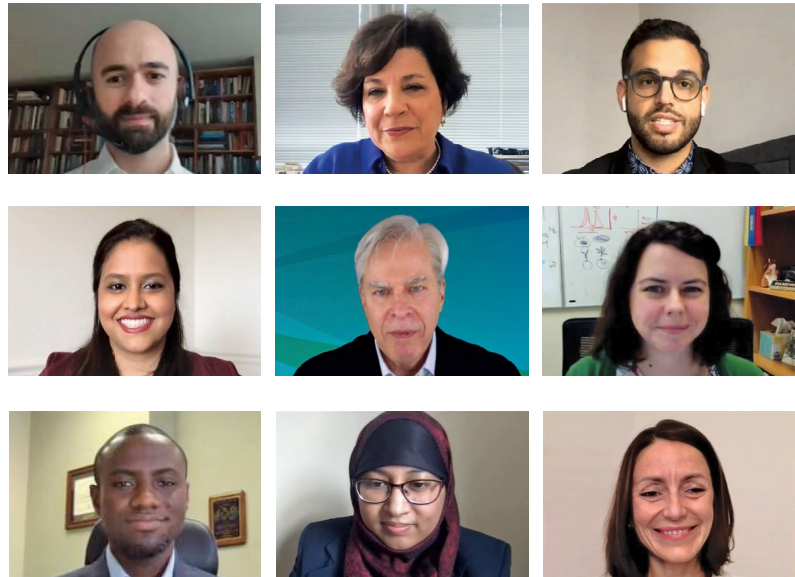


STATE *of the* SCIENCE REPORT

27 Twenty-Seventh Annual Prostate Cancer Foundation SCIENTIFIC RETREAT

VIRTUAL SCIENTIFIC PROGRAM



Highlights from
the 27th Annual
PCF Scientific Retreat
October 22-23, 2020

Provided compliments of the
Prostate Cancer Foundation



Prostate Cancer
Foundation
Curing Together.



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Introduction

The 27th Annual Prostate Cancer Foundation (PCF) Scientific Retreat was the first-ever open-access, global, virtual PCF Annual Scientific Retreat, and was held virtually from October 20-23, 2020. This is the foremost scientific conference in the world focusing on the biology and treatment of prostate cancer. The diversity, novelty, and extremely high impact of the topics presented as well as the diversity and excellence of the invited attendees make this a unique conference.

The Annual PCF Scientific Retreat reflects the unyielding commitment of PCF to ending death and suffering from prostate cancer. This investment by PCF has fostered a collaborative culture unparalleled in any other cancer research area and has accelerated the understanding of prostate cancer biology and the treatment landscape. 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 27th Annual Scientific Retreat featured the following:

- 33 presentations in the Plenary Session including a debate on whether prostate cancer genomic classifiers are ready for use in standard of care clinical practice, and a panel discussion on underlying causes, effects, and solutions surrounding racial and ethnic health care disparities in prostate cancer care and COVID-19
- 185 virtual poster presentations
- 23 different scientific disciplines related to prostate cancer research presented and discussed
- 68% of speakers presented first-in-field, unpublished data at a PCF Scientific Retreat for the first time
- 2,335 individuals from 36 countries registered for the Retreat, including 1,024 PhDs, 457 MDs, 253 MD PhDs, 51 PharmDs, 13 DVMs, 1 DDS, 2 DMDs, 1 DO, 1 OD, 1 DNP, 1 DPM, 1 DC, 7 JDs, 682 with Master's degrees (including MS, MPH, MBA, MA, MHA, MPA, MSN, MMSc, and MSW degrees), 2 PA-Cs, and 4 RNs
- Retreat registrants included 1,576 academic researchers or health care professionals, 66 government researchers or health care professionals, 413 biopharmaceutical industry professionals, 73 representatives from non-profit and other professional health care organizations, 6 private practice health care professionals, 5 media and journalism professionals, 148 patients, survivors, caregivers, advocates or other interested members of the general public, and 27 undergraduate and high school students
- 270 academic institutions, 72 biopharmaceutical companies, and 17 medical research foundations
- NIH, NCI, Dept. of Defense, and Veterans Affairs research leaders
- Attendance by 221 PCF Young Investigators, and 264 researchers who have been on a PCF Challenge Award team
- Attendance by 19 PCF Board of Director members and major donors
- The 5th Annual PCF Women in Science Forum was held with 701 attendees

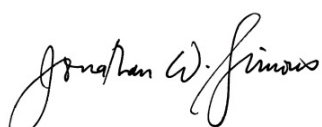
PCF is the world's leading philanthropic organization funding and accelerating prostate cancer research. The PCF “Global Research Enterprise” currently extends to 22 countries and funds a robust research portfolio. Founded in 1993, PCF has raised more than \$865 million and provided funding to more than 2,085 research programs at more than 244 cancer centers and universities. This includes \$65 million awarded to 314 PCF Young Investigators since 2007 and over \$225 million to PCF Challenge Award teams since 2008.

We thank the sponsors of the Retreat for their generous support: Sanofi Genzyme, Janssen, Advanced Accelerator Applications, Amgen, Bayer, Bristol-Meyers Squibb, Clovis Oncology, Daiichi Sankyo, Pfizer, Astellas, AstraZeneca, Foundation Medicine, Genentech, Constellation Pharma, Dendreon, Essa Pharma, and Merck.

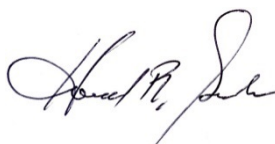
The 2020 State of Science Report was prepared by the Prostate Cancer Foundation to summarize the scientific presentations from the Retreat in order to globally disseminate this knowledge to researchers, clinicians, patients, the public, philanthropists, industry, and other interested stakeholders. We 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 if you have any questions about this Report.

All of the presentations and discussions from the 27th Annual Prostate Cancer Foundation (PCF) Scientific Retreat can be viewed in full here: <https://www.pcf.org/scientific-retreat/27th-annual/video-replays/>

Yours sincerely,

A handwritten signature in black ink that reads "Jonathan W. Simons".

Jonathan W. Simons, MD
President & CEO

A handwritten signature in black ink that reads "Howard R. Soule".

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

A handwritten signature in black ink that reads "Andrea Miyahira".

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

Session 1: Prostate Cancer, Androgens and COVID-19

Regulation and Targeting of SARS-CoV-2 Entry Factors ACE2 and TMPRSS2 in Human Airway Epithelial Cell Subtypes

Arul Chinnaiyan, MD, PhD

University of Michigan; Michigan Center for Translational Pathology

- TMPRSS2 is an androgen-regulated protein that plays a major role in the initiation and progression of prostate cancer in ~50% of patients. TMPRSS2 is a “protease,” an enzyme which functions to cleave portions off of other proteins to alter their functions.
- Recent studies have demonstrated that entry of the coronavirus SARS-CoV-2 into human cells requires two host cell proteins: TMPRSS2 and ACE2. TMPRSS2 cleaves the SARS-CoV-2 Spike protein into a new formation that can bind to ACE2, which allows the virus to firmly attach and get into the cell.
- Preclinical laboratory studies found that the TMPRSS2 inhibitor camostat mesylate can inhibit SARS-CoV-2 entry into cells. This suggests that inhibiting TMPRSS2 or its expression may be an effective treatment for COVID-19.
- This link between SARS-CoV-2 and prostate cancer resulted in a rapid and productive shift by many cancer scientists to work on solutions for the coronavirus pandemic.
- Dr. Arul Chinnaiyan discussed studies on whether sex hormones and their control of SARS-CoV-2 receptors have a role in COVID-19, and whether drugs targeting TMPRSS2 or androgens, including drugs approved in prostate cancer, may have potential as therapies for COVID-19.
- Demographic studies from several countries have found that COVID-19 outcomes are worse in men compared with women. For instance, data pooled from reported cases in Italy, Spain, Germany and Switzerland found that while rates of infection are similar across gender, men have higher rates of hospitalization and death. These data support the hypothesis that male sex hormones may play a role in COVID-19 pathology by increasing levels of TMPRSS2.
- A large epidemiological study in Italy which evaluated over 9,000 SARS-CoV-2-positive patients found that prostate cancer patients undergoing treatment with androgen deprivation therapy (ADT) were less likely to be SARS-CoV-2-positive than prostate cancer patients not undergoing treatment with ADT. This suggests that prostate cancer hormonal treatment, which lowers male hormone levels and the activity of the androgen receptor (AR), may be protective against SARS-CoV-2.
- Another study from Cleveland Clinic however, did not support these findings.
- A study from Spain found that men with androgen-driven alopecia (a.k.a., “male pattern baldness”) had an increased association with hospitalization for COVID-19. A small clinical trial performed in 77 men with androgen-driven alopecia found that anti-androgen treatment appeared to lower COVID-19 infection and hospitalization rates.
- Dr. Chinnaiyan and team evaluated levels of TMPRSS2, ACE2, and AR in healthy human lung tissue using single cell gene expression data.
- There are several types of cells that make up lung tissue including trachea, bronchi, bronchiole, and aveolar cells. TMPRSS2, ACE2, and AR were found to be expressed in all of these cell types, and were highest in aveolar type 2 cells, which are also the cell type highly targeted by SARS-CoV-2 for infection.

- TMPRSS2, ACE2, and AR were also found to be expressed in key lung cell types in mice, including alveolar type 2 cells.
- Castration of male mice resulted in decreased levels of TMPRSS2, ACE2 and AR in mouse prostate cells and lung cells.
- Female mice had lower natural levels of TMPRSS2, ACE2 and AR in lung cells compared to male mice. The levels of these could be increased in female mice by administering testosterone.
- TMPRSS2, ACE2 and AR were also found to be co-expressed (in same cells) in mouse and human lung cells.
- Studies in human tissues found higher levels of AR in lungs from males over the age of 70, compared to females over the age of 70 and to advanced prostate cancer patients treated with hormonal therapy. AR levels in lung tissues were similar in males and females under the age of 70. Levels of TMPRSS2 and ACE2 were not significantly different between human male and female lung tissue.
- Together, these studies suggest that TMPRSS2 and ACE2 may be regulated by androgens in lung tissues as well as prostate cells, particularly in older males.
- Dr. Chinnaiyan and team then tested the effects of treatments targeting AR or TMPRSS2 on SARS-CoV-2 infection in laboratory models.
- Treatment of cells with remdesivir (the recently FDA-approved treatment for COVID-19), camostat (a TMPRSS2 inhibitor), AR-targeted treatments approved for prostate cancer (apalutamide, enzalutamide, and darolutamide), and an experimental AR-degrading treatment (ARD61b) all reduced or prevented SARS-CoV-2 infection (**Figure**). BET bromodomain inhibitors, which block AR signaling, could also block SARS-CoV-2 infection.
- Further studies demonstrated that AR, FOXA1 and BRD4 (a “BET” family protein) are recruited to the gene regulatory “enhancer elements” on the *TMPRSS2* and *ACE2* genes.
- Together, these studies suggest that inhibiting the AR gene regulatory complex (which includes FOXA1 and BRD4) or using therapies targeting AR or BET, will block expression of TMPRSS2 and ACE2, and may be effective at reducing the pathogenesis of SARS-CoV-2.
- Clinical trials to evaluate various AR-targeted therapies and BET inhibitors in COVID-19 patients are underway.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/prostate-cancer-androgens-and-covid-19/>**

