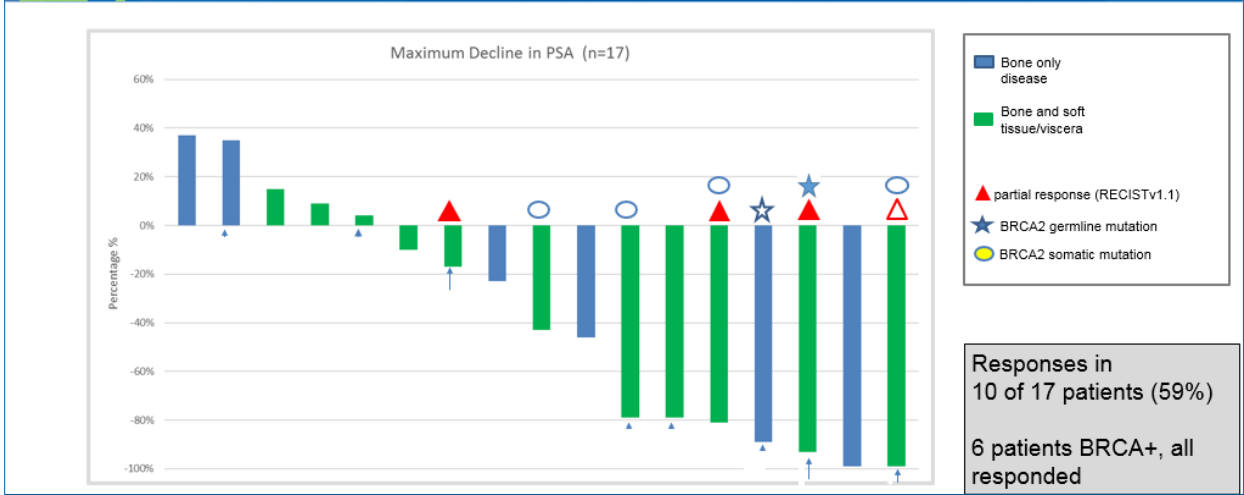
**Ravi Madan, MD**  
**National Cancer Institute**

- Immunotherapy has the potential to eliminate cancer and has cured some patients. Immunotherapies include a variety of treatment types, all of which share the goal of activating or directing immune cells to target and kill cancer cells. These include cancer vaccines, checkpoint inhibitors, CAR T cells, and other strategies of immune activation.
- Checkpoint inhibitor immunotherapy is a type of treatment that works by reactivating anti-tumor immune cells that have naturally developed in a patient, but were forced into a hibernation-like state by a variety of immunosuppressive mechanisms. These treatments have demonstrated efficacy in several cancer types including melanoma and lung cancer.
- Cancer vaccines act by activating immune cells to target and kill cancer cells. However, immune cells activated by cancer vaccines can still be forced into hibernation by immunosuppressive factors.
- In prostate cancer, single agent treatments with checkpoint inhibitors or anti-cancer vaccines have not, to date, demonstrated significant and immediate anti-tumor efficacy, manifested by PSA declines or tumor size reduction. For instance, as discussed by Dr. James Gulley (above), the prostate cancer vaccine ProstVac was recently found to be ineffective as a single agent in a phase III clinical trial.
- For immunotherapy to be successful against prostate cancer, combination treatments might be necessary.
- Dr. Madan discussed results from clinical trials being conducted at the NCI and elsewhere to test immunotherapy treatment combinations in prostate cancer.
- NCI researchers hypothesized that combining the ProstVac vaccine with checkpoint inhibitors would allow anti-tumor immune cells produced by the vaccine to remain active and avoid being turned off by tumors.
- This hypothesis is supported by observations that prostate tumors upregulate immune checkpoints (the proteins that turn off immune cells and are targeted by checkpoint inhibitor immunotherapy) after treatments such as ProstVac or enzalutamide. A clinical trial testing the immune checkpoint inhibitor pembrolizumab in metastatic castrate-resistant prostate cancer (mCRPC) patients progressing on enzalutamide has reported that ~20% of the 20 patients tested experienced a reduction in PSA levels.
- A PCF-funded clinical trial being conducted by Dr. Doug McNeel (University of Wisconsin) is testing a novel prostate cancer vaccine pTGV-HP in combination with pembrolizumab in mCRPC. In this very early clinical trial, patient responses have been observed.
- Dr. Madan reported on a clinical trial at the NCI testing the combination of the immune checkpoint inhibitor durvalumab with the PARP-inhibitor olaparib in mCRPC patients.

- PARP-inhibitors are treatments that impair the cell's ability to repair damaged DNA. These treatments are particularly effective against tumors with mutations that already weaken the cell's DNA repair capabilities. The most common of these mutations are in the BRCA1/2 genes.
- In the durvalumab + olaparib trial, 10 of 17 unselected patients treated thus far had tumor shrinkage or drops in PSA levels (Figure). Six of the responding patients had BRCA1/2 mutations in their tumors and possibly responded simply because of the olaparib therapy. However, the other four responders did not have BRCA mutations and are being studied further to better understand the activity of this promising treatment combination. This study is now being expanded to include 40 more patients in order to better understand why the treatment works and which patients it is most likely to benefit.
- Another NCI clinical trial is evaluating the combination of the prostate cancer vaccine ProstVac with the checkpoint inhibitors ipilimumab and pembrolizumab in prostate cancer.
- In a safety lead-in mCRPC cohort (ten patients will be enrolled), immune-related adverse events in the first two patients led to ipilimumab being dropped from the regimen for subsequent patients.
- Significant drops in PSA levels accompanied by partial radiologic responses have been observed in 2 of 4 evaluable patients treated thus far (88% and 95% PSA declines) (Figure). Scans also revealed shrinkage of metastatic lesions in the two responding patients.
- Following completion of the safety cohort, the ProstVac + pembrolizumab combination will be tested in a neoadjuvant cohort.
- Radiation therapy, including standard radiation and Radium-223, has been demonstrated to have an impact on anti-cancer immune responses by making the cancer cells more easily recognizable and killable by immune cells. Clinical trials are testing radiation in combination with immunotherapies.
- One mechanism by which radiation treatment sensitizes tumors to immune cell killing appears to be tumor cell upregulation of calreticulin, a protein that promotes immune activation.
- However, radiation treatment can also activate expression of immune-suppressive signals, including the negative immune checkpoint pathway PD1/PD-L1. Anti-PD-L1 therapy was highly synergistic with radiation in the treatment of prostate cancer in animal models.
- These data provide rationale for testing the combination of immunotherapy with radiation therapy or Radium-223.
- Ongoing trials at the NCI are testing the combination of Radium-223 with PD1/PD-L1 inhibitors atezolizumab or pembrolizumab in mCRPC.
- Clinical trials are also testing the combination of PARP-inhibitors and anti-PD-L1 in combination with Radium-223 in mCRPC.
- These studies will provide much needed insights into the best therapeutic strategies for activating the immune system to target and kill prostate cancer.

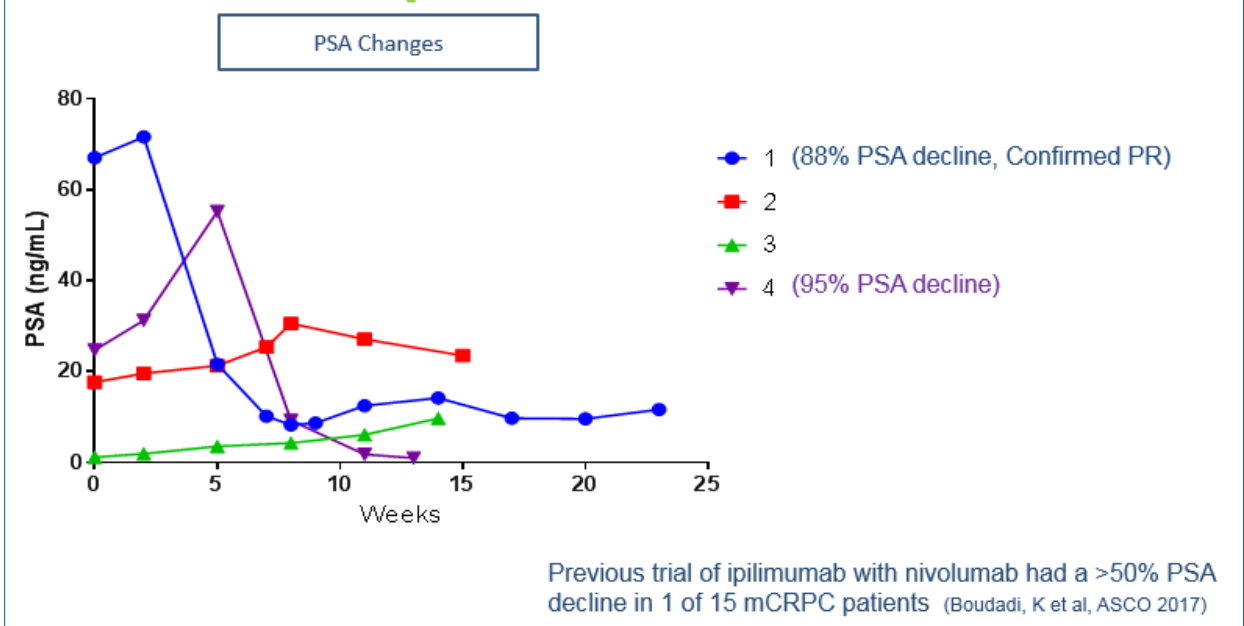
24  
 Twenty-Fourth Annual  
 Prostate Cancer Foundation  
**SCIENTIFIC  
 RETREAT**

## Olaparib + Durvalumab in mCRPC



**Figure:** In a clinical trial at the NCI testing the combination of durvalumab + olaparib, 10 of 17 patients treated thus far had tumor shrinkage or drops in PSA levels. Six of the responding patients had BRCA1/2 mutations in their tumors (denoted by stars and ovals) and possibly responded simply because of the olaparib therapy. The other four responders did not have BRCA mutations and are being studied further to better understand the activity of this promising treatment combination. Source: Karzai FH et al., ASCO, 2017.

## Safety Lead-in Cohort: Prostvac, Ipilimumab, Nivolumab



**Figure:** An NCI clinical trial testing the combination of the prostate cancer vaccine ProstVac with the checkpoint inhibitors ipilimumab and pembrolizumab demonstrate significant drops in PSA levels accompanied by partial radiologic responses in 2 of 4 evaluable patients treated thus far (Patient 1, Patient 4).

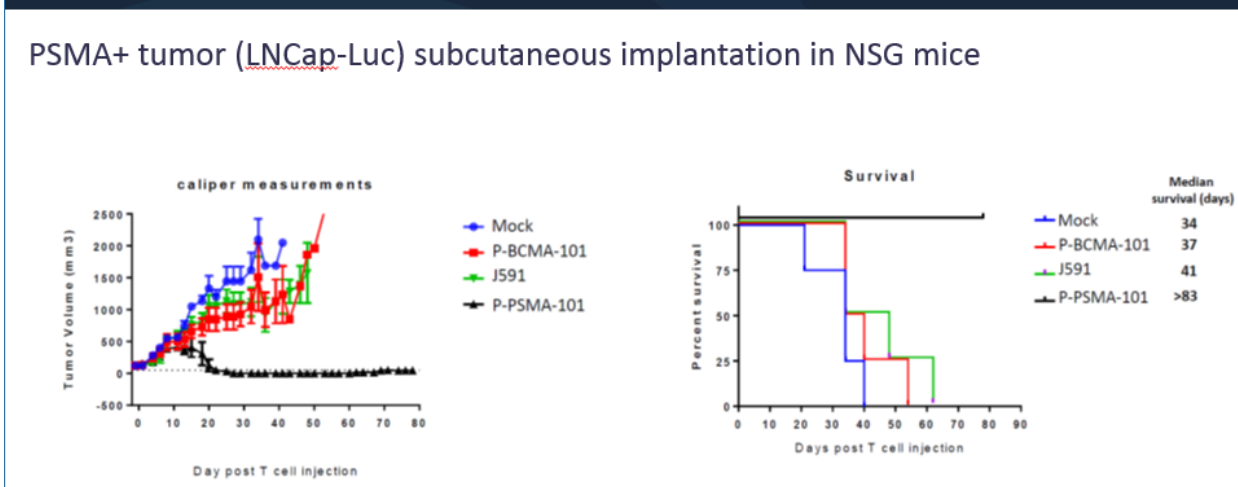
## *P-PSMA-101: An Autologous CART Therapy Comprised Predominantly of T Stem Cell Memory (Tscm) Cells*

Eric Ostertag, MD, PhD  
Poseida Therapeutics, Inc.

- CAR T cells are a novel type of immunotherapy in which a patient's own immune cells are genetically engineered to target and kill their tumor. CAR T cells have recently received FDA approval for the treatment of certain types of leukemia and lymphoma. Several groups are now developing CAR T cells for the treatment of prostate cancer.
- CAR T cells are created by modifying T cells with an engineered CAR molecule, which is composed of an exterior domain that recognizes a tumor-associated protein, and an interior domain that activates the T cell to kill the target cell.
- Dr. Eric Ostertag discussed preclinical results of a new prostate cancer-targeting CAR T cell therapy being developed by Poseida Therapeutics.
- PSMA is a molecule that is highly expressed on the surface of prostate cancer cells and is considered a promising therapeutic target.
- Centyrins™ are a novel class of highly stable, engineered proteins that can be designed to bind tightly and specifically to any protein target.
- A library of Centyrins™ was screened to identify ones which exhibited strong and specific binding to PSMA.
- PSMA-targeting Centyrins™ were then used as the exterior domain to engineer a novel CAR molecule. Standard CAR molecules use tumor-targeting antibody derivatives as the exterior domain. This novel PSMA-targeting “CARTyrin” was named P-PSMA-101.
- The P-PSMA-101 CAR gene was uploaded into T cells using the piggyBac™ transposon method, and was demonstrated to be successfully expressed. Expression was higher on activated T cells than resting T cells.
- T cells expressing P-PSMA-101 exhibited markers of T cell killing activity (such as IFN-gamma expression) only in the presence of prostate cancer cells, but not other cell types.
- P-PSMA-101 CAR T cells also specifically killed PSMA-expressing prostate cancer, but not other cancer cell types in preclinical experiments.
- P-PSMA-101 CAR T cells did not express markers of activation or exhaustion in the absence of tumor cells, indicating that expression of the CAR molecule did not cause premature activation and early exhaustion.
- P-PSMA-101 CAR T cells resulting from the CAR T cell production process consisted primarily (>70%) of a stem cell memory phenotype. Stem cell memory T cells are the T cell subset that has the most longevity and ability to create many copies of themselves and also differentiate into all T cell subsets, such as the effector T cells that perform the killing of cancer cells.

- Use of the piggyBac™ transposon system for uploading the P-PSMA-101 CAR gene into the T cells may underlie the resulting large fraction of stem cell memory T cells. The piggyBac™ method preferentially transposes naïve and stem cell memory T cells, while lentivirus, which is the prototypical method for delivering CAR genes into T cells, prefers differentiated T cells.
- The fraction of stem cell memory T cells in the final CAR T cell product was found to correlate with improved efficacy and longevity in the treatment of mouse models of multiple myeloma.
- Analysis of leukemia patients treated with University of Pennsylvania/Novartis CTL109 CAR T cells found improved responses and long-term persistence of CAR T cells in patients who had higher percentages of stem cell memory T cells in their pre-manufacturing product.
- Treatment of prostate cancer animal models with P-PSMA-101 CAR T cells resulted in complete tumor regression and long-term survival (Figure).
- Following tumor elimination in these mice, P-PSMA-101 CAR T cells were able to persist for at least several months, primarily with a stem cell memory phenotype.
- Thus, the predominantly stem cell memory phenotype of P-PSMA-101 CAR T cells may likely underlie its strong efficacy in preclinical models.
- These results suggest that P-PSMA-101 CAR T cells may be a promising new treatment for prostate cancer and warrant testing in clinical trials.

## P-PSMA-101: Unprecedented Efficacy



**Figure:** Treatment of prostate cancer animal models with P-PSMA-101 CAR T cells (black line) resulted in complete tumor regression (left) and long-term survival (right), compared with controls (blue line = mock treatment; red line = breast cancer-targeting CAR T cells; green line = PSMA-targeting antibody J591).



## *Special Lecture: Where are Disseminated Tumor Cells (DTCs) Hiding at the Time of Radical Prostatectomy?*

**Kenneth Pienta, MD**  
**Johns Hopkins University**

- The bone is the primary location in the body of prostate cancer metastasis. For a bone metastasis to develop, prostate cancer cells must first disseminate from primary or other metastatic tumors and take up residence in the bone marrow. These early colonizers are termed bone marrow disseminated tumor cells (BM-DTCs).
- Studies have identified cells thought to be DTCs in the bone marrow. This has led to the hypothesis that the presence of BM-DTCs in men with early stage prostate cancer indicates an increased likelihood for future recurrence and development of bone metastases.
- Dr. Kenneth Pienta discussed studies on the incidence and implications of BM-DTCs at the time of radical prostatectomy.
- Most cells in the bone marrow are immune cells and do not express epithelial cell markers. Prostate cancer is derived from prostate epithelial cells and can express epithelial cell markers such as EPCAM. Previous studies that examined the presence of DTCs in the bone marrow of patients with localized prostate cancer used EPCAM as a marker to identify BM-DTCs.
- These legacy studies found 72% of patients with localized prostate cancer had EPCAM-expressing cells in the bone marrow. This is vastly higher than the number of patients who will eventually experience a PSA recurrence (~30%) or develop metastatic disease (~12%). This suggests that either BM-DTCs are highly inefficient in the ability to survive long-term in patient bone marrow and grow into tumors, or that EPCAM is marking other non-tumor cells in the bone marrow.
- A PCF-funded multi-institutional collaboration was developed to comprehensively assess prostate cancer BM-DTCs in early stage patients. Several different technologies were used to identify and study DTCs from bone marrow samples collected from the iliac crest (upper edge of pelvic bone) at the time of radical prostatectomy.
- Methods included technologies in which cells from bone marrow samples were smeared on glass slides, labeled with fluorescent-antibodies targeting different cell markers, and examined by an automated microscope scanning system. In a second set of technologies, cells expressing EPCAM were isolated from bone marrow samples, followed by analysis of expressed genes.
- These studies found that EPCAM-expressing cells were present in the bone marrow of 100% of prostate cancer patients undergoing radical prostatectomy and 92% of controls without prostate cancer.
- To determine if these cells were prostate cancer cells or other types of cells, the expression of several other prostate cancer-associated cell markers were examined.
- PSMA is a protein that is expressed by prostate cells and some other cell types. 100% of prostate cancer patients were found to have PSMA-expressing cells in their bone marrow at

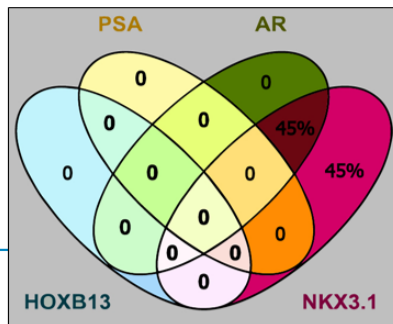
the time of radical prostatectomy suggesting that PSMA is not a prostate-specific marker. It is known to be expressed on types of endothelial cells.

- Several prostate cancer-associated markers were widely present on cells in bone marrow from men without prostate cancer including the androgen receptor (AR, 45%), and NKX3.1 (90%) (Figure). These proteins also have non-prostate cancer-related functions such as the regulation of immune cell development.
- These studies suggest that EPCAM, AR, and NKX3.1 are not suitable for detecting BM-DTCs in prostate cancer patients as they also detect normal cells that reside in the bone marrow.
- The prostate cancer markers PSA and HOXB13 were only expressed on cells in bone marrow from prostate cancer patients, but not controls, suggesting that these may specifically mark prostate cancer BM-DTCs. PSA and HOXB13 were also present on cells from bone marrow and peripheral blood samples from metastatic prostate cancer patients (Figure).
- Based on these results, only four of ~200 patients studied at the different institutions were convincingly found to have BM-DTCs.
- These studies suggest that BM-DTCs are very rare in men with localized prostate cancer.
- As ~30% of patients will experience a PSA recurrence following radical prostatectomy, these studies suggest that DTCs reside either in bone sites outside of the iliac crest (site of intraoperative BM sampling), or somewhere else in the body, such as in lymph nodes.
- PSMA-PET imaging is a highly sensitive new technology for imaging prostate cancer and is being used to identify early sites of prostate cancer metastasis.
- PSMA-PET imaging studies have found that in patients at low PSA recurrence levels (0.2-1ng/ml), about half of the detectable lesions are in the prostate bed and half are in pelvic lymph nodes. Bone marrow lesions are rarely detectable in patients with these PSA levels (~5%).
- In patients at higher PSA recurrence levels (>1 ng/ml), 90% of patients have detectable lymph node metastases (pelvic or non-pelvic), while bone metastases are still very rare.
- Circulating tumor DNA (ctDNA) is DNA released from dying tumor cells into the circulation and can be detected in patient blood draws. ctDNA technologies are being improved to better detect residual disease and early disease recurrence.
- ctDNA technologies still require much improvement as an analysis of four different commercially available tests found poor overlap in the tumor mutations detected in samples from the same patients.
- Overall, these studies suggest that lymph nodes may be the primary reservoirs of residual prostate cancer cells that eventually cause metastases.
- Improving methods that enable earlier identification of patients who will go on to recur is of great need and will improve treatment and outcomes.

Based on RNA detection (and IF), quickly became apparent that there is a need for disease specific markers

- EPCAM present in 100% of patients (92% of controls)
- PSMA present in 100% of patients
- AR in 45% of control bone marrows (regulates hematopoiesis)
- NKX3.1 in 90% of control bone marrows (male and female)

PSA and HOXB13 appear to be Specific at this point



CONTROL BONE MARROW  
 N=12 92% EpCAM+

**Figure:** Several prostate cancer-associated markers were widely present on cells in bone marrow from men without prostate cancer including androgen receptor (AR, 45%), and NKX3.1 (90%). The prostate cancer markers PSA and HOXB13 were only expressed on cells in bone marrow from prostate cancer patients but not controls. These data suggest that PSA and HOXB13 but not AR and NKX3.1 are suitable for identifying BM-DTCs in prostate cancer patients.

