

# STATE *of the* SCIENCE REPORT



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

Highlights from  
the 25<sup>th</sup> Annual  
PCF Scientific Retreat  
October 2018

Provided compliments of the  
Prostate Cancer Foundation



Prostate Cancer  
Foundation  
Curing Together.



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## Introduction

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The 25th Annual Prostate Cancer Foundation (PCF) Scientific Retreat was held from October 26 - 28, 2018, at the Omni La Costa Resort in Carlsbad, California. 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 primary prostate cancer global knowledge exchange event, held to bring together the brightest minds in science to discuss the most significant and promising advancements and new areas of research that may lead to new treatments for prostate cancer. The 2018 Retreat represented a quarter-century of this foundational event and was a celebrated anniversary, due to the immeasurable historical impact the Retreat has had on the prostate cancer research field and community. Attendance at the Retreat has directly led to the establishment of a strongly networked and highly collaborative research community, unparalleled by any other biomedical research field. 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 25th Annual Scientific Retreat featured the following:

- 45 presentations in the Plenary Session including a panel discussion on the principles and practice challenges of precision oncology in advanced prostate cancer
- 154 poster presentations
- 26 different scientific disciplines related to prostate cancer research presented and discussed
- 55% of speakers presented first-in-field, unpublished data at a PCF Scientific Retreat for the first time
- Attendance by 558 participants from 16 countries, including 223 PhDs, 188 MDs, 91 MD PhDs, 10 PharmDs, 1 DMD, 1 DO and 1 RN.
- 110 academic institutions, 43 biopharmaceutical companies, 8 medical research foundations, and 8 other for-profit companies
- NIH, NCI, Dept. of Defense, and Veterans Affairs research leaders
- Attendance by 160 PCF Young Investigators
- Attendance by 15 PCF Board of Director members and major donors and 15 special guests.

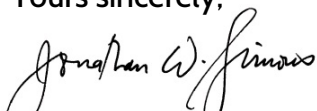
PCF is the world's leading philanthropic organization funding and accelerating prostate cancer research. The PCF "Global Research Enterprise" currently extends to 22 countries and funds a robust research portfolio. Founded in 1993, PCF has raised more than \$770 million and provided funding to more than 2,000 research programs at more than 210

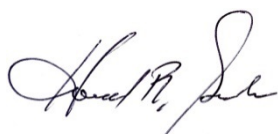
cancer centers and universities. This includes \$53 million awarded to 255 PCF Young Investigators since 2007 and over \$195 million to PCF Challenge Award teams since 2008.


We thank the sponsors of the Retreat for their generous support: Sanofi Genzyme, Pfizer Oncology, Amgen, Bayer, Clovis Oncology, Janssen Oncology, Astellas, Bristol-Myers Squibb, Sun Pharma, Immunomedics, Dendreon, Endocyte, Genentech, AstraZeneca, Constellation Pharmaceuticals, Harpoon Therapeutics, and Merck.

The 2018 State of Science Report was prepared by the Prostate Cancer Foundation to summarize the scientific presentations from the Retreat in order to disseminate this knowledge to the global community of researchers, clinicians, patients, the public, philanthropists, industry, and other interested stakeholders. We hope that this Report advances understanding of the current state of prostate cancer research, encourages discourse and the exchange of new ideas and information, inspires new 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

  
Andrea K. Miyahira, PhD  
Director, Research



## Session 1: Neuronal Control of Prostate Cancer Progression

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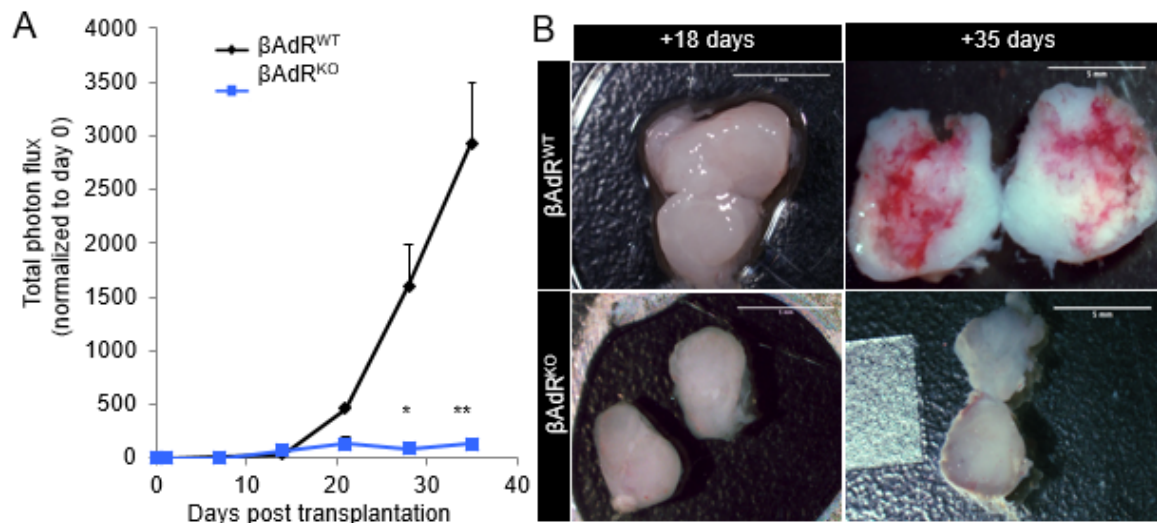
### *Adrenergic Nerves Activate an Angio-Metabolic Switch in Prostate Cancer*

Paul Frenette, MD

Albert Einstein College of Medicine

- Nerves may regulate the growth and progression of prostate cancer. Perineural invasion, a phenomenon in which prostate tumors invade and grow along prostatic nerves, is known to be associated with worse clinical outcomes. In a separate phenomenon, nerves can also grow within prostate tumors and regulate them.
- Dr. Frenette and team discussed the role of signals from prostatic nerve cells in prostate cancer.
- Adrenergic nerves communicate via release of adrenaline, noradrenaline and dopamine. In animal models, adrenergic nerve signaling through  $\beta$ -adrenergic receptors was required for prostate tumor growth and for the development of tumor blood vessels.
- Additionally, cholinergic nerves, which communicate via acetylcholine signals, appear to play important roles in later stages of prostate cancer progression. For example, in animal models, cholinergic nerves were important for prostate cancer invasion into tissues outside of the prostate, which is an initial step in the formation of cancer metastasis.
- Dr. Frenette and team found that in animal models, the expression of  $\beta$ -adrenergic receptors on endothelial cells (the cell type that forms blood vessels) was required for tumor growth and prostate cell division.
- Under low oxygen conditions, endothelial cells are able to form new blood vessels to supply tissues with oxygen, a phenomenon called the “angiogenic switch.” This phenomenon was found to be dependent on  $\beta$ -adrenergic receptor signaling, which directed metabolism of ATP from glucose, thereby supplying the endothelial cells with the energy necessary for this activity. Blockade or deletion of the  $\beta$ -2 adrenergic receptor switched endothelial cell metabolism from glycolysis to oxidative phosphorylation and inhibited new blood vessel formation.
- Together, these studies suggest that adrenergic nerve signaling is important in prostate cancer development and progression by driving the formation of new tumor blood vessels that supply tumor cells with oxygen and nutrients.
- These data indicate that targeting nerve pathways may be a new way to treat prostate cancer, and led to the initiation of a clinical trial by Dr. Benjamin Gartrell (below) to test the efficacy of the beta-blocker Carvedilol as a prostate cancer treatment.

## $\beta$ -adrenergic receptors regulate exponential tumor growth



Zahalka et al. *Science* October 20<sup>th</sup> 2017

**Figure:** In animal models, adrenergic nerve signaling through  $\beta$ -adrenergic receptors was required for prostate tumor growth, and for the development of tumor blood vessels.

### *Clinical Trial of a Beta Blocker in Prostate Cancer*

**Benjamin Gartrell, MD**

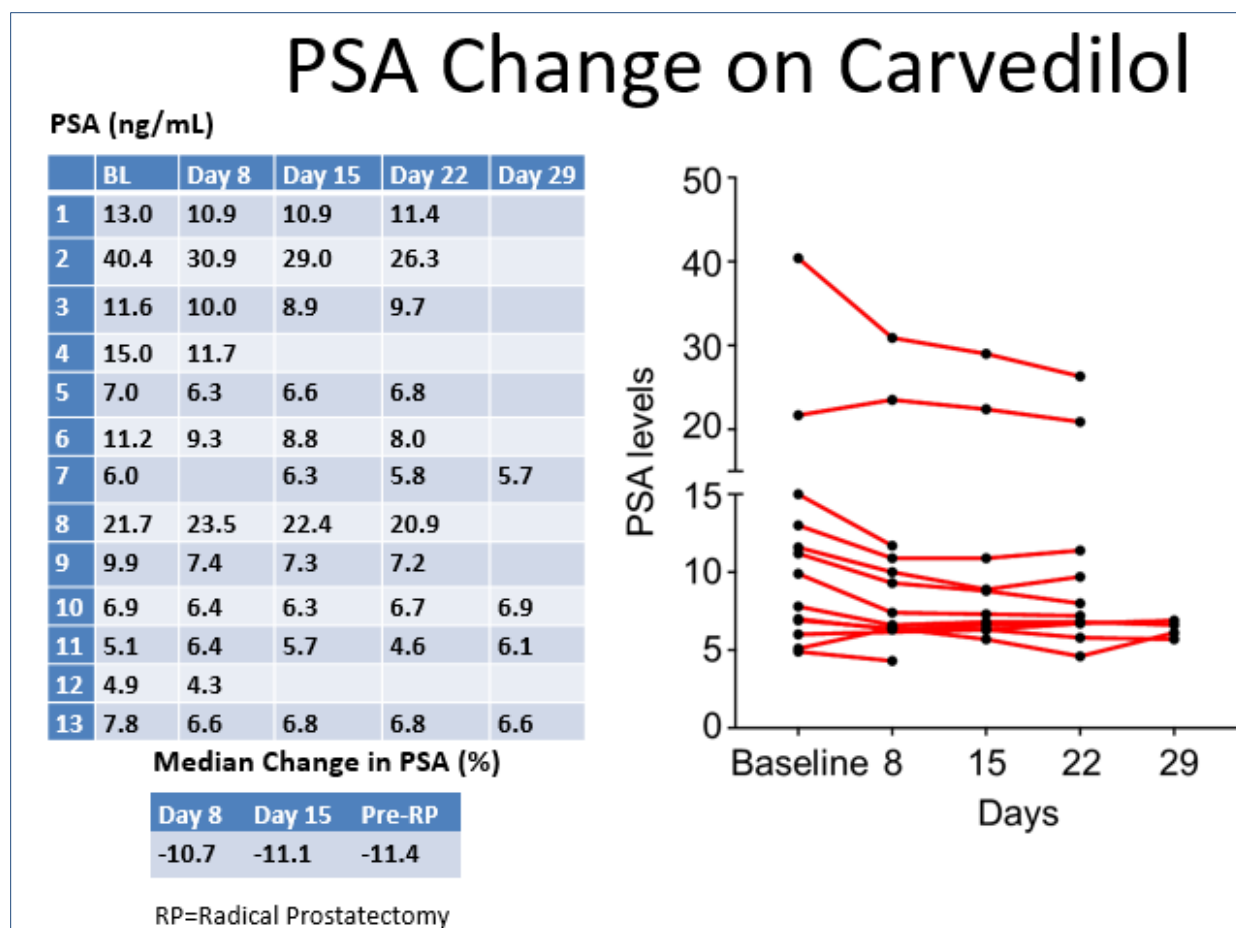
**Albert Einstein College of Medicine; Montefiore Medical Center**

- In the previous talk, Dr. Paul Frenette presented studies indicating that adrenergic nerve cell signaling is critical to prostate cancer progression, in part through directing the formation of new blood vessels that supply tumor cells with the oxygen and nutrients necessary for continued growth and survival.
- Dr. Benjamin Gartrell initiated a clinical trial to test an inhibitor of  $\beta$ -adrenergic receptors, Carvedilol, as a neoadjuvant therapy for prostate cancer. In this trial, Carvedilol was given twice daily for 28 days prior to prostatectomy in men with intermediate-high risk localized prostate cancer.
- Carvedilol is a beta-blocker medication that was FDA-approved in 1995 for the treatment of hypertension and congestive heart failure. Carvedilol is well-tolerated, with the only common adverse effect being dizziness in ~6% of treated individuals.
- Carvedilol is able to target several classes of  $\beta$ -adrenergic receptors, including  $\beta$ -1,  $\beta$ -2, and  $\beta$ -3 classes.
- At the time of this presentation, 14 patients had been accrued to the trial with a total target accrual of 20 patients. Peri-neural invasion, a phenomenon in which tumor cells invade



prostatic nerves, was observed in eight of ten patients analyzed thus far. The team will assess whether there is any relationship between peri-neural invasion and efficacy of the treatment.

- In preliminary analyses, some PSA declines were observed, suggesting there may be promise with this treatment.
- In addition to assessing PSA changes and other outcome measures, the team will investigate whether Carvedilol affects cancer cell division or death rates by comparing pre-treatment biopsy samples with post-treatment prostatectomy samples.
- If this treatment demonstrates evidence of activity in this trial, a randomized clinical trial testing Carvedilol in prostate cancer will be considered.



**Figure:** PSA changes in preliminary analyses from a clinical trial testing Carvedilol as a neoadjuvant therapy in men with intermediate-high risk localized prostate cancer. Some PSA declines were observed among the first 13 men treated on this trial.

## *Sympathetic Nerves, Stress and Anti-Cancer Immunity*

Elizabeth Repasky, PhD

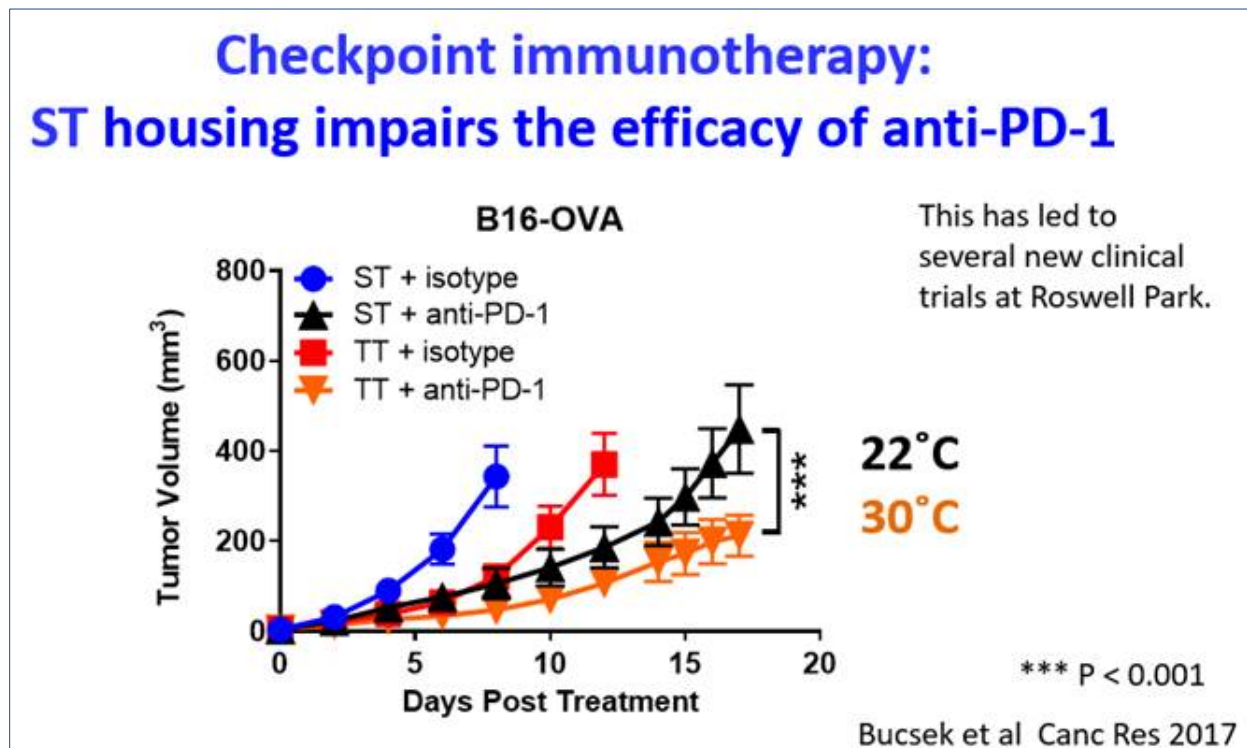
Roswell Park Comprehensive Cancer Center

- The autonomic nervous system (which includes the sympathetic nerves) controls many body functions, such as heart rate, digestion, breathing rate, blood pressure, and production of body fluids including saliva and sweat.
- The autonomic nervous system can also transmit responses to psychological stress (for instance, depression, fear, and anxiety) and different signals from the environment including thermal shifts, chemical exposure and infections. Recent studies have found that tumors attract sympathetic nerves and that signals from these nerves drive tumor growth. This may provide a pathway by which psychological stress could be helping to create a pro-tumorigenic state within the tumor.
- Dr. Elizabeth Repasky and team have recognized that manipulating housing temperature can be a physiologically relevant strategy to study the impact of chronic adrenergic stress on tumor growth and anti-tumor immunity. Studies by others have found that in nature, healthy mice seek out or create “thermoneutral” (approximately 30-31°C or 85-86°F) environments to minimize metabolic stress resulting from extra heat production. A warmer environmental temperature minimizes the extra energy needed for mice to maintain a normal body temperature (~37°C).
- If mice are kept in cooler room temperatures (such as that mandated by animal research regulations for maintenance of mice research colonies), sympathetic nerves will produce norepinephrine, a stress hormone needed to activate heat production in brown fat.
- Dr. Repasky hypothesized that chronic stress, including chronic cold stress, may drain energy away from the anti-tumor immune response, impairing the body’s cancer fighting capabilities and result in increased tumor growth. To investigate this hypothesis, a study was conducted to examine tumor growth in mice kept at thermoneutral (30°C) versus standard room temperature (22°C).
- In several different mouse tumor models, tumors grew slower and developed fewer metastases in mice kept at thermoneutral temperature.
- The ability of thermoneutral housing temperature to slow tumor growth was found to be completely dependent on the adaptive immune system. The ability of anti-tumor CD8+ T cells to enter into tumors and become activated in mice was increased at thermoneutral temperature compared with tumors in mice housed at standard room temperature.
- Checkpoint immunotherapy is a type of cancer treatment which increases the ability of T cells to kill their tumor targets. In Dr. Repasky’s studies, anti-PD-1 checkpoint immunotherapy was more effective in mice kept at thermoneutral temperature compared with those kept at standard room temperature (Figure).
- Dr. Repasky found that combining beta-blockers with checkpoint immunotherapy in mice housed at standard room temperature significantly improved tumor control. Moreover, their team found that energy required by CD8+ T cells as they become activated is suppressed in mice enduring chronic adrenergic stress. Specifically, both glycolysis and oxidative



phosphorylation in mitochondria is impaired in T cells which are activated in the presence of an activator of the  $\beta$ 2-adrenergic receptor (isoproterenol).

- All together, these studies suggest that chronic stress (as induced by cool housing temperatures) caused the autonomic nervous system to divert energy from anti-tumor immune responses in order to maintain body temperature. This work further suggests that reducing adrenergic stress signaling by using beta-blockers may have efficacy as a cancer treatment.
- These findings have led to several new clinical trials being conducted and developed at Roswell Park, which include combinations of immunotherapy or chemotherapy with beta-blockers in the setting of melanoma, breast, pancreas and rectal cancers.
- Finally, radiation therapy can occasionally cause shrinkage of tumors that had not been directly radiated. This “abscopal effect” is thought to be mediated by activation of anti-tumor immune responses by radiation therapy.
- Dr. Repasky’s team found that treatment of mouse tumor models with beta-blockers improved the efficacy of radiation therapy and enhanced abscopal effects (shrinkage of tumors that had not received radiation). The synergy between beta-blockers and radiation therapy was dependent on the presence of immune cells, which supports the hypothesis that abscopal effects are caused by activation of anti-tumor immune responses.
- Thus, treatments such as beta-blockers may also be synergistic with radiation or other immune-activating treatments for prostate and other cancers.



**Figure:** Tumors grew slower in mice kept at thermoneutral temperature (TT; 30°C) compared with standard room temperature (ST; 22°C). Anti-PD-1 checkpoint immunotherapy was more effective at blocking tumor growth in mice kept at thermoneutral temperature (orange triangles) compared with standard room temperature (red squares). Similar enhanced efficacy of anti-PD-1 was seen when tumor bearing mice housed at ST were treated with beta-blockers. Isotype = mice treated with a control antibody and not with anti-PD-1. (Bucsek et al., *Cancer Research*, 2017).

## Session 2: Steroid Receptors in Advanced Prostate Cancer: New Approaches to an Old Target

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### *SPECIAL LECTURE: If We Knew 20 Years Ago What We Know Now, Would We Have Targeted the Androgen Signaling Pathway in Prostate Cancer Differently?*

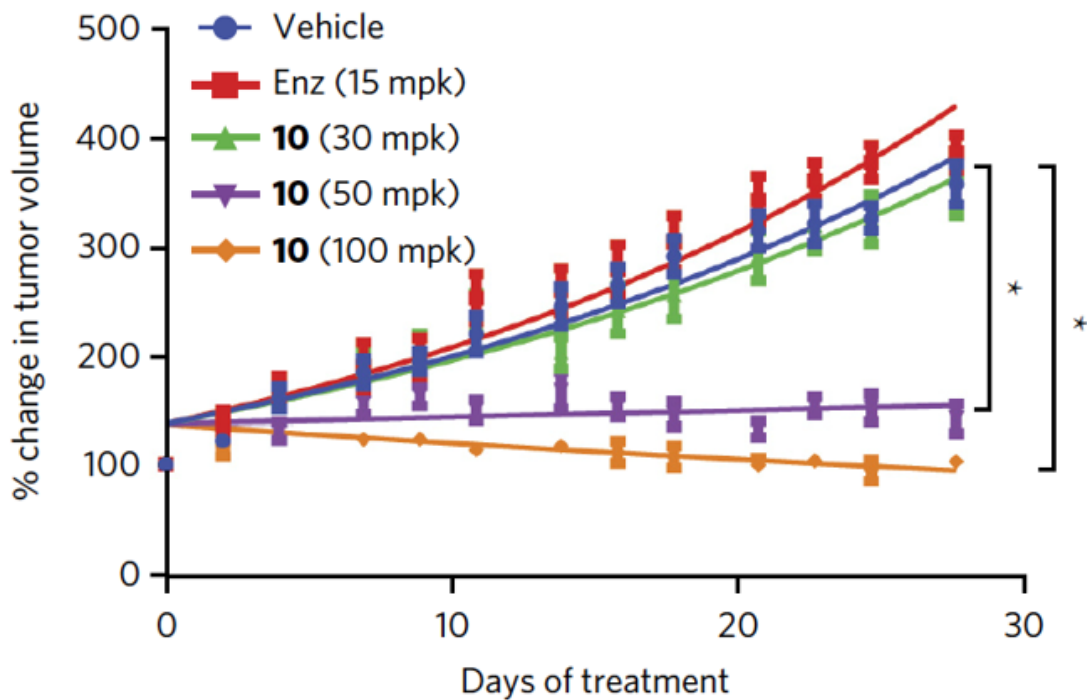
Donald P. McDonnell, PhD  
Duke University School of Medicine

- The androgen receptor (AR) is the major regulator of the processes that drive the growth and progression of prostate cancer. AR is a transcription factor (a protein that binds to DNA and regulates the expression of certain genes), that is triggered by male hormones (androgens) such as testosterone. When activated, AR regulates the expression of genes involved in cell growth and survival.
- Because prostate cancer cells depend on AR, it is the primary therapeutic target for the treatment of advanced prostate cancer.
- AR-targeted therapy includes androgen deprivation therapies (ADT), which work by blocking the production of testosterone or interfering with its effects. Newer “second-generation” AR-targeted therapies include abiraterone, which blocks production of androgens, and enzalutamide and apalutamide, which directly bind to AR and interfere with its function. Dr. Donald McDonnell noted that, in addition to blocking androgen production, abiraterone also directly interacts with and inhibits AR function.
- However, prostate cancer often develops resistance to AR-targeted therapies and continues to progress. Resistance is commonly associated with mutations in AR that (a) decrease the inhibitory activity of existing therapies or (b) allow the receptor to function in a constantly active manner. In these forms of castration-resistant prostate cancer (CRPC), new treatment strategies to block AR in ways different from current medicines are likely to be effective.
- Dr. McDonnell discussed new strategies for therapeutic targeting of AR for the treatment of prostate cancer.
- Dr. McDonnell and team made the important observation that when AR is activated by binding to androgens, the receptor undergoes a conformational change that enables it to partner with other transcription factors and turn on expression of different gene programs.
- Genetic screens performed by the McDonnell lab identified over 300 proteins (co-regulators) that can interact with AR, 160 of which were shown to be important for androgen action. AR requires some of these transcription factors to activate transcription whereas others are required for AR-dependent repression of gene expression. Importantly, these proteins can bind to different surfaces on AR and the team was able to take advantage of the conformational flexibility of AR to identify new classes of drugs that facilitate the interaction of AR with some but not all co-regulators.
- Using this information, the team performed screens to identify new classes of AR-binding compounds that could antagonize prostate cancer-driving functions of AR, while retaining

activities that support bone and muscle metabolism. Some of these compounds, called Selective Androgen Receptor Degradors, are now in clinical development.