AR antagonists inhibit SARS-CoV-2 infection in LNCaP cells

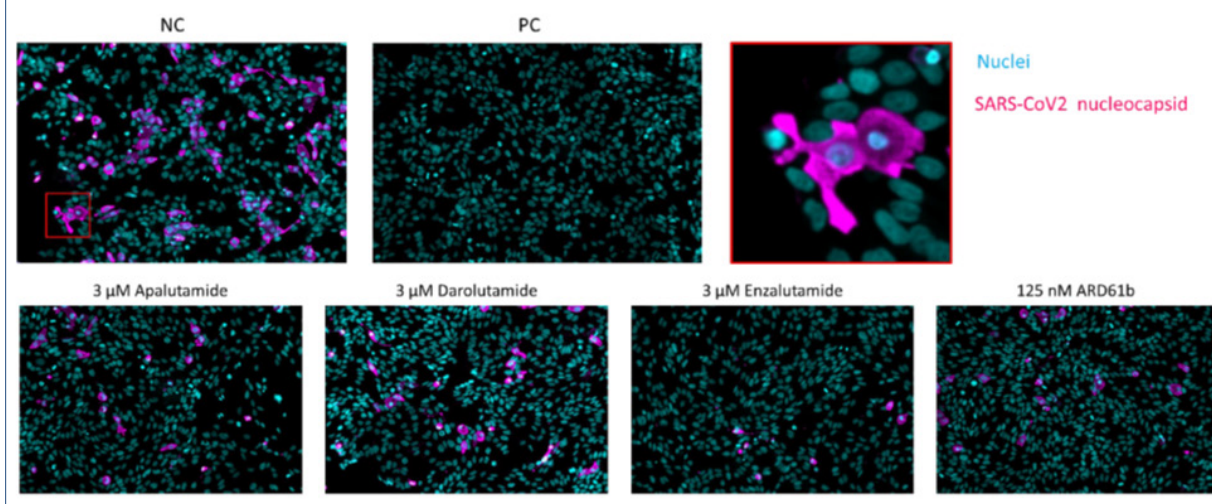


Figure: Treatment of cells with AR-targeted treatments approved for prostate cancer (apalutamide, enzalutamide, and darolutamide), and an experimental AR-degrading treatment (ARD61b) all reduced or prevented SARS-CoV-2 infection. NC = negative control (no treatment); PC = positive control (remdesivir). The pink color indicates cells infected with SARS-CoV-2.

Randomized Clinical Trial of Camostat vs. Placebo in COVID-19 Outpatients

Joseph Vinetz, MD
Yale University

- Dr. Joseph Vinetz discussed an ongoing clinical trial (ClinicalTrials.gov Identifier: NCT04353284) to test camostat mesylate in patients recently diagnosed with COVID-19.
- COVID-19, the disease caused by SARS-CoV-2 infection, can have symptoms including fever, cough, myalgia or fatigue, loss of smell and taste, and other symptoms. In some people, disease progresses to become extremely morbid and lethal, while other people can remain completely asymptomatic yet still transmit the infection.
- Wearing masks reduces transmission and is highly recommended, along with other social distancing measures.
- The natural history of infection has three stages. The first stage (1-6 days) is respiratory illness where patients have high viral loads and some develop pneumonia. The second stage (~6-10 days) is an inter-critical phase, where patients either recover or can progress to respiratory decompensation and viral dissemination to tissues beyond the lungs (10% of patients). Adaptive anti-viral immune responses begin to take effect in this stage. In the third stage, patients have multi-organ infection and can experience acute respiratory distress syndrome (ARDS), shock, disseminated intravascular coagulopathy (DIC), and death.

- Patients with COVID-19 have primarily been managed with supportive care such as oxygen and symptom management. The anti-viral agent remdesivir was FDA-approved in October, 2020, for patients with COVID-19 requiring hospitalization, and can only be administered in a hospital setting. Other anti-viral agents and anti-inflammatory agents are being tested in clinical trials. These treatments are only administered to patients in hospital settings. There are no outpatient treatments (such as pills) yet available for reducing the severity of COVID-19 in infected individuals.
- An ideal new anti-viral drug could be a pill that prevents virus infection and transmission, or treats sick people and reduces disease severity.
- Recent studies have established that the TMPRSS2 enzyme is necessary for infection of human host cells by SARS-CoV-2. Preclinical studies found that SARS-CoV-2 infection can be prevented in cells by the TMPRSS2 inhibitor camostat (**Figure**).
- TMPRSS2 is a protein originally identified and studied in prostate cells, which has a significant role in prostate cancer initiation and progression. This connection between prostate cancer and COVID-19 has resulted in a rapid and impactful shift of cancer researchers to focus on identifying solutions for the COVID-19 pandemic.
- Dr. Joseph Vinetz and team are conducting a clinical trial (ClinicalTrials.gov Identifier: NCT04353284) to test camostat mesylate, a TMPRSS2 inhibitor, in patients who have recently tested positive for SARS-CoV-2 infection. This drug is a pill taken by mouth, and is used for the treatment of pancreatitis in Japan. It has an established safety record.
- This randomized, double-blind, placebo-controlled trial will be performed in two stages, and will compare camostat pills, taken 3 times per day for 7 days, to placebo pills.
- The pilot phase will test whether camostat reduces viral load compared to placebo, in 114 patients. Viral loads in patients will be measured every 2 days by nasal swab or saliva test.
- In the second stage, the trial will determine the impact of camostat vs. placebo on clinical outcomes, including progression of disease symptoms, oxygenation and hospitalization, in 600 patients. Measurements will include daily symptom scores and oxygen measurements using a pulse oximeter.
- Dr. Vinetz and team will also perform correlative studies to evaluate the immune system biology of patients treated with camostat, and to confirm the impact of camostat on TMPRSS2 levels in patient samples.
- The Prostate Cancer Foundation (PCF) is funding some of the correlative studies through a PCF team science “Challenge Award” to Dr. Vinetz and team.
- This trial is ongoing and is open at Yale University in Connecticut.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/prostate-cancer-androgens-and-covid-19/>**

Basics of SARS-CoV-2 (the virus): Identification of a potential drug, **camostat**

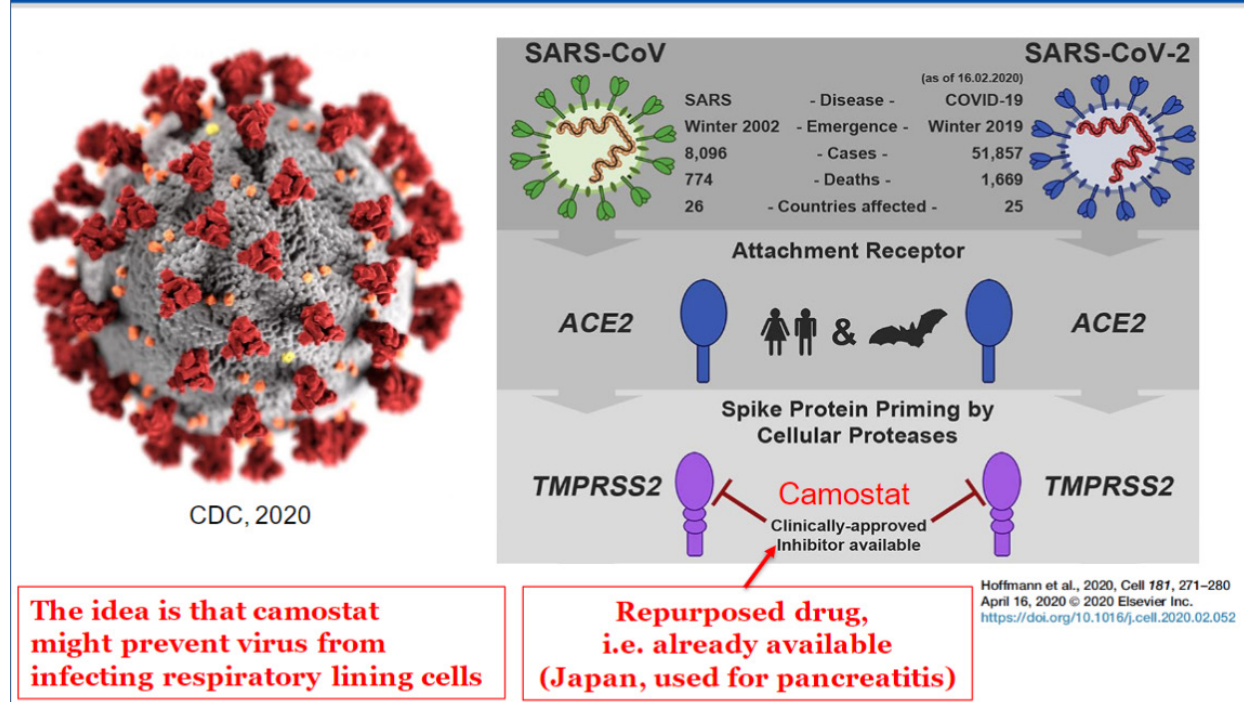


Figure: Entry of the coronavirus SARS-CoV-2 into human cells requires two host cell proteins: TMPRSS2 and ACE2. TMPRSS2 cleaves the SARS-CoV-2 Spike protein into a new formation that can bind to ACE2, which allows the virus to firmly attach and get into the cell. Preclinical studies found that SARS-CoV-2 infection can be prevented in cells by the clinically available TMPRSS2 inhibitor camostat.

Hormonal Intervention for the Treatment of Veterans with COVID-19 Requiring Hospitalization (HITCH)

Matthew Rettig, MD

University of California, Los Angeles; VA Greater Los Angeles Healthcare System

- TMPRSS2 is an androgen-regulated gene that is required for host cell infection by the SARS-CoV-2 coronavirus.
- Targeting TMPRSS2 directly, or blocking TMPRSS2 expression by targeting androgens, may be effective treatments for COVID-19.
- Studies from several European countries and China have found that COVID-19 infection rates are similar in men and women, but outcomes are far worse in men. This includes ~2-fold greater rates of death, and increased rates of hospitalization, ICU rates, and intubation rates in men compared with women.

- These gender differences in COVID-19 outcomes may be related to behaviors, such as smoking, co-morbidities, or to biological factors such as androgen and estrogen levels.
- Together, these data have led to the hypothesis that androgens, which are present at higher levels in men than women, cause higher TMPRSS2 levels and result in enhanced COVID-19 pathology in men compared with women.
- Several observational studies have evaluated the relationship between androgen deprivation therapy (ADT), a standard prostate cancer treatment, and COVID-19 outcomes.
- A study in Italy by M. Montopoli, *et al.* found a significantly reduced incidence of COVID-19 in prostate cancer patients on ADT compared with prostate cancer patients not on ADT and with all cancer patients not on ADT. However, this study had small numbers and no multivariate analysis.
- In contrast, a study by E. Klein, *et al.* found that ADT was not associated with reduced incidence. This study had a larger number of patients and a multivariate analysis. However, it only evaluated tested patients and did not include statistical tests to account for the likelihood of being tested.
- The United States Department of Veterans Affairs (VA) is the largest integrated health care system in the United States. Approximately 9 million Veterans are enrolled in the VA. Approximately 500,000 Veterans are currently living with prostate cancer, of which ~17,000 have metastatic prostate cancer. The VA has the oldest medical record system in the U.S., which is integrated into a database called VINCI.
- Dr. Rettig and team performed a study to evaluate the effects of ADT on COVID-19 incidence amongst Veterans using data from VINCI. This study evaluated 248,264 Veterans tested for SARS-CoV-2, of whom 23,817 were positive. Whether or not Veterans have prostate cancer or are currently on ADT was also determined.
- This study found that Veterans on ADT had a 25% lower risk of testing positive for COVID-19 compared to all Veterans not on ADT, and a 14% reduction in risk of testing positive for COVID-19 compared to Veterans with prostate cancer who were not on ADT. These findings suggest a modest protective effect of ADT from COVID-19 infections.
- Veterans on ADT who tested positive for COVID-19 also had better outcomes than all COVID-19-positive patients not on ADT, including a reduced risk of ICU, ventilation assistance, intubation, and death. These studies suggest ADT reduced COVID-19 disease severity.
- Based on these studies, Dr. Matthew Rettig and team hypothesize that ADT may improve outcomes in men with COVID-19. The protective effects of ADT are hypothesized to be due to either reducing levels of TMPRSS2 and ACE2 (which are regulated by androgens), and/or by reducing immune system suppression caused by androgens.
- Studies by Dr. Rettig's colleagues at UCLA found that AR, TMPRSS2, and ACE2 are expressed together in bronchial and nasosinus cells in male humans and mice. Castration of male mice led to a reduction in TMPRSS2, ACE2, and AR levels in nasosinus cells.
- In addition, castration of male mice also leads to a regrowth of the thymus. The thymus is an important immune organ that produces T cells. The thymus shrinks (involutates) with age, which is attributed in part to the increase of sex steroids at puberty.
- Dr. Rettig and team initiated a prospective randomized phase 2 clinical trial (HITCH; Hormonal Intervention for the Treatment in Veterans with COVID-19 Requiring Hospitalization) to test the efficacy of ADT in Veterans hospitalized with COVID-19 (**Figure**). This trial will enroll ~200 male Veterans admitted to a VA Hospital for COVID-19. Patients will be randomized (2:1) to best supportive care (BSC) plus the ADT treatment degarelix vs. BSC alone. BSC treatments can include remdesivir, convalescent plasma, and dexamethasone (a corticosteroid).