## Session 5: DNA Damage Repair

---

### *Processes of DNA Damage in Localized Prostate Cancer*

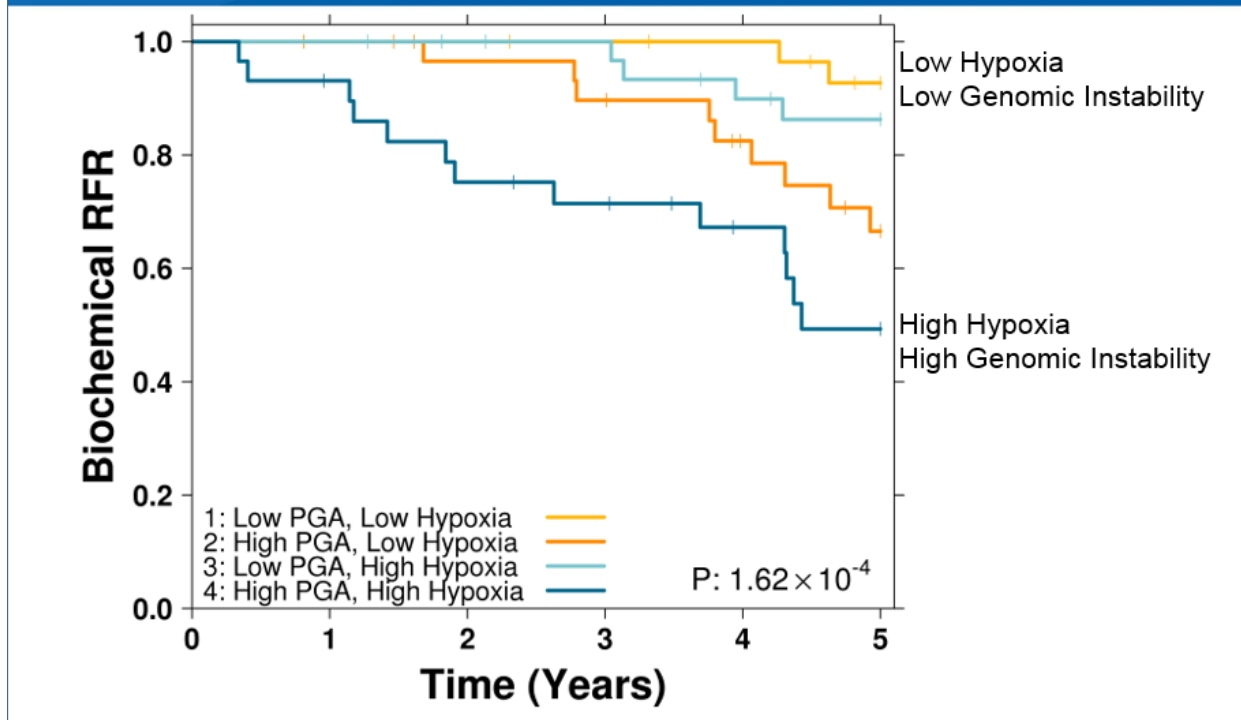
**Paul Boutros, PhD**

**Ontario Institute for Cancer Research**

- In patients with localized prostate cancer, the decision to undergo active surveillance or immediate treatment is based on prognosis for risk of disease progression. Currently, clinical parameters including how the tumor looks under a microscope, are used to classify patients into categories of low, intermediate, or high risk for progression.
- Unfortunately, these prediction tools are not perfect and some patients recommended for immediate treatment do not actually have aggressive cancer, and would have been better off on active surveillance, while other patients have more aggressive disease than predicted, and would benefit from more intensive treatment.
- New methods to better stratify a patient's risk of progression will reduce under-treatment and over-treatment and lead to improved outcomes and quality of life.
- Dr. Paul Boutros discussed the development of genomic biomarkers to better predict risk in patients with localized prostate cancer.
- To identify genomic biomarkers that can improve patient prognostication, the Canadian Prostate Cancer Genome Project (CPC-GENE) performed whole genome sequencing on tumors from patients with localized prostate cancer. Tumor mutations and standard clinical prognostication factors were correlated with clinical outcomes to identify genomic biomarkers that improved risk prognostication.
- Primary prostate cancer is often multifocal, meaning different areas of the prostate can develop into unique sites of cancer. Not all of these tumors will progress into clinically significant disease.
- To optimally identify genomic biomarkers predictive of risk, prostatectomy specimens from some patients were micro-dissected to obtain regions with different Gleason scores that were separately genomically sequenced. Mutations in the different regions were compared and used to reconstruct a map of how the tumor(s) evolved. For instance, a lack of shared mutations indicates tumors are distinct from one another, while tumors with shared mutations likely evolved from the same tumor cell ancestor.
- Some patients had multiple distinct primary tumors, while others exhibited multifocal tumors that arose from the same initial tumor, but then evolved separately. Different tumor regions from the same patient varied greatly in the number of mutations present, by up to 10-fold.
- Patients whose tumor cells remained genomically similar had far better outcomes than patients whose tumors evolved into multiple different clones with different mutations.
- Identifying genomic biomarkers that can be used for prognosis and treatment selection is complex when more than one tumor is present, as biopsies of different prostate regions could have different results.

- To address this issue, Dr. Boutros and team focused on mutations that occur early in tumor evolution and would be present in all tumors that evolved from the same initial tumor cell. Specifically, the team focused on alterations in the number of gene copies, which occur when segments of the genome are deleted or duplicated, and indicate the level of DNA damage.
- Bioinformatics were used to classify patients into groups that shared certain copy number alterations. These groupings were found to be predictive of clinical outcome.
- Prostate cancer patients whose tumors had fewer copy number alterations (<7.5% of the genome altered) had better outcomes than patients whose tumors had a higher level of copy number alterations (>7.5% of the genome altered). This phenomenon is only mirrored in breast cancer, while in other types of cancer, patients whose tumors have more mutations typically have better outcomes.
- Prostate cancer aggressiveness was not associated with the number of point mutations (mutations in single nucleotides or very short genome sequences), or chromothripsis (a phenomenon in which chromosomes collapse and cause massive gene loss).
- Dr. Boutros and team sought to further refine the identification of patients who are likely to relapse, by examining other types of biomarkers.
- Hypoxia is a lack of oxygen, a phenomenon common in tumors due to insufficient blood supply. Hypoxia increases the level of reactive oxygen species, which are toxic molecules that damage DNA.
- The level of hypoxia in tumors had no correlation with the level of mutations.
- However, classification of tumors based on both hypoxia and copy number alterations improved prediction of relapse. Patients with low levels of hypoxia and fewer copy number alterations had far better outcomes than patients with high levels of hypoxia and more copy number alterations (Figure).
- A biomarker was developed that combined data on copy number alterations and hypoxia levels. The biomarker was validated as a strong predictor of disease progression in additional cohorts of localized disease patients, with an overall accuracy rating of ~80%.
- Mitochondria are the energy powerhouses of the cell. They also have their own genome separate from the genome in the cell nucleus.
- The mitochondrial genome was found to be highly and frequently mutated in prostate cancer cells, particularly at the site at which genome replication begins (the “origin of replication”).
- Certain mutations in mitochondria were associated with certain mutations in the nuclear genome. This suggests an interplay between mutations in the mitochondria genome and in the nuclear genome that contribute to prostate cancer development and progression.
- Overall, these studies will contribute to development of a composite biomarker that will improve prediction of disease aggressiveness and selection of optimal treatment strategies.

# Synergy: Hypoxia & Instability



**Figure:** Classification of localized prostate tumors based on levels of hypoxia and levels of copy number alterations (genomic instability, PGA) was highly predictive of relapse (biochemical RFR). Patients with low levels of hypoxia and low levels of genomic instability (yellow line) had far better outcomes than patients with high levels of hypoxia and high levels of genomic instability (dark blue line).

## Implementing Germline Genetics into Prostate Cancer Clinical Care

Heather Cheng, MD, PhD  
University of Washington

- Approximately 10% of men with metastatic prostate cancer have inherited (germline) mutations in DNA damage repair (DDR) genes (which include BRCA2 and BRCA1) that likely promoted the development of their cancer.
- Identification of these men is critical, as tumors with DNA repair gene mutations are believed to be very sensitive to treatment with PARP-inhibitors or platinum chemotherapy.
- In addition, the presence of inherited DDR mutations has significant implications for a patient's family, as family members who also inherited the mutation may be at increased risk for prostate, breast, ovarian, and other cancers. Genetic counseling for these men and their families is critical, so family members can be informed about their personal cancer risks and

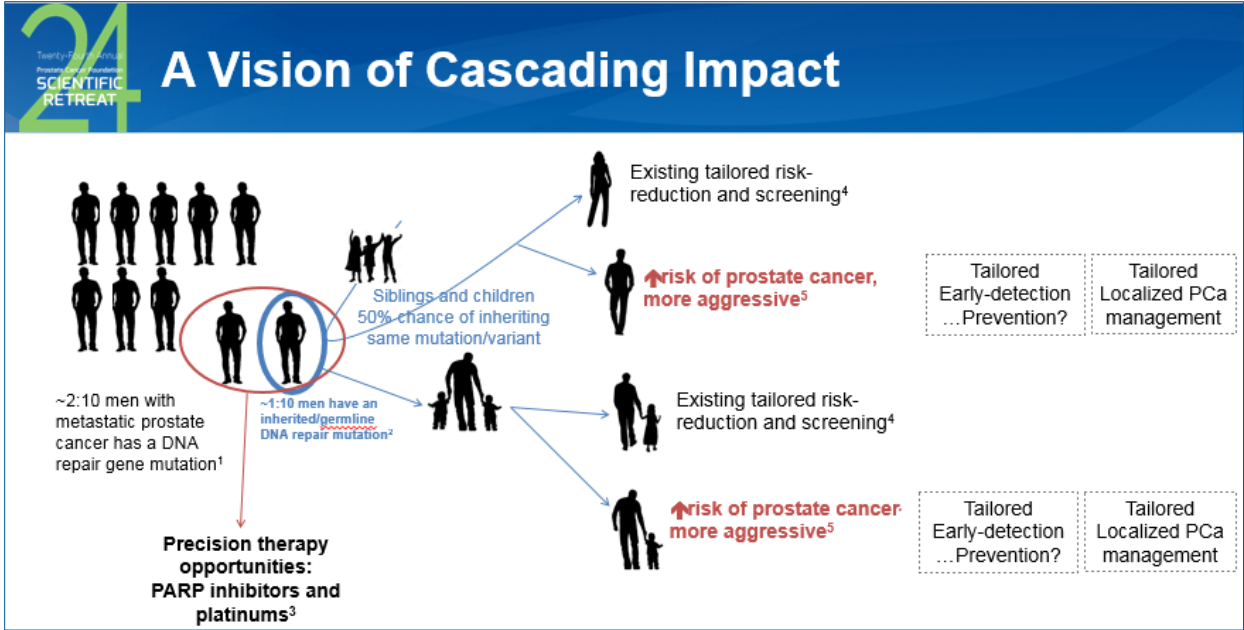
recourses for cancer. The practice of testing family members of an affected individual for inherited cancer risk genes is termed “cascade genetic testing.”

- While many men with inherited DDR gene mutations have a family history of cancer, many others have no family history of cancer. Thus, family history is not sufficient to identify men who carry inherited mutations in DDR genes and are at increased risk for prostate cancer.
- These findings have now been integrated into the 2018 NCCN Guidelines for Prostate Cancer and for Genetic/Familial High-Risk Assessment: Breast and Ovarian. The guidelines recommend consideration for all men with a family history of prostate cancer, and all men with metastatic or high-risk localized prostate cancer be offered genetic counseling and genetic testing for inherited DDR gene mutations.
- Dr. Cheng discussed efforts being made to implement germline genetics into prostate cancer clinical care.
- This goal requires changes in paradigms that have governed patient care over past decades. It is important to bring together the fields of prostate cancer oncologists, including doctors focused on treatment for men with advanced prostate cancer, with medical genetics and counseling, which focus on risk assessment largely based on family history, managing early stages of disease, and strategies for managing unaffected people at risk.
- Dr. Cheng has opened the Prostate Cancer Genetics Clinic at the Seattle Cancer Care Alliance. This clinic is dedicated to screening prostate cancer patients for inherited DDR gene mutations, and counseling patients and family members on treatment options and cascade genetic testing. The clinic brings together medical oncologists, urologists, and genetic counselors, with patients and their families.
- Prostate cancer patients receive genetic testing of their tumor and germline, and genetic counseling. Patients who are found to be inherited mutation carriers receive counseling on choosing precision medicine treatments that may be effective, access to clinical trials and registries, and screening for other cancers. Family members are provided with access to cascade genetic testing and genetic counseling, and education on their risk and recourse for prostate, breast, ovarian, and other cancers.
- Since its official opening in 2016, the clinic has seen over 60 prostate cancer patients.
- For example, a patient with late stage metastatic prostate cancer who enrolled in the clinic was found to have an inherited mutation in the DDR gene BRCA2. The patient was enrolled on a clinical trial for the PARP-inhibitor, olaparib, and went on to have a dramatic response that significantly improved his quality of life.
- In another example, a patient with a strong family history of cancer was not found to have a hereditary mutation in any of the DDR genes that are screened for in the standard test performed by the clinic. This patient was enrolled in a family study that will look for other, yet-unidentified, inherited mutations that increase cancer risk.
- These experiences highlight needs for improved patient education on genetics and precision medicine concepts.
- Major barriers to implementing germline genetics as a standard of care for prostate cancer patients include insufficient numbers of accessible genetic counselors, gaps in insurance



coverage for genetic testing, and counseling and concerns about potential genetic discrimination.

- Dr. Cheng and team have established the GENTLEMEN study as a new model to remove barriers to genetic testing for men with metastatic prostate cancer.
- The GENTLEMEN study is an entirely web- and telephone-based study that offers genetic testing and counseling to all men with metastatic prostate cancer living in Washington State.
- Patients enroll using a web-based consent form, complete an online 40-minute survey and upload certain medical data. Once this is completed, patients are mailed a Color Genomics saliva germline genetic test kit, the costs of which are covered by the study. Patients then receive results via telephone-based genetic counseling.
- The purpose of this study is to identify men who carry inherited DNA repair gene mutations, which may be helpful for their treatment planning, and may be helpful for family members' health decision-making.
- Male family members found to carry cancer risk genes may be able to enroll in clinical trials of tailored prostate cancer screening and, if diagnosed earlier, may improve the chance for cure.
- Enrollment for the GENTLEMAN study can be accessed at: [www.gentlemenstudy.org](http://www.gentlemenstudy.org).
- In another effort, Dr. Cheng and colleagues are working to improve early prostate cancer detection in men known to carry germline DNA repair gene mutations. Men enrolled in this study will begin prostate cancer screening at age 40 with annual digital rectal exams and PSA testing. Men with abnormal results will undergo prostate biopsy and imaging, if necessary. Men found to have low grade disease will be considered for active surveillance or clinical trials for new biomarkers, while patients with high grade disease will receive tailored treatment plans including consideration for clinical trials.
- These efforts will improve treatment options for prostate cancer patients, and facilitate better understanding of the biology, natural history, and treatment sensitivities of tumors with these mutations, including in newer, less characterized genes.



**Figure:** The implementation of germline genetics into prostate cancer clinical care will enable the identification of patients with inherited cancer risk mutations and lead to precision medicine opportunities for patients and counseling for family members on cascade genetic testing. At-risk family members can consider tailored risk-reduction, screening, and early cancer management strategies.

## **STATE OF THE SCIENCE 2017**

**Jonathan Simons, MD**  
President & CEO  
Prostate Cancer Foundation

*Introduced by Howard Soule, PhD*  
*Prostate Cancer Foundation*

*This talk can be viewed in full at:*  
<https://www.pcf.org/c/24th-annual-scientific-retreat/>

## **KEYNOTE ADDRESS**

**Michael Milken**  
Founder & Chairman  
Prostate Cancer Foundation

*Introduced by Stuart Holden, MD*  
*Prostate Cancer Foundation*

*This talk can be viewed in full at PCF.org:*  
<https://www.pcf.org/c/24th-annual-scientific-retreat/>

## Session 6: PSMA Imaging and Radioligand Therapy

---

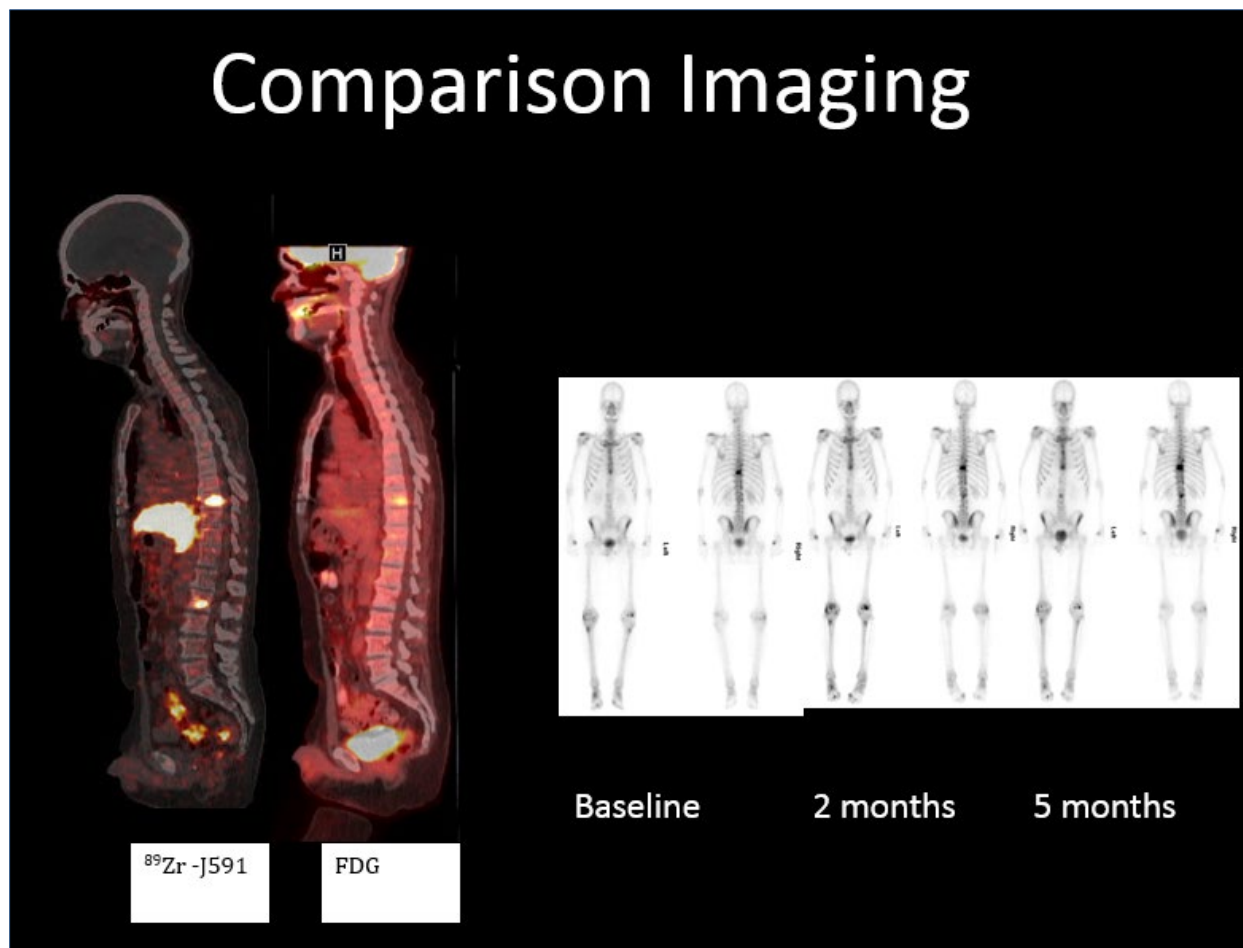
### *Radioantibody Imaging of Prostate Specific Membrane Antigen*

Steven Larson, MD

Memorial Sloan Kettering Cancer Center

- PSMA (prostate-specific membrane antigen) is a protein that is highly expressed on the surface of prostate cancer cells and increases with prostate cancer progression. PSMA is expressed on some normal cell types rarely, and usually at lower levels. PSMA is considered a highly promising target for imaging and treatment of prostate cancer.
- Dr. Steve Larson discussed the use of PSMA-targeting antibodies for prostate cancer imaging.
- Labeling of antibodies with radioactive isotopes creates positron emission tomography (PET) imaging agents, as PET detects certain types of radioactive decay.
- J591 is a PSMA-targeting antibody. J591 labeled with radioactive isotopes for prostate cancer imaging or treatment has been widely studied. Dr. Larson reported on the first use of 89-Zirconium-labeled J591 (89Zr-J591) for PET imaging.
- In a phase I trial, 89Zr-J591 was tested as a prostate cancer PET imaging agent. 89Zr-J591 was found to be a highly sensitive PET tracer for imaging of metastatic prostate cancer, and dosimetry was found to be acceptable for study of patients with advanced disease.
- A phase I/II study compared the specificity and sensitivity of 89Zr-J591 PET with conventional imaging (bone scans and CT), and with FDG PET. Sites of disease were detected by all imaging modalities and were compared. 21 bone sites and 25 soft-tissue sites were biopsied to determine sensitivity and specificity of the different imaging modalities.
- Overall, 692 lesions were detected in 50 patients across all imaging modalities (532 in bone and 160 soft tissue).
- 17% of bone lesions and 11% of soft tissue lesions detected by 89Zr-J591 PET were not detected by the other imaging methods (Figure).
- 89Zr-J591 PET was more sensitive and specific for detecting bone metastases than bone scan, CT, or FDG, in that order. Performance of 89Zr-J591 was superior in bone compared to soft-tissue metastases. Of sites detected by 89Zr-J591 PET, 18/19 (94%) bone sites and 60% of soft tissue sites were confirmed as prostate cancer upon biopsy.
- Statistical tests were used to infer the number of sites detected by each imaging modality that would have been positive upon biopsy. Based on this test, ~91% of the 470 bone lesions detected by 89Zr-J591 PET were predicted to be actual sites of tumor metastases.
- Overall, 89Zr-J591 PET was found to be the most sensitive method for detecting bone metastases, while CT was the most sensitive method for detecting soft-tissue metastases.