- One of the most important practical implications of the McDonnell lab's work on the molecular pharmacology of AR, is that the overall structure of AR is flexible and is influenced by the structures of the drugs with which it interacts. These findings enabled the team to demonstrate that it is possible to discover compounds that promote different interactions between AR and co-regulators and/or allow AR to adopt different conformations with distinct functions.
- Enzalutamide is an AR inhibitor that directly binds to AR. However, at clinically relevant concentrations, enzalutamide actually activates AR, a property which is often overlooked and likely contributes to drug resistance.
- Based on these new insights into AR biology and pharmacology, this group developed strategies to identify: (a) pure AR-antagonists, (b) AR-inhibitors that lead to the degradation of the receptor, (c) drugs that induce novel AR conformations that prevent interactions with certain co-regulators, and (d) drugs that directly block co-regulator binding sites on AR.
- A screen of 180,000 compounds identified a class of cyclobutanes that bind to AR and induce a conformational state that prevented the interaction of the receptor with any known co-regulator. These compounds functioned in animal models of CRPC as pure antagonists and were effective against enzalutamide-resistant prostate tumors in animals.
- The team identified HOXB13 as a key co-regulator of AR that can drive the development of prostate cancer. Interestingly others have shown that mutations in HOXB13 are associated with increased risk for prostate cancer. The HOXB13-AR complex has been found to block expression of cell differentiation genes and promote expression of genes that cause cell growth. Treatment with the HOXB13-inhibitor digoxin prevented the growth of prostate tumors in preclinical animal models.
- These studies demonstrate that new AR inhibitors which block interactions between AR and co-regulators may have strong promise for the treatment of prostate cancer.
- In addition to targeting AR, targeting the cancer growth genes that are turned on by AR may also be a promising therapeutic strategy. Dr. McDonnell's research efforts are now focused on defining how AR inhibitors impact prostate tumor immunity.

## Novel Clinically Relevant AR Degraders/ Antagonists Should have Efficacy in Xenograft Models of Enzalutamide Resistance



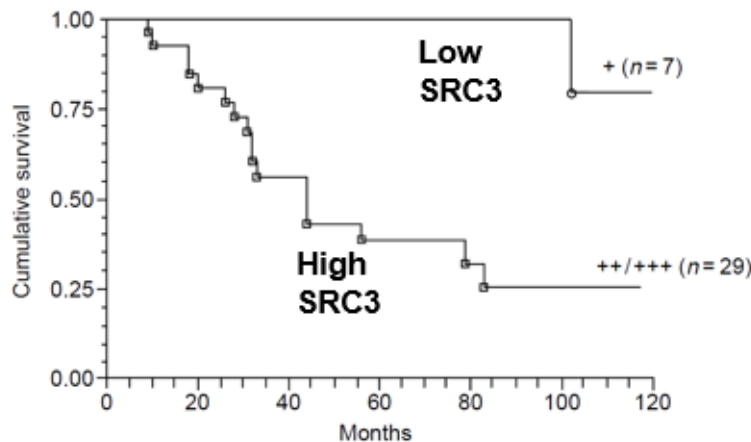
**Figure:** A novel AR-inhibitory cyclobutane ("10") which prevents interactions with co-regulators and inhibits the activity of AR is able to inhibit the growth of enzalutamide-resistant prostate cancer models.

## *Moving Beyond the Androgen Receptor: Targeting Transcriptional Coregulators for the Treatment of Castration-Resistant Prostate Cancer*

Salma Kaochar, PhD  
Baylor College of Medicine

- Castration-resistant prostate cancer (CRPC) is an advanced state of prostate cancer that has developed resistance to therapies that target the androgen receptor (AR). It is critical to understand the biological factors that cause resistance to AR-targeted therapy and to develop new treatments that are effective against CRPC.
- The p160 Steroid Receptor Coactivators (p160 SRCs) are proteins that interact with and modulate the activity of numerous cancer-driving transcription factors. Transcription factors are proteins that act to turn on and off the expression of specific groups of genes and are the master regulators of many cellular activities.
- Levels of p160 SRCs are frequently increased in CRPC and are associated with resistance to AR-targeted therapy and poorer clinical outcomes.
- Dr. Salma Kaochar and team found that p160 SRCs drive prostate cancer cell growth and promote the activity of AR and several other prostate cancer-driving oncogenes.
- These studies suggest that targeting p160 SRCs may be an effective new treatment strategy for CRPC.
- In collaboration with Dr. Bert O'Malley (Baylor College of Medicine), Dr. Kaochar and team identified a small molecule inhibitor of p160 SRCs that had anti-cancer activity in preclinical animal studies without any apparent toxicities. This inhibitor is currently undergoing continued preclinical development in preparation for testing in clinical trials.
- Altogether, these studies demonstrate that targeting p160 SRCs may be a promising new treatment strategy for advanced prostate cancer. Ongoing studies are being conducted to advance these agents into clinical trials.

## Increased Expression and Activity of SRCs are Associated With Inferior Clinical Outcomes



Gnanapragasam et al.  
British Journal of Cancer (2001)

**Figure:** Increased expression and activity of p160 SRCs is associated with poorer clinical outcomes in prostate cancer patients.

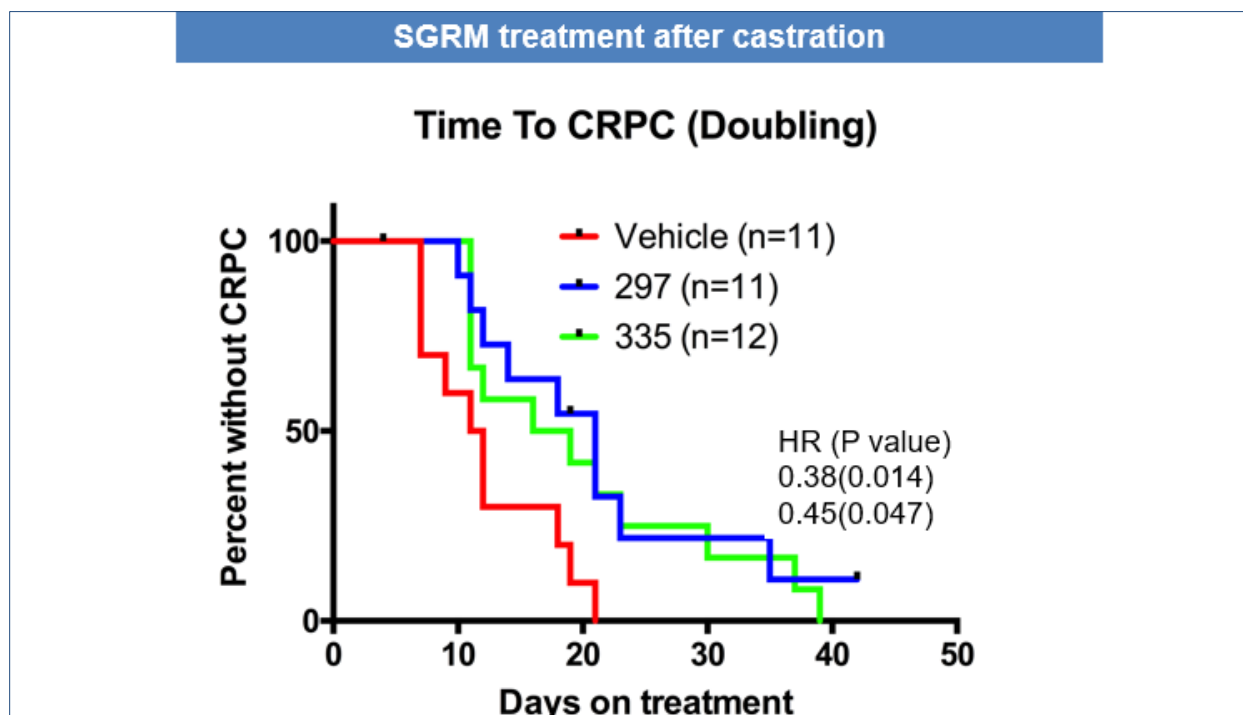
## Surprising Aspects of Androgen and Glucocorticoid Receptor Crosstalk Revealed by Selective Receptor Antagonism

Suzanne Conzen, MD  
University of Chicago

- The glucocorticoid receptor (GR) is a protein that is evolutionarily related to the androgen receptor (AR), and can perform some overlapping functions. Both of these proteins are in the nuclear steroid receptor protein family, but are activated by different hormones or hormone-related molecules and function to turn on expression of certain genes.
- Cholesterol is the precursor of the five major classes of steroid hormones: progestogens, glucocorticoids, mineralocorticoids, androgens, and estrogens.
- AR is the major driver of prostate cancer and is activated by male hormones (androgens) such as testosterone.



- Hormone receptor-positive breast cancers express the estrogen receptor (ER) and/or progesterone receptor (PR), which are activated by estrogens or progesterone, respectively, and/or HER2. Breast cancers that express these receptors can be treated with hormone therapy and/or trastuzumab, which targets HER2.
- Triple-negative breast cancers (TNBC) do not express ER, PR, or HER2, and cannot be treated with hormone therapy or trastuzumab.
- Dr. Suzanne Conzen found that 30% of TNBCs express GR which is activated by glucocorticoids and that GR expression is associated with worse outcomes in patients with TNBC. GR expression in TNBC was found to promote cell survival and metastasis. Thus, GR may be a possible treatment target in patients with GR-positive TNBC.
- In contrast, GR was also expressed in a subset of ER-positive breast cancer, but was associated with better outcomes. These studies suggest that GR may influence the activity of ER, and has context-dependent effects on breast cancer outcomes.
- To investigate the potential for targeting GR in GR-positive TNBC, Dr. Conzen and team developed a set of highly selective GR modulators.
- GR-selective modulators were demonstrated to block the activity of GR by preventing the binding of GR to glucocorticoids and to other proteins that activate GR.
- Treatment of TNBC models with GR-modulators increased their sensitivity to chemotherapy.
- Dr. Conzen and others have also found that GR is expressed in a subset (~20%) of castration-resistant prostate cancer (CRPC) and may be a treatment target. Expression of GR was found to increase in prostate cancer after treatment with androgen deprivation therapy (ADT) or after progression to CRPC, and was associated with a poor response to enzalutamide.
- These studies suggest that targeting GR may be effective in preventing the development of castration-resistance and in GR-positive CRPC.
- In prostate cancer models, treatment with GR-modulators delayed the development of resistance to AR-targeted therapy.
- GR was found to activate the expression of many of the same genes turned on by AR. This suggests that GR may compensate for AR when AR is inhibited.
- GR was also found to activate a unique set of genes that are not regulated by AR. These included immune-regulatory genes. Whether these genes influence CRPC is not yet clear.
- Dr. Conzen and colleagues have initiated clinical trials testing GR-modulators in breast cancer, prostate cancer, and other cancer types.
- In advanced prostate cancer, there are at least three ongoing clinical trials testing GR-modulators: 1) enzalutamide alone vs. with the GR-modulator mifepristone; 2) the GR-modulator CORT125134 plus enzalutamide; and 3) the GR-modulator CORT125181 plus enzalutamide.
- These mutually informative studies of breast and prostate cancer have allowed identification of GR as a common mediator of therapy resistance and a promising therapeutic target.



**Figure:** In prostate cancer models, treatment with selective GR-modulators (SGRM; 297, blue; 335, green) delayed development of castration resistant prostate cancer (CRPC) compared with untreated vehicle controls (red).

## *In the Thicket of an Aberrant Genome: Interpreting the Role of AR-V7*

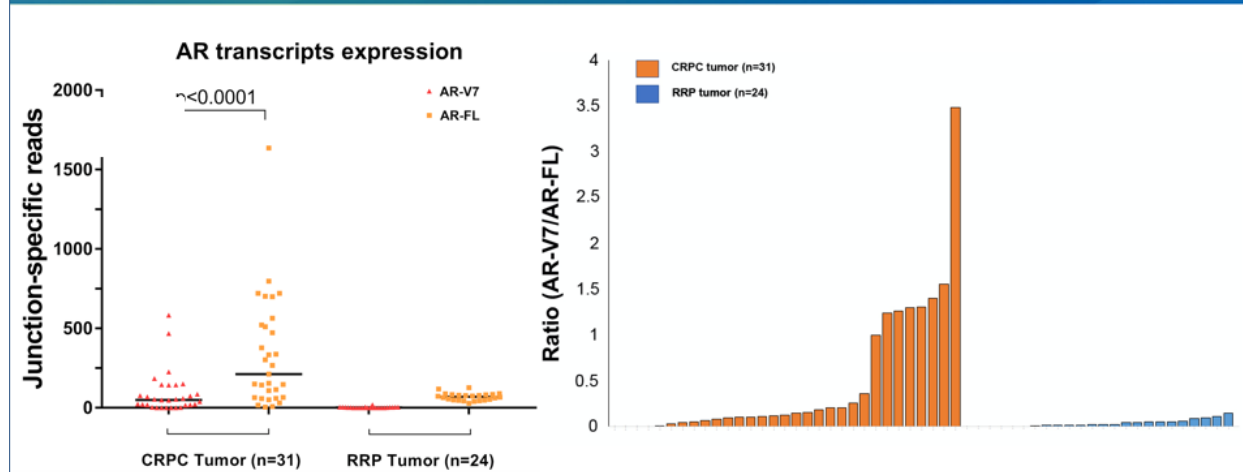
Jun Luo, PhD

Johns Hopkins University

- The androgen receptor (AR) is the primary driver of prostate cancer and turns on genes required for growth and survival. AR is activated by male hormones such as testosterone, then enters the cell's nucleus and binds to target genes, turning on their expression. Because of this dependence, therapies which target either the production of male hormones or AR itself have been the cornerstone of treatment for advanced prostate cancer for decades.
- Unfortunately, in many patients, resistance to AR-targeted therapy develops, resulting in castration-resistant prostate cancer (CRPC), for which no curative treatments yet exist.
- In many cases of CRPC, the disease may continue to be driven by AR, due to mutations that amplify the AR gene or increase AR activity, and/or expression of constantly active AR-variants such as AR-V7.

- AR-variants are shorter forms of the AR protein that do not require the presence of hormones to become activated, and are unable to be bound and inhibited by enzalutamide or apalutamide. It is currently unclear if expression of AR-V7 and other AR-variants drive the development of CRPC or are only associated with it.
- Dr. Jun Luo is investigating the role of AR-V7 in CRPC, and the potential for AR-V7 as a biomarker for predicting response versus resistance to AR-targeted therapies.
- Expression of AR-V7 is very low in untreated primary prostate cancer, but significantly increases following treatment with androgen deprivation therapy (ADT) and second generation AR-targeted therapies (abiraterone, enzalutamide, apalutamide). However, even in CRPC, AR-V7 levels appear to be much lower than levels of normal AR.
- Dr. Luo and team are developing better assays that more accurately measure the levels of AR and AR-V7. With a new assay, the team found that both normal AR and AR-V7 levels are highly increased in CRPC compared with primary prostate cancer. In CRPC, AR-V7 levels tended to be lower than normal AR levels. However, AR-V7 levels in CRPC were similar to normal AR levels in primary prostate cancer.
- AR-V7 may interact with normal AR and cause normal AR to become activated in the absence of hormones. However, Dr. Luo's studies found that AR-V7 and normal AR did not interact in two different prostate cancer cell lines.
- HOXB13 is a transcription factor that can drive the development of prostate cancer. In prostate cancer cell lines and patient samples, AR-V7 but not normal AR was found to bind to the same sites on the genome as HOXB13. AR-V7 only bound to a subset of genomic sites bound by normal AR.
- In prostate cancer cell lines, eliminating the expression of normal AR did not affect levels of AR-V7. However, AR-V7 levels were reduced by HOXB13-targeting drugs. HOXB13-targeting drugs also reduced the growth of prostate tumors in animal models.
- Together, these findings suggest that AR-V7 may drive prostate cancer through interactions with HOXB13 but not normal AR.
- Dr. Luo and team have also developed an assay to measure AR-V7 levels in circulating tumor cells (CTCs) from patients, and are validating this as a test to identify CRPC patients unlikely to respond to second-line AR-targeted therapy.
- It is yet unclear if targeting AR-V7 may be an effective treatment approach for CRPC. Drugs targeting AR-V7 are currently in development.

## AR-V7 is not a low-abundance transcript (in CRPC, AR-V7 levels on par with AR-FL in CSPC)



**Figure:** Normal AR and AR-V7 levels are highly increased in CRPC compared with primary prostate cancer from radical prostatectomy samples (“RRP”). While AR-V7 levels tended to be lower than normal AR levels in CRPC, AR-V7 levels in CRPC were similar to normal AR levels in primary prostate cancer. Left: AR and AR-V7 levels in CRPC and primary prostate cancer. Right: Ratio of AR-V7 to normal AR levels in CRPC and primary prostate cancer.

## Session 3: PSMA-Targeted Theranostics for Prostate Cancer

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### *SPECIAL LECTURE: PSMA Theranostics: Latest Evidence-Base, Promise and Uncertainties*

Michael Hofman, MBBS

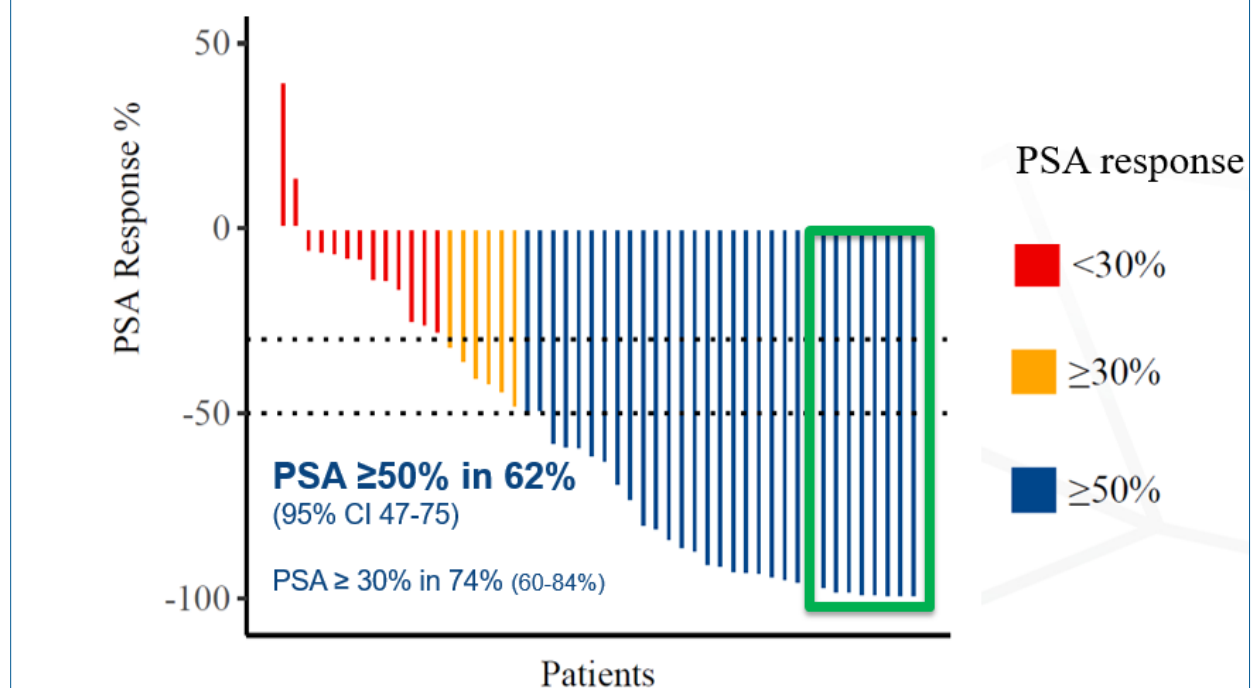
Peter MacCallum Cancer Centre, Australia

- PSMA (prostate specific membrane antigen) is a protein that is highly expressed on the surface of prostate cancer cells, and in a few other normal cell types at lower levels. PSMA on prostate cancer cells increases with disease progression and following androgen deprivation or AR-targeted therapies. Because of these properties, PSMA is a highly promising target for prostate cancer therapies and PET (positron emission tomography) imaging.
- Radioligand therapy is an emerging type of cancer treatment consisting of radioactive isotopes attached to cancer-targeting molecules, and enables delivery of radiation directly to tumor cells.
- Several new PSMA-targeted radioligand therapies have been developed and are being tested in clinical trials for prostate cancer. Early reports on PSMA-targeted radioligand therapies are promising, and have prompted further clinical trial testing.
- Dr. Michael Hofman discussed results from a phase II clinical trial testing the PSMA-targeted radioligand therapy  $^{177}\text{Lu}$ -PSMA-617 in men with metastatic castrate-resistant prostate cancer (mCRPC), which was conducted at the Peter MacCallum Cancer Centre in Australia.
- In this trial, mCRPC patients, most of whom had failed previous treatment with abiraterone or enzalutamide and with docetaxel, were treated with up to four cycles of  $^{177}\text{Lu}$ -PSMA-617.
- To determine eligibility for the trial, FDG-PET imaging and PSMA-PET imaging were done to ensure all sites of metastasis expressed the treatment target, PSMA, at sufficiently high levels. Only patients in which all metastatic lesions detected by FDG-PET imaging were also visible on PSMA-PET imaging, and PSMA-PET imaging levels were sufficiently high, were enrolled onto the trial and treated with  $^{177}\text{Lu}$ -PSMA-617.
- Of 75 patients screened for the trial, 25 were found ineligible, eight of whom had low PSMA levels on PSMA-PET imaging, and eight of whom had metastatic sites on FDG-PET imaging that were not seen on PSMA-PET imaging.
- Overall, 50 patients were treated, 21 of whom had less than 4 cycles of treatment.
- Of the 50 patients treated, 74% had  $\geq 30\%$  reductions in PSA levels and 62% had  $\geq 50\%$  reductions in PSA levels (Figure). Ten patients (20%) experienced disease progression. Exceptional responses with consequent early cessation of therapy were observed in eight (15%) patients, four of whom experienced a complete imaging response (Figure).
- The treatment was not curative and almost every patient treated eventually progressed. The median overall survival of the treated patients was 13.4 months.
- Disease progression after therapy occurred predominantly as metastases in bone marrow.

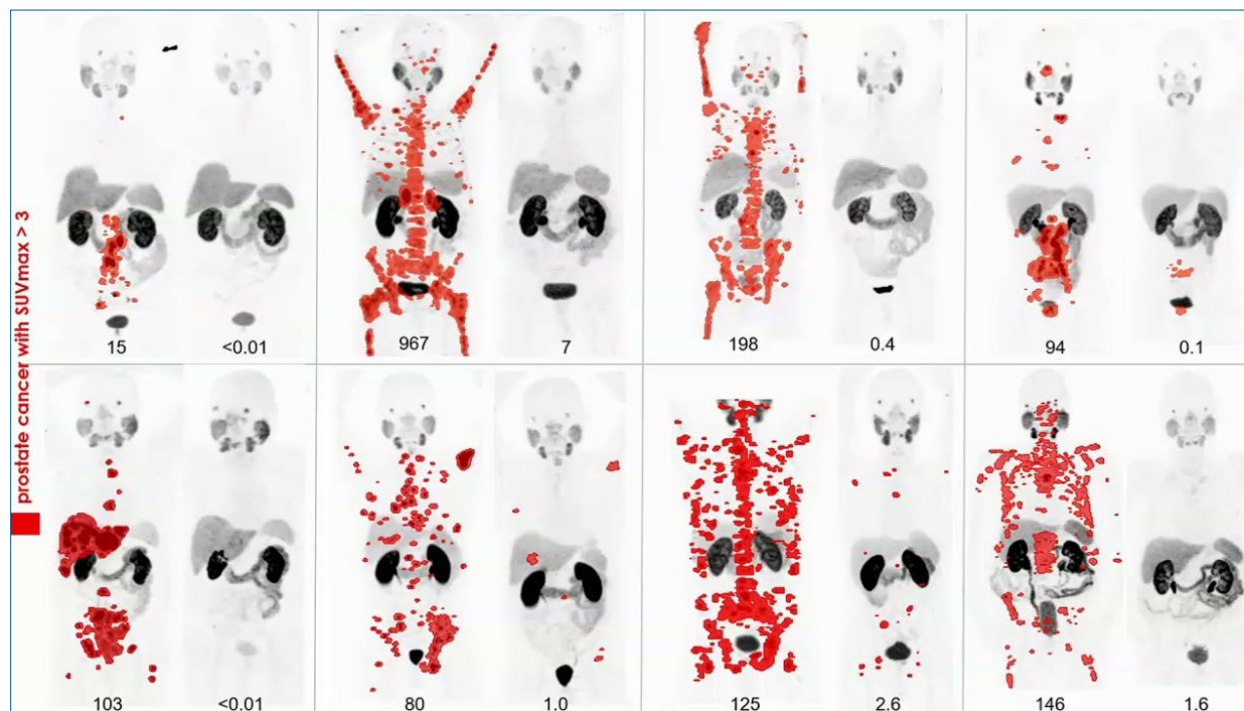
- The treatment was well tolerated. The most common Grade 3 adverse events were anemia (10%), low blood platelet count (8%), and low neutrophil count (6%).
- The most commonly observed Grade 1 adverse event was dry mouth (xerostomia). Grade 1 xerostomia occurred in 66% of patients and grade 2 xerostomia occurred in one patient (2%). These symptoms could be alleviated by increasing oral intake of liquids and moist foods, and were usually reversible after treatment.
- The radioactivity released by  $^{177}\text{Lu}$ -PSMA-617 can be visualized on SPECT molecular imaging, which can be used to estimate the dose of treatment that was delivered to tumors. To estimate the dose of  $^{177}\text{Lu}$ -PSMA-617 that was delivered to tumor sites, SPECT imaging was performed on patients after the first treatment cycle. Results indicated that better PSA responses were seen in patients who received larger treatment doses to their tumors.
- Altogether, these results indicate that  $^{177}\text{Lu}$ -PSMA-617 is a highly promising treatment for mCRPC. Several new  $^{177}\text{Lu}$ -PSMA-617 clinical trials have been initiated.
- A randomized phase II clinical trial (“TheraP”) testing  $^{177}\text{Lu}$ -PSMA-617 versus cabazitaxel has been opened at several centers in Australia. Over 80 patients have been enrolled on this trial thus far.
- An international open-label randomized phase III trial (“VISION”) testing  $^{177}\text{Lu}$ -PSMA-617 plus best supportive care versus best supportive care alone in men with progressive PSMA-positive mCRPC was opened in 2018. 750 patients will be recruited to this trial. If this trial is positive, it may lead to FDA-approval for this new treatment.
- Planned trials at the Peter MacCallum Cancer Centre include a phase I trial testing  $^{177}\text{Lu}$ -PSMA-617 plus the PARP-inhibitor olaparib, and a phase I/II trial testing  $^{177}\text{Lu}$ -PSMA-617 plus the immune checkpoint inhibitor pembrolizumab.
- Future trials will test whether  $^{177}\text{Lu}$ -PSMA-617 or other PSMA-targeted radioligand therapies, alone or in combination with other treatments, are more effective or possibly even curative when used earlier in the disease course.