- There are several forms of ADT that are used for treating prostate cancer. Degarelix was chosen for this trial because it is the most rapid suppressor of testosterone levels. Degarelix (an LHRH antagonist) is able to reduce testosterone by 95% within 24 hours and to undetectable levels within 3 days. In contrast, other forms of ADT (LHRH analogs) cause a temporary surge in testosterone levels and take ~2 weeks to suppress testosterone completely. The potent AR-targeting agents enzalutamide and apalutamide take ~1 month to reach a steady state of AR suppression.
- Because COVID-19 is a rapidly progressing disease, it would be important to suppress testosterone and AR as rapidly as possible, and to avoid any surges in testosterone levels.
- The primary objective of the HITCH trial is to determine if degarelix improves clinical outcomes of Veterans hospitalized to an acute care ward due to COVID-19. The evaluated outcomes include mortality, ongoing need for hospitalization, or requirement for mechanical ventilation/extracorporeal membrane oxygenation (ECMO).
- As secondary objectives, the trial will determine if degarelix reduces time to clinical improvement, inpatient mortality, length of hospitalization, duration of intubation for mechanical ventilation, time to achieve a normal temperature, or the maximum severity of COVID-19 illness.
- Correlative studies will also be performed to evaluate whether any inherited genetic factors are associated with outcomes, to evaluate the impact of ADT on levels of TMPRSS2, AR, and ACE2 in nasosinus cells (using a nasopharyngeal swab), and to evaluate the impact of ADT on immune responses to COVID-19.
- A mid-term interim analysis of the primary endpoint will be performed when 99 randomized patients complete or are terminated from the study.
- This study is ongoing, and is actively enrolling patients at VA hospitals in Los Angeles, Puget Sound (Seattle), Brooklyn and Manhattan, Philadelphia, Houston, Phoenix, Dallas, Memphis, Miami, Charleston, Little Rock, Tampa, and Long Beach. 13 patients had been enrolled at the time of this presentation.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/prostate-cancer-androgens-and-covid-19/>**

Trial Schema

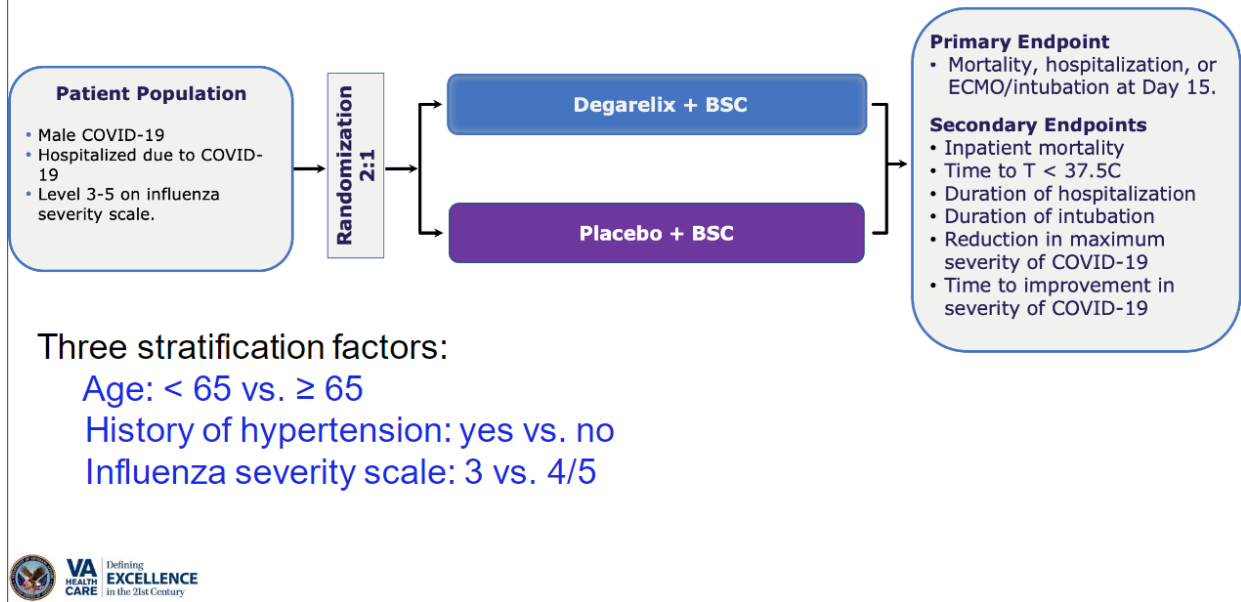


Figure: The HITCH Trial schematic. This trial will enroll ~200 male Veterans admitted to a VA Hospital for COVID-19. Patients will be randomized (2:1) to best supportive care (BSC) plus the ADT treatment degarelix vs. BSC alone.

Session 2: Circulating DNA Methylation Biomarkers for Diagnosis, Prognosis, and Treatment Selection

Using 5-hydroxymethylcytosine Sequencing to Interrogate Biological Drivers of Advanced Prostate Cancer

Martin Sjöström, MD, PhD
University of California, San Francisco

- Although cancer is thought of as a genetic disease, prostate cancer typically has a relatively low number of genomic alterations that result in mutated proteins. In addition to genomic alterations, cancers can also be altered at the epigenetic level.
- Epigenetics is the regulation of gene expression by chemical alterations on DNA that affect its 3D structure. Epigenetics include the addition or removal of chemical groups that affect how “open” or “closed” a region of DNA is, and thus how accessible the genes in that region are to gene expression machinery.
- Epigenetic alterations result in altered levels of expressed genes (proteins and RNAs) that can drastically change the biology of a cell. Epigenetic signatures can be used to indicate gene expression levels.
- Epigenetics are also stable and “heritable,” meaning that as cells divide, their epigenetics are also replicated in the daughter cells.
- Because RNA, DNA, proteins, and other molecules released from dying tumor cells can be found in the blood, studies on tumor biology can now be done using “liquid biopsies” (blood draws). Researchers are working to establish liquid biopsies to assess tumor biology and assist in clinical decision making, in order to avoid the need for invasive tumor biopsies.
- Dr. Martin Sjöström discussed studies to map the landscape of epigenetic alterations in prostate cancer and develop these data into clinical biomarkers.
- DNA methylation is a major type of epigenetic modification, in which methyl groups are chemically linked to cytosine (C) DNA nucleotides (**Figure**). Methylated cytosine nucleotides are called “5-methyl-cytosine” (5mC), and are associated with tightly closed DNA and repressed gene expression. 5mC can be further modified by oxidation of the methyl group, forming “5-hydroxy-methyl-cytosine” (5hmC), which re-opens the DNA region and is associated with active gene expression. The 5hmC site can also be converted back to an un-methylated cytosine.
- The PCF West Coast Prostate Cancer Dream Team (WCDT) previously performed a series of detailed studies on 100 metastatic castration resistant prostate cancer (mCRPC) biopsies, including whole genome RNA sequencing, whole genome DNA sequencing, and whole genome bisulfite sequencing. This series of studies has greatly expanded knowledge of prostate cancer genomics and molecular biology and is an important resource for prostate cancer researchers.
- As a part of the WCDT study, Dr. Sjöström and colleagues performed 5hmC sequencing on these tumor samples. This method provides a genome-wide map of DNA sites which have 5hmC epigenetic modifications.
- 5hmC signatures from mCRPC were compared with 5hmC data from localized prostate cancer. This comparison found that mCRPC had higher 5hmC levels in key mCRPC drivers compared with localized prostate cancer, suggesting that oncogenes gain 5hmC.

modifications, which allows them to be expressed at higher levels during progression to mCRPC. Tumor suppressor genes conversely had the opposite pattern (lower 5hmC levels in mCRPC).

- The genes that mapped to the highest increases in 5hmC levels in mCRPC compared with localized prostate cancer were involved in cellular programs including development and de-differentiation.
- Dr. Sjöström also discussed studies to evaluate whether 5hmC signatures can be used as a biomarker of prostate cancer biology.
- Gene expression levels were found to correlate with 5hmC levels in gene bodies, and to negatively correlate with 5mC levels in gene promoters. Overall, 5mC may function like an “on/off” switch of gene expression, while 5hmC is responsible for fine-tuning gene expression levels. 5hmC and 5mC patterns together were highly predictive of gene expression levels. Androgen response genes were the most highly correlated with these methylation signatures in prostate cancer cells.
- Prior studies have found that levels of tumor DNA in the circulation (in liquid biopsies) correlate with tumor burden and are prognostic for patient outcomes.
- Dr. Sjöström and colleagues performed 5hmC profiling on liquid biopsy samples from a cohort of 64 mCRPC patients. 5hmC levels were found to predict the levels of prostate cancer content in cell-free DNA, and was prognostic for overall survival.
- A biomarker consisting of high 5hmC signatures on critical prostate cancer oncogenes and low 5hmC signatures on tumor suppressor genes was also highly prognostic of patient outcomes. 5hmC signatures on certain tumor oncogenes could also identify patients with a subset of highly aggressive mCRPC.
- Together, these studies demonstrate that 5hmC signatures are a strong indicator of gene activation in advanced prostate cancer, and have potential as biomarkers of prostate cancer burden and patient outcomes.
- Efforts are ongoing to optimize and validate 5hmC signatures as clinical biomarkers that can be used to predict patient outcomes and inform treatment selection.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/circulating-dna-methylation-biomarkers/>**

5hmC is an epigenetic modification associated with active transcription

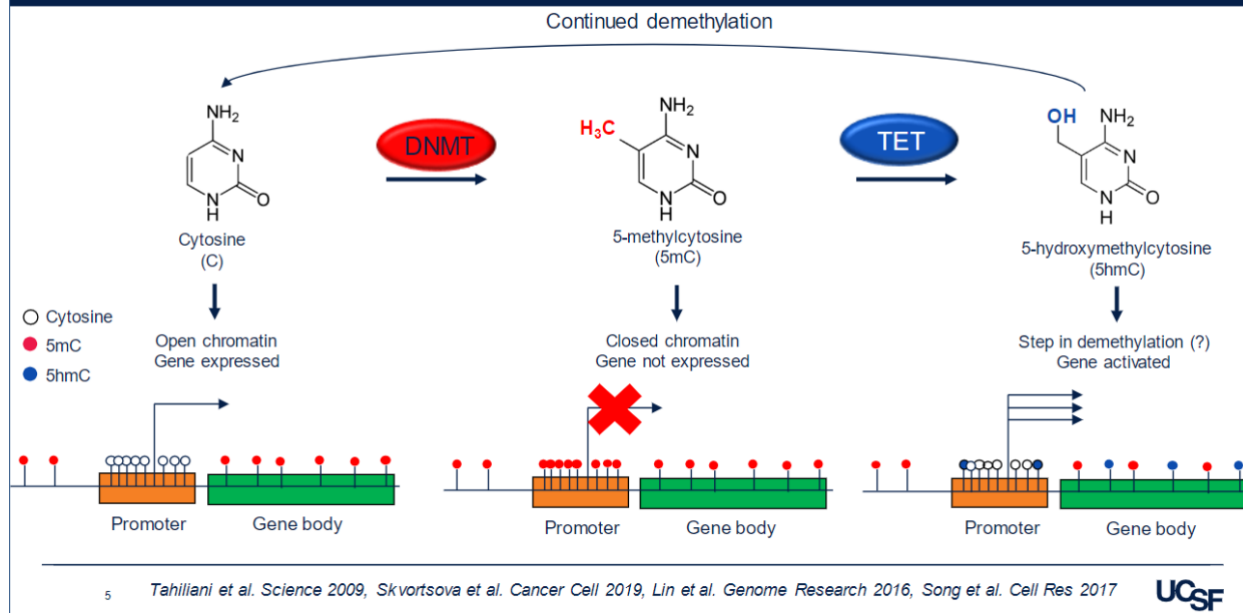


Figure: DNA methylation is a major type of epigenetic modification, in which methyl groups are chemically linked to cytosine (C) DNA nucleotides (Figure). Methylated cytosine nucleotides (5mC) are associated with tightly closed DNA and repressed gene expression. 5mC can be further modified by oxidation of the methyl group, forming 5hmC, which re-opens the DNA region and is associated with active gene expression. 5hmC can also be converted back to an un-methylated cytosine.