- IAB2M is a “minibody” (an engineered antibody fragment) that targets PSMA.
- IAB2M is about half the size of the J591 antibody and therefore has different kinetics in the body, being able to better penetrate tissues at a faster rate.
- 89-Zirconium-labeled–IAB2M (89Zr-IAB2M) is also being tested as a prostate cancer PET imaging agent and may give brighter images than 89Zr-J591 PET due to its higher uptake rate.
- These agents continue to be evaluated for their effectiveness in prostate cancer imaging and may lead to improved and earlier detection of metastatic disease.



**Figure:** Comparison of prostate cancer imaged by  $^{89}\text{Zr}$ -J591 PET (left panel), FDG PET (center panel), and bone scans (right panels). More lesions in the spine can be detected by  $^{89}\text{Zr}$ -J591 PET at earlier time points.

## *Low Molecular Weight PSMA-Based Imaging*

**Steve Cho, MD**

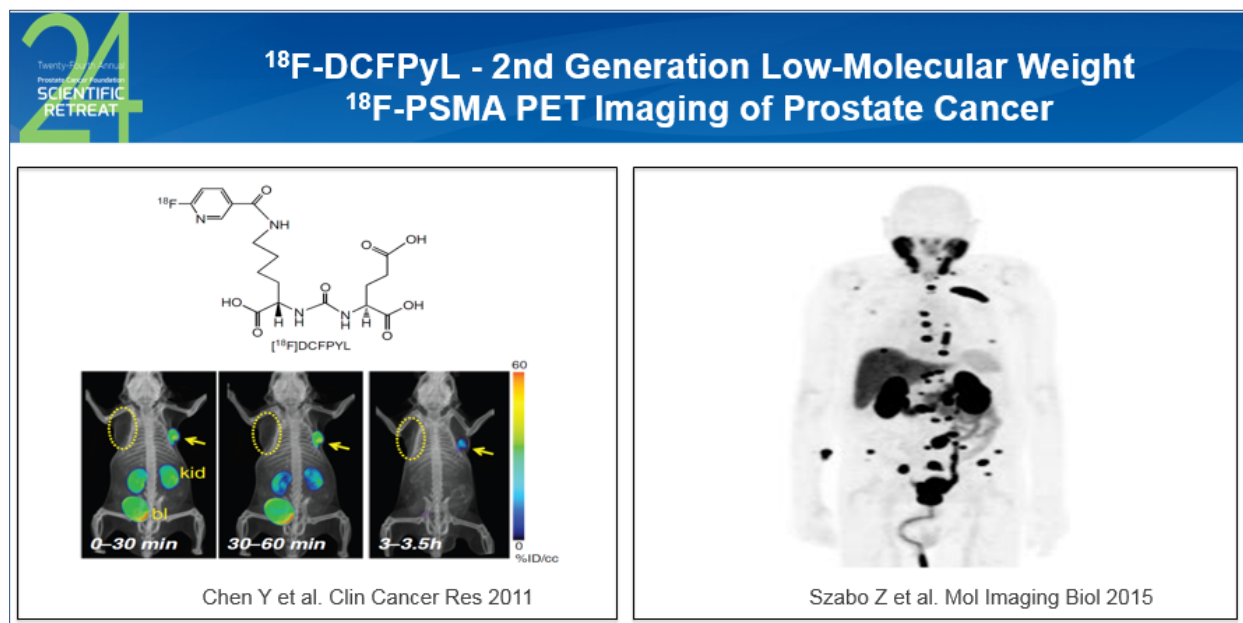
**University of Wisconsin – Madison**

- Prostate specific membrane antigen (PSMA) is a protein that is primarily expressed on the surface of prostate cancer cells. PSMA expression levels increase with prostate cancer progression, being highest in metastatic and castrate-resistant prostate cancer (CRPC).
- Up to 1 million PSMA molecules are expressed on each prostate cancer cell, making PSMA an ideal target for prostate cancer therapy and detection.
- Dr. Steve Cho discussed the use of radiolabeled PSMA-targeting small molecules as imaging agents for the detection of prostate cancer.
- Attachment of PSMA-targeting small molecules to various radioactive isotopes allow them to be visualized by PET (positron emission tomography) imaging machines.
- The isotopes most commonly used to label PSMA-PET imaging agents are 18-Fluorine (18F) and 68-Gallium (68Ga). These radioisotopes have different half-lives (107 and 68 minutes, respectively) and different production and labeling procedures, which must be considered when planning use of these agents.
- At least 12 small molecules that bind to PSMA have been developed and are being tested for their utility as prostate cancer imaging and therapeutic agents.
- 18F-DCFBC, a urea-based small molecule ligand of PSMA, was the first PSMA-targeted small molecule to be developed for PET imaging. 18F-DCFBC was highly promising for imaging primary and metastatic prostate cancer. However, the images produced had higher than desired background in the vascular blood pool, prompting the development of improved imaging agents.
- 18F-DCFPyL, a derivative of DCFBC, was subsequently developed. 18F-DCFPyL exhibited improved sensitivity for imaging of primary and metastatic prostate cancer with significantly lower background, with no accumulation in blood pools (Figure). 18F-DCFPyL is being tested in multiple ongoing clinical trials.
- 68Ga-PSMA is a PSMA-targeted agent that is already in wide use in Germany and Australia, with ongoing studies in the United States.
- 18F-PSMA-1007 is a highly promising new agent being tested in Europe with primarily liver excretion, compared to kidney excretion for 18F-DCFPyL and 68Ga-PSMA.
- The sensitivity and specificity of each of these imaging agents are being tested for detection of primary and metastatic prostate cancer compared with conventional imaging agents (CT and bone scans).
- Benign prostate hyperplasia (BPH) is a non-cancerous condition that can cause elevated PSA levels, prompting unnecessary prostate biopsies. Other new imaging technologies, such as choline-based PET agents (11C-Choline and 18F-FluoroCholine), and Fluciclovine (Axumin<sup>TM</sup>), are not able to differentiate prostate cancer from BPH very well and thus are not as specific for diagnosis of primary prostate cancer.

- Because PSMA is not upregulated in BPH, PSMA-PET imaging is highly specific for the detection of primary prostate cancer.
- 68Ga-PSMA-PET is highly specific, with ~95% of sites detected by imaging being actual sites of cancer. 68Ga-PSMA-PET is also highly sensitive, being able to detect ~78% of all sites of known disease recurrence versus only about 27% detected by conventional imaging (CT or MRI).
- 68Ga-PSMA-PET was shown to be superior to CT scans for imaging and staging lymph node metastases in patients prior to prostatectomy, particularly for identification of small sites of disease.
- PSMA-PET is being tested for use in early detection of disease sites in patients with a rising PSA following treatment of primary prostate cancer.
- In one study, 68Ga-PSMA-PET detected metastatic sites in 58% of men with very low PSA levels (0.2-0.5ng/ml), and vastly outperformed conventional imaging methods for this early state of disease recurrence.
- In a study comparing 18F-Choline vs 68Ga-PSMA PET imaging in patients with a rising PSA post-prostatectomy, PSMA imaging detected twice as many metastatic lesions than Choline, and increasingly outperformed Choline in patients with lower PSA levels. Positive PSMA-PET findings changed overall clinical management of 63% of patients in this study.
- In another study, 139 patients with rising PSA levels after surgery or radiation were imaged using 18F-Choline-PET. 68Ga-PSMA PET imaging was used in the 25% of patients who had negative Choline-PET scans, and detected lesions in almost half of them.
- Compelling clinical and research questions that remain to be addressed in regards to PSMA PET imaging include whether 18F or 68Ga PSMA PET agents are superior. Studies suggest they are likely similar in sensitivity, although 18F imaging may produce slightly clearer images, and 18F PET agents can be more easily produced in bulk and allow for wider distribution for clinical use.
- Studies are also investigating whether combining imaging modalities further improves sensitivity and specificity for detecting prostate cancer.
- Combination of MRI with 68Ga-PSMA-PET imaging (using a specialized PET-MR machine) resulted in an 88% performance rate for detection of primary prostate cancer, which was more sensitive and specific than either imaging modality alone (68Ga-PSMA-PET alone had an 83% performance rate, while MRI imaging alone had a 73% performance rate).
- PSMA expression is lost in some very aggressive, late-stage, androgen receptor-independent CRPC subtypes, including poorly-differentiated neuroendocrine prostate cancer. In such cases, PSMA-PET imaging is not useful. A novel PET imaging tracer 68Ga-DOTA-NOC, which detects the somatostatin protein, has been developed and appears useful for imaging neuroendocrine prostate cancer for this very small subset of patients.
- As PSMA-PET imaging appears to be more sensitive than current gold standard imaging methods, researchers are aiming to attain FDA approval for these agents and bring this new technology to patients as well as incorporate PSMA-PET imaging into clinical trials testing new treatments.



- FDA approval will require further clinical trials that validate sensitivity and specificity and demonstrate that PSMA-PET imaging changes treatment plans and results in improved patient outcome.



**Figure:**  $^{18}\text{F}$ -DCFPyL PET imaging exhibits high sensitivity for imaging of primary and metastatic prostate cancer in animal models (left) and patients (right).

## *PSMA Targeted Radionuclide Therapy for Prostate Cancer*

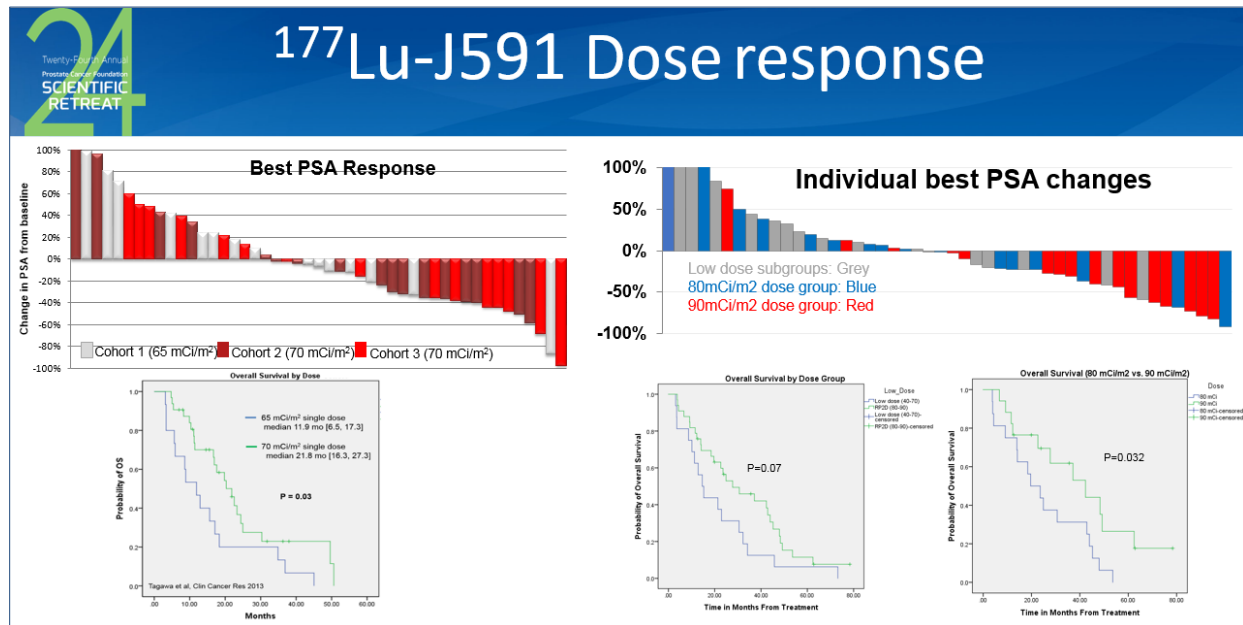
Scott Tagawa, MD  
Weill Cornell Medical College

- External beam radiation therapy is a common and effective treatment for localized prostate cancer for cure, as well as palliation of limited metastatic disease.
- Radiotherapy can be delivered as external beam radiation, brachytherapy, which are implanted radioactive “seeds,” and injected radioactive isotopes, such as Radium-223 which treats metastatic prostate cancer in bone.
- PSMA (prostate specific membrane antigen) is a protein expressed by prostate cancer cells. PSMA is considered an optimal therapeutic target for prostate cancer because it is highly expressed on the surface of prostate cancer cells but absent or very low on normal cells. Its expression on prostate cancer cells increases with disease progression and especially following initiation of hormone therapy.
- PSMA-targeted radionuclide therapy is a promising new type of treatment consisting of a radioactive isotope attached to a molecule or antibody that can target PSMA.

- Dr. Scott Tagawa discussed ongoing studies testing various types of PSMA-targeted radionuclide therapy for the treatment of prostate cancer.
- J591 is an antibody that targets PSMA and is being developed as a treatment and imaging agent for prostate cancer. J591 can be attached to various radioactive isotopes that can kill prostate cancer cells or can be detected by imaging technologies such as PET.
- Radiolabeled-J591 has been tested as a prostate cancer treatment in at least eight phase I and II clinical trials with promising results. J591 labeled with the radioactive isotope 177-Lutetium (177Lu-J591) has been the best evaluated, with demonstrated safety and efficacy.
- The total dose of administered PSMA-directed radionuclide therapy can safely be increased by dividing the total dose into fractions that are given days or weeks apart. This treatment strategy is known as dose fractionation.
- In a study comparing different doses of 177Lu-J591, even slightly higher doses of 177Lu-J591 resulted in improved patient responses and extended survival (Figure).
- These results led to trials testing fractionated doses of 177Lu-J591 in combination with docetaxel chemotherapy. Safety has been demonstrated for this combination with standard (full) dose chemotherapy.
- Overall these trials demonstrated that radiolabeled-J591 therapies were more effective against prostate cancer at higher doses and resulted in PSA responses and improved overall survival. However, the most efficacious doses had the highest toxicity, which was reversible myelosuppression (decreases in blood counts which recover after days to weeks).
- PSMA-targeting small molecules attached to radioactive isotopes have also been developed and are being tested for the treatment of prostate cancer. The most commonly tested of these small molecules is PSMA-617.
- 177Lu-PSMA-617 has been tested in patients and appears promising. Case studies have reported some dramatic PSA declines, improved PSMA-PET scans, and improved quality of life, without significant side effects.
- A meta-analysis examining all reports of patients treated with 177Lu-PSMA-617 therapy in Germany (145 patients across 12 centers) found that of the patients with follow-up data (99 patients), 60% experienced any PSA decline, and 45% experienced at least a 50% PSA decline. However, the patients treated at these centers were not part of a controlled clinical trial, and nearly a third did not have follow-up data.
- In Australia, the first prospective phase II clinical trial is being completed for 177Lu-PSMA-617 therapy in prostate cancer. In early results from the first 30 patients treated, 57% of men experienced a >50% PSA decline, and 43% of men experienced a >80% PSA decline. Median PSA progression free survival was 6.3 months and median overall survival for patients was 12.7 months.
- Very little high-grade toxicity was reported in this phase II trial. Low grade symptoms of dry mouth were reported in 63% of patients. No patients reported high-grade dry mouth toxicity, which has been a significant issue with the similar agent 225Ac-PSMA-617 (a PSMA-targeting ligand bound to a powerful alpha-particle emitter).

- Results from this trial have led to the initiation of three additional clinical trials: a randomized trial comparing <sup>177</sup>Lu-PSMA-617 with cabazitaxel, and trials combining <sup>177</sup>Lu-PSMA-617 with a PARP-inhibitor or PD-1 checkpoint immunotherapy.
- Other recently initiated prospective trials testing PSMA-targeted radionuclide therapy in prostate cancer patients include a phase I dose escalation study of <sup>131</sup>I-MIP1095, and the phase II PERCIST trial testing two different doses of <sup>177</sup>Lu-PSMA-617.
- At Weill Cornell Medicine, Dr. Tagawa has initiated a PCF-funded dose-escalation study of fractionated-dose <sup>177</sup>Lu-PSMA-617 in metastatic castrate-resistant prostate cancer (mCRPC). Three patient cohorts have been completed thus far with no dose-limiting toxicity reported. Once an optimal dose has been established, the trial will be expanded at additional sites.
- In an anecdotal case from this study, a highly-pretreated patient with widespread mCRPC who received two doses of <sup>177</sup>Lu-PSMA-617 experienced a PSA decline of >50% by two weeks with only low grade adverse effects. However this patient progressed after 6 months.
- Two additional studies are being conducted by Dr. Tagawa and team to define optimal doses of PSMA-targeted radionuclide therapy.
- Because the J591 antibody and the PSMA-617 small molecule bind to PSMA at different sites and have different organ exposure and toxicities, these treatments could be combined. With a higher dose to tumor, but less to areas leading to side effects, there is the possibility to achieve greater effects to tumor at lower doses of each molecule with even lower toxicity. To test this hypothesis, Dr. Tagawa is initiating a trial testing the combination of <sup>177</sup>Lu-PSMA-617 and <sup>177</sup>Lu-J591.
- There are two classes of radioactive isotopes that are used for these treatments; those that emit alpha particles, and those that emit beta particles. Alpha particles have 4,000-times more energy but can only travel a very short distance (can pass through a few cells), while beta particles have lower energy but can travel much further (approximately an inch through tissue). <sup>177</sup>Lu is a beta-emitter while <sup>225</sup>Actinium (<sup>225</sup>Ac) and <sup>223</sup>Radium are alpha-emitters.
- In Germany, <sup>225</sup>Ac-PSMA-617 is being used to treat patients, and anecdotal cases of exceptional responses have been reported, with complete remissions of mCRPC. However, these patients have experienced a severe dry mouth syndrome, as the salivary glands express low levels of PSMA and are destroyed by this treatment, and there is the possibility of kidney damage.
- Because the J591 antibody is far larger than the PSMA-617 small molecule, it is likely less able to penetrate and damage normal tissues that express low levels of PSMA such as the salivary glands. Thus, it may be better to use alpha-emitters attached to J591 to reduce these toxicities. To address this hypothesis, Dr. Tagawa initiated a clinical trial that will examine the efficacy and toxicity of <sup>225</sup>Ac-J591.
- Overall, PSMA-targeted radionuclide therapy is a promising experimental treatment for prostate cancer patients, but requires systematic and controlled clinical trials to determine true efficacy and the optimal way to give these treatments to reduce toxic effects to normal organs.

- The clinical trials led by Dr. Tagawa and others will determine efficacy and optimize dose and treatment strategies for these novel therapies alone and in combination with other treatments.



**Figure:** Clinical trials demonstrated that even slightly higher doses of <sup>177</sup>Lu-J591 resulted in improved patient responses and extended survival. On the left are PSA responses and overall survival of patients receiving 65mCi/m<sup>2</sup> vs 70mCi/m<sup>2</sup> of <sup>177</sup>Lu-J591. On the right are PSA responses and overall survival of patients receiving fractionated doses totaling 80mCi/m<sup>2</sup> vs 90mCi/m<sup>2</sup> of <sup>177</sup>Lu-J591. Fractionated doses of <sup>177</sup>Lu-J591 could be delivered for higher overall doses with less toxicity. Source: Tagawa et al., *Clin Cancer Res*, 2013 Sep 15, 19(18):5182-91; Tagawa et al., *J Clin Oncol* 31, 2013 (suppl 6; abstr 121).

## Session 7: Meeting Reports

---

### *Second Bi-Annual Strategy Meeting to Accelerate Progress in the Understanding and Treatment of Prostate Cancer; Athens, Greece 2017*

Christopher Logothetis, MD  
The University of Texas MD Anderson Cancer Center

- Dr. Christopher Logothetis reviewed the proceedings of the Second Bi-Annual Strategy Meeting to Accelerate Progress in the Understanding and Treatment of Prostate Cancer, held from March 6-7, 2017 in Athens, Greece.
- The goal of the Meeting was to discuss why past prostate cancer clinical trials have failed, particularly those testing docetaxel in combination with other therapies, in order to facilitate the design of successful, future clinical trials.
- Challenges to the successful development of new cancer treatments include poor model systems that do not faithfully recapitulate clinical prostate cancer, lack of applying knowledge of biology to clinical decision making, and heterogeneity of cancer within an individual and across individuals.
- To overcome these challenges, physicians have typically conducted large, inclusive phase III trials that do not recapitulate the conditions of phase II trials, most of which ultimately fail.
- However, promising progress has been made against these challenges.
- Approximately 60% of patients with castrate resistant prostate cancer (CRPC) can now be classified into molecular subtypes based on underlying tumor biology.
- Liquid biopsies (blood draws) contain DNA from dying tumor cells that was released into the circulation, and can be used to assess tumors mutations. Liquid biopsies can be repeated many times to evaluate changes in tumor biology throughout the course of treatment.
- Advances in tumor biopsy techniques and the ability to profile tumor DNA from liquid biopsies have accelerated our ability to assess mechanisms of treatment resistance and response.
- These have led to the identification of promising new treatment strategies, and have shortened the time it takes new treatments to go from the lab to clinical trials.
- The androgen receptor (AR) is the primary driver of prostate cancer and therefore the primary therapeutic target. However, resistance to AR-targeted therapy is common and leads to the development of CRPC.
- CRPC tumors can be divided into subtypes driven by several major mechanisms including those which remain driven by AR (due to mutations that increase the activity of this pathway), and AR-indifferent subtypes which often exhibit mutations in the tumor suppressor genes p53, RB1, and/or PTEN.