## Best PSA Response (N=50)



**Figure:** Best PSA response in 50 patients treated with  $^{177}\text{Lu}$ -PSMA-617. Of the 50 patients treated, 74% had  $\geq 30\%$  reductions in PSA levels and 62% had  $\geq 50\%$  reductions in PSA levels.



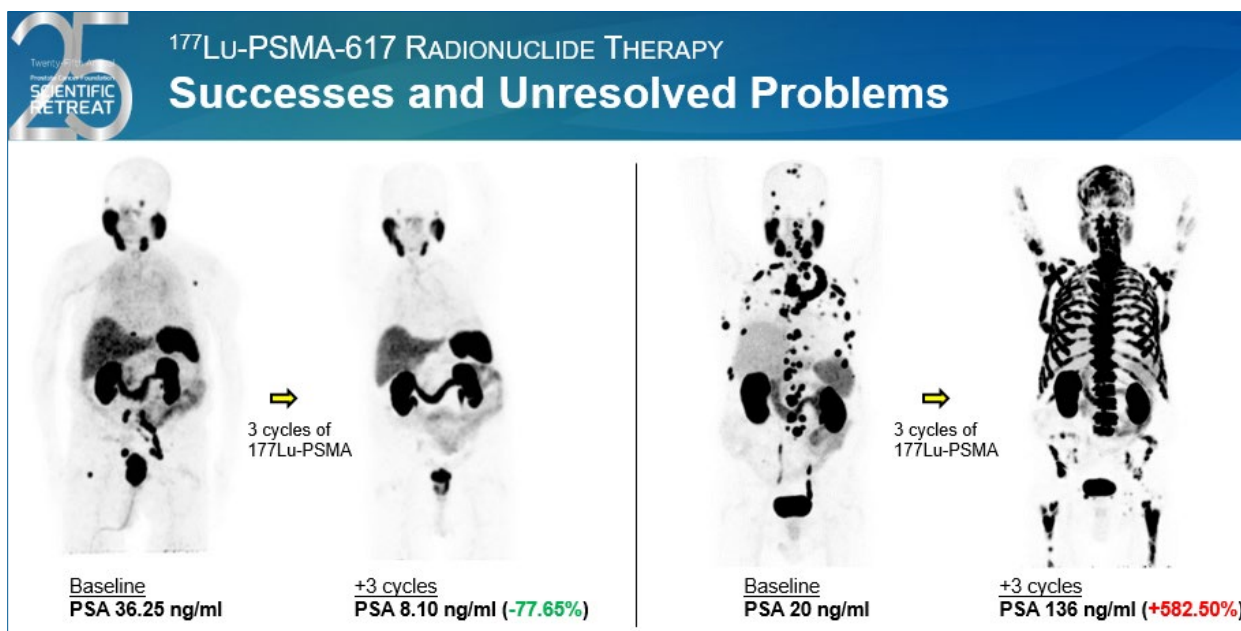
**Figure:** PSMA-PET imaging of metastatic prostate tumors and PSA levels before and after  $^{177}\text{Lu}$ -PSMA-617 treatment in the eight patients with the best responses.

## *Elucidating Mechanisms of Effectiveness and Resistance to PSMA Targeted RadioLigand Therapy (RLT) using <sup>177</sup>Lu-PSMA-617*

Jeremie Calais, MD  
University of California, Los Angeles

- PSMA is a protein that is highly expressed on the surface of prostate cancer cells and is thus a promising therapeutic and imaging target in prostate cancer.
- PSMA-targeted radioligand therapy is a new type of treatment composed of a radioactive isotope attached to a PSMA-targeting molecule, and acts to deliver radiation directly to prostate cancer cells.
- There are several PSMA-targeted radioligand therapies that are under development for the treatment of prostate cancer, including <sup>177</sup>Lu-PSMA-617, which is composed of the beta particle-emitting isotope 177-Lutetium attached to the PSMA-targeting small molecule PSMA-617.
- Dr. Jeremie Calais discussed preliminary results from a bi-phasic phase II trial (“RESIST-PC”) being conducted at UCLA and Excel Diagnostics in Houston, testing <sup>177</sup>Lu-PSMA-617 in men with progressive metastatic castration-resistant prostate cancer (mCRPC). Eligible patients must have previously failed treatment with abiraterone or enzalutamide, and have PSMA-positive tumors on PSMA-PET imaging.
- Patients enrolled on the trial were randomized to receive up to four cycles of either 6.0 GBq or 7.4 GBq of <sup>177</sup>Lu-PSMA-617.
- Of 64 men treated with at least one cycle of <sup>177</sup>Lu-PSMA-617, 27% experienced a PSA decline  $\geq 50\%$  at 12 weeks post-treatment, and 33% experienced a PSA decline  $\geq 50\%$  at some time point. 50% of patients had no PSA response at 12 weeks and 41% had no PSA response at any time after therapy. 10% of patients experienced a deep and durable response with  $>90\%$  PSA decline.
- The treatment was well tolerated. Mild and reversible xerostomia (dry mouth) occurred in 70% of patients, with no grade 3-4 cases seen. Over 40% of patients had Grade 1-2 nausea or vomiting. Grade 4 low blood platelet counts were seen in 2% of patients. Grade 3 adverse events included anemia (8%), low white blood cell count (5%), and low neutrophil count (3%). Grade 3 kidney failure occurred in two patients (3%). No toxicity differences were observed in patients who received lower versus higher doses (6.0 vs 7.4 GBq).
- At least six different patterns of PSA responses were observed in patients treated with <sup>177</sup>Lu-PSMA-617. Response patterns included: 1) immediate PSA declines after the first treatment that became deep and durable after treatment cycles 2-4; 2) initial PSA increases followed by decreases after subsequent treatment cycles; 3) short-term PSA declines followed by increases after later cycles; 4) stabilization or slowing down of PSA progression; 5) continuous PSA progression; and 6) an immediate increase in PSA progression kinetics (burst). These variable PSA responses likely reflect a difference in the underlying biology of the metastatic prostate cancer. Studies are underway to understand the biology underlying the spectrum of different PSA and imaging response patterns seen.

- Dr. Calais and colleagues in Europe and Australia are performing studies to identify biomarkers that can predict which patients will respond to PSMA-targeted radioligand therapy.
- One factor that may result in poor responses, may be an inability to deliver sufficient doses of radiation to tumors. In the previous talk by Dr. Hofman (above), it was demonstrated that better responses were seen in patients who had higher radiation doses reach their tumors. Dr. Calais and team are investigating whether this is observed in this clinical trial cohort.
- Molecular mechanisms underlying response versus resistance to PSMA-targeted radioligand therapy are also under investigation.
- The team is performing studies to identify protein pathways that are activated in tumors in response to  $^{177}\text{Lu}$ -PSMA-617 in animal models.
- DNA damage response/repair pathways (ATR and ATM) were activated by treatment while cell division pathways (*CDK1*, *CDK2*) were turned off. This suggests that prostate cancer cells are attempting to fix DNA damaged by the treatment before continuing to divide.
- Dr. Calais and team performed preclinical studies to indicate whether inhibition of DNA damage response/repair pathways would be synergistic with  $^{177}\text{Lu}$ -PSMA-617. In mouse prostate cancer models,  $^{177}\text{Lu}$ -PSMA-617 was synergistic with an ATR-inhibitor.
- There are several ATR and ATM inhibitors that are currently being tested in clinical trials.
- These studies suggest that clinical trials testing  $^{177}\text{Lu}$ -PSMA-617 in combination with ATR or ATM inhibitors may be warranted.
- Studies are ongoing to identify other targetable signaling alterations that occur in response to treatment with  $^{177}\text{Lu}$ -PSMA-617, and to identify rational combination therapies that may be more effective against prostate cancer.
- There are multiple ongoing prostate cancer clinical trials testing PSMA-targeted therapies and PSMA-PET imaging at UCLA. These include the international randomized phase III “VISION” trial testing  $^{177}\text{Lu}$ -PSMA-617 plus best supportive care versus best supportive care alone in progressive PSMA-positive mCRPC.



**Figure:** PSMA-PET imaging and PSA levels following <sup>177</sup>Lu-PSMA-617 treatment in patient examples of response good responder (left) and of massive PSA and bone marrow progression in a non-responder (right).

### Optimization of PSMA-Targeted Radionuclide Therapy

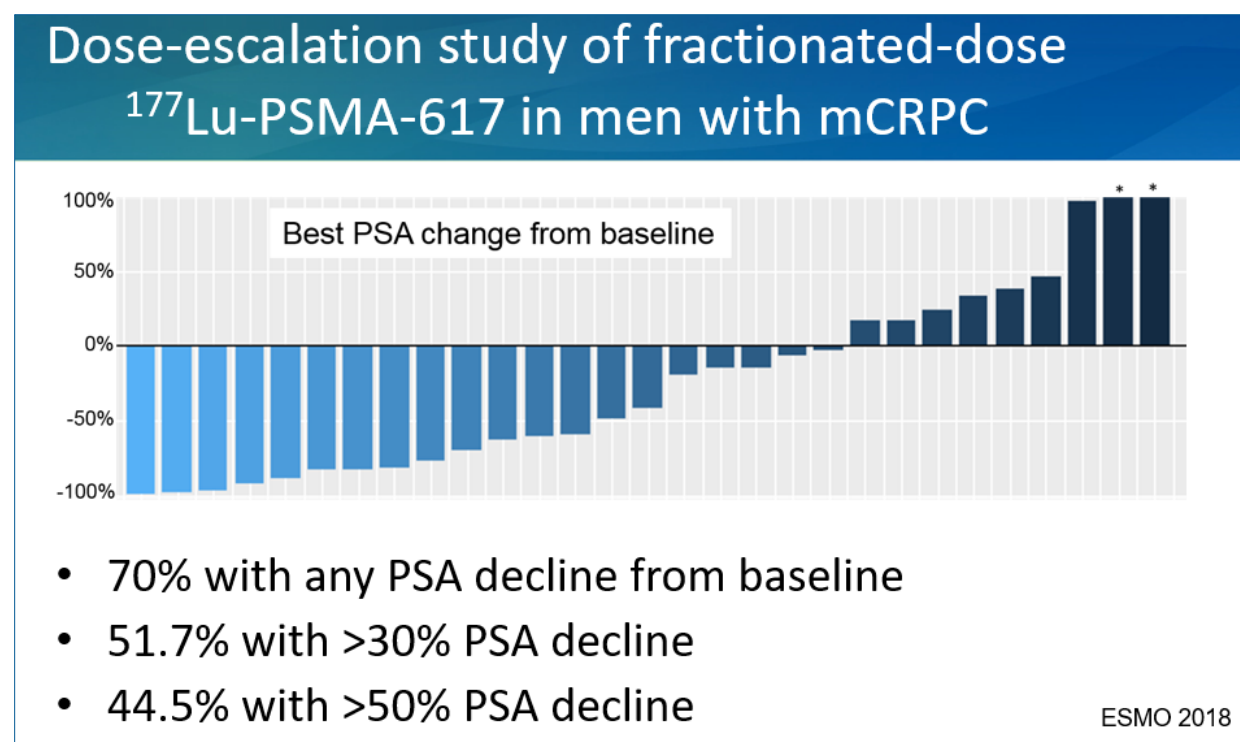
**Scott Tagawa, MD**  
Weill Cornell Medicine

- PSMA (prostate-specific membrane antigen) is a protein that is highly expressed on prostate cancer cells and is a promising therapeutic and imaging target. Studies are underway to develop PSMA-targeted treatments and PSMA-PET imaging agents.
- PSMA-targeted agents that have been developed for therapy and imaging include small molecules and antibodies.
- Antibodies are approximately 100-times larger than the PSMA-targeted small molecules that have been developed. These size differences result in differences in circulation time in the body (antibodies have a circulation time of days, whereas the small molecules have a circulation time of hours), differences in tissues that can be accessed and penetrated (antibodies primarily target vasculature while small molecules rapidly diffuse to all tissue sites expressing PSMA), and toxicity (PSMA-targeted antibody toxicities include infusion reactions and toxicity to bone marrow and liver, while PSMA-targeted small molecules are more toxic to the kidney, salivary glands, and small intestine).

- Dr. Tagawa and team have developed a PSMA-targeted antibody (J591) and are testing various forms of the J591 antibody in prostate cancer clinical trials. These forms include “naked” J591 (the antibody alone or in combination with other agents), antibody-drug conjugates in which various chemotherapies or toxins are attached to J591, and radioligand therapies, in which radioactive isotopes are attached to J591.
- Eight different phase I and phase II trials have been completed at Weill Cornell Medicine to date, which have demonstrated safety and indicated efficacy for various J591-radioligand agents. Six of these trials tested  $^{177}\text{Lu}$ -J591 at various doses or dosing strategies.
- Collectively, these trials have found that patient outcomes are better at higher doses of  $^{177}\text{Lu}$ -J591. In one study, median overall survival was 21.8 months in patients who received a  $^{177}\text{Lu}$ -J591 dose of 70 mCi/m<sup>2</sup> compared with median overall survival of 11.9 months in patients who received a slightly lower dose of 65 mCi/m<sup>2</sup>.
- Dose fractionation, in which several successive small doses are given instead of single larger doses, can achieve higher cumulative radiation doses with lower toxicities, and may result in better patient outcomes. In one fractionated dosing trial, median overall survival was 42.3 months in patients receiving a cumulative dose of 90 mCi/m<sup>2</sup>, 19.6 months in patients receiving a cumulative dose of 80 mCi/m<sup>2</sup>, and 14.6 months in patients receiving a cumulative dose of 40-70 mCi/m<sup>2</sup>.
- Dr. Tagawa conducted a phase I clinical trial testing escalating fractionated doses of  $^{177}\text{Lu}$ -PSMA-617 in men with mCRPC. No dose-limiting toxicities or maximum tolerated dose were defined. In the 29 patients treated, 70% exhibited a PSA decline from baseline at some point after treatment, 51.7% exhibited a >30% PSA decline, and 44.5% exhibited a >50% PSA decline (Figure). A reduction in circulating tumor cell (CTC) levels was observed in 10 of 17 (59%) patients assessed.
- Differences in the tissues targeted and the associated toxicities of PSMA-targeted small molecule versus antibody-based radioligand therapies have been observed.
- In the phase I clinical trial testing the PSMA-targeted small molecule  $^{177}\text{Lu}$ -PSMA-617 in 29 patients, the greatest toxicities were damage to salivary glands (48.3%), low platelet counts (37.9%), nausea (31%), fatigue (31%), and low neutrophil counts (20.7%).
- In combined phase I and II trials testing the PSMA-targeted antibody  $^{177}\text{Lu}$ -PSMA-J591 in 131 patients, the greatest toxicities were low platelet counts in 80.9% (32.2% were grade 4), low neutrophil counts in 73.3% (21.4% were grade 4), fatigue (42.7%), and nausea (17.6%), while salivary gland toxicities were observed in <1% of patients. Blood cell-based toxicities were fully recovered after treatment ended, in most cases.
- Differences in the toxicities caused by small molecule versus antibody-based PSMA-targeted radioligand therapies have led to the hypothesis that combining these treatments may achieve higher efficacy without significantly increasing toxicity. To investigate this possibility, Dr. Tagawa and team are conducting clinical trials testing the PSMA-targeted small molecule  $^{177}\text{Lu}$ -PSMA-617 alone or in combination with  $^{177}\text{Lu}$ -J591.
- There are various radioactive isotopes that can be attached to tumor-targeting agents to generate radioligand therapies. Beta-emitting isotopes emit lower energy over longer distances, while alpha-emitting isotopes emit 4,000-fold greater energy that travels much shorter distances. Isotopes being tested in PSMA-targeted radioligand therapies include the beta-emitting isotope 177-Lutetium ( $^{177}\text{Lu}$ ) and the alpha-emitting isotope 225-Actinium ( $^{225}\text{Ac}$ ).



- Previous studies have found that treatment with  $^{225}\text{Ac}$  attached to a PSMA-targeted small molecule ( $^{225}\text{Ac}$ -PSMA-617) resulted in significant salivary gland toxicities, as salivary glands express low levels of PSMA. It is possible that less toxicity would occur using an alpha emitter attached to an antibody (due to the poorer ability of the antibody to penetrate salivary tissue). To test this hypothesis, Dr. Tagawa is conducting a clinical trial testing escalating doses of  $^{225}\text{Ac}$ -J591.
- Altogether, these clinical trials will help to determine the most promising form, dose, and therapeutic strategy for PSMA-targeted radioligand therapy.
- Dr. Tagawa is also conducting studies to identify biomarkers that will help to determine which patients are most likely to benefit from these treatments.



**Figure:** Best PSA responses in a phase I clinical trial testing escalating fractionated doses of  $^{177}\text{Lu}$ -PSMA-617 in men with mCRPC. In the 29 patients treated, 70% exhibited a PSA decline from baseline at some point after treatment, 51.7% exhibited a >30% PSA decline, and 44.5% exhibited a >50% PSA decline.



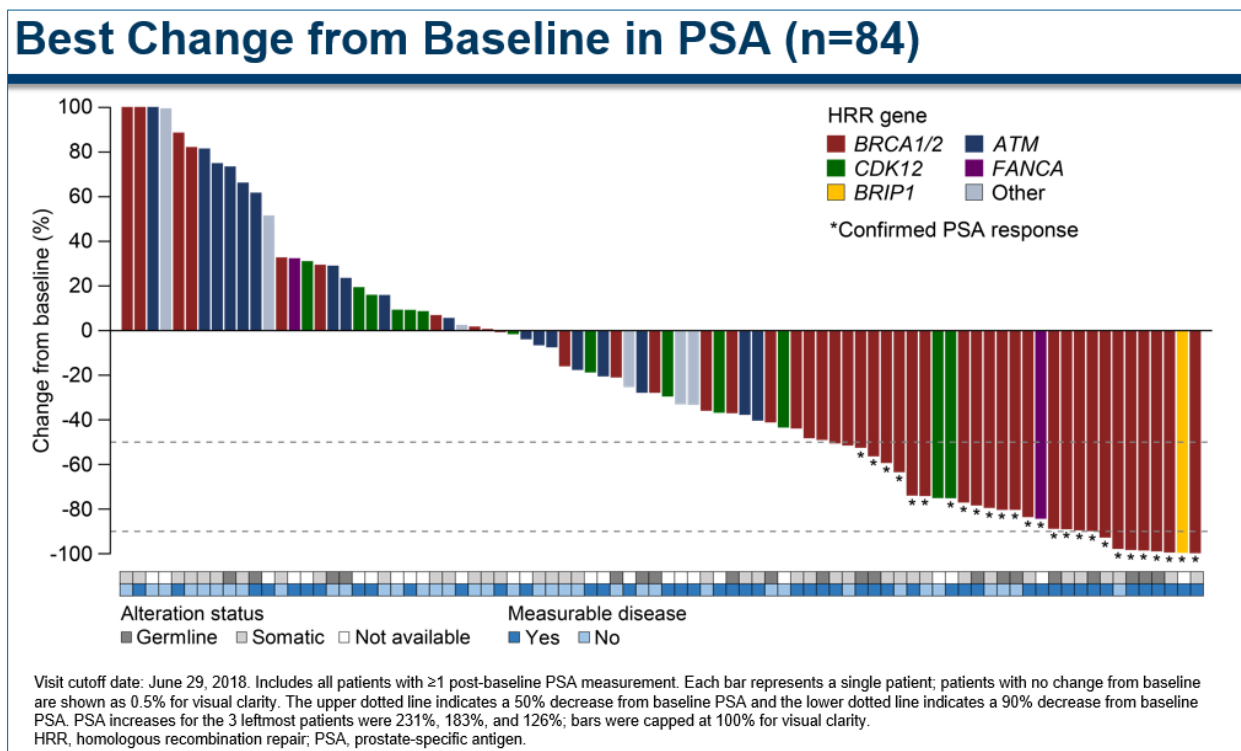
## SPECIAL LECTURE: Results from TRITON2: Treatment of mCRPC with Rucaparib

Alan Bryce, MD  
Mayo Clinic

- Precision medicine offers the prospect of selecting treatments based on the unique genetic alterations present in an individual's cancer. Many studies are now underway to identify precision medicine treatment options for patients with metastatic castration-resistant prostate cancer (mCRPC), a currently lethal form of this disease.
- Approximately 25% of mCRPC patients have tumors with defects in DNA damage repair (DDR) genes such as *BRCA1*, *BRCA2*, and *ATM*. DDR-deficient tumors can become highly reliant on the PARP DNA repair pathway to maintain sufficient integrity of DNA, and are therefore sensitive to treatment with PARP inhibitors.
- Several PARP inhibitors are now being tested in prostate cancer clinical trials.
- A previous phase II clinical trial, TOPARP-A, investigated the efficacy of the PARP inhibitor olaparib in mCRPC. Genomic analysis performed on tumors from the 49 patients on this trial demonstrated that DDR-alterations were strongly associated with responses, based on a composite endpoint looking at radiographic imaging, PSA levels, or circulating tumor cell levels: of 16 patients who responded to olaparib, 14 had alterations in DDR genes including *BRCA1* (1 patient), *BRCA2* (7 patients), and *ATM* (4 patients).
- The phase II TRITON2 clinical trial is testing the PARP inhibitor rucaparib in mCRPC patients who have somatic (tumor) or germline (inherited) DDR gene alterations. Dr. Alan Bryce presented preliminary results from 85 patients treated thus far in TRITON2.
- Only patients with a DDR gene alteration identified in their tumor or germline were eligible for enrollment on this trial. Patients must also have previously failed treatment with both an androgen receptor (AR)-directed therapy (abiraterone, enzalutamide, or apalutamide) and taxane-based chemotherapy.
- Of the 85 patients enrolled thus far, 45 had *BRCA1/2* alterations, 18 had *ATM* alterations, 13 had *CDK12* alterations, and 9 had other DDR gene alterations.
- In a preliminary analysis, rucaparib was found to have encouraging antitumor activity in patients with *BRCA1* or *BRCA2* alterations. In 25 patients with germline or tumor *BRCA1/2*-alterations who were treated with rucaparib and had measurable disease, 44% experienced a confirmed radiographic response (tumors shrank on imaging), 36% had stable disease, and 16% had progressive disease. No complete responses were observed. Among the 45 patients overall with *BRCA1/2* alterations, 51% had a confirmed PSA response.
- Two patients with *BRIP1* or *FANCA* alterations also had confirmed radiographic and PSA responses.
- Alterations in the *ATM* or *CDK12* genes were not associated with responses to rucaparib.
- 95.3% of patients on the trial experienced at least one treatment-related adverse event, with grade 3 events occurring in 52.9% of patients. 52.9% of patients had a dose reduction or treatment interruption due to an adverse event. The most common adverse events leading

to dose reduction were fatigue (8.2% of patients), anemia (7.1%), decreased platelet count (5.9%), and nausea (4.7%). Five patients (5.9%) discontinued treatment altogether due to adverse events.