Opportunities for Tracking the Prostate Cancer Methylome in Plasma

Gerhardt Attard, MD, PhD

University College London Cancer Institute, UK

- The immune system has the powerful potential to detect and kill cancer cells, yet anti-tumor immune responses are often suppressed in patients with progressive cancer.
- Epigenetics is a major mechanism that enables cells to control which genes encoded in DNA can and cannot be expressed. Epigenetics consist of chemical modifications to DNA that affect its 3D structure and control whether the DNA region is “closed” or “open”. Open DNA is accessible to gene expression regulators while closed DNA cannot be accessed and the genes in that region are inactivated.
- Alterations in a cell’s epigenetic landscape greatly impact the cell’s functions and behaviors. Epigenetic alterations commonly drive cancer progression. The epigenetic landscape of prostate cancer cells is an important field of study, as it provides insights into tumor biology, and may also be useful as biomarkers to predict the cancer’s clinical behavior.

- A patient's tumor biology is classically studied using biopsy or surgical samples. More recently, it has been established that tumors release their contents into the bloodstream, allowing researchers to study tumor biology using simple blood draws (a.k.a. "liquid biopsies"). For instance, tumor mutations can be identified by sequencing the DNA found in patient plasma, as some of that DNA is from tumor cells.
- Dr. Gerhardt Attard and team have been working to establish a liquid biopsy test that can assess tumor biology, and be used as a biomarker to predict clinical outcomes, inform precision medicine treatment selections, and measure disease progression and treatment responses.
- This team has found that liquid biopsy studies using tumor epigenetic profiles are more informative biomarkers compared to tumor mutational profiles.
- Dr. Attard presented a study which compared tumor genomic profiles (using targeted and whole genome DNA sequencing) to epigenetic (DNA methylation) profiles from liquid biopsies from patients with metastatic castration resistant prostate cancer (mCRPC).
- The mCRPC patients analyzed in this study were starting either abiraterone or enzalutamide treatment. Plasma samples were obtained from the patients prior to starting treatment and at the time of disease progression on treatment. Approximately half of the patients had been treated previously with docetaxel.
- The type of epigenetic modifications assessed in this study were DNA methylation profiles. DNA methylation, in which a methyl chemical group is added to a DNA nucleotide, results in "closed" DNA and inactivates the genes in that region.
- The tumor DNA methylation status in mCRPC samples was found to strongly correlate with the tumor DNA fraction (the proportion of DNA in the liquid biopsy sample that came from tumor cells vs non-tumor cells) (**Figure**).
- A tumor DNA methylation signature ("ct-Meth-Sig") which strongly correlated with tumor DNA fraction was developed, using the most highly methylated and most highly unmethylated tumor genes.
- The most highly methylated genes in mCRPC included a set of epigenetic regulators named polycomb repressor complex 2 (PRC2), as well as genes that are typically regulated by PRC2.
- The ct-Meth-Sig tumor DNA methylation signature was found to include both prostate cancer-specific DNA methylation patterns as well as normal prostate cell-specific DNA methylation patterns. Thus, methylation signatures from mCRPC DNA could easily be distinguished from methylation patterns from non-tumor cell DNA in the blood.
- Tumor DNA methylation signatures were identified that defined unique mCRPC subtypes. One signature was enriched for unmethylated DNA regions near androgen receptor (AR) binding sites. This suggests that this mCRPC subgroup is driven by high AR activity. AR is a major driver of prostate cancer, and functions to control the expression of genes important for prostate cell growth and survival.
- One challenge to liquid biopsies, is that it is difficult to accurately assess tumor mutations when there are low levels of tumor DNA in blood. This is because one circulating DNA molecule may contain only a single mutation, DNA from normal tissues can also carry mutations, and because some tumors do not carry mutations that are easily assessed by DNA sequencing.
- Tumor DNA methylation is a better approach, particularly in patients with a low tumor burden, as a single circulating DNA fragment can carry many methylation alterations, and the methylation patterns found in prostate cancer have a distinct pattern compared to normal cells. Thus, tumor DNA methylation has better sensitivity for detecting prostate cancer signatures using liquid biopsies.

- Studies are ongoing to develop validated tumor DNA methylation signatures and technologies that can be used in the clinic for improving precision medicine for prostate cancer patients.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/video/circulating-dna-methylation-biomarkers/>

Principal component 1 highly correlates with genomically determined tumour fraction

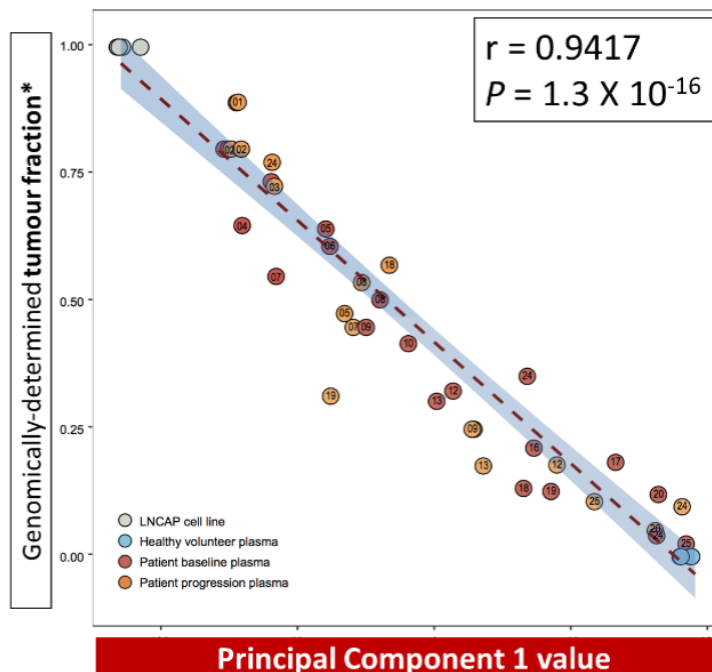


Figure: Tumor DNA methylation status strongly correlated with tumor DNA fraction in mCRPC liquid biopsy samples. Source: *J Clin Invest.* 2020;130(4):1991-2000.

Circulating Methylation Biomarkers for Neuroendocrine Prostate Cancer Differentiation

Francesca Demichelis, PhD

University of Trento, Italy

- Prostate cancer growth and survival is in part driven by and dependent on signals received from male hormones (androgens such as testosterone) transmitted by the androgen receptor (AR).
- The androgen receptor (AR) is the primary driver of prostate cancer, and functions to turn on genes that are critical to prostate cell growth and survival. Androgen deprivation therapies (ADT) have been a cornerstone of treatment for advanced prostate cancer for decades.
- Unfortunately, most tumors eventually develop resistance to ADT as well as more potent forms of AR-targeted therapy (including abiraterone, enzalutamide, apalutamide, and darolutamide) and continue to progress to lethal disease.
- Prostate cancer that has developed resistance to ADT is commonly known as “castration-resistant prostate cancer” (CRPC).
- While a large number of CRPC cases remain driven by AR pathway alterations, ~15-20% of CRPC are no longer driven by AR. Mechanisms that contribute to the development of AR-independent CRPC include activation of alternate/bypass cellular programs that cause the cells to no longer rely on AR for growth and survival, selection of resistant clones during treatment, and lineage plasticity which enables transition to alternate cell phenotypes.
- Small cell/neuroendocrine prostate cancer (SC-NEPC) is a highly aggressive form of AR-independent CRPC. SC-NEPC differs from “typical” adenocarcinoma-type CRPC (Adeno-CRPC), in that it has lost prostate epithelial cell features, and gained features of small cells and/or neuroendocrine cells. There are currently no effective treatments for SC-NEPC.
- The diagnosis of SC-NEPC currently relies on examination of metastatic tumor biopsies by a pathologist. However, metastatic tissue biopsies are invasive and not all patients have access to clinical settings capable of performing metastatic biopsies. Furthermore, tumor heterogeneity can result in biopsies sampling some but not all phenotypes present in a tumor.
- Dr. Francesca Demichelis discussed studies to develop a liquid biopsy test to diagnose and study SC-NEPC.
- Liquid biopsies are tests that use blood samples, which contain tumor cells and tumor cell contents such as DNA and RNA, to assess tumor biology.
- To develop a liquid biopsy test, a study was performed which evaluated matched tumor tissue and liquid biopsy samples from patients with metastatic prostate cancer. Included were patients with hormone-naïve metastatic prostate cancer, Adeno-CRPC, and SC-NEPC. For some patients, metastatic biopsies were obtained from different metastatic tumor sites, and/or samples were obtained at different times during the clinical course.
- Samples were evaluated by whole exome sequencing to evaluate tumor genomic alterations and whole genome bisulfite sequencing to evaluate epigenetic alterations across the genome.
- In some patients, there were no differences in genomic alterations found in metastases taken from different tissue sites from the same patients, including liquid vs. tissue biopsies (**Figure**). In other patients, both shared and unique alterations were seen in tissue vs. liquid biopsy samples, indicating differences in representation of tumor sub-clones.