- AR-driven CRPC may still respond to second-generation AR-targeted therapy (abiraterone or enzalutamide), while AR-indifferent CRPC is typically resistant to AR-targeted therapy.
- AR-targeted treatment is given to patients after treatment of the primary tumor, either in high-risk patients or in those experiencing a PSA rise.
- However, it is hypothesized that earlier treatment with stronger AR-targeted therapy may be of benefit. Ongoing clinical trials are testing AR-targeted therapy (with multiple AR pathway-inhibitors) in high-risk, localized disease patients, prior to prostatectomy.
- A randomized clinical trial at the University of Texas MD Anderson Cancer Center (MDACC) tested 6 months of either abiraterone plus androgen deprivation therapy (ADT), or abiraterone plus enzalutamide plus ADT prior to prostatectomy in patients with high-risk, localized prostate cancer.
- Examination of post-treatment prostatectomy samples found that the glucocorticoid receptor (GR), a relative of AR that can recapitulate much of AR's activity, and cortisol (which activates GR), were upregulated in non-responsive tumors in the abiraterone + ADT group (Figure). Tumors with upregulated GR did not have activation mutations in the AR pathway.
- These data suggest that GR pathway activation can drive resistance to AR-targeted therapy in some patients and should be a biomarker to identify patients who will likely not benefit from AR-targeted treatment.
- GR-expressing CRPC tumors exhibited altered expression of metabolic genes. These data suggest that GR-positive tumors may be driven by changes in tumor metabolism.
- A second clinical trial is being conducted to further understand efficacy and mechanisms of response and resistance in high-risk, localized disease patients treated with neoadjuvant AR-targeted therapy. In this trial, patients will be randomized to 6 months of either abiraterone + ADT, apalutamide + ADT, or abiraterone + apalutamide + ADT, followed by prostatectomy.
- Biomarkers are being developed to identify patients who are unlikely to respond to AR-targeted treatments. These include expression of AR-V7, a short variant of AR that is constantly activated regardless of the presence of androgens and cannot be inhibited by existing AR-targeted treatments.
- At MDACC, a biomarker based on the ratio of AR-V7 to total AR (which includes full-length AR and all AR-variants) has been clinically validated and certified by regulatory agencies (CLIA).
- The AR-V7/AR biomarker is being applied in clinical trials to identify patients who may not benefit from AR-targeted treatment and should be excluded from such trials. Exclusion of "diluting" patients from these clinical trials is proposed to improve determination of the efficacy of AR-therapy in the remainder of patients.
- In one such trial, CRPC patients will be selected based on the AR-V7/AR biomarker and those deemed likely to respond will be enrolled. Patients will be treated with abiraterone plus apalutamide.
- Clinical trials in metastatic hormone therapy naïve prostate cancer (patients who have not yet received ADT) may also benefit from the use of the AR-V7/AR or similar biomarkers to

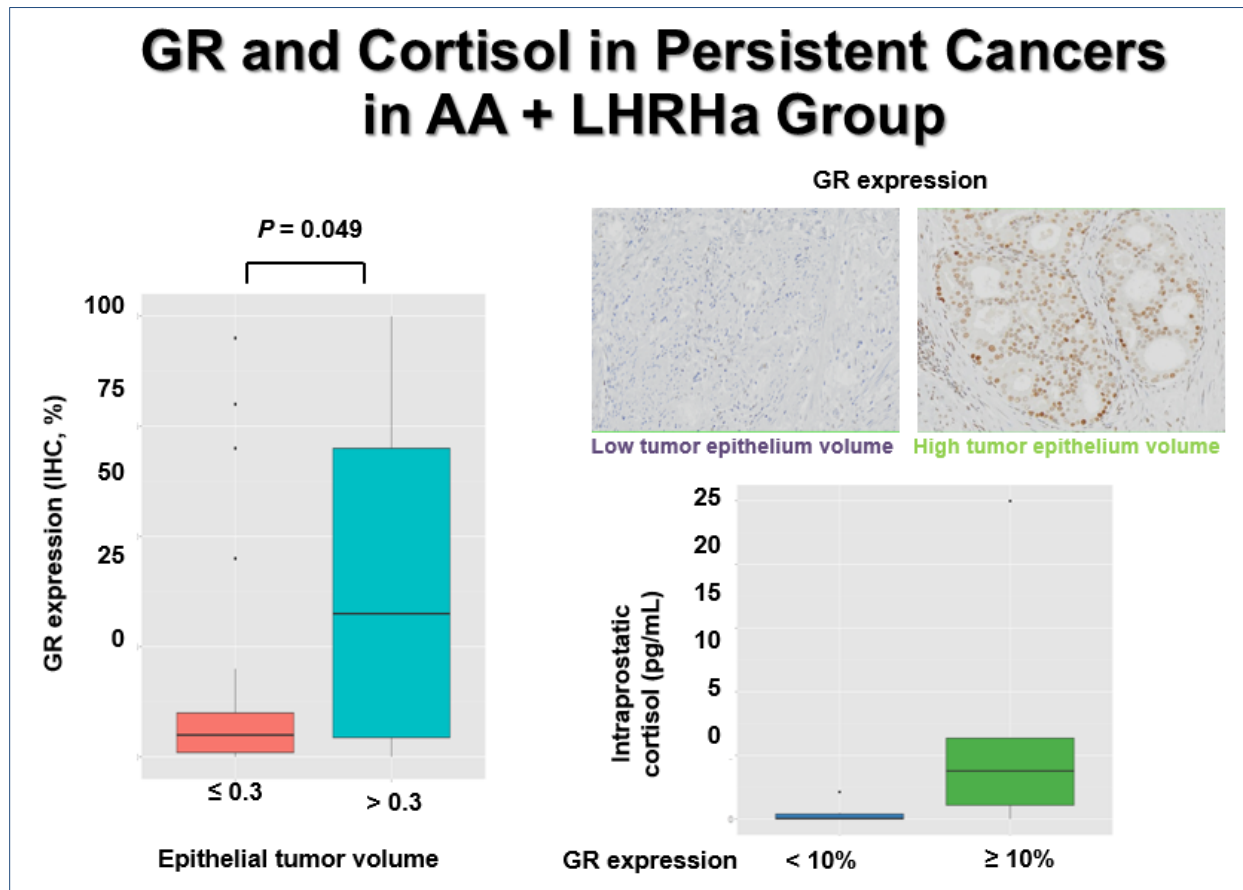


select patients. This is because some of these patients may have pre-existing resistance to AR-targeted therapy.

- Aggressive variant prostate cancer (AVPC) are a heterogeneous group of highly aggressive androgen-indifferent metastatic CRPC. AVPC is characterized by having any of the following clinical features: small cell prostate carcinoma, visceral metastases only, lytic bone metastases, bulky nodes or prostate mass, low PSA relative to volume, neuroendocrine markers & serum CEA or LDH, and early castration-resistance.
- AVPC can be driven by mutations in the tumor suppressor genes p53, RB1, and/or PTEN. AVPC may also be driven by alterations in the “epigenome,” the chemical marks on DNA that control which genes a cell can express.
- AVPC are commonly sensitive to treatment with platinum-based chemotherapy, such as carboplatin or cisplatin.
- AVPC also often have alterations in DNA damage repair (DDR) pathways. DDR alterations are associated with sensitivity to PARP-inhibitors such as olaparib.
- Based on these data, a clinical trial has been initiated to examine the efficacy of treating AVPC patients with cabazitaxel plus carboplatin, followed by olaparib versus observation.
- Another subtype of CRPC is driven by the bone-signaling proteins FGF, OSF, and RANK. These factors promote interactions between prostate cancer cells and bone cells, and promote a bone environment permissive to prostate cancer growth. Therapeutic targeting of these factors is being explored in clinical trials and preclinical studies.
- Radium-223 is an FDA approved treatment that targets prostate cancer bone metastases. Radium-223 is a radioactive element that resembles calcium and is taken up in place of calcium at highly active bone sites, which are typically areas of tumor growth.
- Tumors resistant to Radium-223 were found to differentially express genes including bone markers, DNA repair genes, and immune genes. This suggests that some patients may benefit from the addition of PARP-inhibitors or immunotherapies to Radium-223 treatment.
- Studies in animal models of human prostate cancer bone metastases have identified interactions that occur between AR signaling and immune cells. These findings may help to define strategies for combining AR-targeted therapy with immunotherapy.
- The feasibility of clinical trials and drug development is also an area in need of improvement.
- Because tumors evolve mutations that contribute to drug resistance, the ability to sequence the tumor genome every time a treatment appears to be failing will enable improved precision medicine treatment decisions to be made.
- Technologies to sequence tumor DNA in liquid biopsies are vastly improving and will provide clinicians the ability to reassess tumor mutations throughout treatment. In contrast, the use of invasive tumor biopsies to evaluate tumor mutations has significant limitations in feasibility, as they can be painful, costly, and tumors often grow in areas that cannot be biopsied.
- To further improve patient outcomes, MDACC is developing a program to present patient compliance, toxicity, and monitoring data on a timely basis to clinicians.



- Overall, the development of high impact, biomarker-driven, precision medicine clinical trials will lead to vastly improved treatment and outcomes for patients.



**Figure:** High-risk localized disease patients treated with abiraterone plus ADT prior to prostatectomy in a clinical trial. Examination of post-treatment prostatectomy samples found upregulation of the glucocorticoid receptor (GR) (left, top right) and cortisol (right bottom) in persistent tumors, suggesting that GR upregulation contributes to resistance to AR-targeted therapy.

## *MARS2: Androgen Receptor Splice Variants Update*

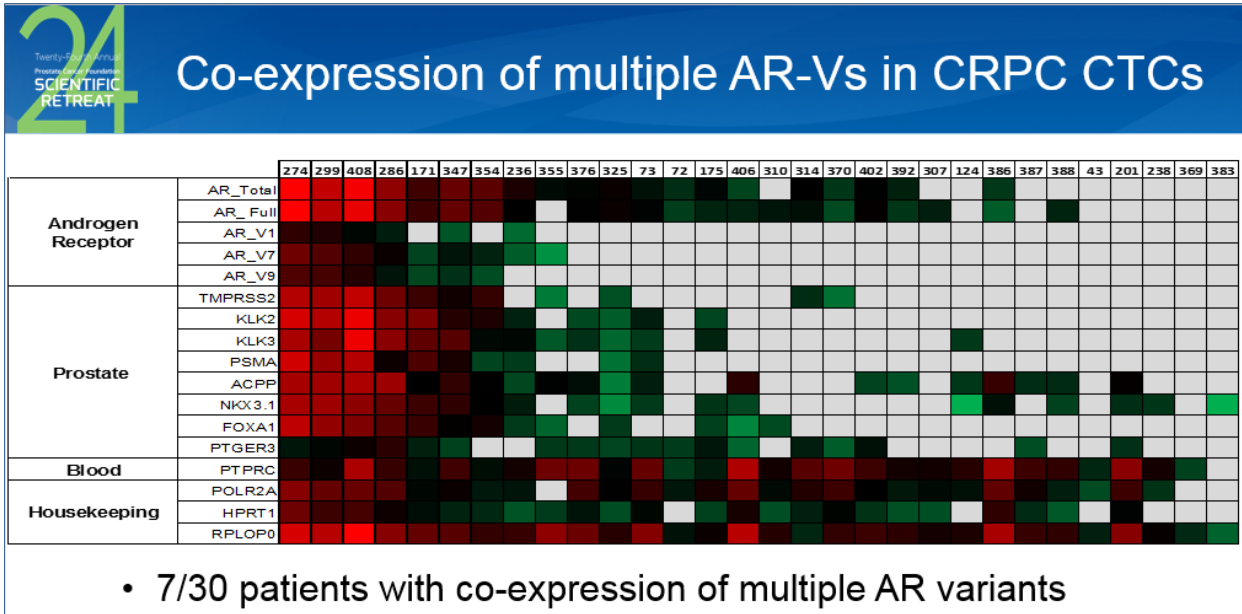
Ganesh Raj, MD, PhD

The University of Texas Southwestern Medical Center at Dallas

- The MARS2: Androgen Receptor Splice Variants Meeting was held in Boston, MA, on May 11, 2017.
- This meeting focused on advancing the understanding of the biology and targeting of androgen receptor (AR) splice variants in prostate cancer.
- AR is the primary driver of prostate cancer, and acts by turning on genes required for growth and survival. AR is consequently the primary therapeutic target for the treatment of prostate cancer. However, resistance to AR-targeted therapy inevitably occurs, necessitating research into mechanisms of resistance and design of alternate treatment strategies.
- One major mechanism of resistance to AR-targeted therapy is the expression of AR-variants, short forms of the AR protein which are constantly active and not effectively targeted by current therapies.
- AR-variants are shorter forms of AR that are produced by using select and alternate gene segments, called exons, to create the protein through a process known as alternative splicing.
- Full-length AR has a “ligand-binding domain” (LBD), which binds to androgens. Full-length AR only becomes activated when the LBD binds androgens. All current FDA approved drugs target the full-length AR by preventing androgens from binding to the LBD.
- AR-variants such as AR-V7 lack the LBD and instead incorporate other small domains into the protein. AR-variants lacking the LBD are constantly active, and are not affected by the presence or absence of androgens. AR-variants are also not responsive to any of the currently approved drugs targeting the full-length AR.
- Many questions remain about the role of AR-Vs in CRPC, including whether AR-Vs can be used as biomarkers of therapeutic resistance or response, whether AR-Vs are molecular drivers of CRPC, and whether AR-Vs can be therapeutically targeted.
- Validated assays have been developed to examine the expression of AR-V7 in clinical prostate cancer samples.
- Studies using these assays have demonstrated that AR-V7 is not expressed in prostate cancer cells prior to treatment with androgen deprivation therapy (ADT). Expression of AR-V7 occurs following treatment with AR-targeted therapy and increases with longer courses of ADT and after treatment with the second-generation AR-targeting therapies abiraterone and enzalutamide.
- AR-V7 expression is associated with poorer prognosis.
- Studies into the expression of different AR-Vs in prostate cancer are limited by the lack of specific tests that can uniquely assess each one.

- RNA-ISH is a specialized assay that evaluates expression levels of RNA (not protein). The RNA of different AR-Vs has a different sequence and this assay has the potential to differentiate between full-length AR and the various AR-Vs. However, RNA levels of a gene do not always correlate with protein levels.
- A RNA-ISH assay for AR-V7 has been developed, and was used to demonstrate that AR-V7 RNA, like the protein, was absent prior to ADT and increased with longer ADT and second-generation AR-targeted therapy.
- Circulating tumor cells (CTCs) are dispersed tumor cells that can be found in patient blood. Assays have been developed to examine the expression of AR-V7 in CTCs. These studies have found that the presence of AR-V7-expressing CTCs was prognostic for resistance to abiraterone and enzalutamide.
- The VERSA system is a technology to isolate CTCs which can be used to examine gene expression and mutational status. VERSA can determine expression of multiple AR-variants simultaneously. Studies using this technology found that prostate cancer cells can express AR and multiple AR-Vs at the same time, including AR-V7, AR-V9, and AR-V1 (Figure).
- These studies suggest that AR-Vs can be biomarkers of therapeutic response or resistance. However, further validation and optimization of these tests are necessary before they can become a standard of care practice.
- Although AR-V expression is highly associated with AR-therapy resistance, more studies are needed to determine whether AR-Vs drive AR-therapy resistance.
- The vast majority of genes that are activated by AR-V7 overlap with genes activated by full-length AR.
- AR must form dimers (two AR proteins bound to each other) in order to activate gene expression. AR-Vs maintain the ability to form dimers and can even partner with full-length AR, activating it in the absence of androgens. Thus, AR-Vs may serve as AR activators.
- AR-Vs were also found to interact with most proteins that full-length AR interacts with.
- The findings that AR-Vs can perform the vast majority of activities that full-length AR does, support the hypothesis that AR-Vs can function as drivers of AR-therapy resistance.
- Studies are underway to identify strategies to therapeutically target AR-Vs.
- The development of AR-V-inhibitors is complicated by the inability to determine the 3D structure of AR-Vs due to an intrinsically disordered structure.
- Strategies for targeting AR-Vs have focused on targeting the DNA-binding domain present in AR-Vs and full-length AR. This would enable targeting of AR and all AR-Vs.
- Novel inhibitors have been developed that target the DNA-binding domain of AR, and have shown activity against enzalutamide-resistant prostate cancer in animal models.
- Drug screens have identified niclosamide as a specific inhibitor of AR-Vs but not full length-AR. Niclosamide was also found to have activity in preclinical enzalutamide-resistant prostate cancers models and is now being tested in phase Ib/II clinical trials.

- These studies suggest that AR-Vs can be therapeutically targeted, though the utility of these agents in prostate cancer still needs to be clinically proven. Combining AR-V-targeting therapies with standard AR-therapy may also be a promising strategy.
- A review of this meeting was published in the scientific journal European Urology: [http://www.europeanurology.com/article/S0302-2838\(17\)31030-8/fulltext](http://www.europeanurology.com/article/S0302-2838(17)31030-8/fulltext)



**Figure:** Studies using the novel VERSA technology found that prostate cancer cells can express AR and multiple AR-Vs at the same time, including AR-V7, AR-V9, and AR-V1. Rows indicate expressed genes and columns indicate different patients.

## *Report from the 2017 Coffey-Holden Prostate Cancer Academy Meeting, Beyond the Androgen Receptor II: New Approaches to Understanding and Treating Metastatic Prostate Cancer*

Heather Cheng, MD, PhD  
University of Washington

- The 2017 Coffey-Holden Prostate Cancer Academy (CHPCA) Meeting was held in Carlsbad, California, from June 14-17, 2017. The CHPCA Meeting is an annual action-tank meeting hosted by PCF that is attended by roughly 75 investigators, half of whom are young investigators.
- The meeting is uniquely designed to produce extensive and constructive discussions on the most urgent and impactful topics concerning research into the biology and treatment of metastatic prostate cancer.
- The theme of the 2017 CHPCA meeting was “Beyond the Androgen Receptor II: New Approaches to Understanding and Treating Metastatic Prostate Cancer.”
- Dr. Heather Cheng, who chaired the organizing committee, overviewed some of the most important topics discussed at the meeting.
- One major theme of the meeting was understanding the transition of prostate cancer to “aggressive variant prostate cancer” (AVPC), a subtype of highly aggressive mCRPC that does not express or require the androgen receptor (AR) and may be resistant to AR-targeted therapy.
- AVPC often exhibit properties of other cell types such as stem cells and neuroendocrine cells rather than prostate epithelial cells. Understanding the mechanisms enabling the ability to gain features of other cell types will be critical to developing new treatment strategies for AVPC.
- Studies into mechanisms that drive the development of AVPC have uncovered a role for mutations in TP53, RB1, and BRN2. In addition, activation of SOX2, which can be driven by these mutations, is a critical driver of AVPC.
- Studies have also identified EZH2 as a driver of AVPC. EZH2 is a regulator of a cell’s epigenetic program, which consists of chemical modifications on DNA that determine which genes a cell can and cannot express. EZH2 activity may be altered by AVPC-driving mutations, including RB1-loss and N-MYC gain.
- Novel experimental methods in which prostate cancer cells are grown as mini-tumors in the lab (“organoids”) have enabled screening of drugs for efficacy against AVPC. These screening studies identified inhibitors of EZH2 as promising for the treatment of AVPC organoids.
- AVPC cells have been found to express the protein CEACAM5. These findings have led to efforts to develop CAR T-cells that target CEACAM5, which are now in preclinical studies.
- Another major theme of the meeting was the role of the glucocorticoid receptor (GR) in driving resistance to AR-targeted therapy and the development of CRPC.

- GR expression and glucocorticoid metabolism have been shown to enable resistance to AR-targeted therapies including enzalutamide.
- Therapies targeting GR are in development and are also being tested for the treatment of breast cancer.
- The role of DNA damage repair (DDR) mutations in prostate cancer was actively discussed. Mutations in DDR genes have been identified in ~25-30% of patients with metastatic prostate cancer, about half of whom inherited this mutation. Tumors with these mutations are highly sensitive to treatment with PARP-inhibitors and platinum chemotherapy.
- Biomarkers for identifying these patients are necessary for optimizing treatment. In breast and ovarian cancer, in which these mutations are also common, biomarkers for DDR alterations that are being explored include mutations, as well as non-mutational alterations that cause defects in DNA repair pathways and render tumors sensitive to the same treatments.
- Some DDR alterations may not cause tumors to be sensitive to treatment with PARP-inhibitors. These occurrences are being studied to understand the biology and identify potential new combination treatment approaches that may be effective.
- Combining PARP-inhibitors with inhibitors of the TWIST1-HOXA9 pathway can promote DNA repair defects and are promising in preclinical models.
- DDR mutations are more common in the SPOP-mutant prostate cancer subtype. Studies are underway to understand the interaction between SPOP mutations and DDR mutations and identify therapeutic strategies.
- The findings that inherited DDR mutations occur in ~12% of metastatic prostate cancer patients has necessitated a need to integrate genetic information into clinical practice.
- These same mutations, if inherited by women, may be associated with increased risk of breast or ovarian cancer and have established recommended screening guidelines. Thus, identifying men who carry these inherited mutations and encouraging family members to determine their own risk and recourse for cancer is a significant need.
- Urologists and medical oncologists are creating new models of prostate cancer clinics that focus on improving identification and management of these patients and providing education and resources for them and their families.
- Patient partnership is critical for increasing the identification of these patients and being able to use this information to impact families.
- Efforts are also being made to address disparities that lead to poorer outcomes in patients of African descent in the US and worldwide.
- Other major topics discussed at the CHPCA meeting were new imaging and radionuclide therapies.
- Improved prostate cancer imaging methods include PSMA-PET and Choline-PET imaging. Each of these agents has different properties that need to be considered.