- Altogether, these data demonstrate that rucaparib may be promising in patients with *BRCA1* or *BRCA2* alterations.
- Based on these results, in October 2018, the FDA granted Breakthrough Therapy designation, (a process to fast-track FDA review of highly promising drugs) for rucaparib in patients with *BRCA1/2*-mutated mCRPC who have received at least one prior AR-directed therapy and taxane-based chemotherapy.
- In 2016, rucaparib was FDA-approved for ovarian cancer patients with *BRCA1/2* alterations who have been treated with two or more prior chemotherapy regimens. In 2018, rucaparib was FDA-approved as maintenance treatment for patients with recurrent ovarian cancer who are in a complete or partial response to platinum-based chemotherapy.
- Enrollment in the TRITON2 trial is ongoing. The safety and efficacy of rucaparib as a treatment for mCRPC patients with a DDR gene alteration continues to be evaluated.



**Figure:** Best change from baseline in PSA in 84 patients treated with rucaparib on the TRITON2 trial. Confirmed PSA responses (\*) were observed in 51.1% of patients with *BRCA1/2* alterations, one patient with a *CDK12* alteration, one patient with a *BRIP1* alteration, and one patient with a *FANCA* alteration.

*PANEL DISCUSSION: Principles and Practice (Challenges) of 2018 Precision Oncology in Advanced Prostate Cancer 4 Nano CPCs: CDK12-/-, BRCA2-/-, AKT-1E17K, and SLC43-BRAF Fusion*

**Introduction:**

Jonathan W. Simons, MD  
Prostate Cancer Foundation

**Moderator:**

Himisha Beltran, MD  
Harvard: Dana-Farber Cancer Institute

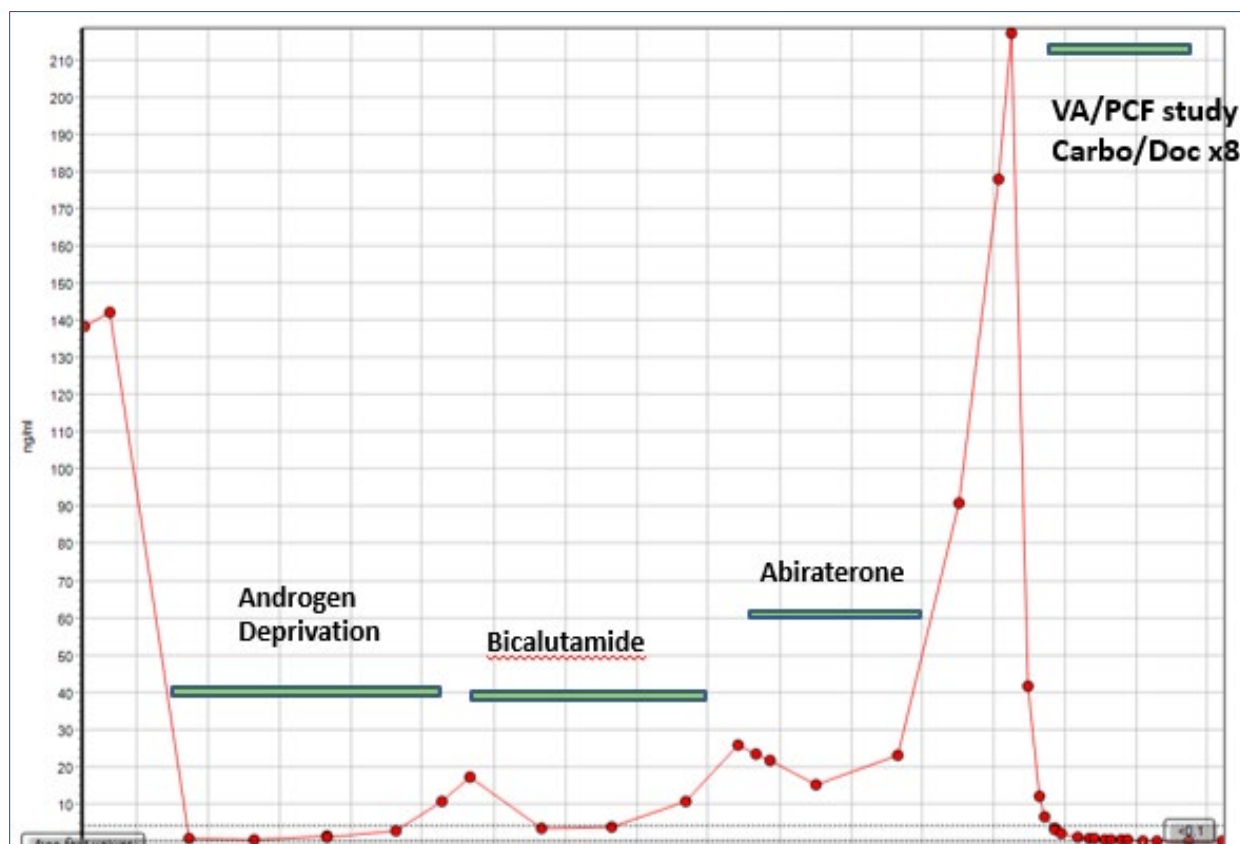
**Panelists:**

Ajjai Alva, MD (University of Michigan)  
Bruce Montgomery, MD (University of Washington; VA Puget Sound)  
Vaibhav Patel, MD (Icahn School of Medicine at Mount Sinai Hospital)  
Matthew Rettig, MD (University of California, Los Angeles)  
Gerhardt Attard, MD, PhD (University College London Cancer Institute, UK)

- Precision oncology is an emerging clinical strategy to match individual patients to treatments most likely to provide benefit, based on the unique biology of their tumor.
- There are a multitude of new treatments being tested in clinical trials, several of which have demonstrated activity in individual patients with specific genomic mutations.
- A panel discussion, moderated by Dr. Himisha Beltran, was held to share several individual prostate cancer precision medicine experiences involving different genomic alterations.
- In addition, the panel discussed the critical need for a single centralized platform in which clinicians may report precision medicine successes and failures for various treatments, including data on the biomarkers used to select the treatments (such as mutations or gene expression), and standardized clinical and outcomes data, in order to learn from other experiences, aggregate data, and accelerate the development of precision medicine treatment paradigms for specific tumor mutations.
- Dr. Himisha Beltran discussed the practice of precision oncology and how it can be improved and accelerated.
- In precision medicine, all patients can be considered individual “N=1” cases.
- Each individual has unique patient factors including disease state, alternative options, urgency of therapy, comorbidities, patient preferences, and insurance and financial considerations.

- Precision medicine decisions must also consider tumor factors, the strength of prior basic science and preclinical studies, and potential impacts of co-occurring alterations, on the efficacy of the treatment.
- Precision medicine decisions also involve consideration of which tests were used to identify mutations and the source of the tumor tissue used.
- Access to drugs is another important factor, including whether the drug is FDA-approved for the indication or another indication, whether the drug may be accessed through clinical trials or compassionate use programs, and out-of-pocket costs to the patient.
- In order to accelerate precision medicine, it is essential that data from prior successes and failures is shared and made accessible. Existing “venues” to disseminate precision medicine data include publication in scientific journals and presentation at scientific meetings.
- A central database to house precision medicine data does not currently exist. An ideal database would incorporate common data elements, be accessible to academic and non-academic precision medicine physicians, report outcomes from biomarker-driven decisions or exceptional responses to standard therapies, and allow the opportunity to provide tissues or blood.
- Other necessary measures to accelerate precision medicine include partnerships with pharmaceutical and biotechnology companies, design of innovative clinical trials (for instance, N=1, basket, umbrella, enriched, and adaptive trials), updating and improving guidelines, and establishing framework for precision medicine decisions based on non-genomic biomarkers, such as protein expression.
- Ultimately, engagement and participation of the broader oncology community and other leading governmental and oncology organizations (such as the NCI, ASCO and AACR) will make it easy to report precision medicine data, collaborate on studies, and secure the funding needed.
- Most importantly, patients must remain the focus. Clinicians must partner with, educate, advise and deliver results for their patients.
- “N=1” precision medicine case reports were presented by several panelists.
- Dr. Ajjai Alva presented a case in which a metastatic castration-resistant prostate cancer (mCRPC) patient with a bi-allelic loss (loss of both gene copies) of the *CDK12* gene in his tumor exhibited a deep PSA and imaging response to checkpoint immunotherapy.
- This patient had previously undergone a radical prostatectomy and serial treatments with ADT, abiraterone and enzalutamide.
- *CDK12* bi-allelic alterations have been shown to result in a high level of tandem duplication mutations which may cause tumors to be sensitive to checkpoint immunotherapy. In addition to a *CDK12* bi-allelic alteration, tumor samples from the patient were infiltrated with T cells, further supporting the likelihood that checkpoint immunotherapy could be of benefit.
- The patient received 15 cycles of the checkpoint immunotherapy anti-PD1 through a compassionate use program. The patient’s PSA levels dropped into normal ranges and tumors markedly shrank on imaging. At the time of this presentation, the patient was still on treatment and continued to experience a deep PSA response.

- A clinical trial (IMPACT: NCT03570619) has been opened, which will test the efficacy of the checkpoint immunotherapies nivolumab + ipilimumab in patients with either mCPRC or non-prostate solid tumors who have bi-allelic loss of the *CDK12* gene in their tumors.
- Platinum chemotherapy has previously been demonstrated to be effective in *BRCA2*-deficient ovarian cancer and breast cancer.
- Dr. Bruce Montgomery presented a case in which a mCPRC patient with a bi-allelic *BRCA2* gene alteration experienced complete PSA and imaging responses following treatment with carboplatin plus docetaxel chemotherapy (Figure). The patient had previously been treated with ADT, bicalutamide, and abiraterone, and had symptomatic metastatic disease at the time the treatment was initiated. At the time of this presentation, the patient continued to be on carboplatin/docetaxel treatment with an ongoing complete response.
- Dr. Vaibhav Patel discussed identifying a precision treatment for a mCPRC patient who had progressed on abiraterone/prednisone. Subsequent treatment choices for this patient included enzalutamide +/- targeted radiation, docetaxel, or a clinical trial. To aid in this decision, genomic analysis of the tumor was conducted, which identified a bi-allelic alteration in the *AKT1* gene (a gene amplification and an activating mutation, both of which cause hyper-activation of the oncogenic AKT pathway).
- AZD5363 is an inhibitor of *AKT1*, *AKT2* and *AKT3*, that has previously indicated promise in patients with various solid tumor types with *AKT1* alterations. Consideration for enrollment of this patient onto a trial testing AZD5363 in AKT-mutant solid tumors was discussed. This trial has an arm specifically for prostate cancer patients with mCRPC who have previously progressed on enzalutamide. The patient is currently being treated with enzalutamide, and will be enrolled onto the AZD5363 trial at the time of progression on enzalutamide.
- Dr. Matthew Rettig presented a case in which a mCPRC patient with an *AK-G469A* (activating mutation) was treated with the MEK inhibitor trametinib. BRAF activates the MEK oncogene pathway which may drive prostate cancer, thus it was hypothesized that inhibiting MEK might be effective in this patient.
- The patient experienced some tumor shrinkage on imaging following treatment with trametinib. The patient also experienced a fluctuating PSA response which did not correlate with imaging responses. Unfortunately, the patient passed away due to complications from a surgery to treat a colo-vesical fistula. The fistula may have been a side effect caused by a prior brachytherapy implantation procedure.
- Alterations in the RAF/MEK/ERK pathway are common in advanced prostate cancer. However, it is yet unclear how best to apply precision medicine to target this complicated oncogenic pathway.
- Altogether, while these case reports demonstrate that precision medicine treatments which target tumor alterations can be of benefit in advanced prostate cancer, much more information and experience is needed in order to successfully apply this approach to every patient. A collective understanding of which treatments benefit which patients, is imperative for the advancement of precision oncology.



**Figure:** PSA levels over time in a prostate cancer patient with a bi-allelic alteration in the *BRCA2* gene who was treated serially with ADT, bicalutamide, abiraterone, and carboplatin plus docetaxel (Carbo/Doc) chemotherapy.



## *SPECIAL LECTURE: VAlor Awards and VA Center of Excellence Update*

Bruce Montgomery, MD

University of Washington; VA Puget Sound

Matthew Rettig, MD

University of California, Los Angeles

- On November 29, 2016, the United States Department of Veterans Affairs (VA) and the Prostate Cancer Foundation (PCF) announced a partnership to advance precision medicine for U.S. veterans. As part of this announcement, PCF pledged \$50 million to support the PCF Veterans Health Initiative to expand prostate cancer precision oncology research among veterans to speed the development of new precision treatment options and cures for prostate cancer patients.
- This initiative includes funding for investigators conducting studies involving veteran prostate cancer patients and the VA, establishing PCF-VA Centers of Excellence, and the establishment of prostate cancer precision medicine clinical trials within the VA.
- The VA is the largest integrated healthcare system in the U.S., comprising 1,243 facilities, with over 9 million veterans enrolled.
- Approximately 50,000 U.S. veterans are diagnosed and treated for cancer each year, making up 3.5% of all cancer cases in the U.S.
- Prostate cancer is the most frequently diagnosed cancer among veterans. Approximately 13,000 veterans are diagnosed with prostate cancer each year. The high prevalence of prostate cancer in veterans may be due in part to exposure to battlefield chemicals including Agent Orange.
- In 2018, PCF funded the establishment of ten VA hospitals as “PCF-VA Centers of Excellence” (Figure) to advance best-in-class precision oncology treatment and care for prostate cancer patients. PCF-VA Centers of Excellence include VA Medical Centers in Chicago, Los Angeles, Tampa, Bay Pines, Seattle, Ann Arbor, Manhattan, the Bronx, Washington DC, Durham, and Philadelphia.
- Drs. Bruce Montgomery and Matthew Rettig have led the implementation of the VA/PCF Precision Oncology Program for Cancer of the Prostate (POPCAP) program, which has opened several prostate cancer precision medicine clinical trials within the VA.
- The POPCAP program aims to provide genomic sequencing for germline (inherited) and somatic (tumor) mutations to develop a comprehensive precision oncology approach for veterans with prostate cancer, provide access to precision medicine clinical trials and off-label use of FDA-approved drugs for patients found to have targetable mutations, and implement best practices in precision oncology across the VA. There is also a goal to establish a biorepository for primary and metastatic tumor samples and circulating tumor DNA.
- Precision oncology resources currently available in the VA include no-cost genomic sequencing and telephone-based genetic counseling services.

- The POPCAP program has thus far opened seven prostate cancer precision medicine clinical trials in the VA. Many of these trials are available at cancer centers outside of the VA, and this program provides access for veterans to these trials. Several VA sites participate in each trial, and travel is provided for eligible patients to enroll in studies at sites distant from their primary VA hospital.
- Clinical trials being opened in the VA as part of the POPCAP program include the following:
  - A phase II clinical trial testing the efficacy of carboplatin plus docetaxel in men with metastatic castration-resistant prostate cancer (mCRPC) who have bi-allelic alterations (both gene copies are inactivated) in DNA repair genes.
  - A phase II trial testing the efficacy of carboplatin followed by docetaxel versus docetaxel followed by carboplatin in mCRPC patients who have genomic alterations in *BRCA1/2* or *PALB* genes.
  - A study testing the utility of PSMA-PET imaging for the diagnosis and management of prostate cancer.
  - A phase II trial (CHOMP) testing the efficacy of the checkpoint inhibitor pembrolizumab in mCRPC patients with genomic alterations in mismatch repair (*MMR*) or *CDK12* genes.
  - A phase II trial (TRITON2) testing the efficacy of the PARP inhibitor rucaparib in mCRPC patients with genomic alterations in DNA repair genes. This trial is open at seven VA medical centers. Preliminary results from the TRITON2 trial were presented by Dr. Alan Bryce (see above).
  - A phase III trial (TRITON3) testing the efficacy of the PARP inhibitor rucaparib versus physician's choice of best therapy in mCRPC patients with genomic alterations in DNA repair genes. This trial is now open at six VA medical centers.
  - A phase III trial (VISION) testing the PSMA-targeted radionuclide agent <sup>177</sup>Lu-PSMA-617 in mCRPC patients.
- To date, PCF has provided \$36 million in funding commitments to advance our Veterans Health Initiative. This includes \$25 million to support our 10 Centers of Excellence, \$8 million to 8 team science "Valor Awards", and \$3.2 million to 14 PCF-VA Young Investigators.
- The projects supported by these awards include studies to identify mechanisms and biomarkers of prostate cancer metastasis and treatment resistance, develop biomarkers to identify patients with early-onset imminently lethal prostate cancer, understand the biology of prostate cancer in African American men, and elucidate the effects of exposure to battlefield chemicals such as Agent Orange on the development and progression of prostate cancer. Funded team science projects include VA Medical Centers in Houston and Portland as funded sites of collaborative investigations.

## PCF-VA NETWORK OF CENTERS OF EXCELLENCE

-  **Manhattan, NY** – The John and Daria Barry Foundation Precision Oncology Center of Excellence at the VA Manhattan
-  **Bronx, NY** – The Blavatnik Family Foundation Precision Oncology Center of Excellence at the VA Bronx
-  **Ann Arbor, MI** – The Stewart J. Rahr Foundation Precision Oncology Center of Excellence at the VA Ann Arbor
-  **Chicago, IL** – The Robert Frederick Smith Precision Oncology Center of Excellence at the VA Chicago
-  **Seattle, WA** – The Stephen J. Cloobek Precision Oncology Center of Excellence at the VA Puget Sound
-  **Los Angeles, CA** – The Michael and Lori Milken Family Foundation Precision Oncology Center of Excellence at the West Los Angeles VA
-  **Philadelphia, PA** – Corporal Michael J. Crescenz Philadelphia VA Medical Center



**Figure:** In 2018, PCF funded the establishment of ten VA hospitals as “PCF-VA Centers of Excellence” to advance best-in-class precision oncology treatment and care for prostate cancer patients. The first seven centers that were selected to receive PCF funding are shown in this figure.

## *SPECIAL LECTURE: The Evolving Landscape of Life-Prolonging Treatments for Advanced Prostate Cancer: The New World Order*

**Maha Hussain, MD, FACP, FASCO**

**Robert H. Lurie Comprehensive Cancer Center, Northwestern University**

- Prostate cancer is driven by male hormone (androgen) signaling through the androgen receptor (AR). Thus, androgens and AR have been the main treatment targets in advanced prostate cancer for decades.
- In the 1980s and 1990s, research for treatment advances focused on improving and optimizing AR-targeted therapy, chemotherapy, and bone-targeted therapy, and investigating the role for local therapy in patients with metastatic disease.
- Resistance to AR-targeted therapy eventually occurs in most patients, and results in the development of castration-resistant prostate cancer (CRPC), an aggressive form of the disease for which there are currently no curative treatments.
- Studies have found that despite being “castration-resistant,” CRPC is often still driven by AR, due to AR mutations and gene amplifications that make the cancer able to grow in low-androgen conditions or resistant to therapies that directly bind AR.
- In addition, some forms of CRPC are AR-independent, and are driven by mechanisms which bypass the requirement for AR.
- Life-prolonging treatments that have been FDA-approved for metastatic CRPC since 2004 include docetaxel, sipuleucel-T, cabazitaxel, abiraterone, enzalutamide, and radium-223.
- Two treatments have been FDA-approved treatments for skeletal-related events in prostate cancer: zoledronic acid and denosumab.
- Mitoxantrone, strontium, and samarium are treatments that have been FDA-approved for pain palliation.
- Issues that must be addressed in future clinical trials include advancing effective therapies to earlier disease states, maximizing the anti-tumor effect of treatments, better characterization of the molecular profile and the biology of the cancer at an individual patient level to better personalize therapy, enhancing survivorship, and addressing cost and value of treatments.
- Recent clinical studies have demonstrated that certain therapies are more effective if used earlier in the disease course. Trials have demonstrated that the use of docetaxel chemotherapy or abiraterone at the time patients initiate androgen deprivation therapy (ADT) (instead of waiting until tumors develop resistance to ADT and progress to CRPC), dramatically improves overall survival and extends the time until tumors progress clinically. These trials have led to new standards of care in prostate cancer and the FDA-approval of docetaxel and recently in 2018 of abiraterone + ADT for metastatic hormone-sensitive prostate cancer.
- Unfortunately, a significant proportion of men with metastatic hormone-sensitive prostate cancer progress to CRPC within a short time (<1 year) of initiating ADT ± docetaxel or

abiraterone. Dr. Hussain and others are investigating clinical, hereditary and environmental causes and biomarkers for these more aggressive forms of prostate cancer.

- Non-metastatic CRPC is a clinical state in which men who are being treated with ADT have their PSA levels begin to rise, but the growing tumors cannot yet be seen on scans. Two recent clinical trials have demonstrated that the addition of the AR-targeted therapies enzalutamide or apalutamide to continual ADT in these patients significantly extends the time before metastases become evident on scans. In 2018, the FDA approved both apalutamide and enzalutamide in addition to continual ADT for men with non-metastatic CRPC.
- Ongoing phase III clinical trials are testing the efficacy of combining different types of hormone and AR-targeted therapies in order to maximize shutdown of the AR pathway. This strategy is being tested in both metastatic CRPC and metastatic hormone-sensitive prostate cancer settings.
- Approximately one-third of the patients who die from prostate cancer are diagnosed with metastatic disease. Whether treatment of the primary tumor is beneficial for these patients is an important clinical question.
- Recently presented results from the phase III STAMPEDE clinical trial demonstrated that radiotherapy to the primary tumor for newly diagnosed metastatic prostate cancer prolonged survival in the subset of men with a low burden of metastatic disease, but did not benefit men with a high burden of metastatic disease. The results from this study were discussed in greater detail by Dr. Silke Gillessen (see below).
- The phase III PEACE-1 clinical trial is comparing the efficacy of several different treatment combinations in patients with newly diagnosed (hormone-sensitive) metastatic prostate cancer. In this trial, patients are randomized to one of four treatment combinations: ADT + docetaxel; ADT + docetaxel + abiraterone/prednisone; ADT + docetaxel + radiotherapy; and ADT + docetaxel + abiraterone/prednisone + radiotherapy.
- The randomized phase II EA8153 CHARTED-2 study is testing ADT plus abiraterone/prednisone with or without cabazitaxel in patients with metastatic CRPC who were previously treated with docetaxel.
- Following the FDA-approval of docetaxel in 2004, numerous treatments tested in phase III clinical trials failed to show a further improvement (over docetaxel alone) in survival for metastatic CRPC, despite promising biological, preclinical, and phase II trial data. Several of these treatments are FDA-approved in other types of cancer.
- These failures include bone-targeting agents tested alone or in combination with docetaxel (docetaxel +/- dasatinib; atrasentan; docetaxel +/- atrasentan; zibotentan; and radium-223 + abiraterone), angiogenesis-targeting agents tested alone or in combination with docetaxel (docetaxel +/- bevacizumab; docetaxel +/- aflibercept; docetaxel +/- lenalidomide; sunitinib; cabozantinib; tasquinimod), prostate cancer vaccines (GVAX; PROSTVAC), and other targets (satraplatin; docetaxel + DN101; TAK700; ipilimumab; custericin).
- Significant efforts are underway to optimize precision medicine for advanced prostate cancer.
- In 2015, the International PCF Prostate Cancer Dream Team published a study in which the genomes of 150 mCRPC cases were sequenced to identify mutations. Approximately 90%

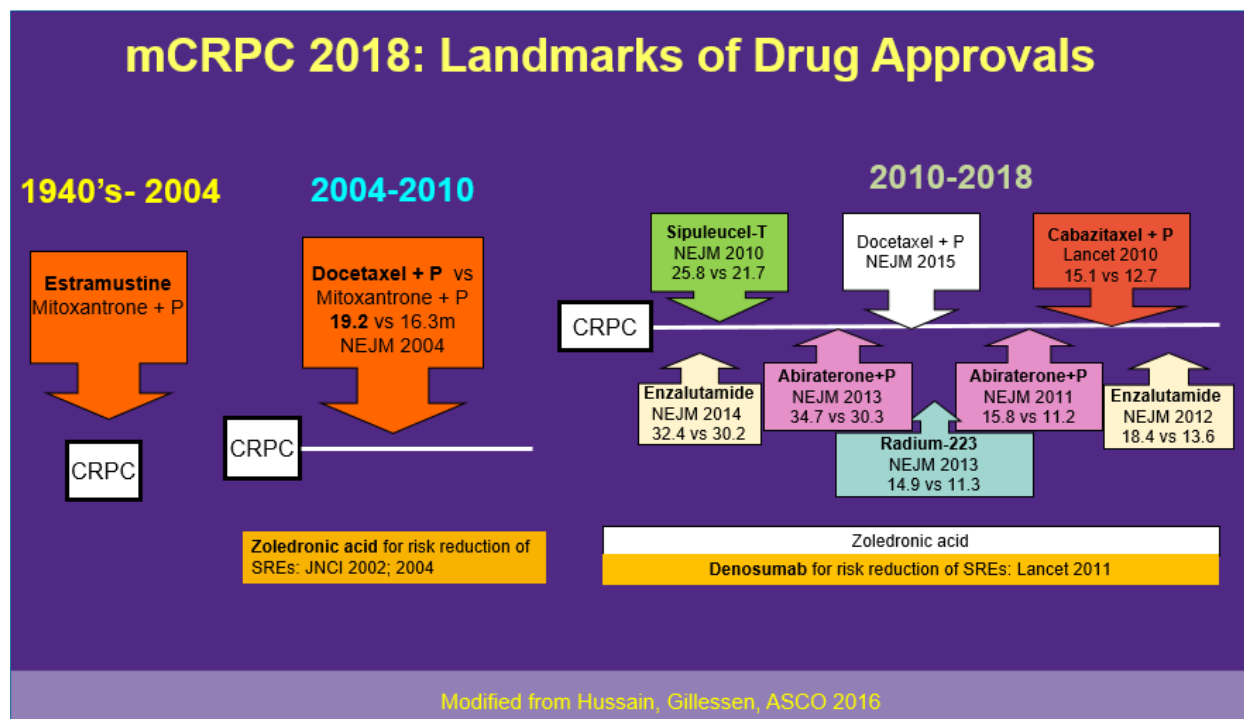
of mCRPC cases were found to have clinically potentially actionable mutations (those which may be targetable by existing approved or experimental therapies).