- A prostate cancer DNA methylation signature was developed using data from tissue biopsies. This signature could successfully identify and predict levels of tumor DNA in plasma. Overall, DNA methylation alterations found in tumor tissue and plasma were highly similar.
- Interestingly, SC-NEPC cases had unique DNA methylation signatures compared to Adeno-CRPC, which could be observed using either tissue or liquid biopsy samples. Intermediate signals could be seen in patients who had a mixed phenotype (both SE-NEPC and Adeno-CRPC).
- This data suggests that SC-NEPC has unique genomic and DNA methylation features, and these can be identified using plasma samples from patients.
- Dr. Demichelis and colleagues developed a SC-NEPC “genomic-methylation score”, which combines alterations found from genomic and epigenetic sequencing. This score can be used to identify patients who have SE-NEPC vs. Adeno-CRPC, using a liquid biopsy.
- Challenges that remain to be overcome with liquid biopsy assays include those posed by tumor polyploidy. This phenomenon, in which tumor cells progressively gain altered numbers of chromosomes, makes it more difficult to determine exact changes in gene copy numbers (especially gene losses) using plasma.
- Another challenge, is that patients with low tumor burden can also have low levels of tumor DNA in plasma.
- The team is currently working to improve the sensitivity and specificity of the genomic-methylation score and validate this as a non-invasive liquid biopsy test to diagnose mCRPC patients who have developed SE-NEPC.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/video/circulating-dna-methylation-biomarkers/>

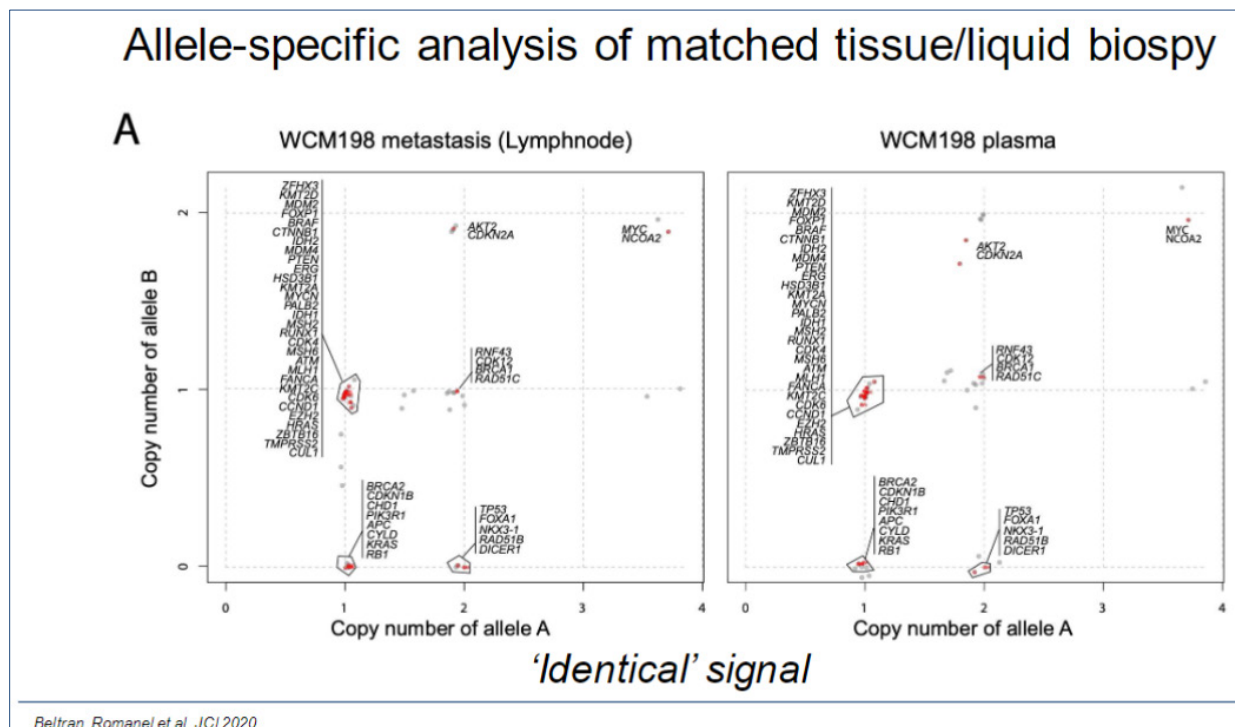


Figure: An example of a patient with identical genomic alterations in tissue (a lymph node metastasis) and plasma (liquid) biopsy samples.

SPECIAL LECTURE: Dual Functions of SPOP and ERG Dictate Androgen Therapy Responses in Prostate Cancer

Jean-Philippe Theurillat, MD
Institute of Oncology Research, Switzerland

- Prostate cancer is a heterogeneous disease. Comprehensive genomic sequencing efforts have enabled the identification of several molecular subtypes, characterized by distinctive genomic alterations.
- Dr. Jean-Philippe Theurillat discussed studies on the biology of the driver mutations of certain prostate cancer molecular subtypes.
- Approximately 50% of prostate cancers harbor *TMPRSS2-ERG* fusions. This fusion brings the ERG oncogene under the control of the androgen receptor (AR), resulting in high levels of ERG.
- Another ~10% of prostate cancer cases have point mutations in the protein SPOP, which inactivate its function.
- Interestingly, *TMPRSS2-ERG* fusions and *SPOP*-inactivating mutations are almost never seen together in the same prostate cancer. Previous studies suggested this “mutually exclusive” relationship was due to a functional redundancy by these alterations, in which SPOP mutations were thought to stabilize ERG and thereby increase its levels. However, this finding was not validated in later studies.
- To understand the mutual exclusivity of *TMPRSS2-ERG* fusions and *SPOP* mutations, Dr. Theurillat and team created tumor cell lines containing either alteration or both.
- In this study, both *TMPRSS2-ERG* fusions and SPOP mutations alone could drive formation of mini-tumors (“organoids”) in the laboratory, though with different physical characteristics.
- However, tumor cells with both alterations stopped growing and were unable to form organoids.
- In a separate assay, if the second alteration was put into tumor cell lines that had the other alteration, they were no longer able to form tumors in mice. If tumors with both alterations were treated with ERG-inhibitors, they began to slowly grow again.
- This data suggests that *TMPRSS2-ERG* fusions and SPOP mutations have an antagonistic relationship and together are incompatible with cell growth.
- Prior studies on human tumor tissues have found that tumors with *TMPRSS2-ERG* fusions have low levels of AR signaling, while tumors with SPOP mutations have high levels of AR signaling. Normal SPOP acts to promote AR degradation, while SPOP-mutations stabilize AR.
- The gene expression profiles of prostate tumors with *TMPRSS2-ERG* fusions vs. SPOP mutations were compared and found to be very different.
- AR and ERG are both “transcription factors,” which control gene expression programs by driving expression of certain genes and repressing expression of others.
- Dr. Theurillat and team found that SPOP-inactivating mutations, when added to prostate cancer cells, resulted in higher levels of AR activity and reduced ERG activity. Higher levels of AR activity were observed as higher levels of AR-driven genes and lower levels of AR-repressed genes. Reduced ERG activity was observed as lower levels of ERG-driven genes and higher levels of ERG-repressed genes.
- AR and ERG can also together drive expression of certain genes, including cell cycle arrest and senescence (anti-growth) genes.

- This data suggests that SPOP-inactivating mutations and *TMPRSS2-ERG* fusions are incompatible because together they would cause high activity of AR that overrides the repressive function of ERG on cell cycle arrest and senescence genes, resulting in an arrest of cell growth.
- In other words, normal SPOP appears to be required for the growth of tumors driven by ERG. This hypothesis was supported by the data that tumors with *TMPRSS2-ERG* fusions had higher levels of normal SPOP than other tumor subtypes.
- Dr. Theurillat and team then explored the hypothesis that SPOP-inactivating drugs could prevent growth of prostate tumors driven by *TMPRSS2-ERG* fusions. When mice with *TMPRSS2-ERG* fusion-driven tumors were treated with a SPOP-inhibiting drug, tumor growth was significantly reduced (**Figure**).
- AR is the primary driver of prostate cancer and AR-targeted therapies are the primary treatment for patients with advanced disease. However, most tumors eventually develop resistance to AR-targeted therapies and will continue to progress to castration resistant prostate cancer (CRPC).
- Tumors with SPOP-mutations however, appear to be more sensitive to standard androgen deprivation therapy (ADT) than other molecular prostate cancer subtypes.
- Clinical trials have also been exploring bipolar androgen therapy (BAT) as a treatment in patients with CRPC. BAT therapy is a treatment method in which androgen levels are alternated between being extremely high and extremely low. Approximately 1/3 of CRPC patients have had good responses with this treatment in clinical trials.
- Dr. Theurillat found that ERG-driven prostate cancer cells were highly sensitive to high androgen levels. This suggests that patients with ERG-driven prostate cancer may benefit from BAT therapy.
- In summary, this study defined the molecular basis for incompatibility of SPOP-inactivating mutations and *TMPRSS2-ERG* fusions in prostate cancer, and suggests that SPOP-inhibitors or BAT therapy may be promising treatments for prostate cancer with *TMPRSS2-ERG* fusions and high expression of the ERG oncogene.
- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/dual-functions-of-spop-and-erg-dictate/>

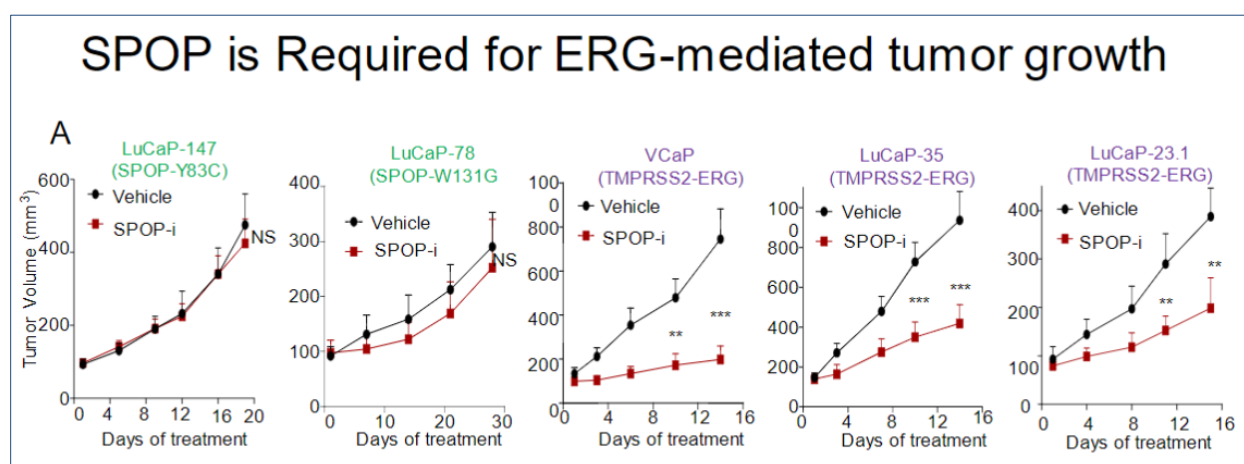


Figure: An example of a patient with identical genomic alterations in tissue (a lymph node metastasis) and plasma (liquid) biopsy samples.

SPECIAL LECTURE: A Community Resource of Genetically-Engineered Mouse Models that Recapitulate the Phenotypic Spectrum of Prostate Cancer

Cory Abate-Shen, PhD
Columbia University Irving Medical Center

- Dr. Cory Abate-Shen discussed the development of a series of prostate cancer genetically-engineered mouse models (GEMMs) as an available resource for the cancer research community.
- Dr. Abate-Shen and colleagues have generated a series of GEMMs that have genetic alterations in different critical prostate cancer pathway genes, in order to study the full spectrum of prostate cancer disease phenotypes in the context of a native tumor microenvironment in a whole organism. Tumors cells from these GEMMs can also be extracted and studied in other types of assays, including as allografts (grown as tumors in mice with different genetic backgrounds) and grown as mini tumors (“organoids”) in the laboratory. Together, these GEMMs provide a whole toolkit for molecular and co-clinical studies.
- Due to challenges in cost, infrastructure and time-consuming institutional regulatory processes, it would be difficult to establish GEMMs as a research community resource within Dr. Abate-Shen’s lab alone.
- To make these GEMMs available to the entire cancer research community as needed, Dr. Abate-Shen has partnered with Jackson Laboratories (JAX), an independent, 501(c)3 nonprofit biomedical research institution that maintains and provides more than 11,500 strains of genetically defined mice for the global biomedical research community. JAX will now house and provide these prostate cancer GEMM mice for any researchers who wish to order them.
- The GEMMs developed by Dr. Abate-Shen harbor prostate-specific genetic alterations, in which the genetic alteration can be specifically induced only in prostate epithelial cells. Researchers choose when to induce the alterations by administering tamoxifen, which triggers the genetic recombination event. Additionally, cells which undergo the alteration will also express a marker gene to enable visualization and lineage tracing.
- Dr. Abate-Shen’s mice all carry the *NKX3.1*^{CreERT2+/-} alteration, which triggers replacement of the *NKX3.1* gene with the Cre enzyme on one allele, only in prostate cells. Loss of one copy of *NKX3.1* results in development of low-grade prostatic intraepithelial neoplasia (PIN), a precursor to prostate cancer. Because *NKX3.1* is only expressed in prostate cells, these mice also now express the Cre enzyme only in prostate cells. When these mice additionally have any genes that are engineered to be placed between “flox” sites, the Cre enzyme will delete those genes in prostate cells when tamoxifen is administered.
- Dr. Abate-Shen’s mice additionally have a *PTEN*^{flox/flox} alteration, which enables deletion of the *PTEN* tumor suppressor gene by Cre and results in the development of prostate cancer.
- The series of mouse models also enable a variety of different additional alterations in oncogenes and tumor suppressor genes that are commonly seen in patients, such as *BRCA2* and *p53*.
- These allow modeling of different prostate cancer disease phenotypes including a range of grade/aggressiveness (**Figure**), neuroendocrine prostate cancer (NEPC), and phenotypes which metastasize with varying degrees to different body organs including a new model which metastasizes to the bone. This resource allows researchers to also study specific

prostate cancer genotypes, including identification of possible treatments for patients with similar genetic alterations.