- Clinical trials that demonstrate that improved sensitivity and specificity compared with current standards are needed to obtain FDA approval. Trials must also demonstrate that information from these new methods changes patients' treatment plan and improves clinical outcomes.
- Novel strategies to help immunotherapy work more effectively in prostate cancer were another major topic of discussion.
- Promising approaches include combining checkpoint immunotherapy with novel prostate cancer vaccines, Radium-223, AR-targeted therapy, and PARP-inhibitors. Clinical trials testing each of these new combinations are underway.
- Other novel strategies to activate anti-tumor immune responses in prostate cancer include targeting the soluble NKG2D ligand sMIC in order to activate natural killer (NK) cells (a cell type with strong cancer killing ability), and activating T-cells with OX40 agonists.
- Overall, over 400 questions were asked over the course of 34 presentations. The discussions held will accelerate new research into the most critical areas needed to improve treatment and outcomes for men with advanced prostate cancer.
- A review of the CHPCA meeting was published in the scientific journal *The Prostate*: <http://onlinelibrary.wiley.com/doi/10.1002/pros.23424/full>

## *Overview of the 2017 Advanced Prostate Cancer Consensus Conference (APCCC2017)*

**Silke Gillessen, MD**  
Kantonsspital, Switzerland

- The Advanced Prostate Cancer Consensus Conference (APCCC) is a bi-annual gathering of prostate cancer experts from around the globe (Figure) to discuss and create consensus treatment recommendations for situations of advanced prostate cancer patients for which evidence to guide the choice of optimal treatment is lacking or controversial.
- The 2017 APCCC was held in St. Gallen, Switzerland, from March 9-11, 2017, and consisted of a panel of 61 prostate cancer experts from 21 countries.
- Ten areas of controversy were discussed at the 2017 APCCC. These included: management of castration-sensitive/naive prostate cancer (CSPC); sequencing/combo treatment for metastatic castration-resistant prostate cancer (mCRPC); the use of novel imaging modalities; tissue and blood based biomarkers for use in daily clinical practice; germline and somatic mutations; management of high risk and locally advanced prostate cancer; oligometastatic and oligo-progressive prostate cancer; prevention and management of the side effects of systemic treatment; palliative and supportive/preventive care; and global access to prostate cancer drugs and treatment in countries with limited resources.



- Each topic was extensively discussed, then assembled into 150 patient management questions that were voted on by 51 panel members.
- Consensus was defined as having 75% or more of the panelists voting in agreement on one option. In many of the questions, no consensus was reached.
- For instance, docetaxel in addition to ADT was recommended by 96% of panelists for the treatment of men diagnosed with metastatic CSPC and high-volume disease (visceral metastases and/or four or more bone lesions).
- Docetaxel in addition to ADT was not recommended by 90% of panelists for treatment of men with non-metastatic CSPC.
- No consensus for the addition of docetaxel to ADT was reached for four other disease states, including for men relapsing with high volume metastatic CSPC after prior treatment for localized prostate cancer.
- Consensus was reached for three of six factors voted on for defining patients as unfit to receive docetaxel, including severe hepatic impairment, grade  $\geq 2$  neuropathy, and low platelet or neutrophil counts.
- Consensus was also reached for the following recommendations:
  - Lymph node dissection was recommended in high-risk localized prostate cancer patients undergoing prostatectomy, and consensus was reached on which regions to sample and the information to include in the pathology report.
  - For oligometastatic prostate cancer, PSMA was recommended as the tracer of choice if PET/CT imaging was being considered.
  - In asymptomatic patients with CRPC, abiraterone or enzalutamide was recommended as first line treatment.
  - No predictive biomarker was deemed ready for use in daily routine clinical practice.
  - Taxane chemotherapy (as opposed to abiraterone or enzalutamide) was recommended as second line treatment for symptomatic CRPC patients who did not respond to first line treatment with abiraterone or enzalutamide.
  - Patients should be advised about strong evidence that ADT increases risk of bone loss and fractures. Regular physical exercise was recommended in men starting ADT.
  - Many areas of discussion had no consensus reached, indicating the topics that need more research and may necessitate prioritization for trial conduct.
  - For example, no consensus was reached for treatment of oligometastatic disease, for best use of novel imaging, and for treatment of patients with DNA repair defects in their tumor.
  - Many clinical trials in these areas are ongoing.
- An open-access report on the 2017 APCCC Consensus Meeting can be accessed at: [http://www.europeanurology.com/article/S0302-2838\(17\)30497-9/fulltext](http://www.europeanurology.com/article/S0302-2838(17)30497-9/fulltext)

**Panel APCCC17**  
*Inspired by Eleni Efsthathiou*

Legend:  
 ◆ urologist  
 ◆ medical oncologist  
 ◆ radiation oncologist  
 ◆ others

Name	Country	Category
N. Clarke	UK	urologist
G. Attard	UK	medical oncologist
J. De Bono	UK	medical oncologist
R. Eeles	UK	radiation oncologist
T. Beer	US	urologist
H. Beltran	US	urologist
C. Evans	US	urologist
P. Kantoff	US	urologist
K. Mastris	UK	urologist
N. James	UK	medical oncologist
A. Padhani	UK	radiation oncologist
C. Parker	UK	radiation oncologist
M. Sydes	UK	others
C. Drake	US	urologist
B. Carver	US	urologist
W. Oh	US	urologist
H. Scher	US	urologist
M. Smith	US	urologist
M. Roach	US	urologist
H. Suzuki	JP	urologist
E. Efsthathiou	US	urologist
C. Logothetis	US	urologist
M. Rubin	US	urologist
N. Shore	US	urologist
C. Sweeney	US	urologist
H. Soule	US	urologist
S. Halabi	US	radiation oncologist
F. Feng	US	radiation oncologist
O. Sartor	US	urologist
C. Higano	US	urologist
C. Ryan	US	urologist
A. Morgans	US	radiation oncologist
M. Morris	US	urologist
C. Pritchard	US	urologist
F. Saad	CA	urologist
R. Bristow	CA	urologist
I. Tannock	CA	urologist
M. Gleave	CA	urologist
R. Dos Reis	BR	urologist
F. Maluf	BR	urologist
P. Ost	BE	urologist
B. Tombal	BE	urologist
A. Heidenreich	DE	urologist
T. Wiegel	DE	urologist
G. Daugaard	DK	urologist
G. Kramer	AT	urologist
A. Sella	IL	urologist
V. Murthy	IN	urologist
B H Chung	KR	urologist
K Fizazi	FR	urologist
R. Khauli	LB	urologist
N. Mottet	FR	urologist
A. Bossi	FR	urologist
M. Frydenberg	AU	urologist
I. Davis	AU	urologist
P.L. Kellokumpu-Lehtinen	FL	urologist
S. Gillissen	CH	urologist
D. Castellano	ES	urologist
S. Fanti	IT	urologist
C. Sternberg	IT	urologist
R. Valdagni	IT	urologist

## Session 8: Potential Applications of Artificial Intelligence in Prostate Cancer

---

### *Machine Learning Methods for Automated MRI Imaging in Prostate Cancer*

Ronald Summers, MD, PhD  
National Institutes of Health

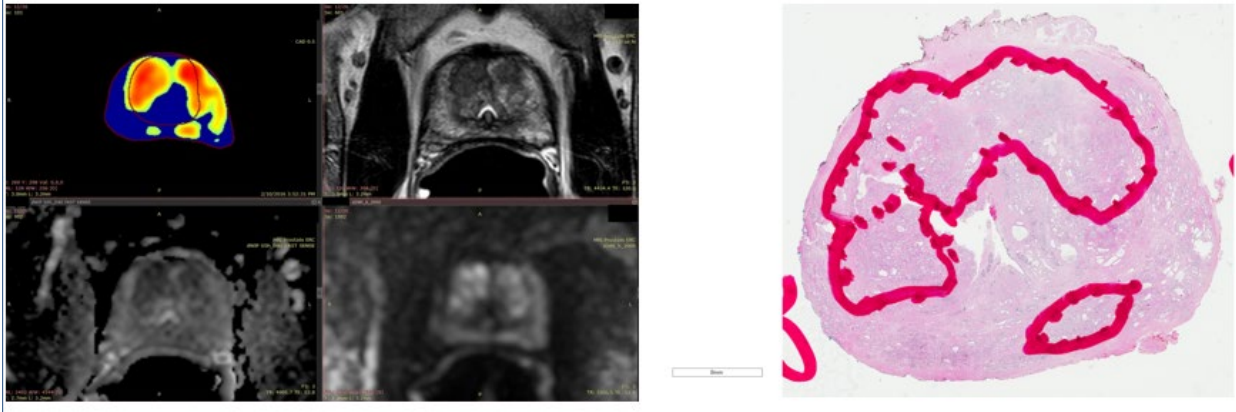
- Advances in artificial intelligence are being used to facilitate and accelerate scientific research and improve the practice of precision medicine.
- Machine learning is a methodology in which computer programs learn from and make predictions and decisions based on raw data inputs, without being explicitly programmed.
- Machine learning algorithms are being developed to recognize cancer versus normal tissues in magnetic resonance imaging (MRI) and improve the accuracy of cancer diagnoses.
- Dr. Ronald Summers discussed the use of machine learning to automate MRI for improved prostate cancer diagnosis.
- MRI is a complex molecular imaging technology that is being developed for improved diagnosis and prognosis of prostate cancer.
- MRI produces several types of images that depict the distribution and movement of water molecules in tissues in response to a series of magnetic pulses applied to the body. MRI images can also be obtained in conjunction with the administration of an MR contrast agent, a method referred to as Dynamic Contrast-Enhanced (DCE) MRI.
- In standard radiology practice, these images are read by an experienced radiologist to identify different tissues and characteristics and make a diagnosis.
- “Radiomics” is a new field that relies on extraction and analysis of measurable features from radiology images. These features include signal intensity, texture, shape, edges, and contrast. For example, cancer frequently has a different texture on MRI images compared with normal tissue.
- Due to the complexity of MRI images and the many layers of data they represent, machine learning may vastly increase the accuracy of MRI in making diagnoses and prognoses.
- There are two paradigms for machine learning. In one paradigm, the program is fed data along with pre-defined features deemed important for making the predictions. The program then uses these features to build a “classifier” (a computer algorithm) that can make the predictions. For instance, the program could be told that certain tissue features indicate prostate cancer. However, this is dependent on humans knowing the most important features from the data for making the predictions.
- In a second paradigm, the machine learning program is only given the raw data and learns from it to define its own features that best make the prediction. In this case, the program would be fed the images, the anatomical location at which they were taken, and told which

images have prostate cancer, but would define the features that best identify prostate cancer itself.

- Several dozen machine learning algorithms have been developed to diagnose prostate cancer using MRI.
- For example, a machine learning algorithm to predict the presence of prostate cancer was developed using MRI images that had been corrected for patient movement during the scan, and in which different regions of the prostate had been outlined by a radiologist. The algorithm was validated and refined by feeding the program data on the anatomic locations of tumors in surgical specimens from patients who underwent prostatectomy after MRI (Figure).
- Machine learning systems can now identify the regions of the prostate in MRI images with an accuracy of ~90%.
- However, the performance of these algorithms for diagnosis of prostate cancer is in the range of 80-90%. This indicates a need for further improvement.
- MRI-based machine learning algorithms are also being developed to guide confirmatory diagnostic prostate biopsies.
- Deep learning is a growing field of study, particularly in radiology. Deep learning is a method that enables the use of many more layers of data and data processing to make more accurate predictions. Deep learning has demonstrated great success in applications such as object recognition in the computer vision field.
- Deep learning is being developed to predict patient survival after a cancer diagnosis.
- There are several competitions that are being conducted by scientific societies to advance machine learning for using MRI for prostate cancer diagnosis.
- Currently, there are only three publicly available prostate MRI datasets representing ~600 patients. This leads to problems including the inability of machine learning programs to detect prostate cancer in less common or more complex scenarios.
- Further advancements in machine learning and deep learning for diagnosis and prognosis of prostate cancer require additional, large datasets that are well annotated (data are not missing parameters). Scientists are encouraged to make data public following publication of studies.
- Overall, these studies demonstrate that machine learning is a highly promising field that will enable large improvements in the accuracy of MRI for prostate cancer diagnosis and prognosis.

# Detection

- Identifying the presence and location of disease
- Requires appropriate standard of reference, e.g., whole mount histopathology



**Figure:** Machine learning algorithms were used to predict the location of prostate cancer in MRI images. Upper left: algorithm-predicted location of tumors; bottom left and center columns: raw prostate MRI images. Tumor location was confirmed based on examination of surgical specimens (right, tumor location outlined in red). Images courtesy of Drs. Nathan Lay (NIH Clinical Center) and Baris Turkbey (NIH National Cancer Institute).

## *Integrating Imaging and Pathologic/Genomic/Biomarker Data Using Machine Learning Methods*

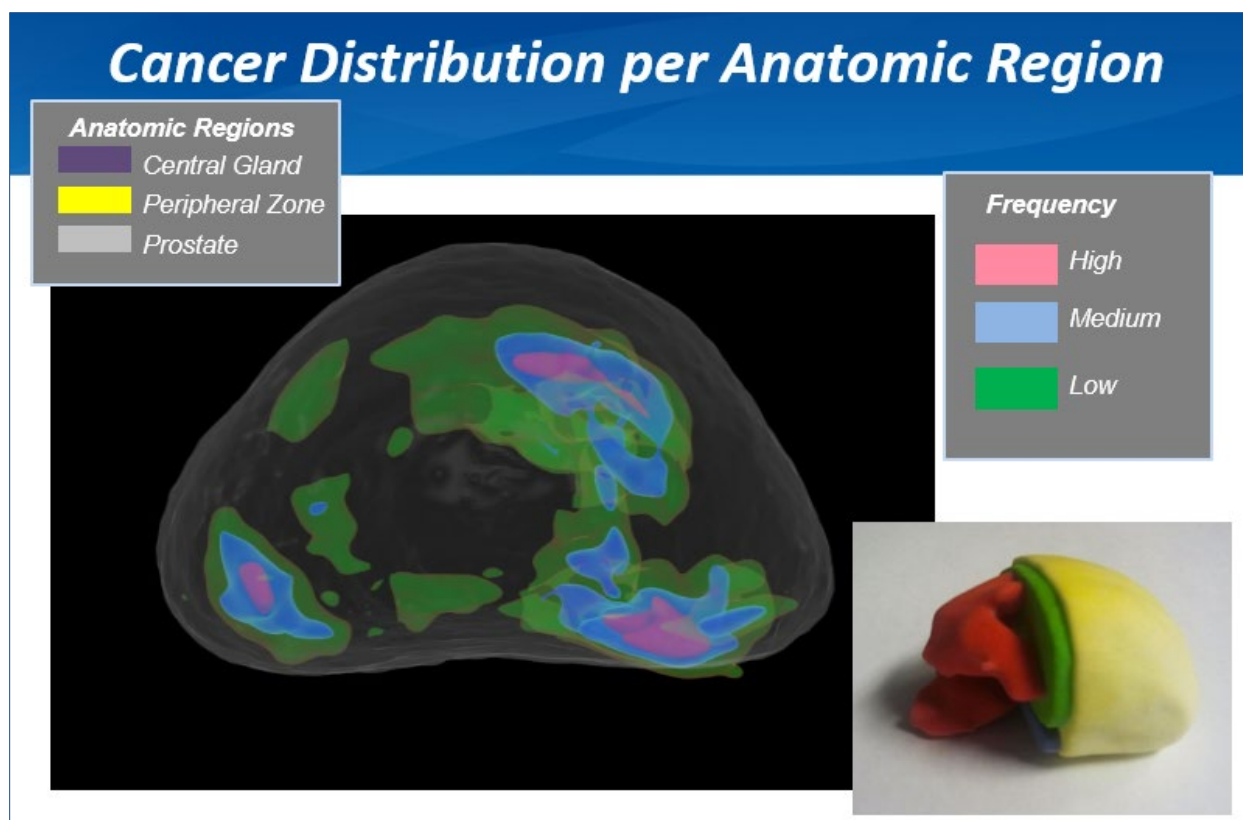
Anant Madabhushi, PhD  
Case Western Reserve University

- Prostate cancer is studied at multiple levels, including by radiologists who study scans, pathologists who study disease at the tissue and cellular levels, and molecular biologists who study genomics, gene expression, and other molecular mechanisms regulating the disease.
- Processes to integrate these different types of data will accelerate our understanding of prostate cancer biology and improve diagnosis, prognosis, and treatment.
- Because of the complexity of these data, high-level bioinformatics methods incorporating machine learning may be necessary to gain a complete understanding.

- Machine learning is a method in which computer programs are not explicitly programmed but instead are fed raw data and learn from it to build algorithms that make predictions and decisions.
- Dr. Anant Madabhushi discussed efforts to integrate different types of prostate cancer data and use machine learning to improve patient diagnosis and management.
- Machine learning is being used to create algorithms that can accurately diagnose prostate cancer from magnetic resonance imaging (MRI) images.
- In one study, data were used from patients who underwent prostate MRI prior to prostatectomy. The program was fed data including MRI images and location-matched images of surgical specimens in which the regions of tumor growth had been outlined by pathologists. These data were used to identify MRI features that could accurately identify prostate cancer and create an algorithm to diagnose prostate cancer using MRI.
- In another study, prostate pathology images and MRI images from 80 patients were overlaid to create a 3D atlas depicting where cancer most often occurs within the prostate (Figure).
- Different MRI features were found to be better at identifying cancer in different regions of the prostate, for instance in the peripheral zone versus the transitional zone. Based on this, algorithms were created to best use MRI data to identify cancer in different prostate regions.
- In another study in 80 patients who had received MRI followed by radical prostatectomy, pathologists mapped regions of prostate cancer as well as atypical findings such as inflammation, atrophy, and high grade premalignant lesions on pathology slides. These pathology slide images were then mapped onto MRI images to identify MRI features that could distinguish atypical benign features from prostate cancer.
- MRI imaging studies revealed that the prostate gland changes shape (indentations and distentions) when cancer is present. In contrast, the volume (size) of the prostate can change in both prostate cancer and benign instances. How to best incorporate prostate gland shape abnormalities in diagnosing prostate cancer is being studied.
- The current standard for evaluating MRI is the PI-RADS system, which is a scoring system based on radiologists' interpretation of the images. However, PI-RADS scores are not always concordant with findings from prostate biopsies. Machine learning-based MRI algorithms have been found to improve the accuracy of the PI-RADS scoring system and reduce both false-positive and false-negative PI-RADS errors.
- In addition to distinguishing cancer from benign prostate in MRI images, machine learning algorithms are also being developed to distinguish low vs. high risk prostate cancer and predict the likelihood of recurrence.
- A study in a cohort of patients who had MRI imaging of their prostate prior to treatment, identified MRI features that could predict biochemical recurrence within 5 years of radical prostatectomy, with an accuracy rating of ~89%.
- The shape of the prostate was also found to correlate with biochemical recurrence.
- Other prostate tissue characteristics are being assessed to identify biomarkers that can predict risk and improve patient diagnosis and prognosis.

- The relationship between MRI, pathology features, and vascular patterns within the prostate were examined. MRI features that correlated with vascular features and predicted Gleason grade of the tumor were identified.
- A study that evaluated the appearance of prostate glands in surgical specimens found that organized gland orientations were associated with non-aggressive disease, while disordered gland orientations were associated with aggressive disease. This measurement of “gland disorder entropy” was also found to predict the risk for biochemical recurrence within 5 years following prostatectomy.
- African-American men have a significantly higher risk for aggressive and lethal prostate cancer compared with Caucasian American men. African-American men were found to have higher measures of prostate gland disorientation and prostate shape irregularity than Caucasian patients with tumors of the same Gleason grade.
- Another study found that morphological features of benign regions of the prostate were highly predictive of biochemical recurrence and metastasis and were more prognostic than tumor features.
- The combination of imaging and pathology features with molecular features such as gene expression is also being studied for utility in improving machine learning based predictions.
- Collectively these studies have identified multiple imaging, pathology, and molecular characteristics that can be integrated into machine learning programs for improved accuracy of prostate cancer diagnosis and prognosis.
- Further development of these technologies into validated clinical tools will improve prognosis, and stratification of patients who should receive active surveillance versus immediate treatment, and predictions of treatment responses.





**Figure:** A 3D atlas that depicts where cancer most often occurs within the prostate was created by fusion of prostate pathology and MRI imaging maps for 80 patients.

## Computational Pathology

Thomas Fuchs, PhD

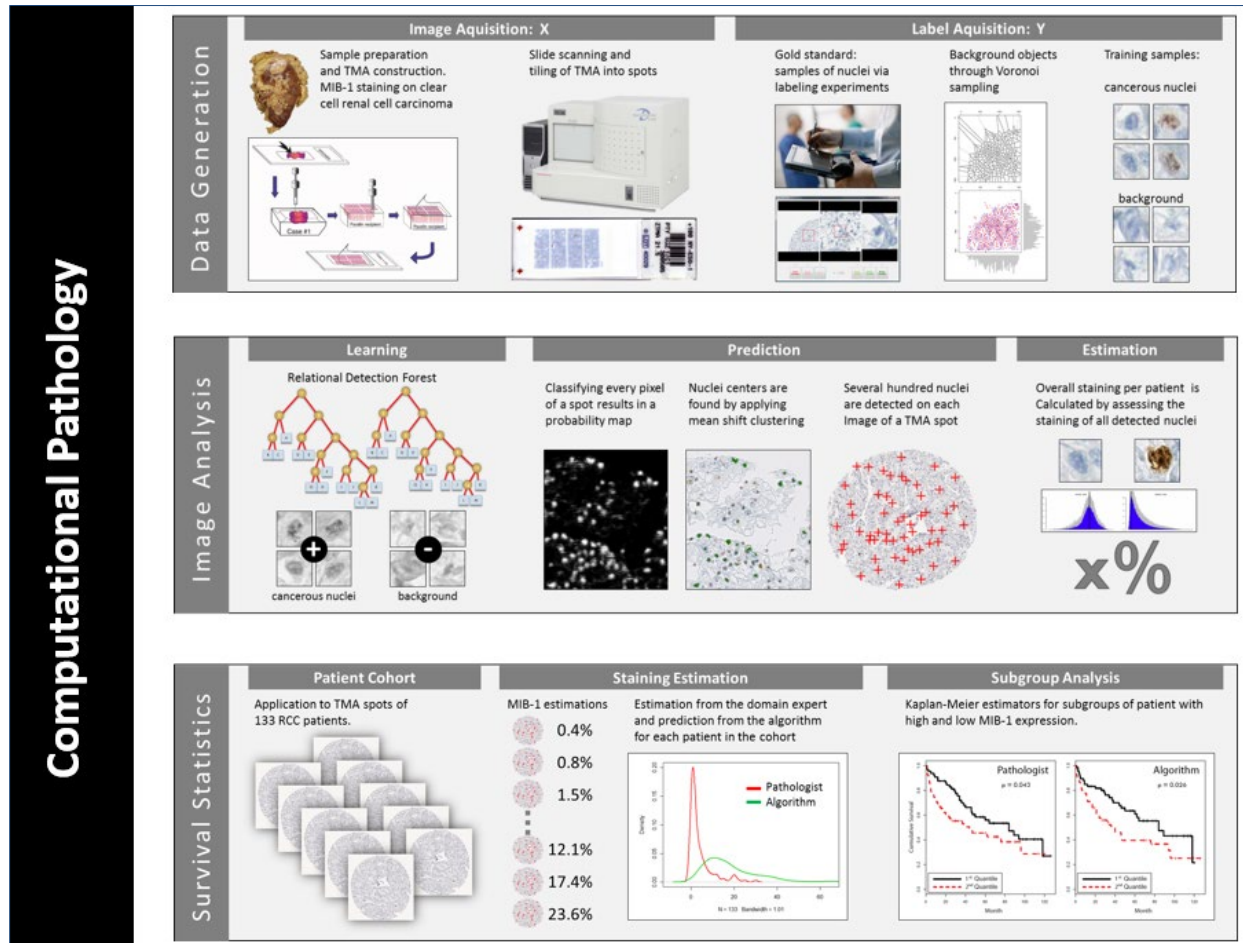
Memorial Sloan Kettering Cancer Center

- Pathology is an arm of the medical field that studies the microscopic features of tissues to answer critical questions such as whether tissues in biopsy or surgical samples are benign or malignant, to examine surgical margins, and to study the biology of disease.
- In traditional pathology, tissues from patients collected by biopsy or during surgery are thinly sliced and mounted onto glass slides. The slides are then stained with special dyes that label different molecules or proteins within the cell, and an experienced pathologist examines the slide under a microscope.
- Based on the cells' appearance, location, and staining with the dyes, pathologists are able to tell what kind of cells are present, whether they are normal or abnormal, and what is likely going on regarding certain aspects of biology.