- Over 20% of mCRPC cases were found to have mutations in DNA repair genes (*BRCA1*, *BRCA2*, *ATM*, others) which may be sensitive to PARP inhibitors.
- In 8-10% of mCRPC patients, DNA repair gene alterations were inherited. This finding has implications for family members, as those who also carry these alterations may have increased risk for prostate, breast, ovarian, or other cancers.
- Several different PARP inhibitors are currently in clinical trials for prostate cancer, including olaparib, rucaparib, niraparib, talazoparib, and BCB-290. Trials are also testing PARP inhibitors in combination with other agents including abiraterone, checkpoint immunotherapies and radiation therapy.
- African American men are at a significantly higher risk than Caucasian-American men for diagnosis and death from prostate cancer. The factors that contribute to this disparity are yet unclear and likely complex.
- Findings from a study that compared overall survival in men with hormone-naïve metastatic prostate cancer treated with similar ADT before versus during the prostate specific antigen (PSA) screening era, suggested that racial disparities in survival have decreased in the PSA utilization era.
- Current 10-year survival rates for men diagnosed with metastatic prostate cancer have been estimated at 17%, using data from the S9346 study. Data from the CHAARTED clinical trial indicates a 7-year survival rate of 17.5% for men diagnosed with high-volume metastatic prostate cancer treated with ADT alone, and 33.3% for men receiving ADT + docetaxel. For men diagnosed with low-volume metastatic prostate cancer, 7-year survival rates in the CHAARTED trial were 54.2% for men treated with ADT alone and 48.1% for men receiving ADT + docetaxel.
- Survivorship, which aims to improve quality of life in cancer survivors, is a critical area of research. Prostate cancer treatments can have long term effects on certain body functions (hormonal, metabolic, cardiac, urinary, bowel, cognitive, and sexual functions), and can increase risk for future cancers. Developing strategies to reduce these side effects is critical.
- Prostate cancer diagnosis and treatment also affects a person's psychology by causing fear of recurrence, changes in body image, distress about enduring symptoms, loss of role functions, and loss of self-esteem.
- A prostate cancer diagnosis also may impact social aspects of a patients' life, for instance by causing absence from or loss of work, loss of income, resulting economic distress, changes in sexual relationships, and distress in family life.
- Prostate cancer treatments can be very costly and are getting more expensive with earlier and longer-term use of newer AR-targeted therapies. 6-month prescriptions can range from \$2,200 - \$9,000 for ADT, approximately \$2,900 for docetaxel, and \$62,000-\$68,000 for newer AR-targeted therapies (enzalutamide, abiraterone, apalutamide). It is critical to address these issues surrounding cost and value of treatments.
- Metastatic prostate cancer is a complex "smart cancer" that exhibits significant heterogeneity. Therapy development must focus on the totality of disease biology and identification of the most effective combination therapies. Studies must be conducted to



thoroughly validate candidate treatment targets and biomarkers of treatment response and resistance.

- We now know that each patient's disease biology and clinical characteristics are unique, and require personalized treatment selection and treatment timing to achieve the best possible outcomes.
- As patients live longer, survivorship and treatment-related physical effects and monitoring costs demand serious attention.
- Ultimately, it is critical to provide the right care at the right time, for the right patient at the right cost.



**Figure:** Timeline of FDA approvals for treatments for metastatic CRPC.

## **STATE OF THE SCIENCE 2018**

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

*Introduced by Howard Soule, PhD  
Prostate Cancer Foundation*

*This talk can be viewed in full at:  
<https://www.pcf.org/scientific-retreat/25th-annual/>*

## **SPECIAL RECOGNITION OF NOBEL PRIZE**

**James Allison, PhD  
The University of Texas MD Anderson Cancer Center  
2018 Nobel Prize in Medicine**

**Padmanee Sharma, MD, PhD  
The University of Texas MD Anderson Cancer Center**

*Introduced by Howard Soule, PhD  
Prostate Cancer Foundation*

*A special tribute video can be viewed at:  
<https://www.youtube.com/embed/bzxmzcQ-6pA>*

## KEYNOTE ADDRESS

Michael Milken  
Founder and 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/scientific-retreat/25th-annual/>*

## Session 4: New Insights into the Biology and Role of Prostate Cancer Stem Cells

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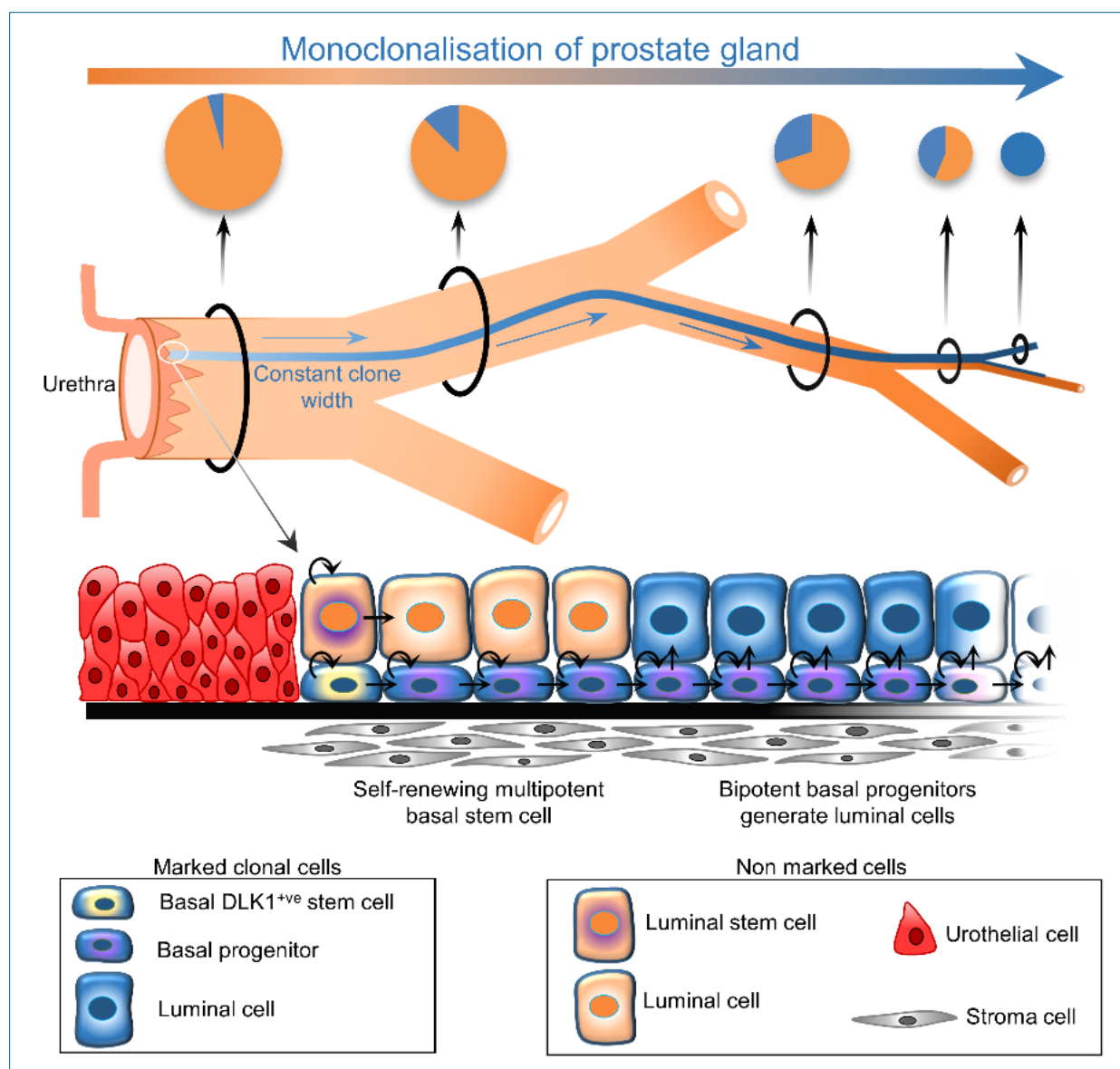
### *Multipotent Basal Stem Cells, Maintained in Localized Proximal Niches, Support Directed Long-Ranging Epithelial Flows in Human Prostates*

Rakesh Heer, MBBS, PhD  
Newcastle University, UK

- To maintain the integrity of the tissues in our bodies, cells are constantly being “turned over” – old cells die off and are replaced by new cells. Each body tissue has its own set of unique tissue “stem cells,” to supply new “daughter” cells throughout life.
- Because stem cells live for a very long time, they can acquire and pass on multiple genomic mutations, and are hypothesized to be the origins of cancer. It is of critical importance to identify tissue stem cells and determine whether and how they may contribute to initial cancer formation.
- Dr. Rakesh Heer discussed studies to identify human prostate stem cells and determine their role in prostate cancer.
- The prostate gland is composed primarily of two major cell types: luminal prostate cells and basal prostate cells.
- Previous studies have identified putative prostate stem cells based on expression of proteins including TROP2. However, these studies were done using cells that had been removed from their normal tissue environment, which may change their behavior and characteristics. Further studies are needed to confirm the identity and biology of prostate stem cells.
- In addition, previous animal studies have come to different conclusions about the nature of prostate stem cells, and whether the same or different populations of stem cells generate luminal and basal prostate cell lineages.
- Dr. Heer undertook studies to identify and study human prostate stem cells “*in situ*” (in their original place).
- In animal models, stem cells can be identified *in situ* using “lineage tracing” techniques. In this method, putative stem cells are engineered to uniquely express certain markers that can be switched on, such as a blue dye. If the marked cell is indeed a stem cell, all daughter cells would also express the marker, and it would be seen in cells throughout the tissue over time. This method has been used to identify colon stem cells in mice.
- In humans, *in situ* lineage tracing studies have become possible with the identification of genetic marks that naturally occur in stem cells.
- Mitochondrial DNA mutations are unique “genetic marks” that accumulate exclusively in stem cells during aging. These marks produce chemical alterations in the DNA, which can be detected in tissue samples using enzyme-activated dyes. Previous studies have used mitochondrial marks to map tissues generated by unique sets of stem cells.

- The prostate gland functions to produce the fluids important for semen. The prostate is structured as sets of tree-like branched ducts that attach (at their trunks) to the urethra, into which the fluids are secreted (Figure).
- Using human prostatectomy specimens, Dr. Heer used a series of MRI and pathology imaging techniques to create a map of the prostate gland attached to the urethra, and identify cells generated by unique sets of stem cells.
- One major lineage tracing pattern was observed, in which cells ranging from the trunk (at the urethra) to the far (distal) ends of the prostate gland all shared the same mitochondrial marks.
- In 88% of these cases, both basal and luminal prostate cells shared the mark, suggesting a “multi-potent” stem cell was able to generate both cell lineages.
- In rare cases, the marks were observed only in basal (7%) or only in luminal (5%) prostate cells. In the cases where only basal prostate cells were marked, Dr. Heer hypothesized that the stem cell lineage had not yet expanded to produce luminal cells, and represented an early picture of prostate lineage development from a single stem cell. In the cases where only luminal prostate cells were marked, Dr. Heer hypothesized that this indicates the existence of a rare set of stem cells that are only able to produce luminal prostate cells.
- Evaluation of a cell proliferation protein (Ki67) demonstrated that most of the cells that are dividing are basal cells and not luminal cells. In addition, cell division occurred more frequently near the trunk (proximal to the urethra) and less frequently at the far ends of the gland.
- In contrast, evaluation of a cell death marker (caspase) found that almost all of the dying cells are luminal cells, and the rate of cell death increases toward the far ends of the gland.
- These studies suggest that prostate stem cells are located near the trunk of the gland, where more cell division is occurring, while the far end of the gland contains the older, dying cells (meaning new cells are generated at the trunk, and are progressively pushed toward the far ends of the gland).
- These studies also suggest that basal cells are the progenitors of both basal and luminal cells, and act to replenish the dying luminal cells.
- To identify the prostate stem cell population, Dr. Heer used laser capture microdissection to dissect the small patch of cells at the trunk, nearest to the urethra, and performed molecular analyses.
- Putative prostate stem cell markers identified included DLK1, LIN28A, and KLF4. DLK1 is a protein that signals to Notch, a protein which is associated with stem cell biology.
- To validate whether DLK-expressing cells were prostate stem cells, DLK-positive and DLK-negative cells were extracted from human prostate samples and grown in laboratory cultures.
- DLK-negative cells produced predominantly luminal cells, which died after a few weeks in culture, suggesting they lack long-lived stem cell characteristics.

- DLK-positive cells were able to grow for a long time and generated both basal and luminal cells, suggesting they contain stem cells. DLK-positive cells could also generate mini-organs in culture with characteristics that resembled normal prostate glands.
- Together, these studies identify a population of putative prostate stem cells located in the trunk area of the prostate, which can be marked by DLK-expression (Figure). These basal prostate stem cells are “bi-potent,” meaning they can give rise to both the basal and luminal lineages of cells that make up the prostate gland. The flow of replenished cells is maintained by a continuous process of asymmetrical cell division, which pushes cells from the trunk to the distal ends of the prostate and gives rise to luminal cells that are continually lost by cell death.



**Figure:** Putative prostate stem cells are located in the trunk area of the prostate (adjacent to the urethra). These DLK-positive basal prostate stem cells give rise to both the basal and luminal lineages of cells that make up the prostate gland. The flow of replenished cells is maintained by a continuous process of asymmetrical cell division, pushing cells from the trunk to the distal ends of the prostate.



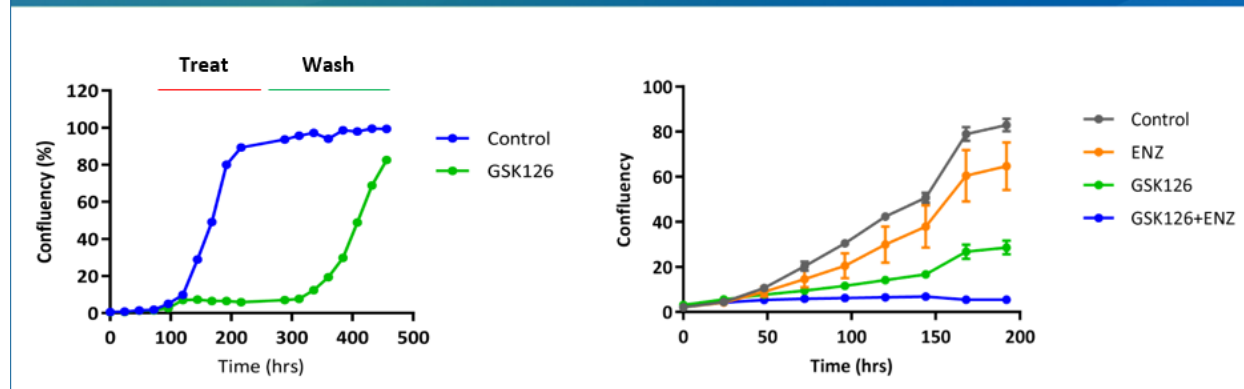
## *Cellular Plasticity and the Neuroendocrine Phenotype in Prostate Cancer*

Amina Zoubeidi, PhD

Vancouver Prostate Centre

- Normal prostate and prostate cancer cells are completely reliant on the androgen receptor (AR) pathway, which regulates the genes required for growth and survival. Because of this dependency, AR-targeted therapy is the cornerstone of treatment for advanced prostate cancer.
- However, constant pressure from AR-targeted therapy selects for prostate cancer cells that can survive in low-androgen conditions or no longer rely on AR for growth and survival (aka, castration-resistant prostate cancer, CRPC).
- Neuroendocrine prostate cancer (NEPC) is a highly aggressive and lethal form of CRPC in which cells have adopted a neuroendocrine cell biology and no longer rely on AR for growth and survival.
- Approximately 17% of patients with advanced CRPC develop NEPC. There is an urgent need to develop new and effective treatments for patients with NEPC.
- Dr. Amina Zoubeidi and team have found that a subset of NEPC continue to express AR. The team created experimental models to study the function of persistent AR expression in NEPC.
- AR is a transcription factor – a protein that binds to DNA to regulate expression of specific genes. In NEPC, AR regulated the expression of a different set of target genes compared with CRPC. Unique AR-regulated genes in NEPC included stem cell and neuronal genes. This suggests that AR plays a role in the ability of CRPC to convert to NEPC. This process of conversion may occur through stem cell-like pathways.
- Dr. Zoubeidi and team found that the ability of prostate cancer cells to express genes from the neuroendocrine cell lineage is also driven by altered expression and activity of stem cell factors and the epigenetic regulator EZH2.
- In AR-positive NEPC, EZH2 was found to interact with AR and direct AR to drive the expression of genes associated with metastatic and neuronal features.
- EZH2 inhibition caused AR therapy-resistant cell lines to revert to an AR-dependent state and regain sensitivity to enzalutamide (Figure).
- These results suggest EZH2 inhibition may have potential in combination with AR inhibitors to prevent and/or reverse NEPC.
- EZH2 inhibitors are now in clinical trials for advanced prostate cancer.

## EZH2 inhibition re-sensitizes AR-indifferent cells to Enzalutamide



**Figure:** EZH2 inhibition (GSK126) caused AR therapy-resistant cell lines to revert to an AR-dependent state and regain sensitivity to enzalutamide (ENZ).

## SPECIAL LECTURE: Canine and Machine Olfaction in Human Prostate Cancer Diagnosis

Claire Guest, HonDSc  
Medical Detection Dogs

Andreas Mershin, PhD  
Massachusetts Institute of Technology

- Dogs have unique nose physiology and highly concentrated olfactory (scent) receptors, which enables them to have the remarkable ability to detect and distinguish trace levels of volatile organic compounds. Traditionally, dogs have been trained to sniff out substances that identify bombs and drugs. Dogs can also be trained to detect volatile organic compounds associated with various diseases including cancer.
- Dr. Claire Guest has been training dogs to detect various types of cancer and other diseases such as Parkinson's disease, with promising success rates for positive and negative identification (Figure).
- Prostate cancer may release volatile organic compounds into urine, which could enable detection of men with high-risk prostate cancer by dogs at an earlier stage than is currently possible with PSA testing.
- Dr. Guest has trained several dogs to identify urine samples from prostate cancer patients. Urine samples from patients and controls were placed onto a carousel, and the dogs are able to go from one sample to the next, in this process. The dogs are taught to indicate a positive sample by standing/ sitting/ staring (alerting). Further research with an interactive

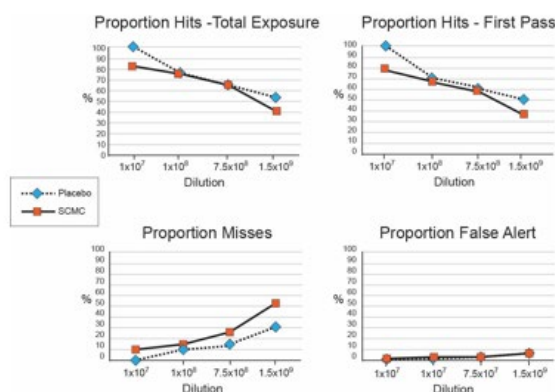
plate is enabling the team to measure the length of time and amount of pressure the dog applies to a plate when indicating the odor in question. In the future, the dog's interactions with samples will be measured with pressure plates to quantitatively evaluate its responses.

- In collaboration with Dr. Guest, Dr. Andreas Mershin is working to develop a “bionic nose” – a diagnostic device able to detect the prostate cancer-associated volatile organic compounds in urine that were found by the dogs. The dogs will assist Dr. Mershin in building a detection algorithm.
- An international cross-disciplinary team of researchers has been assembled to achieve these goals.

## Canine Olfactory Thresholds



**We can influence the canine sensitivity and specificity through reinforcement schedules**



**Figure:** Dogs can be trained to detect various types of cancer and other diseases, with a promising success rate for positive and negative identification.

## Session 5: Ecology of Prostate Cancer

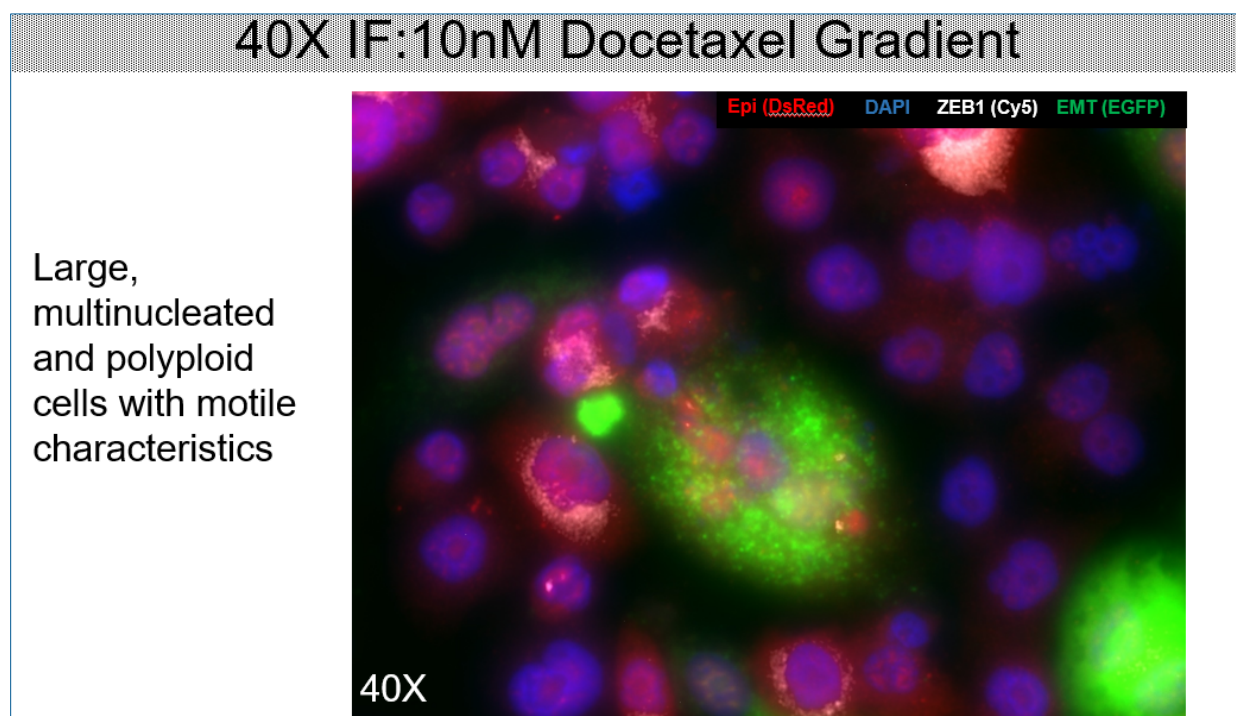
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### *The Changing Primary Tumor Environment – Why an Invasive Species Migrates*

Kenneth Pienta, MD  
Johns Hopkins University

- Ecosystems consist of a physical environment and all of the organisms that live and interact within that environment. Within an ecosystem, there is a flow or cycling of energy, materials, and resources, which upholds the structure of the ecosystem and diversity of the organisms.
- Tumors can be viewed as ecosystems. Tumors are composed of cancer cells that co-exist and interact with a number of non-tumor cell types, including normal tissue cells (which differ depending on whether the tumor is a primary tumor or has metastasized to a different tissue), immune cells, blood vessels, and nerves. Non-cellular factors include the extracellular matrix, oxygen, nutrients, minerals, hormones, immune system communication proteins, platelets, and red blood cells.
- It has been observed that sites of cancer metastasis are not simply determined by blood flow patterns. Instead, different types of cancer preferentially metastasize to specific tissues. In prostate cancer, bone is the primary site of metastasis. This suggests that preferred sites of metastasis represent a hospitable “soil” for that type of cancer “seed.” However, it is unclear what causes a cancer cell to leave the primary tumor site.
- Dr. Kenneth Pienta and team hypothesized that an eutrophication-like process may play a role in driving tumor cells to leave the primary tumor site. Eutrophication is a process that occurs in an unhealthy aquatic environment where excessive nutrient input into a body of water results in an algal bloom, thereby reducing sunlight to underwater plants, and followed by algae die-off and decomposition. Ultimately, this results in a low-oxygen and low-pH environment that causes the death of fish and other aquatic animals.
- In tumors, an analogous process may occur. Proliferation of cancer cells may outstrip vascular supply of oxygen and nutrients, altering metabolism of the cells in the tumor and ultimately selecting for tumor cell “super-clones” that can survive in such poor environments and drive the formation of metastases.
- To determine whether a stressed environment can promote the development of a resistant and migratory tumor cell population, Dr. Pienta and team developed a microfluidic system to study how different gradients of nutrients, pH, drugs, or other factors can affect tumor cell properties.
- When a gradient of docetaxel chemotherapy was applied to the system, while many cells died, some cells were able to adapt and grow. The docetaxel-resistant prostate cancer cells that arose were large and had multiple nuclei due to altered cell division (Figure). These cells were highly mobile and could repopulate areas where other cancer cells had died off. The multi-nucleated cells also had stem cell-like characteristics, and could undergo asymmetric cell division to produce one multi-nucleated cell and one daughter cell with a single nucleus.