- Dr. Abate-Shen presented results from a study on a new prostate cancer GEMM model which metastasizes to the bone. By comparing tumor cells from the bone metastasis and the primary tumor, a gene expression signature that is highly enriched in human bone metastases was identified. This signature was also significantly associated with a more rapid time to metastasis and time to treatment failure in patients.
- Dr. Abate-Shen, in collaboration with Dr. Andrea Califano, have also developed a cross-species bioinformatics approach to identify master regulators of prostate cancer in GEMMs, and match these with patients whose tumors are driven by the same master regulators. These models can then be used in drug screening tests to identify treatments that may be effective for the matching patient. An example was presented in which four possible treatments were identified for an individual patient in the drug screening test, all of which were effective in the GEMM model.
- Overall, this “Oncoloop” strategy, is a generalizable method to “match” patients with predicted drugs and then evaluate the response in real time, demonstrating the clinical value of these GEMM models.
- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/mouse-models-that-recapitulate/>

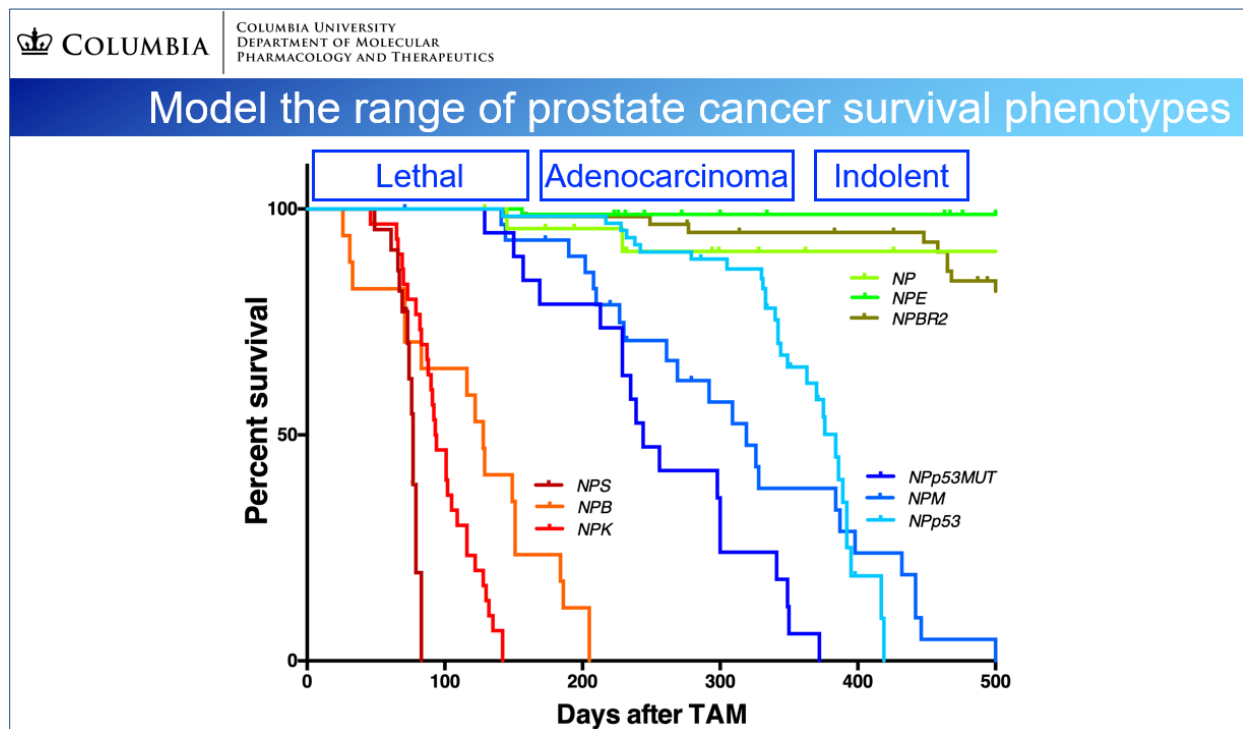


Figure: Dr. Shen’s GEMM models represent a range of prostate cancer phenotypes with different aggressiveness, including forms that are rapidly lethal (red/orange), adenocarcinoma that are eventually lethal (blue), and indolent (green). The graph indicates the percentage of the different GEMM mice that remain alive after the genetic alteration is triggered by tamoxifen (TAM) administration.

SPECIAL LECTURE: The Genomic Evolution of Prostate Cancer

Paul Boutros, PhD, MBA
University of California, Los Angeles

- Localized prostate cancer is a heterogeneous disease, and can present as a range of disease phenotypes, from a slow growing “indolent” disease that will not ultimately cause clinical complications, to those that are highly aggressive and ultimately lethal.
- The ability to distinguish indolent from aggressive disease when it is still localized will aid greatly in directing more appropriate treatment decisions, including which patients can have less intensive treatments vs. which patients need more intensive treatment. Biomarkers to accomplish this are an urgent clinical need.
- Dr. Paul Boutros discussed studies to identify the genomic drivers of prostate cancer, determine when in disease history they arose, and determine the contribution of inherited (germline) genes to prostate cancer development and progression. One critical question under investigation is the evolutionary timing of the key genomic alterations that transform an indolent prostate cancer cell into one with lethal potential.
- To evaluate the genomic landscape of localized prostate cancer, Dr. Boutros and team performed whole genome sequencing on tumors from a cohort of 666 patients with localized disease.
- Different types of genomic alterations were assessed, including point mutations (a single nucleotide change in a coding region of a gene), indels (mutations that insert nucleotides or delete a segment of a gene), genomic rearrangements (different segments of chromosomes rearrange by fusing to one another), and copy number losses and gains (genes are deleted or multiplied, respectively).
- Approximately 55% of primary prostate tumors had between 100-1,000 point mutations and only 0.6% had 1,000 or more point mutations. Almost 50% of primary prostate tumors had no detectable copy number gains and ~10% had no detectable copy number losses in the initiating tumor cells, although more of these alterations were later gained in tumor subclones.
- When the numbers and types of mutations were evaluated based on tumor grade, it was found that low grade tumors had very few mutations and high-grade tumors had the highest numbers of mutations (**Figure**).
- The numbers of tumor driver gene alterations also increased with tumor grade, ranging from 3-4 driver mutations in ISUP grade group 1 (indolent) tumors to 10-11 driver mutations in ISUP grade group 5 tumors (**Figure**).
- By combining the total number of tumor alterations and tumor driver alterations, Dr. Boutros and team were able to identify seven “integrated molecular” subtypes of localized prostate cancer.
- To determine when tumors evolved different mutations, samples from several regions in the primary prostate tumor were sequenced and compared. An example was presented in which 9 different tumor regions from one patient were compared, and each region had a different number of mutations.
- It is surprisingly common for an individual prostate to have multiple independent tumors growing. These observations have led to the hypothesis that the prostate environment is highly conducive to tumor initiation and progression. Hypoxia, a lack of sufficient oxygen in the microenvironment, may be one mechanism that contributes to tumor development in the prostate, as it can promote DNA damage.

- A “hypoxia score” was determined for each tumor sample based on RNA abundance of hypoxia-response genes.
- Tumors with high hypoxia scores tended to have higher levels of “chromothripsis,” a phenomenon of chromosomal shattering, in which extremely high levels of chromosomal rearrangements have occurred.
- High hypoxia scores were also associated with intraductal carcinoma (IDC) a prostate tumor sub-histology that is associated with poorer outcomes.
- Tumors with both high hypoxia scores and an IDC sub-histology were more likely to be visible on MRI imaging.
- A global crowd-sourcing challenge was held, where teams were invited to develop algorithms that could use this data to build a tumor evolutionary tree, to identify how different tumor regions from a single prostate were related to one another, and at what time in disease history they arose.
- Some index (originating) tumors were found to be monoclonal, meaning all the tumor cells in the sample had the same mutations. Other index tumors were polyclonal, meaning multiple subclones carrying different mutations were present in the sample.
- Patients with monoclonal tumors had less aggressive disease and better clinical outcomes than patients with polyclonal tumors. Tumors with the highest levels of polyclonality were associated with the poorest outcomes.
- Another study evaluated the relationship between germline genetics and tumor evolution.
- *BRCA2* is a DNA repair gene, in which germline alterations are known to increase risk for prostate cancer. To study the role of germline *BRCA2* alterations in tumor evolution, primary prostate tumors from 19 patients with germline *BRCA2* alterations were genomically sequenced. Many differences were found when these were compared with tumors that did not have germline alterations. For example, tumors with germline *BRCA2* alterations had a higher frequency of *MYC* oncogene mutations, and lower frequency of *NKX3.1* mutations.
- In a different study, the presence of germline prostate cancer risk single nucleotide polymorphisms (SNPs) were found to be associated with an increased level of epigenetic alterations in tumor samples. Overall, over 12,000 epigenetic alterations were found to be strongly associated with germline prostate cancer risk SNPs. Epigenetic alterations were preferentially located in gene enhancer regions, and appear to regulate gene expression levels.
- A subset of germline prostate cancer risk SNPs was prognostic for patient outcomes.
- Altogether, Boutros and colleagues have created an atlas of mutations in localized prostate cancer, and have identified when certain mutations arise in tumor evolution, how they impact disease aggressiveness, and how they are impacted by germline genetics.
- Ongoing studies are evaluating the function of these mutations, validating their potential as biomarkers, and studying the associations between tumor mutations and gene expression.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/genomic-evolution-of-prostate-cancer/>**

Higher Grade = More Mutations + More Drivers

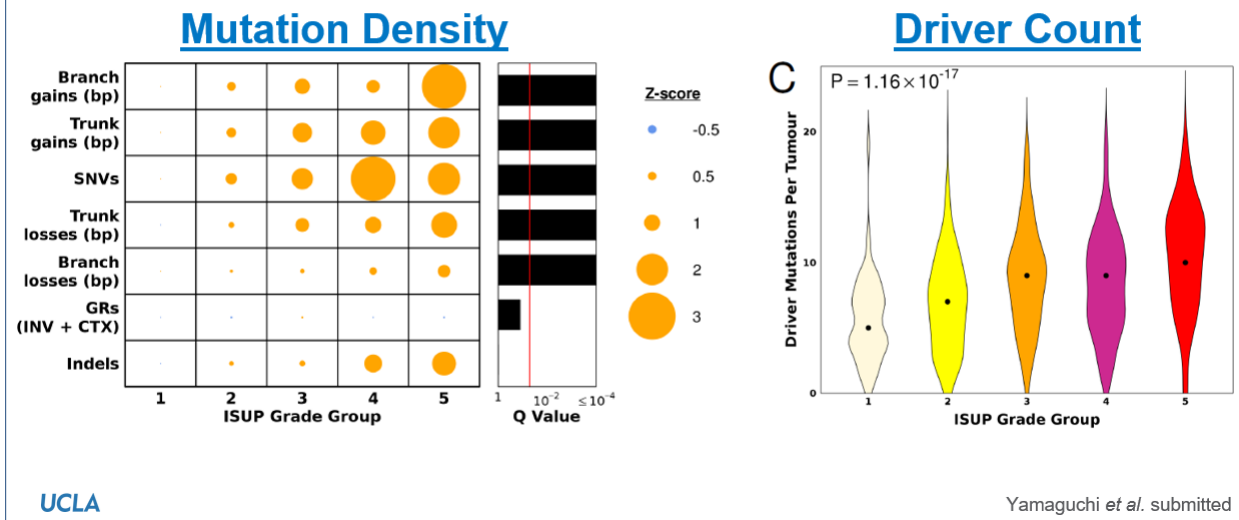


Figure: The numbers of all types of mutations (left) and tumor driver gene alterations (right) correlated with ISUP tumor grade; low grade tumors had very few alterations and high-grade tumors had the highest numbers of mutations.