- Computational pathology is a developing field in which automated imaging and machine learning algorithms are used to analyze patient tissues for disease phenotypes.
- Computational pathology has been accelerated in recent years by the development of automated microscope slide scanning and analysis technology. These automated technologies are able to image the entire slide with digital cameras attached to microscopes, and use machine learning software to analyze the tissues and cells on the slide (Figure).
- Dr. Thomas Fuchs discussed the growing role for computational pathology in improving tissue analysis, patient treatment, and the understanding of cancer biology.
- Each tissue slide, when imaged under a microscope at a level that allows visualization of cells and sub-cellular structures, creates ~6 billion pixels of data. As a frame of reference, all of the data in ImageNet's image recognition database comprise ~2.8 trillion pixels, the equivalent of just 474 tissue slides. This is far more than can be analyzed by human eyes in a reasonable amount of time, necessitating automated artificial intelligence and deep learning systems to comprehensively analyze these specimens.
- Computational pathology will also help with the problem of variability between different pathologists in characterizing disease tissues. For instance, classification of benign versus tumor tissues by a single pathologist can vary by as much as 20% by simply flipping and rotating a tissue slide.
- Artificial intelligence has been developed to distinguish cell shapes and sizes associated with various disease states, recognize normal and abnormal cellular and tissue structures, and create 2D and 3D maps of different cell types within tissues.
- Because there are many different cancer subtypes and tissue pathologies that can occur, large sets of high quality data are needed to advance this field.
- At Memorial Sloan Kettering Cancer Center (MSKCC), approximately one million new glass slides of tissue specimens are collected per year. MSKCC archives currently contain about 25 million slides. About 500,000 of these slides have been digitally imaged so far, generating one petabyte of compressed image data.
- Dr. Fuchs and colleagues are using this collection of samples to identify correlations between tissue pathology and genomic alterations in the tumor. For example, prostate cancer pathology features have been identified that associate with mutations in the SPOP gene.
- The MSKCC program is working to improve quality control of slide scanning to avoid blurry images.
- Portals are being created to enable all MSKCC researchers to access and analyze data from different image scanning systems, use various analysis software, and link imaging data to genomics, gene expression, and clinical outcomes data from the same patient. Expert pathologists are integrated into this program to ensure that the automated image analysis programs are being properly trained to accurately recognize different disease states.
- To enable high performance computing for analyzing this data, the Computational Pathology group at MSKCC built the largest dedicated deep learning cluster for pathology comprising six DGX-1 supercomputers with a total of 6 petaFlops. This supercomputer cluster facilitates training of deep neural networks from tens of thousands of digital slides at once. Deep

neural networks are multi-layer statistical models which are capable of learning complex representations, such as to differentiate prostate cancer from normal tissue.

- Validation that artificial intelligence programs can accurately recognize and diagnose diseases will lead to confidence in these systems to analyze data without human supervision.
- Another method of developing artificial intelligence systems is through “generative adversarial networks.” In this method, two systems work in tandem; one produces real and fake images, and the other works to identify which images are real and which are not. This method allows introspection into what the algorithms are actually recognizing and enables improvement of the systems.
- These efforts will result in the development of clinical grade computational pathology systems that can accurately diagnose disease from pathology slides. This will lead to new understandings in disease biology and improve clinical management of patients.



**Figure:** Computational pathology systems include automated microscope slide scanning and analysis technology. These automated technologies are able image the entire slide with digital cameras attached to microscopes and use machine learning software to analyze the tissues and cells on the slide. Incorporation of clinical data into this system enables correlations to be made between tissue pathology and clinical outcomes.

## Session 9: Recent Advances in Genetically Engineered Mouse Models (GEMMs) of Lethal Prostate Cancer

---

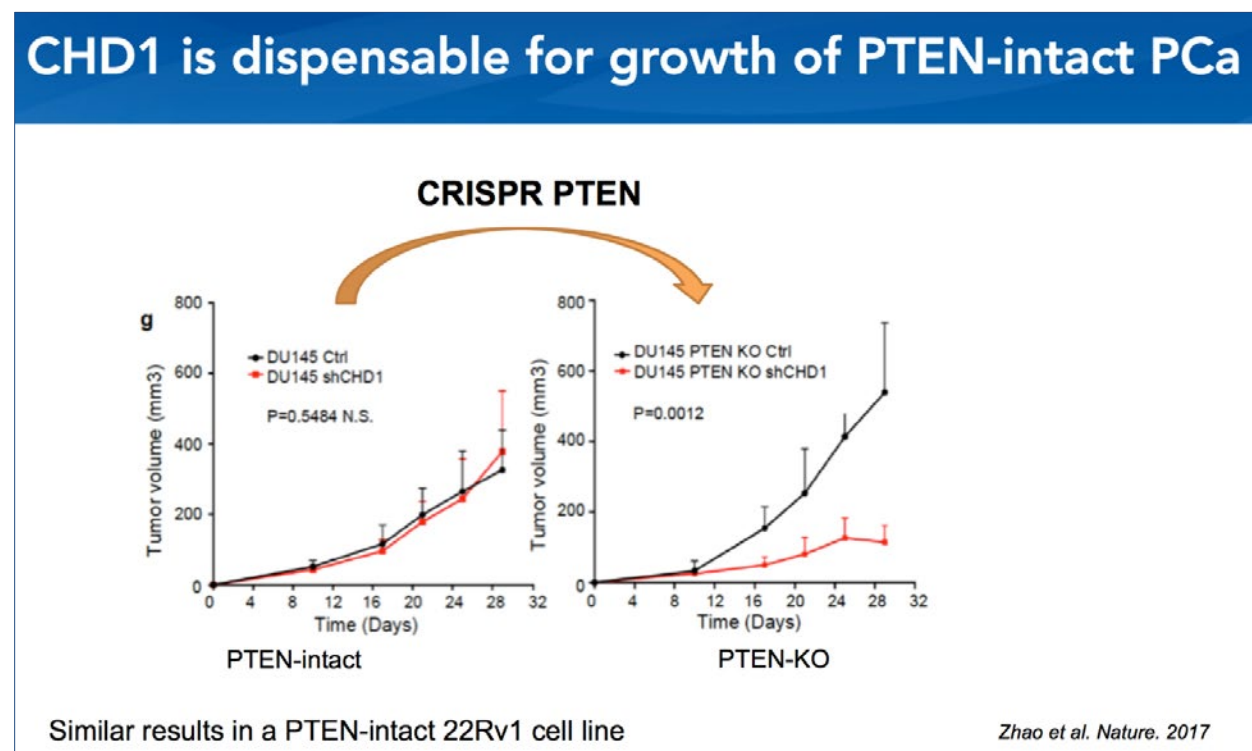
### *Synthetic Essentiality: Targeting Cancer-Specific Vulnerabilities*

Ronald DePinho, MD

The University of Texas MD Anderson Cancer Center

- As cancer cells evolve, they continuously acquire more mutations to survive in different parts of the body and evade therapy. However, under certain conditions these mutations can also be weaknesses and represent treatment opportunities.
- Synthetic lethality is a concept in which tumor cells that have lost activity of one molecular pathway (typically via mutations) become highly dependent on a second related pathway for survival. Therapeutically targeting the second pathway achieves selective killing of the cancer cells while sparing normal cells in which the first pathway is still intact.
- Sometimes deletion of a tumor suppressor gene (which tumor cells acquire to gain growth and survival advantages) inadvertently results in deletion of a neighboring essential, but redundant “house-keeping” gene. Again, the cancer cell would become reliant on a backup house-keeping pathway for survival. Collateral lethality is a concept in which cancer cells that have lost house-keeping genes are selectively killed by targeting the backup pathway.
- Dr. Ronald DePinho discussed studies to identify targetable synthetic-lethal and collateral-lethal relationships in prostate cancer.
- PTEN is a tumor suppressor gene that is commonly deleted in prostate and other cancers. PTEN acts to suppress the activity of the cancer-driving PI3K pathway.
- Examples of collateral-lethal mutations have been documented in prostate and other cancers. For example, in tumor cells with PTEN deletions, deletions of neighboring house-keeping genes with roles in metabolism and cell division have also been observed (GLUD1, MINPP1, PAPSS2, KIF20B, PANK1, and ATAD1).
- Dr. DePinho and team hypothesized that possible synthetic-lethal relationships can be found by identifying genes which are occasionally deleted in cancer but never co-deleted in the same tumor cell. This concept was termed “synthetic-essentiality.”
- For example, the DNA repair genes BRCA1 and PARP are never co-deleted in prostate cancer cells and are a targetable synthetic-lethal gene pair. BRCA1-deficient prostate, breast, and ovary tumors are highly sensitive to treatment with PARP-inhibitors.
- PTEN and PARP are also never co-deleted in prostate cancer cells and may be a synthetic-lethal pair.
- Examination of prostate cancer genomics datasets revealed mutually exclusive occurrences between CHD1-deletions and either PTEN-deletions, or PI3K-pathway activating mutations. This suggests that CHD1 may be synthetic-lethal with PTEN- or other PI3K-pathway genes.

- CHD1 is a protein that promotes a stem cell-like state by maintaining DNA in an open and accessible formation and activating gene expression.
- When CHD1 was deleted in PTEN-deficient prostate cancer cells, they lost the ability to grow in mice (Figure). In contrast, in PTEN-normal prostate cancer cells, deletion of CHD1 had no effect on tumor growth (Figure).
- Further studies found that PTEN promotes CHD1 degradation.
- CHD1 was found to bind to and regulate genes that are activated by the survival gene NF- $\kappa$ B1.
- These studies suggest that when PTEN is deleted, cancer cells are able to survive and progress due to NF- $\kappa$ B1 activation by CHD1.
- Dr. DePinho and team have generated animal models to better study and understand the relationship between PTEN and CHD1 in prostate cancer.
- Overall, these studies indicate that CHD1 may be a promising therapeutic target in PTEN-deficient prostate cancer.



**Figure:** Deletion of CHD1 (red line) has no effect in PTEN-normal prostate tumors (left) but stops the growth of PTEN-deficient prostate tumors (right).

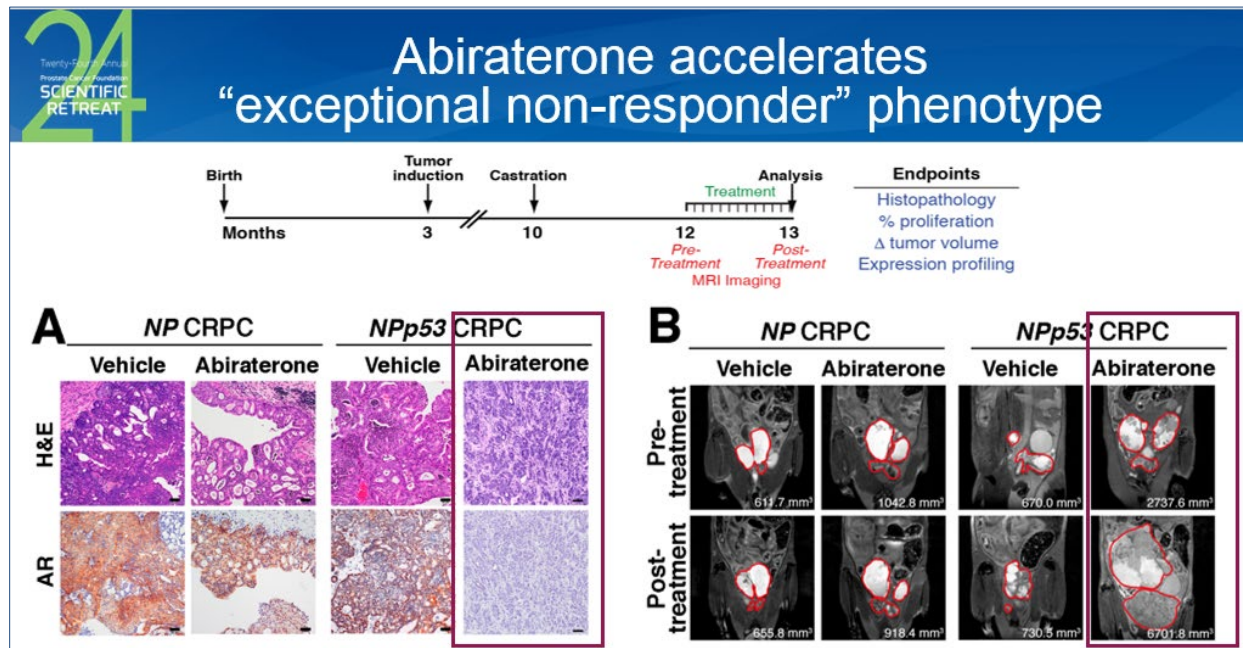


## *Lineage Plasticity as a New Mechanism for Drug Resistance*

Cory Abate-Shen, PhD  
Columbia University Medical Center

- Stem cells were once thought to be a unique type of cell from which all other cells differentiate in a one-directional manner. However it is now known that under certain conditions such as cancer, differentiated cells can revert to a stem cell-like state.
- The ability of differentiated cells to revert to stem cell-like states or to differentiate into other cell types is referred to as “lineage plasticity.”
- Lineage plasticity allows cancer cells to adapt to growing in other areas of the body and to develop resistance to cancer therapy.
- Dr. Cory Abate-Shen discussed studies to understand the mechanisms of lineage plasticity that enable prostate cancer cells to acquire treatment resistance.
- Dr. Abate-Shen and team have developed a series of animal models of prostate cancer with different mutations that represent prostate cancer at different stages of progression. These models are being studied to better understand human prostate cancer progression and treatment resistance.
- NKX3.1 is a gene that is commonly mutated or deleted early in the development of prostate cancer.
- Dr. Chen and colleagues developed genetically engineered mice in which NKX3.1-deletion can be induced in prostate cells, and leaves a mark in the cells in which it was deleted. This allows the researchers to control when the deletion takes place and to track which cells have deleted NKX3.1.
- PTEN and p53 are tumor suppressor genes that are co-mutated in about a quarter of castrate resistant prostate cancer (CRPC) cases.
- Mouse models of NKX3.1/PTEN/p53-deficient prostate cancer were created to better understand how PTEN and p53 deletions drive prostate cancer progression. Tumors from these mice were found to express similar genes as human prostate tumors with PTEN/p53-deletions and neuroendocrine prostate cancer (NEPC), an aggressive form of CRPC in which tumor cells take the phenotype of neuroendocrine cells.
- Treatment of NKX3.1/PTEN/p53-deficient prostate cancer mouse models with abiraterone actually accelerated tumor growth instead of suppressing it (Figure).
- Effective treatments would be hypothesized to reverse abnormal patterns of gene expression. However, in these mice, abiraterone treatment exacerbated the effects of PTEN/p53-loss by further increasing expression of genes turned on by PTEN/p53-loss and further decreasing expression of genes turned off by PTEN/p53-loss.
- These genes were highly enriched for neuroendocrine differentiation. This indicates that PTEN/p53-loss may enable lineage plasticity, which is further encouraged by treatment with abiraterone.

- Two types of cancer phenotypes were observed in mice with NKX3.1/PTEN/p53-deficient prostate cancer. Tumors either had small, focal areas of tumor cells expressing neuroendocrine genes (focal NEPC), or the entire tumor was composed of NEPC cells (overt). In both cases, all of the prostate cancer cells, regardless of neuroendocrine gene expression, had the marker indicating PTEN/p53-deletion had occurred.
- This suggests that PTEN/p53-deletion drives aggressive prostate cancer. Some of these cells acquire further changes that enable neuroendocrine differentiation and resistance to androgen-targeted treatments such as abiraterone.
- Overall, these studies reveal mechanisms underlying the development of aggressive, treatment-resistant prostate cancer. This will lead to new treatments for this lethal form of prostate cancer.



**Figure:** Treatment of mice with PTEN/p53-deficient prostate cancer with abiraterone accelerated tumor growth. Top: experimental plan; Bottom: microscope images (left) and MRI imaging (right) of PTEN-deficient (NP CRPC) and PTEN/p53-deficient (NPp53 CRPC) tumors before and after treatment with abiraterone or vehicle control.



## Session 10: New Platforms to Attack Undruggable Targets

---

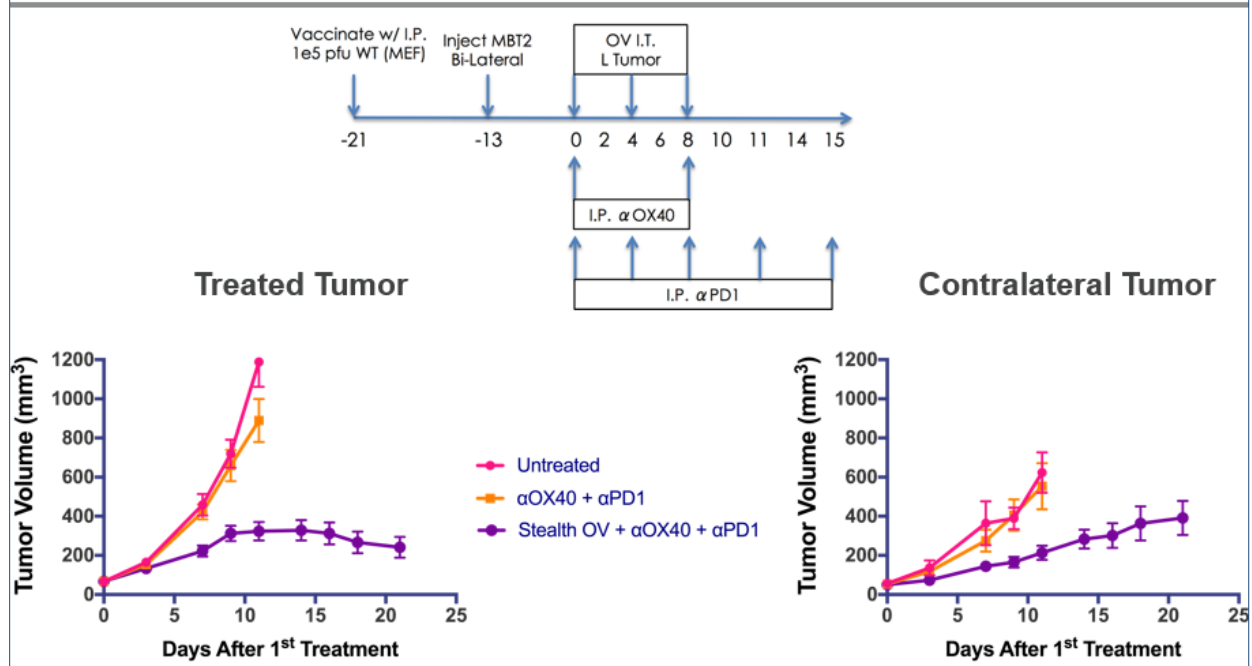
### *T-Stealth Oncolytic Immunotherapy for Solid Tumors*

Matthew Mulvey, PhD  
BeneVir Biopharm, Inc.

- Oncolytic viruses are an emerging type of cancer immunotherapy in which genetically engineered viruses are used to specifically infect and lyse tumor cells. In the process, the virus infection activates the immune system to recognize and eliminate tumor cells throughout the body, which is critical to the efficacy of this treatment.
- Dr. Matthew Mulvey discussed ongoing commercial development of oncolytic viruses for the treatment of cancer.
- Thus far, the oncolytic virus T-Vec (talimogene laherparepvec) is the only treatment in this class that has received FDA approval. T-Vec is used for the treatment of melanoma.
- In the clinical trials that led to FDA approval, T-Vec treatment resulted in partial or complete responses in 26% of metastatic melanoma patients. Half of these patients (16%) had a durable response.
- Pembrolizumab is an immune checkpoint inhibitor, a powerful form of immunotherapy that activates hibernating immune cells that are able to target and kill cancer cells.
- A phase 1b clinical trial was conducted to test the combination of T-Vec and Pembrolizumab in patients with melanoma. Of patients treated with this combination, 62% responded to treatment and 33% exhibited a complete response.
- Pembrolizumab is hypothesized to work better in “hot” tumors, which the immune system has naturally tagged as dangerous and responded to. T cells are observed entering such tumors prior to immunotherapy treatment.
- In the T-Vec + Pembrolizumab combination trial, 83% of patients who exhibited a complete response had “cold” tumors, with low/no numbers of T cells and the immune cell activation protein IFN-gamma observed in tumors prior to treatment.
- Some patients with “hot” tumors responded to the T-Vec + Pembrolizumab combination. However, there was only one complete response in this group. This patient had the highest level of tumor-infiltrating immune cells prior to treatment. This suggests T-Vec played no role in the combination regimen, and Pembrolizumab alone was sufficient to induce a complete response.
- Advantages to using oncolytic viruses as cancer treatments include their ability to have a vaccine-like effect without expressing any tumor antigens.
- Because viruses encode genes that get expressed in the infected cells, they can be engineered to carry genes that could improve treatment, such as antibodies.