- Multi-nucleated cancer cells can be observed in metastatic prostate cancer samples from patients who have been treated with therapy, suggesting this phenomenon may occur in patients.
- Together, these studies suggest that prostate cancer cells may adapt to chemotherapy drugs by altering characteristics including cell division, and gaining the ability to move through tissues, driving metastasis and disease progression. Multi-nucleated tumor cells may represent a reservoir of treatment-resistant cells that contribute to tumor regression following therapy.



**Figure:** A subpopulation of prostate cancer cells in a microfluidic system were able to develop resistance to docetaxel chemotherapy. Docetaxel-resistant prostate cancer cells were large, had multiple nuclei, displayed stem cell-like characteristics, were highly mobile, and could repopulate areas where other cancer cells had died.

## *Resistance is Not Inevitable – Lessons from Pest Management*

Christopher Whelan, PhD

The Moffitt Cancer Center; University of Illinois at Chicago

- Dr. Christopher Whelan discussed how new perspectives and strategies for improving cancer treatment may be derived by applying knowledge and principles from agricultural pest management with analogies to cancer.
- Agricultural pests, many of which are invasive species, are organisms that cause harm to crops. Corn rootworm for instance, causes over \$1 Billion in control costs and crop losses in the U.S. each year.
- Humans have been battling agricultural pests since the advent of agriculture, and pesticides have been used for over 4,000 years. Pesticide resistance once seemed inevitable, but now can be effectively managed by various strategies.
- Reviewing pesticide resistance management strategies may lead to new ideas for preventing the development of treatment resistance by cancer cells.
- As an example, DDT, an organic molecule first synthesized by scientists in 1874, was recognized as a potent insecticide and widely used in the first half of the 20th century. Although DDT was initially effective against mosquitoes and flies, DDT-resistance had evolved by 1947.
- In response, industry and government (USDA) agencies worked to devise pesticide resistance management strategies.
- One strategy to combat pesticide resistance is “refuge,” in which farmers deliberately do not expose some crop areas to the pesticide in order to maintain populations of pests that are not exposed, and hence, not driven to evolve pesticide-resistance genes. These “refuge” pests would act as reservoirs for pesticide-susceptibility genes in the population, and prevent the entire population from becoming resistant to the pesticide.
- In the U.S., forests may contain 20-30 species of insect-consuming bird species, each of which eat insects in a unique way. No insect is known to have evolved resistance to all of these natural predators.
- Integrated pest management is a strategy which uses environment modification techniques to help suppress pest populations. This includes managing the landscape to provide habitats for natural predators of pests. For example, a flower strip on the margin of a crop would attract birds and other animals that eat insects.
- Cancer clinical practice can learn from pest control, by applying analogous principles to manage the tumor ecosystem. For instance, new strategies to mobilize natural defenses, including various components of the immune system which act as natural “predators” of cancer cells, should be explored.
- Overall, the development of successful plans to manage cancer treatment-resistance will require multidisciplinary approaches and expertise and collaborative efforts from academic researchers, the pharmaceutical industry, clinicians, and funding agencies.





Credit: Connie Loper, USGS. Public domain.

## *Cancer Therapy, Adapting to Change the Game*

Robert Gatenby, MD  
The Moffitt Cancer Center

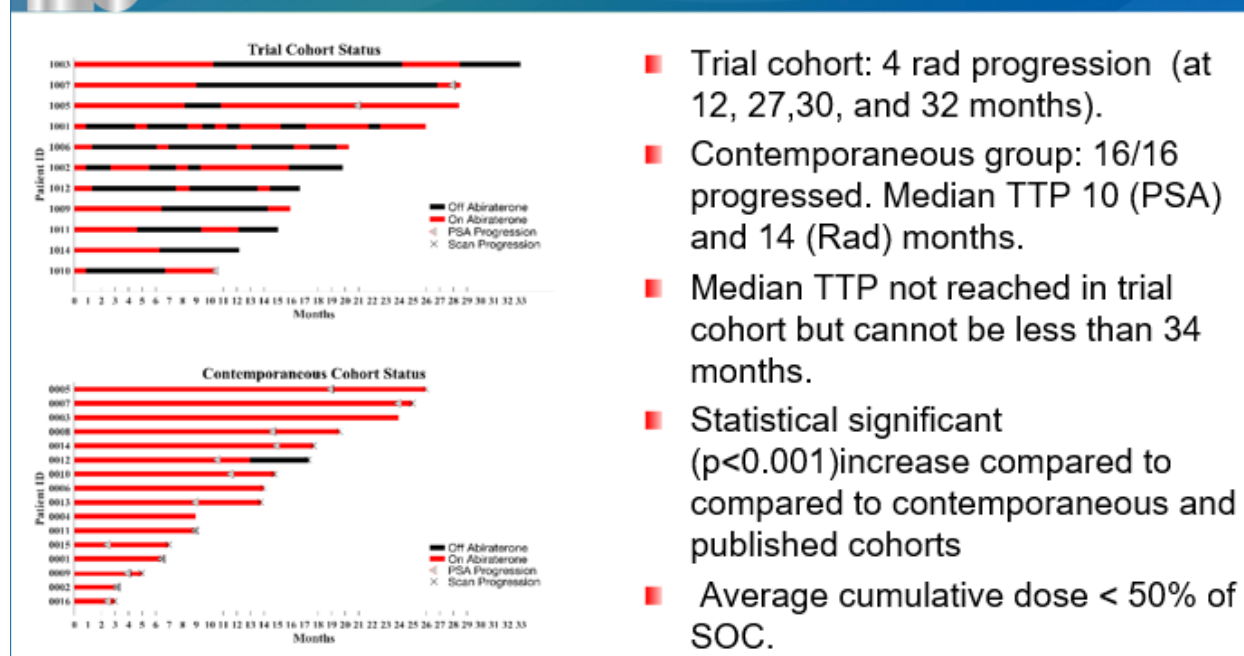
- Cancer is often described as a disease of the genes. While cancer cells clearly accumulate genetic alterations that collectively confer continued proliferation, resistance to normal cell death signals, and the ability to metastasize, cancer cells are imbedded in a temporally and spatially variable tissue ecosystem which ultimately selects the phenotypic properties (and their genotypic counterparts) that are most fit.
- Thus, cancer is more than a disease of the genes. It is a complex, dynamic system with multiple non-linear interactions. Understanding these non-linear interactions will improve our ability to predict the outcomes of treatments that perturb a complex dynamic system and develop improved treatments.
- These complexities can be addressed by recruiting mathematicians and evolutionary biologists to the study of cancer, and linking them with clinicians, to develop theoretical understandings of the dynamics of cancer evolution in cancer treatment. This integrated

research approach is being taken through the Integrated Mathematical Oncology (IMO) Department and the Cancer Biology and Evolution (CBE) program at the Moffitt Cancer Center.

- Dr. Robert Gatenby discussed studies to integrate evolutionary dynamics into prostate cancer therapy.
- Currently, oncology research focuses on developing new drugs which are typically used at “maximum tolerated doses” (MTDs). MTD is the highest concentration of a drug that patients can tolerate without experiencing unacceptable side effects.
- The goal of using cancer drugs at maximum tolerated dose levels, is to kill as many cancer cells as possible. However, this treatment approach typically results in selection for treatment-resistant cancer cells, which eventually proliferate, repopulate the tumor, and cause disease progression.
- Because of the diversity of cancer cells (mutations and gene expression patterns can be different in each cell) and the diversity of the tumor microenvironment (for instance, some areas of the tumor are more accessible to therapy than others), drug-resistant cells are often present prior to therapy, and are selected for by the treatment.
- The field of evolutionary biology has found that genes which are not necessary are often a burden to an organism and will be lost over time. For instance, Charles Darwin discovered a species of fish that live in dark underwater caves and had evolved to lose eyes.
- Similarly, resistance to therapy may be a burden to a cancer cell when it is not necessary because it requires expenditure of resources for synthesis, maintenance, and operation of the molecular machinery of resistance. While the resource costs are exceeded by the corresponding benefit during treatment, they are wasted when therapy is not present. Thus, in the absence of treatment, treatment-resistant cells may be less fit and competitive compared with treatment-sensitive cells.
- These principles led to the hypothesis that treatment of cancer with lower or less frequent doses of cytotoxic drugs may be more effective in the long term, as populations of chemotherapy-sensitive cells would be maintained and would suppress the growth of chemotherapy-resistant cells when the treatment is removed. In this treatment approach, the goal is to maintain a steady-state tumor burden. Lower doses of drug would also be less toxic to patients.
- An “adaptive therapy” treatment approach was tested in animal models, in which the chemotherapy dose was continuously modified to maintain a stable tumor volume. Mice with exponentially growing tumors were initially given chemotherapy frequently, with progressively lower doses. When the tumor ceased to grow exponentially, reaching a “plateau,” tumor control was maintained using low doses of chemotherapy. In this study, treatment could be discontinued for long periods of time (months) in 67% of the mice, and tumor control was maintained indefinitely in 87% of the mice.
- Androgen receptor (AR)-targeted therapy, which acts to block the production or action of testosterone, is a primary treatment for advanced prostate cancer, and is typically given continuously until the tumor develops resistance and disease progression occurs. Unfortunately, treatment resistance to AR-targeted therapy is common, and evolves through various mechanisms, including via tumor cells gaining the ability to produce their own testosterone.

- An adaptive therapy trial was initiated to test intermittent administration of abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC). Abiraterone is a standard-of-care AR-targeted treatment for mCRPC that is typically given continually until disease progression.
- In the adaptive therapy trial, patients were given abiraterone until PSA levels dropped by  $\geq 50\%$ , at which time abiraterone treatment was discontinued. This was hypothesized to allow treatment sensitive cells to repopulate the tumor and suppress growth of treatment-resistant cells. Abiraterone was administered again when a patient's PSA level returned to the pre-treatment level (one cycle), and then withdrawn when the PSA was reduced to 50% of the pretreatment value. Mathematical models predicted that tumor control with this approach could be maintained for 2 to 20 cycles of treatment.
- In preliminary analysis of the first 18 patients enrolled on this trial, cycle lengths (length of time between treatments) ranged from 4 months to 1.5 years (Figure). The earliest disease recurrence in a patient was observed after 2 cycles. The longest survivors are still under treatment after 12 cycles (~4 years). Thus far, four patients have experienced PSA and radiographic progression (at 12, 27, 30, and 32 months). However, the median time to progression for the treatment cohort has not yet been reached.
- These results were compared with a group of mCRPC patients contemporaneously treated with abiraterone in the continuous, standard-of-care manner (Figure). All 16 of the patients in the continuous abiraterone group have progressed, with a median time to radiographic progression of 15 months.
- Based on these results, an adaptive therapy approach for abiraterone in mCRPC appears promising, although a randomized trial comparing these treatment approaches is necessary to validate the superiority of one approach over the other. Notably, on average, patients treated on the adaptive therapy trial received less than half the cumulative dose of abiraterone as patients being treated continuously.
- Data from the patients being treated on this trial is now being used to generate mathematical models to improve the timing and duration of therapy. For instance, simulations using one patient's data predicted that if abiraterone had been withdrawn when PSA reached 80% of the pre-treatment value (instead of 50%), cycle times would have been shorter but tumor control could have been maintained for almost twice the length of time.
- Mathematical simulations also predict that if an adaptive therapy approach is used with two drugs instead of one (abiraterone and docetaxel), time to disease progression could be increased four-fold.
- Based on these types of evolutionary principles and math models, Moffitt Cancer Center has opened four new adaptive therapy trials in several cancer types, including a trial testing first-line androgen deprivation therapy (ADT) for prostate cancer.

## Interim analysis of first 18 trial patients compared to SOC group with initial response of >50% PSA decline



- Trial cohort: 4 rad progression (at 12, 27, 30, and 32 months).
- Contemporaneous group: 16/16 progressed. Median TTP 10 (PSA) and 14 (Rad) months.
- Median TTP not reached in trial cohort but cannot be less than 34 months.
- Statistical significant ( $p < 0.001$ ) increase compared to compared to contemporaneous and published cohorts
- Average cumulative dose < 50% of SOC.

**Figure:** Preliminary analysis of treatment lengths, cycles, and disease progression in mCRPC patients enrolled on a trial testing adaptive therapy with abiraterone (top) versus a group of mCRPC patients contemporaneously treated with abiraterone continuously (standard-of-care, SOC; bottom).

## Session 6: Racial Disparities in Prostate Cancer Treatment and Outcomes: Biology or Access to Care

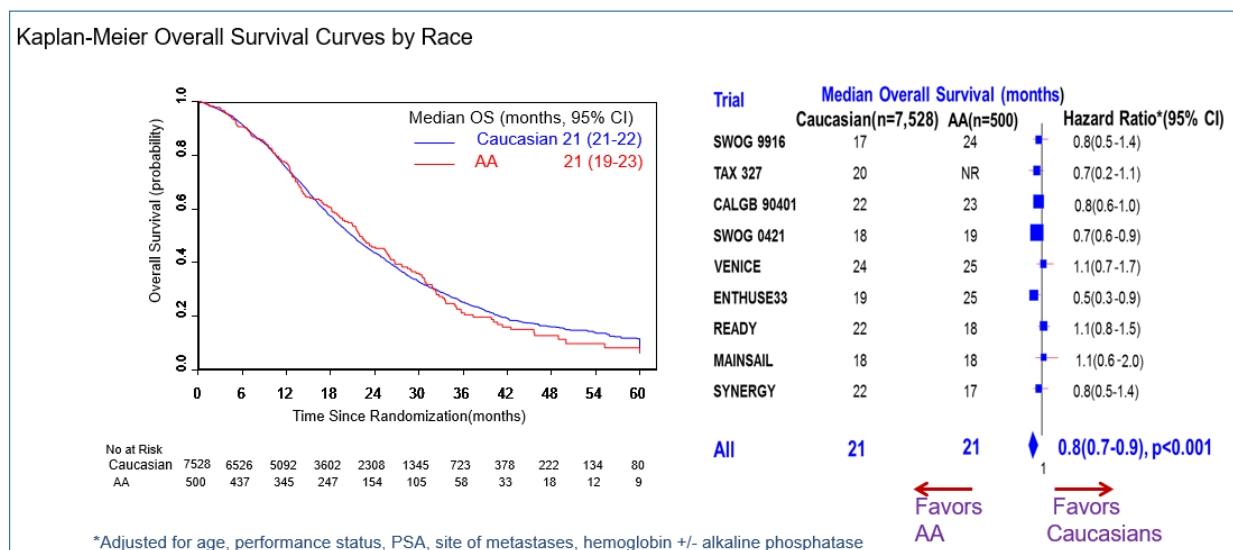
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### *Clinical Outcomes between Black and White Men with Metastatic Castration-Resistant Prostate Cancer*

Susan Halabi, PhD  
Duke University

- African American men have significantly higher prostate cancer incidence and mortality rates compared with Caucasian men, and are typically diagnosed at a younger age with more aggressive disease. Understanding the reasons for these disparities is critical for improving outcomes for African American men.
- To identify factors influencing disparities, Dr. Susan Halabi investigated overall survival outcomes of African American versus Caucasian men with metastatic castration-resistant prostate cancer (CRPC) in randomized phase III clinical trials testing the efficacy of docetaxel or docetaxel-containing regimens.
- Nine phase III trials with outcomes for 8,028 patients were used in this meta-analysis. Of these patients, 85% self-identified as Caucasian and 6% as African American.
- Fewer African American men were accrued to industry trials versus National Clinical Trials Network trials (4% vs 12%).
- The African American men on these trials were younger and had higher baseline PSA levels than the Caucasian men.
- Despite differences in baseline characteristics, African American men and Caucasian men had similar median overall survival (time from randomization on the trial to death from any cause) across all of the trials, of 21 months (Figure).
- Progression-free survival (time from randomization to disease progression or death, whichever occurred first) was also similar in African American men and Caucasian men on these trials, with a median of 8 months for both.
- When differences in important prognostic characteristics (age, performance status, PSA, site of metastases, hemoglobin +/- alkaline phosphatase) were adjusted for, African American men had 19% lower risk for death than Caucasian men.
- It is critical to note that these results are from clinical trials, and may not be generalized to the U.S. population.
- Together, these studies suggest that when treatment is similar, disparities are not observed, and support hypotheses that disparities result from unequal access to care. Unequal access to health care for African Americans is a problem that has been well-documented in medical literature.

- Differences in biology may contribute to African American men being diagnosed at higher rates, at younger ages, and with more aggressive disease, and may affect treatment responses.
- Studies to define biological versus demographic and socio-economic contributors to disparities are critical.
- It is also critical to establish and vigorously implement new methods for enrolling higher numbers of African American men and other minority groups onto clinical trials, so these groups may be appropriately represented.



**Figure:** In nine randomized phase III clinical trials testing the efficacy of docetaxel or docetaxel-containing regimens in 8,028 patients, the median overall survival (time from randomization on the trial to death from any cause) was similar for African American men and Caucasian men, of 21 months.



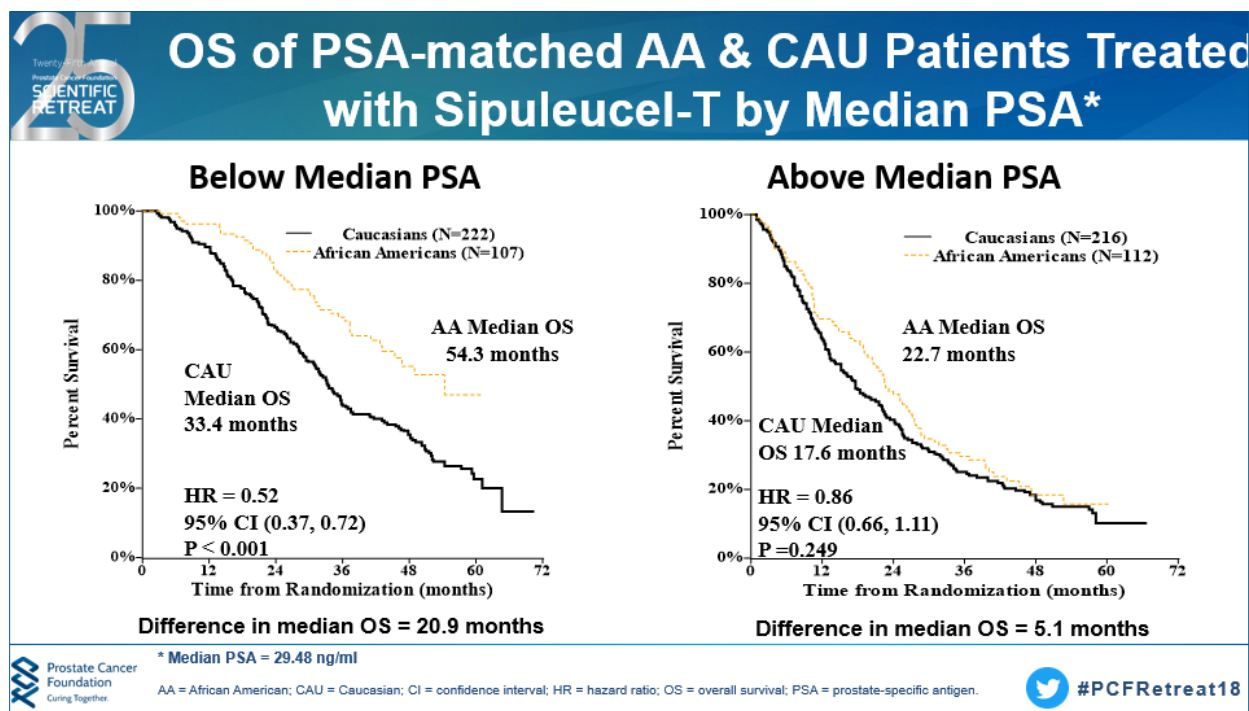
## *Sipuleucel-T in African American Men: Updated Overall Survival Analysis*

Oliver Sartor, MD

Laborde Professor for Cancer Research, Tulane Medical School

- Sipuleucel-T (Provenge®) is an immunotherapy treatment that was approved by the FDA for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in 2010.
- Sipuleucel-T is an immunotherapy that is generated from a patient's own immune cells. To create this personalized therapy, certain types of white blood cells termed antigen presenting cells (APCs) are harvested from a patient by a leukapheresis procedure. The APCs are co-cultured in a clinical laboratory with an engineered fusion protein that consists of the tumor-associated protein PAP (prostatic acid phosphatase) and the immune-stimulating protein GM-CSF. The white blood cells are then reinfused into the patient. This process is repeated for a total of three cellular administrations scheduled two weeks apart. The "loaded" APCs then help to activate the patient's immune system to recognize and react against prostate cells expressing PAP.
- This treatment was FDA-approved based on a median improvement in overall survival by ~4 months.
- African American men are at a significantly higher risk for diagnosis, disease progression after local therapy, and death from prostate cancer compared with Caucasian men. However, the reasons underlying these disparities are unclear.
- As discussed by Dr. Susan Halabi (above), an analysis of pooled data from phase III clinical trials found that African American men with mCRPC actually had similar or better outcomes than Caucasian men with mCRPC when treated with docetaxel-containing regimens in clinical trials.
- Similarly, a pooled analysis of data from phase III clinical trials suggested that African American men may have similar or better outcomes than Caucasian men when treated with sipuleucel-T. Further studies were needed to validate this possibility.
- Dr. Oliver Sartor discussed a study to investigate outcomes in African American vs. Caucasian mCRPC patients following treatment with sipuleucel-T.
- Dr. Sartor and team analyzed data from the PROCEED registry, an FDA-mandated registry to track side effects in patients treated with sipuleucel-T in the "real world" (outside of clinical trials). The PROCEED registry enrolled 1,902 men with mCRPC treated with sipuleucel-T, 12% of whom were African American.
- For this analysis, African American patients were matched 1:2 to Caucasian patients based on baseline PSA levels, and overall survival was compared (the time from treatment to death by any cause). Statistical analyses were performed that corrected for different variables in order to rule out their effects. Patients were matched based on baseline PSA levels because previous studies found that baseline PSA levels were highly correlated with survival times in patients treated with sipuleucel-T. Other baseline clinical characteristics were similar between the African American and Caucasian patient groups evaluated in this analysis.

- Altogether, the study compared overall survival in 219 African American patients and 438 Caucasian patients with mCRPC who were treated with sipuleucel-T.
- The African American patients were found to have a significantly longer median overall survival time compared with baseline PSA-matched Caucasian patients, by a median of 9.5 months (median overall survival of 35.3 months in African American patients vs. 25.8 months in Caucasian patients). This represents a 30% reduction in risk of death in African Americans.
- The differences in outcomes between African American patients vs. Caucasian patients treated with sipuleucel-T were pronounced in patients with lower baseline-PSA levels, and less apparent in patients with higher baseline-PSA levels (Figure). In patients with baseline PSA levels below the median, African American men lived a median of 20.9 months longer than Caucasian men. In patients with baseline PSA levels above the median, African American men lived a median of 5.1 months longer than Caucasian men.
- Non-race-related variables that on their own were associated with differences in survival times following treatment with sipuleucel-T included age, weight, baseline levels of LDH, ALP, and hemoglobin, the presence and number of bone metastases, the presence of non-lymph node metastases, and prior treatments.
- There were no significant differences in the types of treatments received after sipuleucel-T between the African American and Caucasian patients in this analysis.
- Together, these data suggest that African American mCRPC patients do significantly better than Caucasian patients following treatment with sipuleucel-T. More studies are needed to understand the reasons underlying this phenomenon.