DEBATE: Prostate Cancer Genomic Classifiers; Are We Ready for Prime Time?

Moderators:

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

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

Speakers:

Pro: Daniel Spratt, MD (University of Michigan)

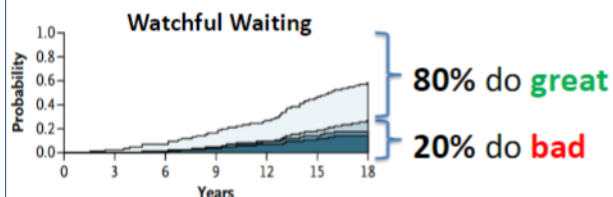
Con: Daniel Lin, MD (University of Washington)

- Dr. Felix Feng and Dr. Rana McKay moderated a debate on whether prostate cancer genomic classifiers are ready for use in standard of care clinical practice. Dr. Daniel Spratt debated the pro argument, and Dr. Daniel Lin debated the con argument.
- Prostate cancer genomic classifiers, such as Prolaris®, Oncotype DX®, and Decipher® are tests which evaluate expression levels of a few dozen genes (17-31 for the three tests mentioned above) that aim to stratify patients with localized prostate cancer for certain treatment decisions. These include decisions on initial therapy at diagnosis and whether or not salvage therapy is necessary following initial therapy.
- The issues discussed and debated included whether the biomarker has a sufficient level of evidence for its use, whether it was developed using appropriate data (were development and validation tests performed in the same patient populations the biomarkers are to be used in), whether the tests significantly improve prognostic accuracy over clinical and pathologic prognosticators alone, whether there is an impact on clinical decision-making, and financial cost considerations.
- Drs. Spratt and Lin each presented an opening argument and a rebuttal argument.
- The audience was polled on their stance on the clinical readiness of prostate cancer genomic classifiers before and after the talks.
- **The full debate can be watched here:** <https://www.pcf.org/scientific-retreat/video/prostate-cancer-genomic-classifiers/>

This is imprecise medicine...our patients deserve better.

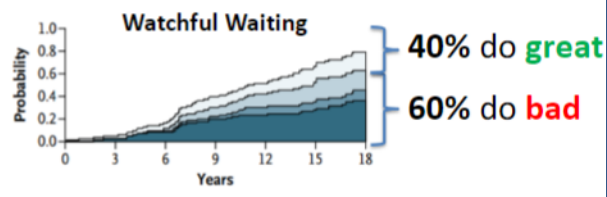
Low enough to do nothing?

LOW RISK



High enough to justify all the toxicity for all men?

HIGH RISK



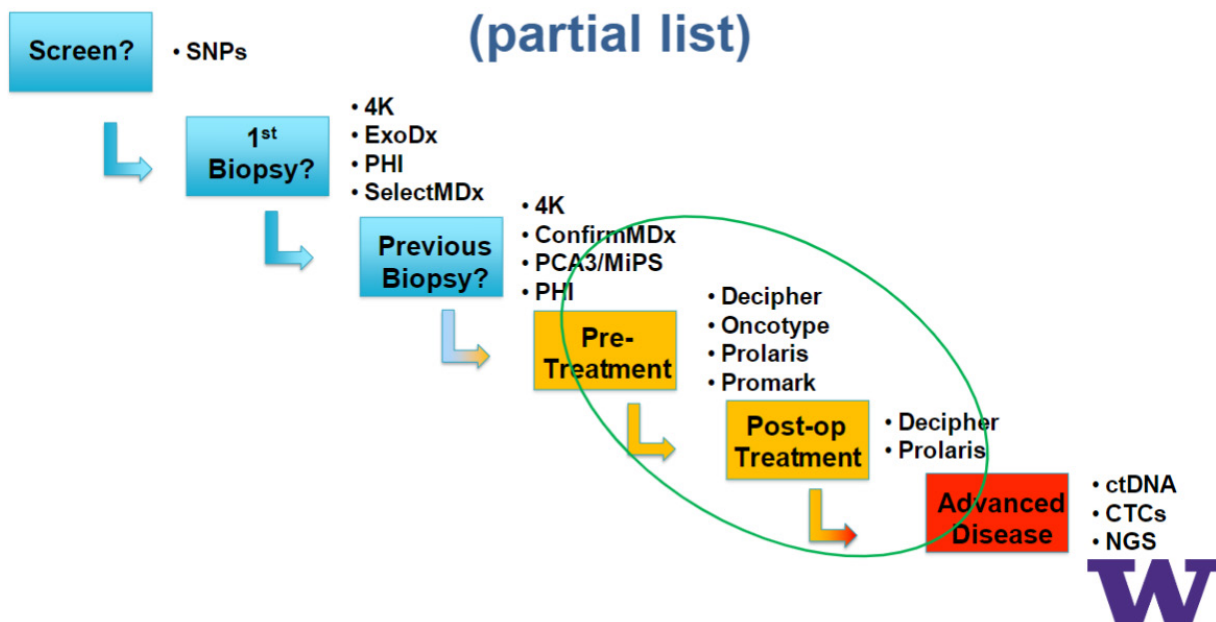
■ Death from prostate cancer ■ Other cause of death, with metastases ■ Other cause of death, with androgen-deprivation therapy ■ Other cause of death, without androgen-deprivation therapy

SPCG-4

RADIATION ONCOLOGY

M MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Prostate Cancer “Candidate” Biomarkers (partial list)



Session 3: Targeting MYC, the Emperor of Oncoproteins

MYC and the Tumor Immune Microenvironment

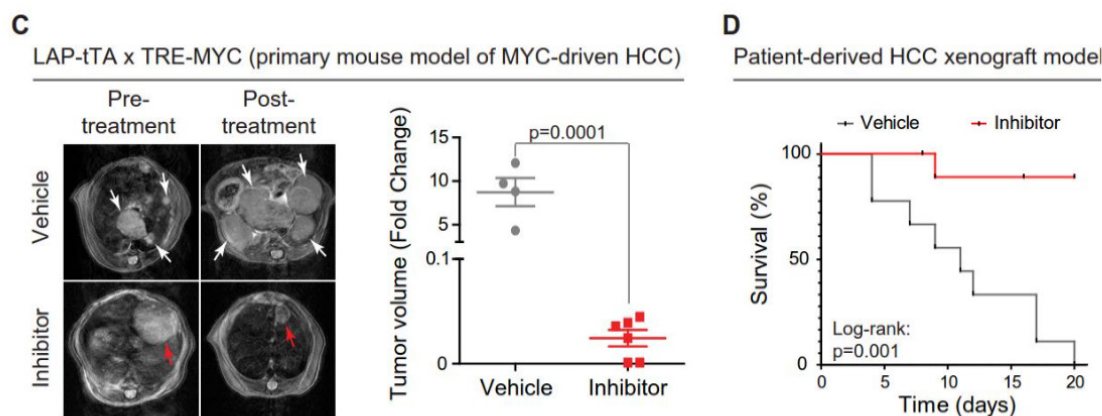
Dean Felsher, MD, PhD
Stanford University

- Oncogenes are normal proteins that when altered (by gaining excessive activity or altered functions), drive the development of cancer.
- MYC is a protein that controls cell growth and division, and is the most important oncogene known, driving an estimated 70% of all cancers.
- Dr. Dean Felsher discussed research on the role of MYC in cancer and its potential as a therapeutic target.
- MYC is a transcription factor (a protein which turns on and off the expression of certain genes), and normally regulates the expression of many genes involved in many cellular processes. Dysregulated MYC, however, turns on all known critical cancer promoting pathways.
- “Oncogene addiction” is a hypothesis that cancers driven by an oncogene are highly dependent on sustained activity of that oncogene for continued growth. Oncogene addiction has been demonstrated for MYC: in preclinical studies, briefly turning off MYC can lead to sustained tumor regression. Thus, constant MYC activity is required for continued growth of MYC-addicted cancers.
- Dr. Felsher and others have recently shown that the MYC oncogene can also regulate the immune system. Cancers that are addicted to MYC also rely on MYC’s effects on the immune system, which allow cancer cells to evade and prevent anti-tumor immune responses.
- Dr. Felsher’s laboratory has developed a series of genetically engineered mouse cancer models in which MYC can be turned on and off, to promote tumor growth or regression, respectively.
- Dr. Felsher and colleagues have found that MYC directly regulates immune responses. MYC was found to increase expression of the immune “checkpoint” proteins PD-L1 and CD47, which turn off immune responses.
- MYC was also found to suppress the activity of natural killer (NK) cells, and prevent NK cells from entering tumors. NK cells are a type of immune cell that target and kill cells infected with pathogens and cancer cells. Turning MYC off in experimental models resulted in NK cell infiltration of tumors and caused tumors to be sensitive to NK cell immunotherapy.
- The role of MYC in the regulation of other immune cell types is under investigation.
- Typical drug development strategies have been unsuccessful in developing drugs that effectively target MYC. This has prompted researchers to look for novel ways to target MYC in cancer.
- A CRISPR gene knockout study was performed to identify proteins that when targeted, would kill specifically MYC-driven cancer cells but not non-MYC-driven cancer cells. Over 100 proteins were identified that may be promising therapeutic targets for MYC-driven cancers. Over 50 of these could be targeted by existing drugs that were not known to be cancer drugs. Several of these proteins were validated as promising therapeutic targets in

preclinical MYC-driven tumor models (**Figure**). Ongoing work is seeking to further develop and validate these drugs as cancer therapies.

- Studies into the biological function of MYC can also reveal strategies for targeting MYC-driven cancers. MYC is a regulator of cell metabolism, including lipid metabolism. Targeting lipid metabolism was found to limit growth of MYC-driven cancer. A novel small molecule was identified that targeted lipid metabolism and had efficacy in MYC-driven liver cancer models.
- Dr. Felsher and colleagues are also developing new technologies to identify novel anti-cancer drugs and measure their effects in very small specimen sizes.
- Dysregulated MYC also can lead to other diseases, including cardiovascular disease, autoimmune diseases, stem cell disorders, and neurological disorders. Thus, treatments that target MYC may be effective in many diseases beyond cancer.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/video/targeting-myc/>

MYC Pathway Screen: Drug Induces Regression of Liver Cancer



Li, Deutzmann et al, *in revision*

Stanford University

Figure: A CRISPR gene knockout study identified promising new therapeutics for MYC-driven cancers. Molecular imaging scans (left) and measured size (right) of tumors before and after treatment with a novel drug (“inhibitor”) vs. placebo (“vehicle”). Right: Survival times of mice with MYC-driven tumors that were treated with the drug vs. placebo.