- The ability of the immune system to block the growth and transmission of viral infections is a major challenge to using viruses as cancer treatments.
- To address this issue, the team at BeneVir has engineered “T-Stealth™” oncolytic HSV-1 (Herpes Simplex Virus-1) viruses that can evade the immune system, including the interferon system (which acts to prevent viral replication), and T cells that kill virus-infected cells.
- T-Stealth™ viruses were also engineered to remove genes that damage the central nervous system and to replicate only in tumor cells and not normal cells.
- Checkpoint inhibitors boost anti-viral immune responses. However, because T-Stealth™ viruses can evade T cells, they are designed to be given simultaneously with checkpoint inhibitors.
- In mice with two tumors on opposite sides of the body, injection of stealth oncolytic viruses into one tumor resulted in regression of both tumors due to activation of a systemic immune response. The combination of stealth oncolytic viruses with checkpoint inhibitors (anti-PD1 plus anti-CTLA4) was found to be synergistic.
- The combination of stealth oncolytic viruses with the T cell activator anti-OX40 was also synergistic in blocking tumor growth in mice. Oncolytic viruses lacking the stealth features (“visible” viruses) were less effective.
- The combination of stealth oncolytic viruses plus anti-PD1 + anti-OX40 was also synergistic in treating tumors in mice. Anti-PD1 + anti-OX40 without stealth viruses had no effect (Figure).
- Overall, these studies detail promising activity for a novel type of immunotherapy that uses engineered viruses to activate the immune system to kill tumor cells.

## Stealth OV Combination with $\alpha$ OX40 & $\alpha$ PD1 Superior to $\alpha$ OX40 & $\alpha$ PD1



**Figure:** Stealth oncolytic viruses synergized with anti-PD1 + anti-OX40 in treating tumors in mice, while anti-PD1 + anti-OX40 alone had no effect. Top: treatment outline. Left: The growth of the tumor injected with the treatment. Right: Growth of tumors on the opposite side of the mouse that were not directly treated.

## *Special Lecture: IronMan - An International Registry of Men with Advanced Prostate Cancer*

**Philip Kantoff, MD**  
**Ironman Executive Committee**  
**Memorial Sloan Kettering Cancer Center**

- There is a tremendous global burden of prostate cancer, with an estimated 366,000 men dying from the disease each year.
- The clinical landscape for the treatment of prostate cancer is complex and changing. Six new life-extending treatments have been FDA approved since 2010 and many more are in development. However, the optimal way to sequence or combine these treatments is not yet known and requires significant further study.
- Because the biology of the disease influences the response to treatment, there is an urgent need to improve our understanding of prostate cancer to improve the treatment and outcomes of men with advanced prostate cancer.
- Dr. Philip Kantoff discussed the implementation of IRONMAN, a global registry to document variations in prostate cancer patient management, experience, and outcomes. IRONMAN also seeks to create an enduring and expanding data resource for global investigators and patients.
- The objectives of the IRONMAN Registry include: describing global practice patterns in treatments used for advanced prostate cancer; identifying associations between treatment sequences or combinations and clinical outcomes; to evaluate potential interactions with concomitant medications or demographic factors; to describe the patient experience and identify unmet treatment needs; to identify clinical and molecular disease subtypes that predict response to individual treatments, combinations, or sequences; and to understand the reasons that physicians initiate treatment changes in men with advanced prostate cancer.
- At least 5,000 men with advanced prostate cancer (either castration-resistant prostate cancer or metastatic hormone-sensitive prostate cancer) will be prospectively recruited to this study.
- The first phase of the study will target recruitment from Australia, Brazil, Canada, Ireland, Sweden, Switzerland, UK, and the USA.
- Patients enrolled in the study will give blood samples at baseline and at every change of treatment. These samples will be stored and used to investigate biomarkers of various outcomes.
- Funding is also being sought to collect archived original biopsy samples.
- Patient reported outcomes will be collected quarterly for the first two years and semi-annually thereafter through surveys using the Movember Foundation's TRUE-NTH patient-support platform. Questions will address quality of life issues including: physical and emotional health, (fatigue, pain, nausea, sleep, depression, and anxiety), memory and cognitive decline, and urinary and sexual health.

- Clinical data including treatment changes, clinically significant events, hospitalization and other severe adverse events, symptomatic skeletal events, secondary cancers, and overall survival will be recorded.
- Physician questionnaires will also be collected, with the primary focus being the reasons why a therapy was selected and why therapy changes occurred.
- The study opened in July 2017 at 76 global sites and had enrolled 28 patients by October 2017. Accrual is anticipated to be completed by the end of 2019.
- A scientific oversight committee is being established to evaluate and approve research proposals that request to use the samples and data from this project.
- This study is the largest of its kind and will result in understanding global variations in practice, outcomes and unmet needs, improved clinical trial planning and identification of the most promising treatment paradigms for clinical trial testing, improved understandings of disparities, and identification of new biomarkers that will improve patient outcomes.

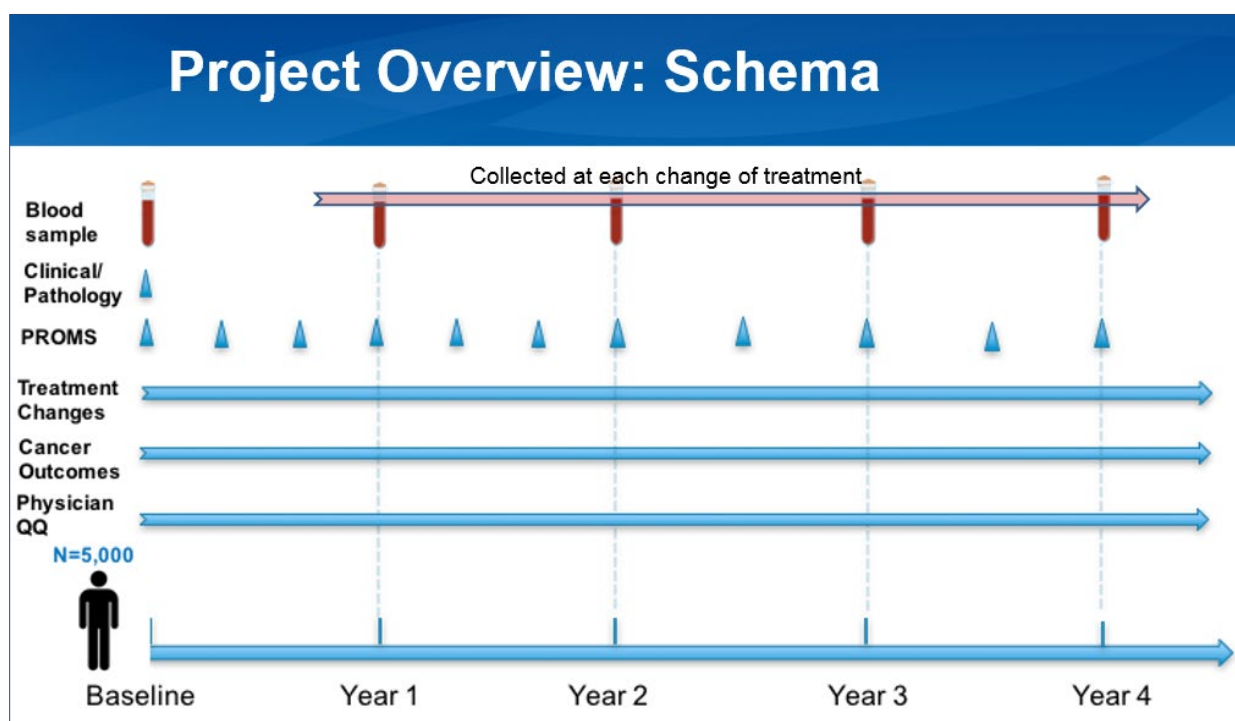


Figure: Timeline for clinical samples and data that will be collected from patients enrolled in IRONMAN.

## *Special Lecture: A Call to Action: Towards a Prostate Cancer Disparities & Health Equity Program*

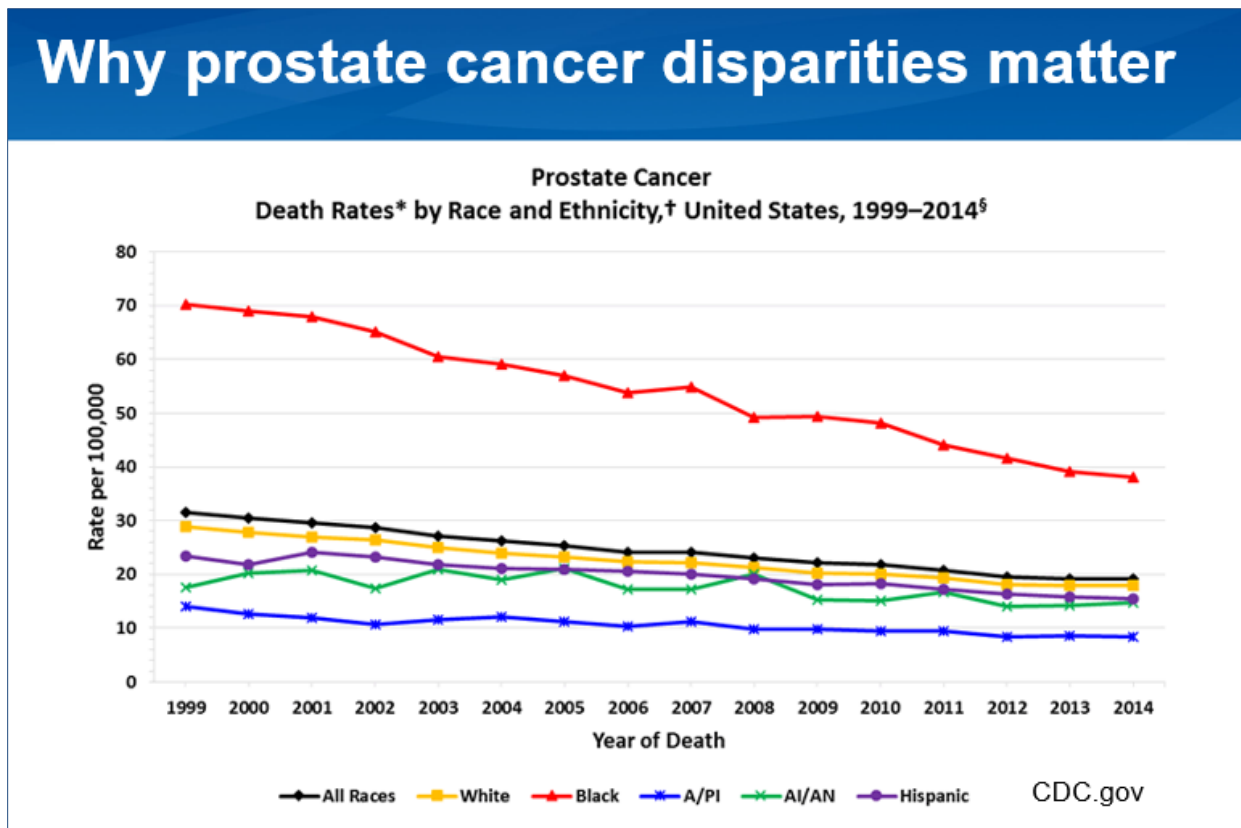
**Franklin Huang, MD, PhD**

**Harvard: Dana-Farber Cancer Institute**

- Men of African descent are at a significantly higher risk for aggressive and lethal prostate cancer compared with men of European descent (Figure). These disparities necessitate studies into the contributing biological, lifestyle, and socio-economic factors.
- Globally, there is also a higher burden of lethal prostate cancer in poorer countries, particularly in Africa and South America, much of which is due to lack of access to quality medical care. In fact, in some developing countries, the vast majority of men diagnosed with prostate cancer do not receive any treatment.
- Dr. Huang discussed studies into the biology of prostate cancer disparities in African-American men and initiatives being developed to address disparities in the U.S. and globally.
- Dr. Huang and Dr. Ami Bhatt of Stanford have created a non-profit organization, Global Oncology ([www.globalonc.org](http://www.globalonc.org)), to improve global cancer care by connecting clinicians and researchers all over the world to work in teams and develop projects to improve patient care.
- Challenges to reducing prostate cancer disparities in the U.S. include poor understanding of the biological features and differences that impact disparities, low accrual of underrepresented minority patients to clinical trials, a need for more translational research at centers that care for large populations of underrepresented minorities, and difficulties in accessing precision medicine cancer therapeutics.
- To better understand the biology of prostate cancer in African-American men, Dr. Huang sequenced and studied the genomes of 102 prostate tumors from African-American patients.
- This study identified several prostate cancer mutations that differed in frequency between African-American and White patients. Most striking were loss-of-function mutations in the ERF gene, which were more common in African-Americans, occurring in ~5% of patients.
- The study also found that African-American prostate cancer has fewer PTEN deletions, uncommon PIK3CA mutations and more common FASN amplifications. Other genomic studies have found African-American prostate cancer has more LSAMP1 deletions, overexpression of MNX1, and differences in the expressed PIK3CD gene product.
- Together these studies suggest that the biology of prostate cancer differs in African-American men, which may contribute to more aggressive disease and poorer outcomes.
- Studies into the biology and clinical responses of African-American prostate cancers are impaired by issues with clinical trial participation. Over 80% of patients participating in cancer clinical trials are White, while only ~6% are African-American.
- To reduce prostate cancer disparities, Dr. Huang and colleagues are working to launch a prostate cancer disparities and health equity program in Boston. This group is composed of

a network of investigators including epidemiologists, health services researchers, clinicians, and basic and translational researchers.

- The goal of this program is to understand the unique biological, environmental, and socioeconomic determinants of prostate cancer disparities and accelerate science and medicine that will reduce disparities.
- This program will also develop a collaborative academic program comprising research and clinical educational and training opportunities in the Boston area and will partner with institutions in other geographic locations.
- Building bridges between academic medical centers, the biotech and pharmaceutical industries, and underrepresented patients and the community health centers and hospitals that care for them, is essential to reducing prostate cancer disparities. Having patients as the center of these relationships will help to drive this goal forward.
- Overall, these collaborative and patient-centered initiatives and studies into the biology of African-American prostate cancer will help reduce the disparities that contribute to higher rates of prostate cancer deaths in African-American men.



**Figure:** Death rates from prostate cancer, per 100,000 men in the United States, by ethnicity. Deaths from prostate cancer in African-American men are approximately double that of other ethnicities.



## *Special Lecture: Long Noncoding RNAs: The Bright Side of the Genomic Dark Matter*

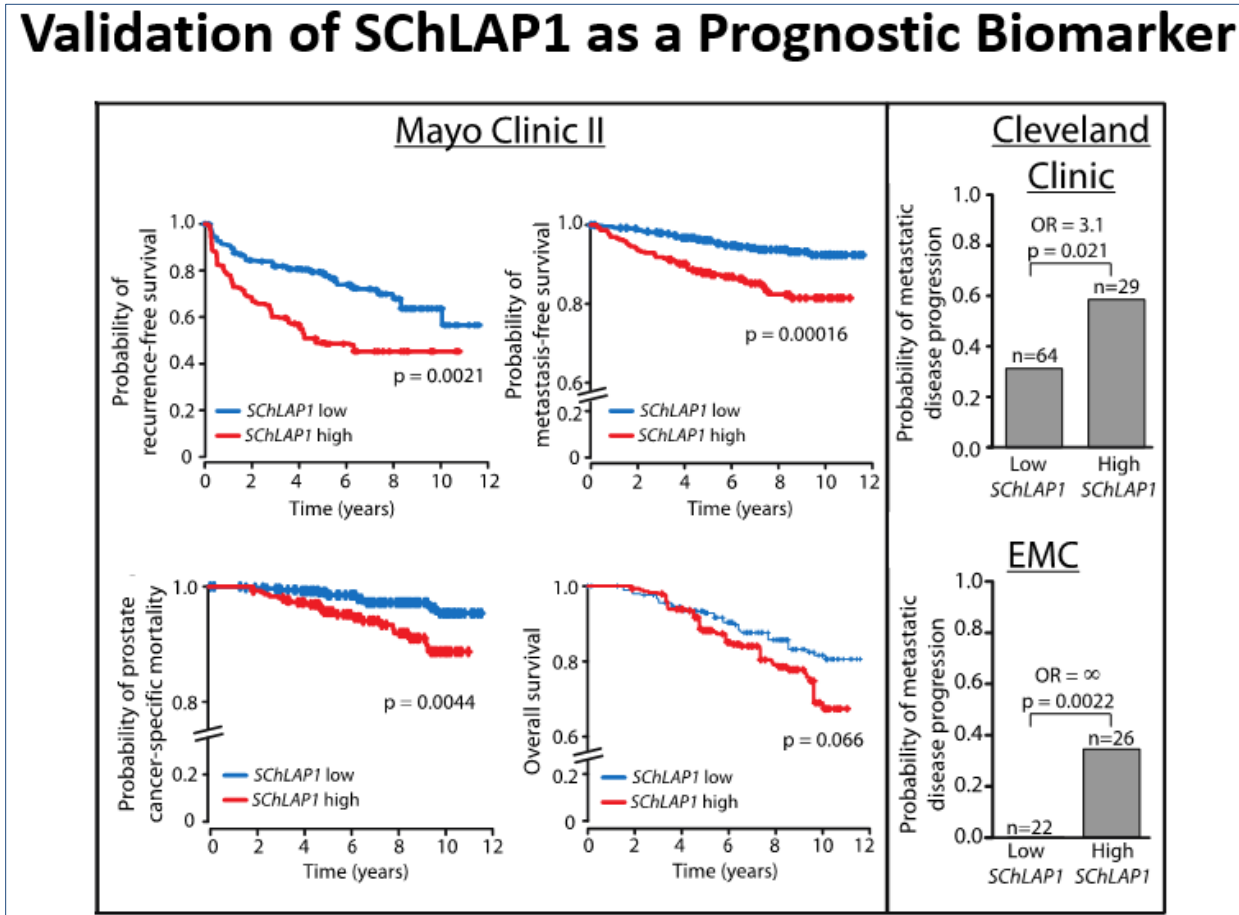
Felix Feng, MD  
University of California, San Francisco

- Cancer is a disease of gene dysregulation. Most studies into the biology of cancer examine alterations in the expression or function of proteins.
- However, over 95% of the genes encoded in the human genome are not used to make proteins, but instead perform cellular functions as RNA. RNA that are not made into proteins are termed “non-coding” RNA.
- There are several classes of non-coding RNA, which have different roles in cell biology.
- Long non-coding RNA (lncRNA), is a class of RNA greater than 200 nucleotides in length that shares many properties with protein-coding RNA. These similarities include synthesis by RNA polymerase II, the presence of multiple exons (the gene is not encoded in DNA continuously but in pieces interrupted by non-gene encoding DNA sequences), similar patterns of alternative splicing (different parts of the gene can be included or excluded from the transcribed RNA), and cell type-specific expression patterns.
- lncRNAs perform various gene regulatory functions, including directly promoting or repressing gene expression, regulating epigenetics (chemical modifications on DNA that control gene expression), and acting as scaffolds to bring together complexes of proteins with DNA.
- lncRNAs are important in a variety of cellular process and diseases including stem cell maintenance, cell lineage differentiation, Alzheimer’s disease, and cancer.
- Dr. Felix Feng discussed the role of lncRNAs in the development and progression of prostate cancer.
- To identify lncRNAs with a possible role in prostate cancer, Dr. Feng and colleagues screened RNA sequencing libraries from over 25 cancer studies.
- Prior to this study, only ~15,000 lncRNAs had been identified in the human genome. This study identified an additional ~50,000 lncRNAs. The number of lncRNAs (estimated at over 60,000) may be far greater than the number of protein-coding genes (~30,000).
- Approximately 8,000 lncRNAs were identified that were differentially expressed in cancer or in different normal tissues.
- To further interrogate lncRNAs with a role in prostate cancer, a microarray-based methodology was established to evaluate expression of RNA from archived, preserved prostatectomy specimens. Over 1.4 million RNA transcripts were evaluated by the microarray, including all known protein-coding genes and most lncRNAs.
- Over 1,000 prostatectomy specimens were evaluated across four patient cohorts. One cohort of 545 patients served as the discovery cohort, in which candidate prostate cancer-associated genes were identified. The other three cohorts (463 patients in total) were then examined to validate the identified genes as being associated with prostate cancer.