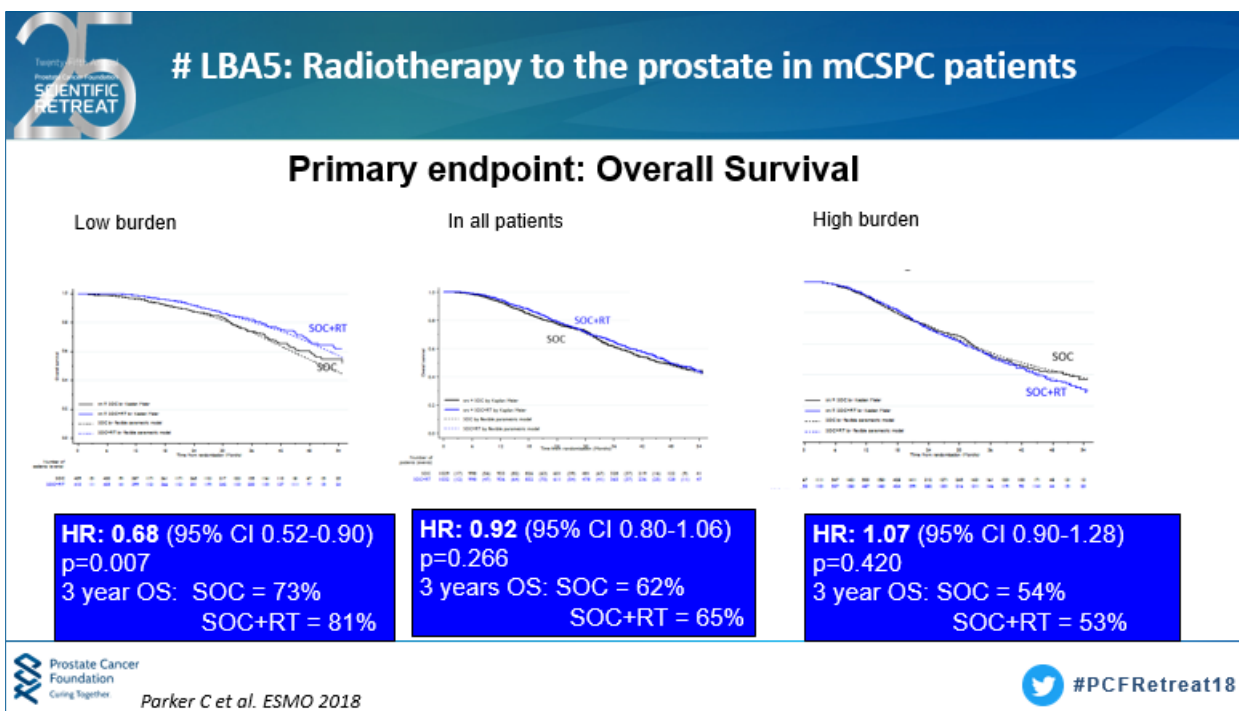
**Figure:** Differences in overall survival (OS) between African American patients vs. Caucasian patients treated with sipuleucel-T were pronounced in patients with lower baseline-PSA levels, and less apparent in patients with higher baseline-PSA levels. In patients with baseline PSA levels below the median (left), African American men lived a median of 20.9 months longer than Caucasian men. In patients with baseline PSA levels above the median (right), African American men lived a median of 5.1 months longer than Caucasian men.

## *SPECIAL LECTURE: ESMO Hot Points*

Silke Gillesen, MD

University of Manchester, UK

- The European Society for Medical Oncology (ESMO) holds an annual conference at which cancer researchers present results from translational and clinical cancer studies. The 2018 ESMO Congress was held in Munich, Germany, from October 19-23, 2018.
- Dr. Silke Gillesen discussed results from two of the most impactful prostate cancer clinical trials that were presented at the 2018 ESMO Congress.
- STAMPEDE is a multi-arm, multi-stage randomized clinical trial being conducted in Europe (UK and Switzerland) that is comparing the efficacy of several different treatment regimens in men with prostate cancer who are starting long-term androgen deprivation therapy (ADT). These patients either have high-risk localized prostate cancer, biochemical relapse or metastatic prostate cancer.
- Prior and current treatment arms on the STAMPEDE trial include: Standard of care (SOC) alone (long term ADT plus current standard treatment options); SOC + zoledronic acid; SOC + docetaxel; SOC + celecoxib; SOC + zoledronic acid + docetaxel; SOC + abiraterone; SOC + abiraterone + enzalutamide; SOC + metformin; SOC + transdermal oestradiol, and SOC + radiation therapy to the prostate in men newly diagnosed with metastatic prostate cancer. The trial is designed such that if promising new treatments are identified, new treatment arms can be added to the trial and compared to a contemporaneous SOC arm.
- Currently, the SOC treatment for men newly diagnosed with metastatic prostate cancer is ADT combined with abiraterone or docetaxel, depending on disease burden and other patient factors. It has not been prospectively determined if local therapy to the primary tumor (radiation or surgery) is beneficial in men who already have developed metastatic prostate cancer at the time of diagnosis.
- At ESMO, results from the STAMPEDE trial were presented from the treatments arms comparing ADT +/- docetaxel (standard of care) versus ADT +/- docetaxel + radiation therapy to the prostate, in men newly diagnosed with metastatic prostate cancer.
- In the entire patient cohort, no benefit was observed with radiation therapy to the prostate added to ADT +/- docetaxel (Figure).
- However, when only patients with a low metastatic disease burden were assessed, a significant survival benefit was observed with the addition of radiation therapy to the prostate, representing a 32% reduction in the risk of death (Figure).
- No survival benefit was seen with the addition of radiation therapy to the prostate in patients with a high burden of metastatic disease (Figure).
- These data suggest that radiotherapy to the primary can improve survival in men with castration-sensitive prostate cancer and a low burden of metastatic disease who are being treated with ADT +/- docetaxel chemotherapy.
- These STAMPEDE trial results were presented at ESMO by Dr. Christopher Parker (Royal Marsden Hospital, UK).



**Figure:** The addition of radiation therapy to the prostate to standard of care (SOC, ADT + docetaxel) was found to increase overall survival in men newly diagnosed with metastatic prostate cancer who had a low burden of disease, representing a 32% reduction in the risk of death (left), but did not benefit patients with a high burden of disease (right).

- The second trial from ESMO presented there by Dr. Matthew Smith (Massachusetts General Hospital) was ERA-223, a randomized, double-blinded phase III trial which tested abiraterone + prednisone in combination with radium-223 vs. abiraterone + prednisone with placebo in 806 patients with mCRPC who had two or more bone metastases and no brain or visceral metastases.
- 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.
- The primary endpoint of the ERA-223 trial was symptomatic skeletal event-free survival (time from randomization until bone metastases caused symptoms).
- The addition of radium-223 vs. placebo to abiraterone/prednisone did not improve either symptomatic skeletal event-free survival or overall-survival times (no significant difference between the treatment arms).
- There was a numerically higher number of deaths (though not statistically significant) among patients who received radium-223 vs. placebo.
- Notably, bone fractures (all grades) were significantly higher in patients who received abiraterone/ prednisone + radium-223 versus patients who received abiraterone/prednisone + placebo (26% versus 10%).

- An independent review was performed of available scans to better understand what was causing the fractures. In the independent review, 76 patients in the radium-223 group and 23 patients in the placebo group were found to have at least one bone fracture.
- All types of bone fractures (pathological, traumatic, osteoporotic) were more frequent in patients who received radium-223, the most pronounced type being osteoporotic bone fractures (37 fractures in the radium-223 group vs. 4 in the placebo group).
- Most fractures in both treatment groups occurred at bone sites with no detectable metastases.
- Bisphosphonates and denosumab are FDA-approved bone health agents that are used for preventing bone fractures in patients with metastatic prostate cancer. Approximately 40% of the patients on the trial had been receiving treatment with bone health agents at baseline.
- Patients in both treatment arms who had been receiving bone health agents had fewer fractures compared with those who did not receive bone health agents. However, radium-223 increased bone fractures compared with placebo in patients who had been receiving bone health agents at baseline, as well as in those who had not.
- The increased frequency of bone fractures and deaths in the radium-223 arm in this trial resulted in the trial being prematurely un-blinded by the independent review committee.
- Together, the analyses from this trial have found that radium-223 does not improve outcomes when added to abiraterone/prednisone, but instead increases risk for bone fractures and possibly death.
- Based on these data, regulatory agencies have issued warnings that radium-223 should not be given in combination with abiraterone + prednisone.
- Bone health is important for men with prostate cancer and it is important to be aware of osteoporosis induced by treatments, including ADT.



## Session 7: Translational Research on WNT Signaling in Normal and Tumor Cell Biology

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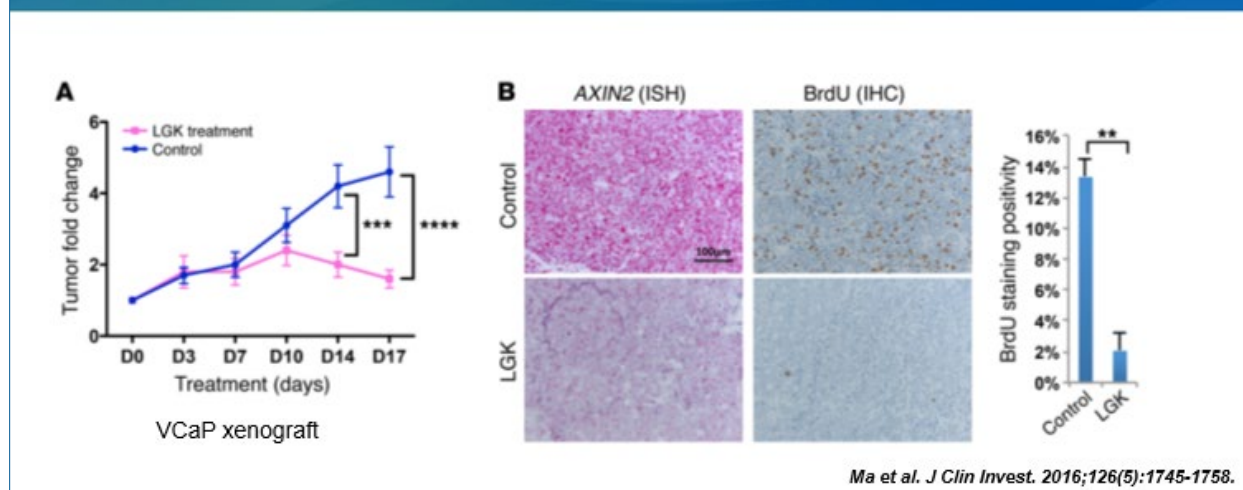
### *WNT Signaling Targets in ADT Resistant CRPC*

Xin Yuan, MD, DSc

Harvard: Beth Israel Deaconess Medical Center

- The WNT signaling pathway is a complex molecular pathway essential for early development and the activities of stem cells, and is also involved in many types of cancer. In colon cancer, WNT pathway alterations drive over 90% of cases.
- Activation of the WNT pathway regulates the expression of genes involved in proliferation, differentiation, stem cell activities, survival, and drug resistance.
- Studies have found that WNT pathway alterations are present in ~18% of metastatic castration-resistant prostate cancer (mCRPC). WNT pathway genes that are altered in mCRPC include *β-catenin*, *APC*, *RNF43*, *ZNRF3*, *RSPO2*, *AXIN1*, and *AXIN2*.
- Dr. Xin Yuan discussed studies to understand the role of the WNT pathway in prostate cancer and to investigate its potential as a therapeutic target.
- A “WNT activity signature” was defined in prostate cancer cell lines by stimulating WNT activities in cells and determining the genes that were activated. A list of 49 genes was identified. These genes included known WNT-regulated genes, negative regulators of WNT signaling, and genes with stem cell functions.
- Using this 49-gene signature, WNT activity was determined in gene expression datasets from primary and metastatic prostate cancer cohorts. Samples with the highest WNT activity signature levels were enriched for WNT pathway genomic alterations.
- WNTs are a family of secreted proteins which mediate their effects by interacting with surface receptors on the cell itself or other cells. WLS is a WNT pathway protein that plays a role in WNT secretion.
- Expression of WLS was found to significantly increase in more aggressive primary prostate cancer and in mCRPC, especially in cases that had developed resistance to enzalutamide.
- The expression of WLS was evaluated in animal models of human prostate cancer. WLS expression was increased following castration, and was even higher following administration of androgen deprivation therapy (ADT) after castration.
- Treatment with the WNT inhibitor LGK974 blocked the growth of human prostate cancer organoids that expressed high levels of WLS.
- LGK974 treatment also blocked the growth of human prostate tumors in animal models (Figure).
- Together these studies demonstrate that WNT signaling may drive a subset of mCRPC. Further studies evaluating the potential for WNT inhibitors as a treatment strategy in mCRPC are warranted.

# Wnt inhibitor blocks PCa xenograft growth



**Figure:** Treatment with the WNT inhibitor LGK974 blocked the growth of prostate tumors in animal models.

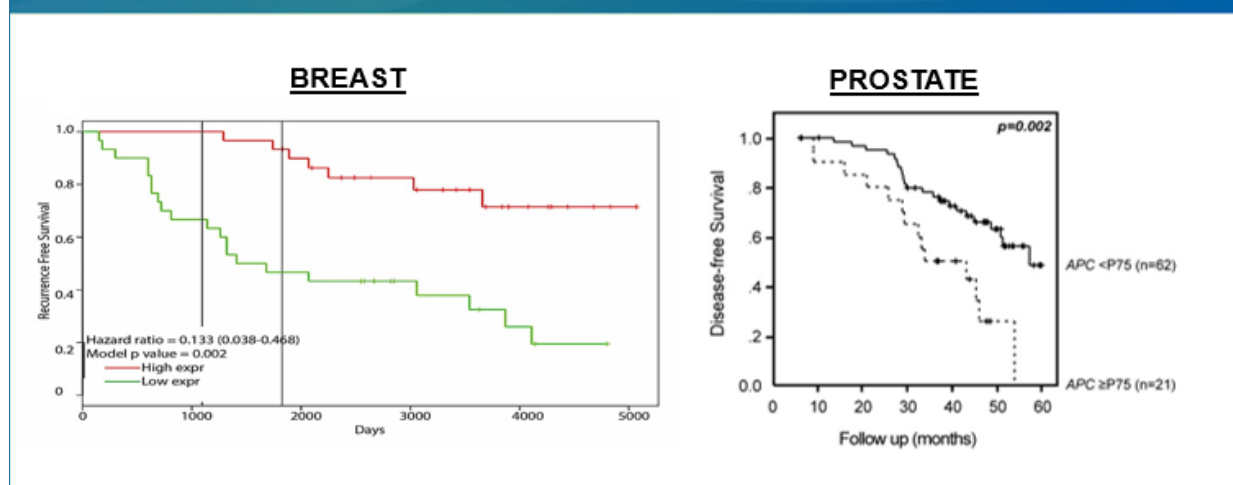
## APC Modulation of Therapy Resistance in Breast Cancer

Jenifer Prosperi, PhD  
University of Notre Dame

- There are several molecular subtypes of breast cancer: Luminal A, Luminal B, HER2-positive, and triple negative. These subtypes are classified based on the expression of the proteins HER2, ER, and PR, which define cancer subtypes that have different biology and clinical features, but also are treated with different therapies.
- Triple-negative breast cancer (TNBC) does not express HER2, ER, and PR, and is the lone breast cancer subtype for which there is no effective targeted therapy. Instead, TNBC is treated with traditional chemotherapy, which is not highly effective and lends to poor prognosis for these women.
- There are several classes of chemotherapy agents that are used in the treatment of TNBC, each of which targets a different cellular activity and has different side effects. Anthracyclines (i.e. doxorubicin, epirubicin) insert themselves into DNA and inhibit DNA replication. Taxanes (i.e. paclitaxel, docetaxel) interfere with cell division by preventing the activity of microtubules, which are tubular structures within cells that move cellular components around. Platinum drugs (i.e. cisplatin) bind and cross-link DNA, causing cell death-inducing DNA damage.
- Adenomatous Polyposis Coli (APC) is a large tumor-suppressor protein that impacts numerous cellular processes. APC can interact with DNA replication enzymes and microtubule components. Thus, APC-loss may impact responses to chemotherapy agents which target these cellular processes.

- Dr. Jenifer Prosperi discussed the role of APC-loss in therapy resistance in patients with breast cancer.
- Loss or inactivation of the APC gene is the primary cause of hereditary colon cancer, driving the development of ~90% of cases.
- APC-loss has also been observed in a number of other cancer types, including 50-75% of breast cancer and 80-90% of prostate cancer.
- APC expression levels can also be impacted in cancer. APC promoter methylation, which shuts down gene expression, has been observed in the majority of breast cancer cases in several studies.
- APC expression levels have been associated with outcomes in breast and prostate cancer; patients whose tumors had lower APC expression levels have poorer recurrence and disease-free survival rates (Figure).
- In breast cancer models, APC-loss was found to cause resistance to doxorubicin chemotherapy.
- This was found to be due in part to increased drug efflux (pumping of drug out of the cell) via the efflux pump protein MDR1. Blockade of MDR1 restored breast cancer cell sensitivity to doxorubicin in the absence of APC.
- APC-loss was also found to decrease DNA damage by doxorubicin. Treatments targeting the DNA repair enzyme ATM, which impair the ability of cells to repair damaged DNA, also restored sensitivity to doxorubicin in the absence of APC.
- Altogether, these data demonstrate that APC-loss can drive resistance to chemotherapy agents through several mechanisms. ATM inhibition and MDR1 inhibition were identified as possible therapeutic options for restoring chemotherapy sensitivity in these tumors.

## APC in breast (and prostate) cancer



**Figure:** Lower APC expression levels are associated with poorer outcomes compared with higher APC expression levels in patients with breast cancer (left) and prostate cancer (right).

## *SPECIAL LECTURE: Movember Foundation Global Prostate Cancer Landscape Analysis*

Mark Buzza, PhD

Movember Foundation

- The Movember Foundation is a global non-profit organization that raises money to fund research on critical men's health issues, with a focus on prostate cancer research, testicular cancer and mental health.
- The Movember Foundation funds research into prostate cancer in different countries in large part through partnerships with "Men's Health Partners," non-profit foundations that focus efforts on funding such research.
- The Prostate Cancer Foundation has been a major partner of the Movember Foundation since 2007. During this time, the Movember Foundation has generously donated more than \$56 million to PCF, to support 45 research awards in the U.S., Canada, and Great Britain.
- Since 2004, the Movember Foundation has invested over \$320 Million AUD (approximately \$232 Million USD) into 589 research projects in 21 countries.
- Other major Men's Health Partners of the Movember Foundation include Prostate Cancer Canada, Prostate Cancer UK, and Prostate Cancer Foundation Australia.
- Dr. Mark Buzza discussed the Movember Foundation's prostate cancer landscape analysis project, which was an effort to understand the gaps and opportunities in the field, and help to determine where the Movember Foundation should make strategic investments over the next 3-5 years that will have the greatest impact for men with the disease.
- As inputs into the landscape analysis, interviews were conducted with 44 thought leaders and 9 patient advocates across the globe. Thought leaders spanned the fields of urology, radiation oncology, medical oncology, pathology, epidemiology, academic translational research, clinical trials, computational biology, radiology, health economics, implementation science, policy, patient advocacy, and included representatives from the National Cancer Institute (NCI) as well as industry.
- Next, the Movember Foundation brought together a Landscape Analysis Committee (LAC) to review the key insights and research needs identified from the interviews, and to determine the highest priority gaps and opportunities in the field. Nine prostate cancer experts from around the world were convened for this workshop.
- High priority research areas were identified across various clinical prostate cancer disease states. The prioritized research areas included:
  - Research focused on earlier stage prostate cancer, from initial diagnosis through oligometastatic disease.
  - Earlier identification and optimizing treatment of men at high risk of disease progression to reduce the number of men who progress from localized to advanced disease.
  - Leveraging existing "Clinical Quality" Movember Foundation investments such as the IRONMAN registry (<https://ironmanregistry.org/>), which will prospectively follow men with

advanced prostate cancer and provide a deeper understanding of optimal treatments and treatment sequences in a real world setting.

- Research on late stage disease (from biochemical recurrence to castration resistant disease) that improves our understandings of disease biology, prediction of disease progression, optimal treatment selection, and treatment resistance.
  - Precision medicine clinical trials that are designed to be adaptive, inclusive, and efficient.
  - Academic drug discovery research that identifies new therapeutic targets.
- The Movember Foundation plans to publish results from the Landscape Analysis in the near future.
  - Dr. Buzza also reported on the status of the Movember GAP1 program, which is a collaborative international effort to create a biobank of patient-derived tumor samples for the research community.
  - Prostate cancer tissue microarrays (TMA) were created as a collaborative effort between 10 teams from the USA, Canada, Finland, and Norway. TMAs are a collection of a large number of patient tumor tissue samples that are arrayed on glass slides in order to study disease biology and pathology.
  - Three sets of TMAs were created by the GAP1 program.
  - One set consists of paired samples of untreated primary tissue and lymph node metastases from 319 patients, to enable biomarker comparisons between primary tumors and soft tissue metastases.
  - A second set consists of samples from the primary tumors of 117 patients with CRPC samples, for profiling biomarker expression in CRPC and a comparison with pre-treatment samples within an individual patient.
  - The third set of TMAs consists of samples from multiple matched metastases from 83 patients, which will enable studies on inter-metastatic heterogeneity of biomarkers in lethal prostate cancer.
  - In addition, the GAP1 program established a series of patient-derived tumor xenograft (PDX) models via a collaborative effort between 11 teams from the USA, Canada, Switzerland, UK, The Netherlands, and Australia (<https://onlinelibrary.wiley.com/doi/abs/10.1002/pros.23701>). PDXs are patient tumor samples that have been successfully established as tumor lines in animal models. These model systems enable the study of human prostate cancer in a live animal.
  - 98 PDX lines have been successfully established and characterized thus far, and an additional 25 will soon be reported on. A TMA slide set has been developed for all 123 PDX lines.
  - The slides from both the TMA and PDX projects (as well as the original PDXs from the xenograft project) will be available to the academic prostate cancer research community upon request through the Prostate Cancer Biorepository Network (PCBN) in early-mid 2019.

## Landscape Analysis Committee (LAC) workshop 10<sup>th</sup>-11<sup>th</sup> December 2017 in Los Angeles

- A Landscape Analysis Committee (LAC) was commissioned to review the key insights and research needs garnered from the interviews and address the six key GSC-approved questions in order to determine the highest priority gaps and opportunities in the field
- The LAC attended a workshop in Los Angeles on 10<sup>th</sup> – 11<sup>th</sup> Dec 2017:
  - Peter Choyke (Radiology, USA)
  - Tony Crispino (Patient Advocate, USA)
  - Suneil Jain (Clinical Oncology, UK)
  - Guido Jenster (Translational Research, Netherlands)
  - Beatrice Knudsen (Pathology, USA)
  - Jeremy Millar (Radiation Oncology, Australia)
  - Nicole Mittmann (Health Economics, Canada)
  - Charles Ryan (Medical Oncology, USA)
  - Bertrand Tombal (Urology, Belgium)



Facilitated by Dr Seanna Davidson, Sax Institute

**Figure:** The Movember Foundation Landscape Analysis Committee (LAC).



## Session 8: Unlocking Innate Immunity for Cancer Therapeutics

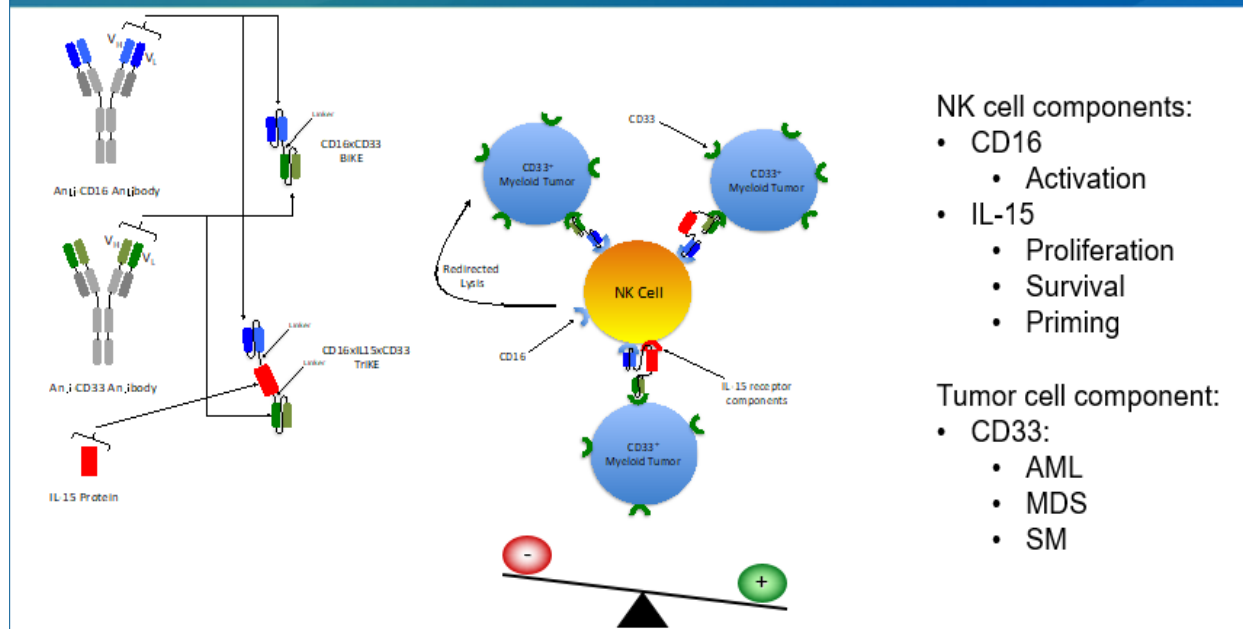
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### *Improving NK Cell Immunotherapy for Cancer*

Martin Felices, PhD  
University of Minnesota

- Cancer immunotherapy is a type of treatment that works by activating a patient's own immune system to fight their cancer. Numerous immunotherapy strategies are being developed for different types of cancer including prostate cancer.
- Many immunotherapy approaches focus on activating T cells, a type of white blood cell that functions to recognize abnormal cells in the body and kill them.
- Natural Killer (NK) cells are a different type of white blood cell that also recognize abnormal cells in the body and kill them, but work very differently from T cells.
- Dr. Martin Felices discussed the development of a novel type of cancer immunotherapy that uses NK cells.
- NK cells are one of the main type of immune cells that infiltrate prostate tumors, and are associated with a better prognosis. These and other studies suggest that NK cells may have activity in prostate cancer.
- Dr. Felices and team have developed a novel NK cell activating platform named "Tri-specific Killer Engager" (TriKE). This treatment consists of a 3-armed protein chimera, which is composed of: 1) an antibody fragment that binds to NK cells; 2) an antibody fragment that binds tumor cells; and 3) the NK cell activating protein IL-15 (Figure).
- In preclinical experiments, a TriKE molecule that targets leukemia cells significantly increased tumor cell killing by NK cells, and also increased NK cell proliferation, survival, and production of immune-activating molecules.
- "Broad-spectrum" TriKEs that are able to target several cancer types including prostate cancer are currently being developed. The team is also planning to develop TriKEs specifically for prostate cancer.
- Altogether, TriKE molecules may represent a novel platform for targeting cancer via NK cells while also driving NK cell expansion. Studies are ongoing to develop this treatment for testing in clinical trials.

## Tri-specific Killer Engager (TriKE) platform



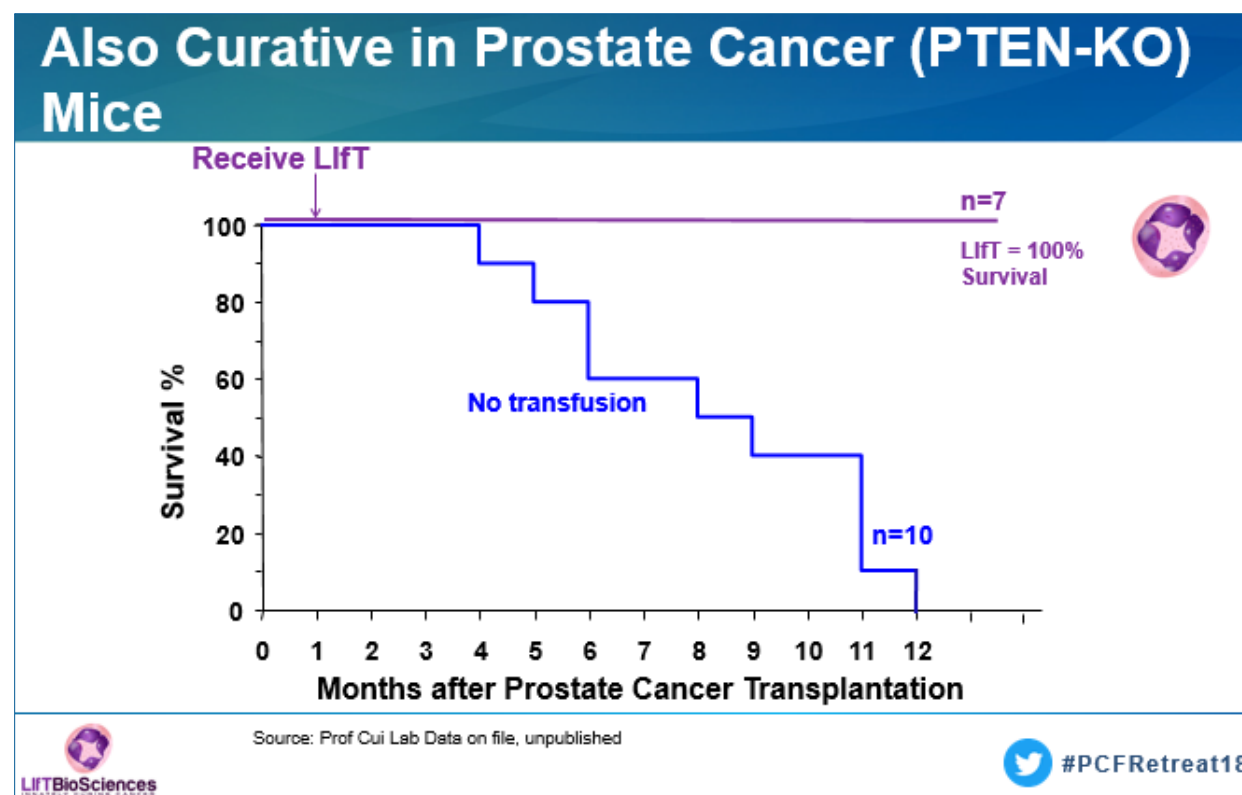
**Figure:** “Tri-specific Killer Engagers” (TriKEs) are a novel NK cell activating platform that consist of 1) an antibody fragment that binds to NK cells (blue); 2) an antibody fragment that binds tumor cells (green); and 3) the NK cell activating protein IL-15 (red).

## Neutrophil Based Cancer Therapeutics

Alex Blyth  
CEO, LiFT BioSciences Ltd

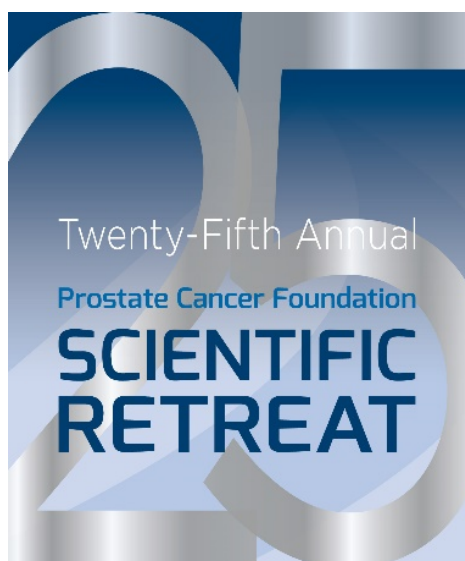
- Neutrophils are a type of white blood cell that act as first responders to pathogen infections and function to ingest pathogens and activate the immune response.
- Dr. Alex Blyth and team have demonstrated that neutrophils also can have exceptional selective cancer-killing activity in preclinical models and in a small FDA approved safety trial.
- LiFT BioSciences is producing a novel neutrophil based cancer therapeutic, N-LiFT, in which large numbers of pure neutrophils with cancer-killing activity are generated from healthy donor hematopoietic stem cells (the type of stem cell from which all red blood cells, platelets, and white blood cells are derived). These neutrophils will be infused into cancer patients. Unlike T cells, neutrophils can be given to MHC-unmatched donors as they do not confer chronic graft-versus-host disease complications.

- N-LIFT-generated neutrophils are a type that are highly cytotoxic to cancer cells and stimulate T cells, as opposed to other neutrophil types which would be less effective against cancer.
- In preclinical models, this neutrophil product was able to kill all types of solid tumors tested, including prostate cancer (Figure).
- N-LIFT neutrophils appear to be safe for advanced cancer patients in early results from a phase I trial.
- Plans to initiate efficacy trials in several cancer types for the end of 2019 are underway, subject to gaining commitments for the outstanding third of the £6M funding still required.



**Figure:** In preclinical models, N-LIFT neutrophils were able to prevent the growth of prostate cancer in 100% of mice tested.

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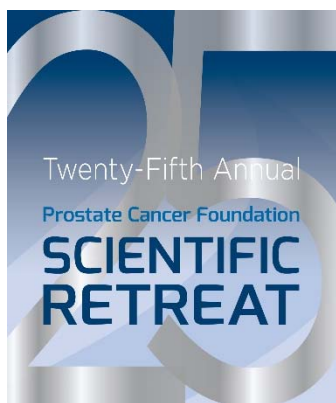


## **APPENDIX:**

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

**OCTOBER 26-28, 2018**

## ***PROGRAM AGENDA***



# AGENDA

**Friday, October 26, 2018**

## GENERAL SESSIONS

**Location: Costa Del Sol Ballroom**

**8:00 AM**

**Registration**

**Costa Del Sol Foyer**

### **Welcome & Introduction**

**2:00 PM - 2:10 PM**

**Howard Soule, PhD**  
Prostate Cancer Foundation

### **Session 1: Neuronal Control of Prostate Cancer Progression**

**2:10 PM - 3:30 PM**

**Moderator: Paul Frenette, MD**  
Albert Einstein College of Medicine

**2:10 PM - 2:25 PM**

***Adrenergic Nerves Activate an Angio-Metabolic Switch in Prostate Cancer***

**Paul Frenette, MD**  
Albert Einstein College of Medicine

***Clinical Trial of a Beta Blocker in Prostate Cancer***

**Benjamin Gartrell, MD**  
Albert Einstein College of Medicine; Montefiore Medical Center

**2:25 PM - 2:30 PM**

**Discussion**

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

***Influence of the Neural Microenvironment on Prostate Cancer***

**Michael Ittmann, MD, PhD**  
Baylor College of Medicine

**2:45 PM - 2:50 PM**

**Discussion**

**2:50 PM - 3:05 PM**

***Neural Control of Cancer***

**Patrick Mantyh, PhD, JD**  
The University of Arizona Cancer Center

**3:05 PM - 3:10 PM**

**Discussion**



**Friday, October 26, 2018**

3:10 PM - 3:25 PM ***Sympathetic Nerves, Stress and Anti-Cancer Immunity***  
**Elizabeth Repasky, PhD**

Roswell Park Comprehensive Cancer Center

3:25 PM - 3:30 PM **Discussion**

**Session 2: Steroid Receptors in Advanced Prostate Cancer: New Approaches to an Old Target**

**3:30 PM - 5:15 PM**

**Moderator: Andrew Armstrong, MD, ScM**

Duke University

3:30 PM - 3:50 PM ***SPECIAL LECTURE: If We Knew 20 Years Ago What We Know Now, Would We Have Targeted the Androgen Signaling Pathway in Prostate Cancer Differently?***

**Donald McDonnell, PhD**

Duke University School of Medicine

3:50 PM - 3:55 PM **Discussion**

3:55 PM - 4:10 PM ***Moving Beyond the Androgen Receptor: Targeting Transcriptional Coregulators for the Treatment of Castration-Resistant Prostate Cancer***

**Salma Kaochar, PhD**

Baylor College of Medicine

4:10 PM - 4:15 PM **Discussion**

4:15 PM - 4:30 PM ***Surprising Aspects of Androgen and Glucocorticoid Receptor Crosstalk Revealed by Selective Receptor Antagonism***

**Suzanne Conzen, MD**

University of Chicago

4:30 PM - 4:35 PM **Discussion**

4:35 PM - 4:50 PM ***The PROPHECY Study: AR-V7, Tumor Heterogeneity, and Hormonal Resistance in Metastatic Prostate Cancer***

**Andrew Armstrong, MD, ScM**

Duke University

4:50 PM - 4:55 PM **Discussion**

4:55 PM - 5:10 PM ***In the Thicket of an Aberrant Genome: Interpreting the Role of AR-V7***

**Jun Luo, PhD**

Johns Hopkins University

5:10 PM - 5:15 PM **Discussion**

Friday, October 26, 2018

**Session 3: PSMA-Targeted Theranostics for Prostate Cancer**

**5:15 PM - 6:20 PM**

**Moderator: Scott Tagawa, MD**  
Weill Cornell Medicine

5:15 PM - 5:35 PM

**SPECIAL LECTURE: PSMA Theranostics: Latest Evidence-Base, Promise and Uncertainties**

**Michael Hofman, MBBS**  
Peter MacCallum Cancer Centre, Australia

5:35 PM - 5:40 PM

**Discussion**

5:40 PM - 5:55 PM

**Elucidating Mechanisms of Effectiveness and Resistance to PSMA Targeted RadioLigand Therapy (RLT) using  $^{177}\text{Lu}$ -PSMA-617**

**Jeremie Calais, MD**  
University of California, Los Angeles

5:55 PM - 6:00 PM

**Discussion**

6:00 PM - 6:15 PM

**Optimization of PSMA-Targeted Radionuclide Therapy**

**Scott Tagawa, MD**  
Weill Cornell Medicine

6:15 PM - 6:20 PM

**Discussion**

**SPECIAL LECTURE**

**6:20 PM - 6:35 PM**

**Results from TRITON2: Treatment of mCRPC with Rucaparib**

**Alan Bryce, MD**

Mayo Clinic

*Introduced by Charles Ryan, MD*

*University of Minnesota*

**6:35 PM - 6:40 PM**

**Discussion**

**Friday, October 26, 2018**

**Dinner**

**7:00 PM - 8:00 PM**

***Dinner Location: Costa Del Sol Patio***

**Poster Session and Dessert**

**8:00 PM - 10:30 PM**

***Poster Session and Dessert Location: Costa Del Sol AB & Foyer***

**Saturday, October 27, 2018**

**6:00 AM - 7:45 AM Breakfast**

**Location: Costa Del Sol Patio**

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

**GENERAL SESSIONS**

**Location: Costa Del Sol Ballroom**

**PANEL DISCUSSION**

**8:00 AM – 9:00 AM**

**Principles and Practice (Challenges) of 2018 Precision Oncology in Advanced Prostate Cancer 4 Nano CPCs: CDK12<sup>-/-</sup>, BRCA2<sup>-/-</sup>, AKT-1<sup>E17K</sup>, and SLC43-BRAF Fusion**

**Introduction: Jonathan W. Simons, MD**

Prostate Cancer Foundation

**Moderator: Himisha Beltran, MD**

Harvard: Dana-Farber Cancer Institute

**Panelists:**

**Ajjai Alva, MD** (University of Michigan)

**Bruce Montgomery, MD** (University of Washington; VA Puget Sound)

**Vaibhav Patel, MD** (Icahn School of Medicine at Mount Sinai Hospital)

**Matthew Rettig, MD** (University of California, Los Angeles)

**Gerhardt Attard, MD, PhD** (University College London Cancer Institute, UK)

**9:00 AM - 9:05 AM    Break**

**Saturday, October 27, 2018**

**SPECIAL LECTURE**

**9:05 AM - 9:20 AM**

**VAlor Awards and VA Center of Excellence Update**

**Bruce Montgomery, MD**

University of Washington; VA Puget Sound

**Matthew Rettig, MD**

University of California, Los Angeles

*Introduced by Jonathan W. Simons, MD  
Prostate Cancer Foundation*

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

**Discussion**

**SPECIAL LECTURE**

**9:25 AM - 9:55 AM**

**The Evolving Landscape of Life-Prolonging Treatments for Advanced Prostate Cancer:  
The New World Order**

**Maha Hussain, MD, FACP, FASCO**

Robert H. Lurie Comprehensive Cancer Center Northwestern University

*Introduced by Felix Feng, MD  
University of California, San Francisco*

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

**Discussion**

**Saturday, October 27, 2018**

**SPECIAL LECTURE**

**10:00 AM - 10:40 AM**

**State of the Science 2018**

**Jonathan W. Simons, MD**

Prostate Cancer Foundation

*Introduced by Howard Soule, PhD*

*Prostate Cancer Foundation*

**10:40 AM - 10:45 AM**

**Discussion**

**SPECIAL RECOGNITION OF NOBEL PRIZE**

**10:45 AM - 10:55 AM**

**James Allison, PhD**

The University of Texas MD Anderson Cancer Center

2018 Nobel Prize in Medicine

**Padmanee Sharma, MD, PhD**

The University of Texas MD Anderson Cancer Center

*Introduced by Howard Soule, PhD*

*Prostate Cancer Foundation*



**Saturday, October 27, 2018**

**KEYNOTE ADDRESS**

**10:55 AM - 11:55 AM**

**Michael Milken**

Founder and Chairman  
Prostate Cancer Foundation

*Introduced by Stuart Holden, MD  
Prostate Cancer Foundation*

**Group Photo**

**11:55 AM - 12:10 PM**

***Location: Costa Del Sol Foyer***

**Lunch**

**12:10 PM - 12:50 PM**

***Location: Costa Del Sol Patio***

**12:50 PM - 1:00 PM Move to Session 4**

**Location: Costa Del Sol Ballroom**

**Session 4: New Insights into the Biology and Role of Prostate Cancer Stem Cells**

**1:00 PM - 2:20 PM**

**Moderator: Rakesh Heer, MBBS, PhD**  
Newcastle University, UK

**1:00 PM - 1:15 PM**

***Inflammation, Aging and Prostate Progenitor Cells***

**Andrew Goldstein, PhD**

University of California, Los Angeles

**1:15 PM - 1:20 PM**

**Discussion**

**Saturday, October 27, 2018**

- 1:20 PM - 1:35 PM ***Multipotent Basal Stem Cells, Maintained in Localized Proximal Niches, Support Directed Long-Ranging Epithelial Flows in Human Prostates***  
**Rakesh Heer, MBBS, PhD**  
Newcastle University, UK
- 1:35 PM - 1:40 PM **Discussion**
- 1:40 PM - 1:55 PM ***Cellular Plasticity and the Neuroendocrine Phenotype in Prostate Cancer***  
**Amina Zoubeidi, PhD**  
Vancouver Prostate Centre
- 1:55 PM - 2:00 PM **Discussion**
- 2:00 PM - 2:15 PM ***Organoids as a New Model System for Cancer Research***  
**Benedetta Artegiani, PhD**  
Hubrecht Institute, Netherlands
- 2:15 PM - 2:20 PM **Discussion**

**SPECIAL LECTURE**

**2:20 PM - 2:35 PM**

***Canine and Machine Olfaction in Human Prostate Cancer Diagnosis***

**Claire Guest, HonDSc**

Medical Detection Dogs

**Andreas Mershin, PhD**

Massachusetts Institute of Technology

*Introduced by Thomas Johnson*

*Prostate Cancer Foundation*

**2:35 PM – 2:40 PM**

**Discussion**

**Saturday, October 27, 2018**

**Session 5: Ecology of Prostate Cancer**

**2:40 PM - 3:40 PM**

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

2:40 PM - 2:55 PM    ***The Changing Primary Tumor Environment – Why an Invasive Species Migrates***

**Kenneth Pienta, MD**  
Johns Hopkins University

2:55 PM - 3:00 PM    **Discussion**

3:00 PM - 3:15 PM    ***Resistance is Not Inevitable – Lessons from Pest Management***

**Christopher Whelan, PhD**  
The Moffitt Cancer Center; University of Illinois at Chicago

3:15 PM - 3:20 PM    **Discussion**

3:20 PM - 3:35 PM    ***Cancer Therapy, Adapting to Change the Game***

**Robert Gatenby, MD**  
The Moffitt Cancer Center

3:35 PM - 3:40 PM    **Discussion**

**Session 6: Racial Disparities in Prostate Cancer Treatment and Outcomes: Biology or Access to Care**

**3:40 PM - 5:00 PM**

**Moderator: Susan Halabi, PhD**  
Duke University

3:40 PM - 3:55 PM    ***Impact of Black Race on Prostate Cancer-Specific and Other-Cause Mortality***

**Daniel Spratt, MD**  
University of Michigan

3:55 PM - 4:00 PM    **Discussion**

4:00 PM - 4:15 PM    ***Clinical Outcomes between Black and White Men with Metastatic Castration Resistant Prostate Cancer***

**Susan Halabi, PhD**  
Duke University

4:15 PM - 4:20 PM    **Discussion**

**Saturday, October 27, 2018**

- 4:20 PM - 4:35 PM ***Sipuleucel-T in African American Men: Updated Overall Survival Analysis***  
**Oliver Sartor, MD**  
Laborde Professor for Cancer Research, Tulane Medical School
- 4:35 PM - 4:40 PM **Discussion**
- 4:40 PM - 4:55 PM ***Metastatic Prostate Cancer Outcomes from National Data on Veterans Treated with Abiraterone and Enzalutamide***  
**Tito Fojo, MD, PhD**  
Columbia University; James J Peter VA Cancer Center
- 4:55 PM - 5:00 PM **Discussion**

**Saturday, October 27, 2018**

**Dinner, Awards Ceremony, and Dinner Speaker**

**7:00 PM - 10:00 PM**

*Location: Costa Del Sol Ballroom*

**DINNER SPEAKER**

**8:00 PM - 8:20 PM**

**Eric Topol, MD**

Scripps Research

*Introduced by: Eric Klein, MD*

*Cleveland Clinic Foundation*

**PCF AWARDS CEREMONY**

**8:45 PM - 9:30 PM**

**2018 PCF Young Investigator Awards**

**2018 PCF VALor Precision Oncology Center of Excellence Awards**

**2018 Movember Foundation-PCF Challenge Awards**



**2018 PCF Challenge Awards**

**2017 PCF Challenge Awards**

**Sunday, October 28, 2018**

**6:00 AM - 7:30 AM** **Breakfast**

**Location: Costa Del Sol Patio**

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

**GENERAL SESSIONS**

**Location: Costa Del Sol Ballroom**

**SPECIAL LECTURE**

**7:45 AM - 7:55 AM**

**ESMO Hot Points**

**Silke Gillesen, MD**

University of Manchester, UK

*Introduced by Howard Soule, PhD  
Prostate Cancer Foundation*

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

**Discussion**

**Session 7: Translational Research on WNT Signaling in Normal and Tumor Cell Biology**

**8:00 AM - 9:20 AM**

**Moderator: Steven Balk, MD, PhD**

Harvard: Beth Israel Deaconess Medical Center

**8:00 AM - 8:15 AM**

***WNT Signaling in the Development of the Prostate***

**Gail Prins, PhD**

University of Illinois

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

**Discussion**

**8:20 AM - 8:35 AM**

***WNT/ $\beta$ -Catenin Signaling in Prostate Cancer Progression***

**Rachana Patel, PhD**

Beatson Institute for Cancer Research, UK

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

**Discussion**



**Sunday, October 28, 2018**

- 8:40 AM - 8:55 AM ***WNT Signaling Targets in ADT Resistant CRPC***  
**Xin Yuan, MD, PhD**  
Harvard: Beth Israel Deaconess Medical Center
- 8:55 AM - 9:00 AM **Discussion**
- 9:00 AM - 9:15 AM ***APC Modulation of Therapy Resistance in Breast Cancer***  
**Jenifer Prosperi, PhD**  
University of Notre Dame
- 9:15 AM - 9:20 AM **Discussion**

**SPECIAL LECTURE**

**9:20 AM - 9:35 AM**

**Movember Foundation Global Prostate Cancer Landscape Analysis**

**Mark Buzza, PhD**

Movember Foundation

*Introduced by Howard Soule, PhD*

*Prostate Cancer Foundation*

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

**Discussion**

**Session 8: Unlocking Innate Immunity for Cancer Therapeutics**

**9:40 AM - 11:15 AM**

**Moderator: Marco Gottardis, PhD**

Janssen Research & Development, LLC

9:40 AM - 9:45 AM ***Introduction***

**Marco Gottardis, PhD**

Janssen Research & Development, LLC

9:45 AM - 10:00 AM ***Improving NK Cell Immunotherapy for Cancer***

**Martin Felices, PhD**

University of Minnesota

10:00 AM - 10:05 AM **Discussion**

**Sunday, October 28, 2018**

10:05 AM - 10:20 AM ***NK Cell Therapeutics and Possible Implications for Treatment of Prostate Cancer***

**James Trager, PhD**  
NKARTA Therapeutics

10:20 AM - 10:25 AM **Discussion**

10:25 AM - 10:40 AM ***CARISMA: Development of a Macrophage-Based Cancer Therapy***

**Michael Klichinsky, PharmD**  
CARISMA Therapeutics; University of Pennsylvania

10:40 AM - 10:45 AM **Discussion**

10:45 AM - 11:00 AM ***Neutrophil Based Cancer Therapeutics***

**Alex Blyth**  
CEO, LIFT BioSciences Ltd

11:00 AM - 11:05 AM **Discussion**

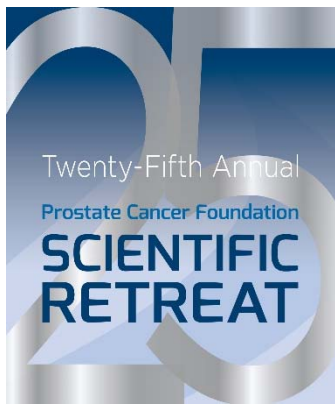
**Closing Remarks**

**11:05 AM - 11:15 AM**

**Howard Soule, PhD**  
Prostate Cancer Foundation  
**Jonathan W. Simons, MD**  
Prostate Cancer Foundation

***Meeting Adjourned***

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



## **Program Committee:**

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

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

**Jonathan W. Simons, MD** (Prostate Cancer Foundation)

**Andrew Armstrong, MD, ScM** (Duke University)

**Steven Balk, MD, PhD** (Harvard: Beth Israel Deaconess Medical Center)

**Paul Frenette, MD** (Albert Einstein College of Medicine)

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

**Susan Halabi, PhD** (Duke University)

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

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

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

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