- Clinical outcomes including development of metastatic disease were available for these patients, enabling the identification of genes associated with poor outcomes.
- Both lncRNA and protein-coding genes were identified that associated with prostate cancer metastasis. While known cancer-promoting proteins were identified in this study, the top 20 most-highly predictive genes for prostate cancer metastasis were lncRNAs.
- The top ranked gene associated with metastatic progression was the lncRNA SChLAP1.
- SChLAP1 expression was found to be a highly prognostic biomarker for biochemical recurrence, metastatic recurrence, prostate cancer mortality, and overall survival (Figure).
- SChLAP1 expression in primary tumors was more prognostic than Gleason score for metastatic progression at 10 years following prostatectomy.
- SChLAP1 expression was also highly specific for prostate cancer and absent in 29 other cancer types evaluated.
- SChLAP1 RNA could be detected in urine samples, and correlated with Gleason score. This suggests that SChLAP1 has potential as a urine biomarker for predicting risk of aggressive prostate cancer.
- SChLAP1 was also highly expressed in prostate cancers with intraductal carcinoma and cribriform architecture phenotypes, which are associated with more aggressive disease. SChLAP1 expression could also be used to differentiate which of the tumors with these features would go on to progress with a PSA relapse.
- The role of SChLAP1 in prostate cancer cell biology was also studied.
- Overexpression of SChLAP1 promoted prostate cancer invasion in cell culture assays. SChLAP1 expression was required for prostate cancer metastasis in mouse models.
- To further examine the function of SChLAP1 in prostate cancer cells, its expression was knocked down and cells were examined for alterations in gene expression.
- Knockdown of SChLAP1 expression resulted in increased activity of the tumor suppressor SWI/SNF gene regulatory complex. Conversely, SChLAP1 overexpression reduced SWI/SNF activity.
- SWI/SNF complexes can either contain the BRG1 protein or its paralog BRM. These different complexes regulate the expression of different gene programs mediated by this tumor suppressor complex. SWI/SNF complexes require the presence of either BRG1 or BRM for function.
- SChLAP1 was found to bind to BRG1 and inhibit the activity of BRG1-SWI/SNF complexes. SChLAP1 did not interact with BRM-SWI/SNF complexes.
- Cells overexpressing SChLAP1 were preferentially sensitive to approaches targeting BRM, suggesting that knockdown of BRM in combination with SChLAP1-mediated inhibition of BRG1-containing complexes results in synthetic lethality of prostate cancer cells.
- These results suggest that SChLAP1 promotes prostate cancer progression by altering the activity of SWI/SNF complexes, and that BRM may represent a therapeutic target in SChLAP1-overexpressing cancers.

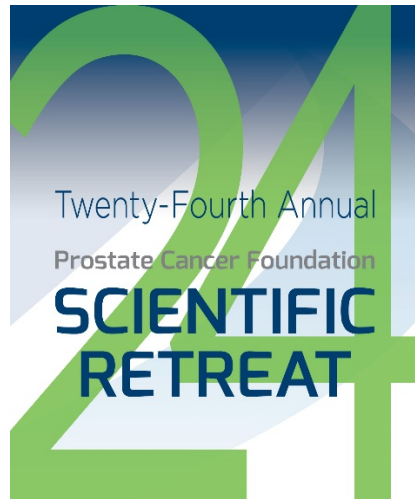
- Ongoing studies are examining the lncRNA landscape of metastatic prostate cancer and identifying lncRNAs that can serve as predictive biomarkers of response to therapy.
- Therapeutic agents that can directly target lncRNAs including SchLAP1 for the treatment of prostate cancer are also being developed.
- Overall, these studies demonstrate that lncRNAs are critical in the biology of prostate cancer and may serve as prognostic and predictive biomarkers and as therapeutic targets.

## Validation of SchLAP1 as a Prognostic Biomarker



**Figure:** SchLAP1 expression in prostatectomy samples was highly predictive for biochemical recurrence, metastatic recurrence, prostate cancer mortality, and overall survival. Source: Prensner J et al., *Lancet Oncology*, 2014 Dec, 15(13):1469-80.





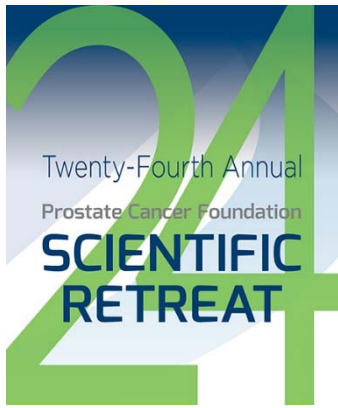
## **APPENDIX:**

# **24<sup>th</sup> ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT**

**OCTOBER 5-7, 2017**

***PROGRAM AGENDA***





# AGENDA

Thursday, October 5, 2017

## GENERAL SESSIONS

Location: Regency Ballroom

8:00 AM

Registration

West Registration Desk

### Welcome & Introduction

2:00 PM - 2:10 PM

Howard Soule, PhD  
Prostate Cancer Foundation

### Session 1: Cell Cycle Dysregulation: Implications for Progression, Plasticity, and Management

2:10 PM - 3:10 PM

Moderator: Karen Knudsen, PhD  
Thomas Jefferson University

2:10 PM - 2:25 PM

*Linking RB/p53 Dysfunction to Prostate Cancer Plasticity and Anti-Androgen Resistance*

David Goodrich, PhD  
Roswell Park Cancer Institute

2:25 PM - 2:30 PM

**Discussion**

2:30 PM - 2:45 PM

*RB Pathway Dysregulation: Mechanisms and Clinical Observations*

Karen Knudsen, PhD  
Thomas Jefferson University

2:45 PM - 2:50 PM

**Discussion**



Thursday, October 5, 2017

- 2:50 PM - 3:05 PM ***CDK4/6 Inhibitors: Learning from Experiences in Breast Cancer, Other Solid Tumors, and Hematologic Malignancies***  
**Geoffrey Shapiro, MD, PhD**  
Harvard: Dana-Farber Cancer Institute
- 3:05 PM - 3:10 PM **Discussion**

**Session 2: Precision Medicine and Targeted Therapies**

**3:10 PM - 4:45 PM**

**Moderator: Wassim Abida, MD, PhD**  
Memorial Sloan Kettering Cancer Center

**SPECIAL LECTURE**

**3:10 PM - 3:40 PM**

**Defining the Actionable Genome**

**David Solit, MD**

Memorial Sloan Kettering Cancer Center

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

**Discussion**

- 3:45 PM - 4:00 PM ***Genomics in Clinical Care of Cancer Patients: Lessons Learned***  
**Vincent Miller, MD**  
Foundation Medicine
- 4:00 PM - 4:05 PM **Discussion**
- 4:05 PM - 4:20 PM ***Finding Exceptional Responders to Targeted Therapy Using Genomics***  
**Louis Staudt, MD, PhD**  
National Cancer Institute
- 4:20 PM - 4:25 PM **Discussion**
- 4:25 PM - 4:40 PM ***Liquid Biopsy Analyses for Detection and Characterization of Human Cancer***  
**Victor Velculescu, MD, PhD**  
Johns Hopkins University
- 4:40 PM - 4:45 PM **Discussion**

Thursday, October 5, 2017

**Session 3: 3D Genomics: The Interface of Genomics, Epigenetics, and Cancer Biology**

4:45 PM - 5:45 PM

**Moderator: Ram Mani, PhD**

The University of Texas Southwestern Medical Center

4:45 PM - 5:00 PM ***3D Genome Organization & Transcription Regulation in Cancer Cells***  
**Yijun Ruan, PhD**

The Jackson Laboratory for Genomic Medicine

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

5:05 PM - 5:20 PM ***Enhancer Mediated Transcriptional Dysregulation in Prostate Cancer***  
**Ram Mani, PhD**

The University of Texas Southwestern Medical Center

5:20 PM - 5:25 PM **Discussion**

5:25 PM - 5:40 PM ***Three-Dimensional Genetic and Epigenetic Disorganisation of the Prostate Cancer Genome***

**Susan Clark, PhD**

Garvan Institute of Medical Research, Australia

5:40 PM - 5:45 PM **Discussion**

**Session 4: Making Immunotherapy Work in Prostate Cancer**

5:45 PM - 7:10 PM

**Moderator: James Gulley, MD, PhD**

National Cancer Institute

5:45 PM - 5:50 PM ***Introduction***

**James Gulley, MD, PhD**

National Cancer Institute

5:50 PM - 6:05 PM ***The Immunological Effects of Epigenetic Agents in Prostate Cancer***  
**Charles Drake, MD, PhD**

Columbia University Medical Center

6:05 PM - 6:10 PM **Discussion**

6:10 PM - 6:25 PM ***Promising Immune Checkpoint Inhibitor Combination Studies in Prostate Cancer***

**Ravi Madan, MD**

National Cancer Institute

6:25 PM - 6:30 PM **Discussion**

Thursday, October 5, 2017

- 6:30 PM - 6:45 PM ***STING-Dependant Innate Immune Signaling and Cancer Immunotherapy***  
**Glen Barber, PhD**  
University of Miami Miller School of Medicine
- 6:45 PM - 6:50 PM **Discussion**
- 6:50 PM - 7:05 PM ***PSMA-Targeted CAR T Cells: Results from the First Patients***  
**Carl June, MD**  
University of Pennsylvania, Abramson Cancer Center
- Naomi Haas, MD**  
University of Pennsylvania, Abramson Cancer Center
- 7:05 PM - 7:10 PM **Discussion**
- 7:10 PM - 7:25 PM ***P-PSMA-101: An Autologous CART Therapy Comprised Predominantly of T Stem Cell Memory (Tscm) Cells***  
**Eric Ostertag, MD, PhD**  
Poseida Therapeutics, Inc.
- 7:25 PM - 7:30 PM **Discussion**

**Dinner**

**7:30 PM - 8:30 PM**

***Dinner Location: Palladian & Diplomat Ballrooms***

**Poster Session and Dessert**

**8:30 PM - 11:00 PM**

***Poster Session and Dessert Location: Ambassador Ballroom & Bird Cage Walk***

Friday, October 6, 2017

6:30 AM - 7:30 AM Breakfast

Palladian & Empire Ballrooms

7:30 AM - 7:45 AM Move to Session

**GENERAL SESSIONS**  
Location: Regency Ballroom

**SPECIAL LECTURE**

7:45 AM - 8:00 AM

***Integrated Tumor and Host Profiling in mCRPC: Updates in Single CTC, Tumor Heterogeneity, & T Cell Profiling***

**Ryan Dittamore**

Epic Sciences

*Introduced by Howard Scher, MD*  
Memorial Sloan Kettering Cancer Center

8:00 AM – 8:05 AM

**Discussion**

Friday, October 6, 2017

**SPECIAL LECTURE**

8:05 AM - 8:20 AM

**Where are Disseminated Tumor Cells (DTCs) Hiding  
at the Time of Radical Prostatectomy?**

**Kenneth Pienta, MD**  
Johns Hopkins University

*Introduced by Howard Soule, PhD*  
Prostate Cancer Foundation

8:20 AM – 8:25 AM

**Discussion**

**Session 5: DNA Damage Repair**

8:25 AM - 9:45 AM

**Moderator: Heather Cheng, MD, PhD**  
University of Washington

**SPECIAL LECTURE**

8:25 AM - 9:00 AM

**Finally!**  
**Genetic Analysis of Inherited Predisposition to Prostate Cancer**

**Mary-Claire King, PhD**  
University of Washington

9:00 AM – 9:05 AM

**Discussion**

9:05 AM - 9:20 AM ***Processes of DNA Damage in Localized Prostate Cancer***  
**Paul Boutros, PhD**

9:20 AM - 9:25 AM Ontario Institute for Cancer Research

**Discussion**

Friday, October 6, 2017

9:25 AM - 9:40 AM ***Implementing Germline Genetics into Prostate Cancer Clinical Care***  
**Heather Cheng, MD, PhD**  
University of Washington

9:40 AM - 9:45 AM **Discussion**

**SPECIAL LECTURE**  
**9:45 AM – 10:15 AM**

**State of the Science 2017**

**Jonathan Simons, MD**  
Prostate Cancer Foundation

*Introduced by Howard Soule, PhD*  
Prostate Cancer Foundation

10:15 AM - 10:20 AM  
**Discussion**

**SPECIAL ADDRESS**  
**10:20 AM – 10:40 AM**

**The Honorable David Shulkin, MD**  
Secretary of Veterans Affairs (VA)

*Introduced by Jonathan Simons, MD*  
Prostate Cancer Foundation

Friday, October 6, 2017

**KEYNOTE ADDRESS**

**10:40 AM - 11:40 AM**

**Michael Milken**  
**Founder and Chairman**  
Prostate Cancer Foundation

*Introduced by Stuart Holden, MD*  
University of California, Los Angeles

**Group Photo**

**11:40 AM - 11:50 AM**

**Lunch**

**11:50 AM - 12:50 PM**

***Location: Palladian & Empire Ballrooms***

12:50 PM - 1:00 PM **Move to Session**

**Regency Ballroom**



Friday, October 6, 2017

**SPECIAL LECTURE**

**1:00 PM - 1:30 PM**

**ER Stress: Remodeling the Tumor Microenvironment**

**Laurie Glimcher, MD**

Harvard: Dana-Farber Cancer Institute

*Introduced by Lorelei Mucci, ScD*

Harvard T.H. Chan School of Public Health; Dana-Farber/Harvard Cancer Center

**1:30 PM - 1:35 PM**

**Discussion**

**Session 6: PSMA Imaging and Radioligand Therapy**

**1:35 PM - 2:35 PM**

**Moderator: Scott Tagawa, MD**

Weill Cornell Medical College

1:35 PM - 1:50 PM

***Targeting PSMA with Antibodies and Antibody Forms***

**Steven Larson, MD**

Memorial Sloan Kettering Cancer Center

1:50 PM - 1:55 PM

**Discussion**

1:55 PM - 2:10 PM

***Low Molecular Weight PSMA-Based Imaging***

**Steve Cho, MD**

University of Wisconsin - Madison

2:10 PM - 2:15 PM

**Discussion**

2:15 PM - 2:30 PM

***PSMA Targeted Radionuclide Therapy for Prostate Cancer***

**Scott Tagawa, MD**

Weill Cornell Medical College

2:30 PM - 2:35 PM

**Discussion**

Friday, October 6, 2017

**Session 7: Meeting Reports**

2:35 PM - 3:35 PM

**Moderator: Howard Soule, PhD**  
Prostate Cancer Foundation

2:35 PM - 2:45 PM

***Second Bi-Annual Strategy Meeting to Accelerate Progress in the Understanding and Treatment of Prostate Cancer; Athens, Greece 2017***

**Christopher Logothetis, MD**  
The University of Texas MD Anderson Cancer Center

2:45 PM - 2:50 PM

**Discussion**

2:50 PM - 3:00 PM

***MARS2: Androgen Receptor Splice Variants Update***

**Ganesh Raj, MD, PhD**  
The University of Texas Southwestern Medical Center at Dallas

3:00 PM - 3:05 PM

**Discussion**

3:05 PM - 3:15 PM

***Report from the 2017 Coffey-Holden Prostate Cancer Academy Meeting, Beyond the Androgen Receptor II: New Approaches to Understanding and Treating Metastatic Prostate Cancer***

**Heather Cheng, MD, PhD**  
University of Washington

3:15 PM - 3:20 PM

**Discussion**

3:20 PM - 3:30 PM

***Overview of the 2017 Advanced Prostate Cancer Consensus Conference (APCCC2017)***

**Silke Gillessen, MD**  
Kantonsspital, Switzerland

3:30 PM - 3:35 PM

**Discussion**

3:35 PM - 3:40 PM

**Break**

Friday, October 6, 2017

**Session 8: Potential Applications of Artificial Intelligence in Prostate Cancer**

3:40 PM - 5:00 PM

**Moderators:**

**Peter Choyke, MD**

National Cancer Institute

**Adam Dicker, MD, PhD**

Thomas Jefferson University

3:40 PM - 4:00 PM

***Machine Learning Methods for Automated MRI Imaging in Prostate Cancer***

**Ronald Summers, MD, PhD**

National Institutes of Health

4:00 PM - 4:20 PM

***Integrating Imaging and Pathologic/Genomic/Biomarker Data Using Machine Learning Methods***

**Anant Madabhushi, PhD**

Case Western Reserve University

4:20 PM - 4:40 PM

***Computational Pathology***

**Thomas Fuchs, PhD**

Memorial Sloan Kettering Cancer Center

4:40 PM - 5:00 PM

***Panel Discussion***

Friday, October 6, 2017

**Dinner, Awards and Dinner Speaker**

7:15 PM - 10:00 PM

*Location: Regency Ballroom*

**DINNER SPEAKER**

7:45 PM - 8:05 PM

**Douglas Lowy, MD**

Acting Director, National Cancer Institute

**PCF AWARDS CEREMONY**

8:30 PM - 9:15 PM

**2017 PCF Young Investigator Awards**

**2017 The Movember Foundation-PCF Challenge Awards**



**2017 PCF Challenge Awards**

**2016 PCF Challenge Awards**

Saturday, October 7, 2017

6:15 AM - 7:15 AM Breakfast

Palladian Ballroom

7:15 AM - 7:30 AM Move to Session

**GENERAL SESSIONS**  
Location: Regency Ballroom

**Interview with a Prostate Cancer Patient: The Journey of Medical Care**

7:30 AM - 8:00 AM

**William Dahut, MD**  
National Cancer Institute

*Introduced by Howard Soule, PhD*  
Prostate Cancer Foundation

8:00 AM - 8:05 AM Break

**Session 9: Recent advances in Genetically Engineered Mouse Models (GEMMs) of Lethal Prostate Cancer**

8:05 AM - 9:05 AM

**Moderator: Cory Abate-Shen, PhD**  
Columbia University Medical Center

8:05 AM - 8:20 AM ***Synthetic Essentiality: Targeting Cancer-Specific Vulnerabilities***

**Ronald DePinho, MD**  
The University of Texas MD Anderson Cancer Center

8:20 AM - 8:25 AM **Discussion**

8:25 AM - 8:40 AM ***Lineage Plasticity as a New Mechanism for Drug Resistance***

**Cory Abate-Shen, PhD**  
Columbia University Medical Center

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

Saturday, October 7, 2017

8:45 AM - 9:00 AM ***Genetics & Metabolic Requirements for Metastatic Prostate Cancer***  
**Pier Paolo Pandolfi, MD, PhD**

Beth Israel Deaconess Medical Center; Harvard Medical School

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

**Session 10: New Platforms to Attack Undruggable Targets**

**9:05 AM – 10:55 AM**

**Moderator: Marco Gottardis, PhD**

Janssen Research & Development, LLC

9:05 AM - 9:15 AM ***Introduction***

**Marco Gottardis, PhD**

Janssen Research & Development, LLC

9:15 AM - 9:30 AM ***STING Pathway Activation to Enhance Cancer Immunity***

**Andrea van Elsas, PhD**

ADURO Biotech, Inc.

9:30 AM - 9:35 AM **Discussion**

9:35 AM – 9:50 AM ***T-Stealth Oncolytic Immunotherapy for Solid Tumors***

**Matthew Mulvey, PhD**

BeneVir Biopharm, Inc.

9:50 AM - 9:55 AM **Discussion**

9:55 AM - 10:10 AM ***Neoantigen Approaches as Cancer Therapeutics***

**Richard Gaynor, MD**

Neon Therapeutics, Inc.

10:10 AM - 10:15 AM **Discussion**

10:15 AM - 10:30 AM ***Novel mRNA Cancer Immunotherapies***

**Robert Jabulowsky, PhD**

BioNTech AG

10:30 AM - 10:35 AM **Discussion**

10:35 AM – 10:50 AM ***The Pentarin Miniature Drug Conjugate PEN-221 Selectively Targets the Somatostatin Receptor SSTR2 that is Over Expressed in Neuroendocrine Cancers***

**Richard Wooster, PhD**

Tarveda Therapeutics, Inc.

10:50 AM - 10:55 AM **Discussion**

Saturday, October 7, 2017

**SPECIAL LECTURE**

10:55 AM - 11:10 AM

**IronMan –**  
**An International Registry of Men with Advanced Prostate Cancer**

**Philip Kantoff, MD**

Ironman Executive Committee  
Memorial Sloan Kettering Cancer Center

*Introduced by Lorelei Mucci, ScD*

Harvard T.H. Chan School of Public Health; Dana-Farber/Harvard Cancer Center

11:10 AM - 11:15 AM

**Discussion**

**SPECIAL LECTURE**

11:15 AM - 11:25 AM

**A Call to Action:**  
**Towards a Prostate Cancer Disparities & Health Equity Program**

**Franklin Huang, MD, PhD**

Harvard: Dana-Farber Cancer Institute

*Introduced by Felix Feng, MD*

University of California, San Francisco

11:25 AM - 11:30 AM

**Discussion**



Saturday, October 7, 2017

**SPECIAL LECTURE**

11:30 AM - 11:50 AM

**Long Noncoding RNAs:  
The Bright Side of the Genomic Dark Matter**

**Felix Feng, MD**

University of California, San Francisco

*Introduced by Franklin Huang, MD, PhD*

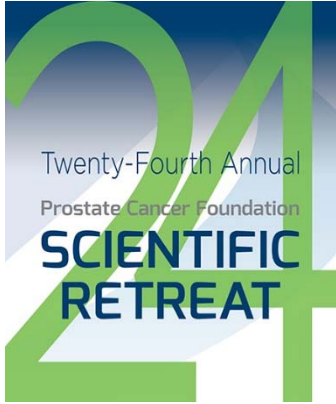
Harvard: Dana-Farber Cancer Institute

11:50 AM - 11:55 AM

**Discussion**

**Meeting Adjourned**

*\*\* A boxed lunch will be provided in Palladian\*\**



## **Program Committee:**

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

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

Cory Abate-Shen, PhD (Columbia University)

Wassim Abida, MD, PhD (Memorial Sloan Kettering Cancer Center)

Heather Cheng, MD, PhD (University of Washington)

Peter Choyke, MD (National Cancer Institute)

Adam Dicker, MD, PhD (Thomas Jefferson University)

Marco Gottardis, PhD (Janssen Research & Development, LLC)

James Gulley, MD, PhD (National Cancer Institute)

Scott Tagawa, MD (Weill Cornell Medical College)

Karen Knudsen, PhD (Thomas Jefferson University)

Ram Mani, PhD (The University of Texas Southwestern Medical Center)

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

SANOFI GENZYME 

Janssen  Oncology  
PHARMACEUTICAL COMPANIES OF *Johnson-Johnson*



CLOVIS  ONCOLOGY

AMGEN®

 *Pfizer* Oncology

 astellas



Bristol-Myers Squibb

Dendreon   
A Division of Valeant Pharmaceuticals International

Genentech  
A Member of the Roche Group

AstraZeneca 

  
BAVARIAN NORDIC





Prostate Cancer  
Foundation  
Curing Together.

© Copyright 2018 Prostate Cancer Foundation

1250 Fourth Street, Santa Monica, CA 90401 | Tel 310.570.4700 Fax 310.570.4701 | [www.pcf.org](http://www.pcf.org)