Advances in MYC Therapeutic Targeting in Cancer

Rosalie Sears, PhD

Oregon Health & Science University

- The MYC protein is the most notorious cancer oncogene, being involved in the development and progression of ~70% of all cancers.
- Dr. Rosalie Sears discussed research on the biology of MYC in cancer and the development of novel MYC-targeting drugs.
- MYC is a transcription factor, meaning it regulates the expression of certain genes by binding to gene regulatory regions on DNA and recruiting enzymes that transcribe the gene into RNA. MYC works in partnership with another transcription factor, MAX.
- Importantly, the genes turned on by MYC-MAX comprise all of the pathways known to be important in cancer. These include cell growth, division, and proliferation, cell differentiation, cell adhesion and motility, metabolism, angiogenesis (new blood vessel development), and immune evasion.
- MYC has been shown to not only drive cancer cells themselves, but also affects the tumor microenvironment, including promoting tumor blood vessel growth and immune cell exclusion. In preclinical studies, turning MYC off reversed all of these activities, demonstrating that MYC is a promising target for cancer therapies.
- MYC protein activity is regulated by environmental signals. These activate cell signaling pathways that phosphorylate MYC, stabilizing it, and activating its ability to bind DNA. Additional downstream signaling pathways destabilize MYC and cause it to be degraded. However, these downstream signaling pathways are often turned off in cancer, allowing MYC to remain in its stabilized active form.
- The enzymes involved in MYC activation include the PIN1 phosphorylation-directed proline isomerase. Isomerases are enzymes that cause structural rearrangements of other molecules. Dr. Sears and colleagues demonstrated that phosphorylation and PIN1-mediated isomerization of MYC boosts its ability to bind to DNA. Mutant versions of MYC that lack the PIN1 recognition phosphorylation site could no longer be regulated by PIN1, and were much weaker at binding DNA.
- Dr. Sears further demonstrated that the PIN1-MYC interaction happens at specific sites in the cell's nucleus, adjacent to nuclear pore sites. These location-dependent activities were important in driving expression of gene programs involved in rapid responses to environmental signals and critical cancer pathways.
- MYC has proven difficult to directly target with drugs. Recent strategies instead focus on targeting factors required for its activity, either by preventing MYC gene expression, or by targeting factors that regulate MYC activation or stability (**Figure**).
- Dr. Sears' lab is developing therapeutics that can reactivate the downstream signaling pathways that destabilize MYC and cause it to be degraded. These include PP2A-activators and PIN1-inhibitors.
- PP2A is an enzyme that promotes MYC degradation. PP2A is normally turned down in cancer.
- A novel small molecule, DT061, which can bind and activate PP2A was developed by colleagues. DT061 caused PP2A to promote MYC degradation, and caused MYC levels to drop in cancer cells.
- DT061 treatment significantly suppressed tumor growth and increased the survival times of mice with pancreatic and triple-negative breast cancer.

- DT061 treatment in mouse cancer models also improved anti-tumor immune responses and demonstrated synergy in combination with checkpoint immunotherapy (anti-PD-L1).
- The MYC-activating isomerase PIN1 is another promising target for anti-cancer therapeutics. Mice genetically engineered to lack PIN1 show a dramatic suppression of tumorigenesis.
- Dr. Sears has shown that PIN1-inhibitors prevent tumor growth and prolong survival of mice with cancer.
- Colleagues of Dr. Sears have recently developed a novel PIN1-inhibitor, sulfopin, and demonstrated this was able to block MYC-driven tumor initiation and growth in mouse models.
- Ongoing work is aiming to further develop these novel therapeutics for MYC-driven cancers.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/video/targeting-myc/>

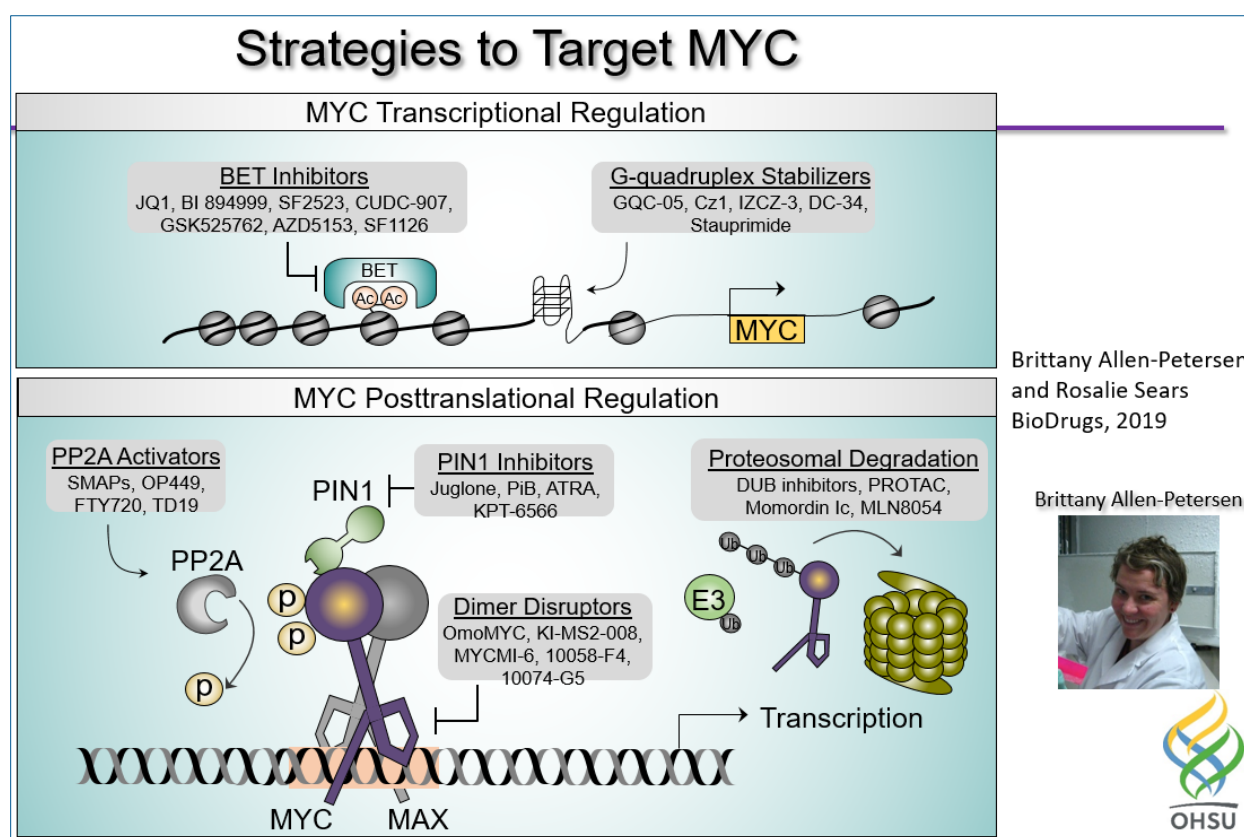


Figure: Left: Strategies to target MYC include targeting factors required for its activity, either by preventing MYC gene expression (BET-inhibitors, G-quadruplex stabilizers), or by targeting factors that regulate MYC activation or stability (PP2A-activators, PIN1-inhibitors, activators of MYC proteosomal degradation, and MYC-MAX dimer disruptors). Figure source: Allen-Petersen, B.L. and Sears, R.C., BioDrugs 33, 539–553 (2019).

N-Myc as a Driver of Lineage Plasticity in Advanced Prostate Cancer

David Rickman, PhD
Weill Cornell Medicine

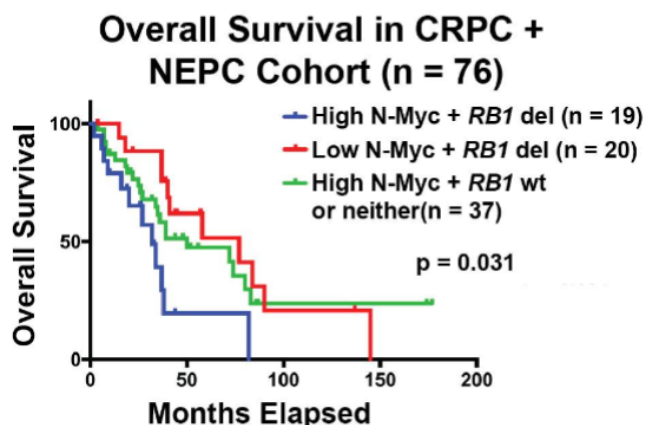
- The androgen receptor (AR) is the primary growth and survival factor for normal prostate and prostate cancer cells. Hence, AR-targeted therapies are the cornerstone of treatment for advanced prostate cancer. Unfortunately, resistance to AR-targeted therapies and progression to castration resistant prostate cancer (CRPC) is common and can occur through several mechanisms.
- One such mechanism is “lineage plasticity,” in which the prostate cancer cells lose dependency on AR by reprogramming their phenotype into that of other cell types which do not need AR for growth and survival, such as neuroendocrine cells. This reprogramming proceeds through epigenetic alterations.
- Epigenetics is a major form of gene expression regulation that is responsible for how our bodies have many different cell types, despite having the same genome. Epigenetics works by adding and subtracting chemical modifications on DNA that affect its 3D conformation, which determines which genes can and cannot be accessed and expressed in that cell.
- Dr. David Rickman discussed the role of N-MYC in driving lineage plasticity in the progression of CRPC to neuroendocrine prostate cancer (NEPC). NEPC is highly aggressive and currently untreatable.
- Dr. Rickman previously showed that N-MYC is increasingly expressed during progression to NEPC. CRPC cases with high levels of N-MYC had worse prognosis than those with low N-MYC levels.
- *RB1* is a critical tumor suppressor gene that is deleted in a subset of prostate cancer and is associated with worse prognosis.
- CRPC patients with both high levels of N-MYC and *RB1*-deletion had shortest survival times, compared to those with low N-MYC levels and/or intact *RB1* (**Figure**).
- Dr. Rickman and colleagues created a series of genetically engineered mouse models to study the role of N-MYC and *RB1* in progression of prostate cancer to CRPC and NEPC. These mice were engineered to lack the tumor suppressor gene *PTEN* in prostate cells, leading to prostate cancer development. Additionally, mice were engineered to overexpress N-MYC and/or have *RB1*-deleted in their prostate cells.
- In these models, prostate tumors that overexpressed N-MYC had low levels of AR-regulated genes, even when AR was present. N-MYC was found to interact with epigenetic regulators on AR-regulated genes, causing epigenetic alterations which turned those genes off (thereby preventing AR from turning them on).
- Castration (orchiectomy) is a surgical method to remove the testes, which are the major source of androgens in the body, and was a common treatment for prostate cancer patients prior to the advent of AR-targeted therapies.
- Castration of prostate cancer mouse models resulted in more aggressive tumors with lower percentages of cells that expressed AR. Prostate cancer cells from castrated mice had higher levels of N-MYC activity and higher expression levels of neural-lineage genes. N-MYC was found to directly turn on neural-lineage genes in prostate cancer cells grown in the absence of androgens.
- “Bivalent” genes are those which contain both activating and repressive epigenetic modifications. In this state they are “off”, but are poised to be turned on upon removal of the repressive modification.

- N-MYC was found to regulate a large number of bivalent genes, many of which are from the neural lineage.
- Mice with N-MYC-high/*RB1*-loss tumors had the most aggressive disease and shortest survival times, similar to what is seen in patients. These mice frequently developed NEPC and all had lung and liver metastases.
- Mice with N-MYC-high/*RB1*-loss tumors were also resistant to treatment with castration (androgen removal). Tumors from these mice were often heterogeneous, having both areas of typical adenocarcinoma and of NEPC. NEPC tumors from these mice had similar gene expression programs as NEPC tumors from patients.
- Analyses of individual cells from N-MYC-high/*RB1*-loss tumors identified those with an NEPC phenotype and gene expression program. NEPC cells also had a distinct epigenetic signature compared with typical prostate adenocarcinoma cells.
- Interestingly, these studies identified two subtypes of NEPC cells with different epigenetic and gene expression patterns in N-MYC-high/*RB1*-loss tumors. Ongoing studies are seeking to determine how these NEPC subtypes are related.
- Comparison of tumors from N-MYC-high/*RB1*-loss tumors vs N-MYC-high/*RB1*-intact tumors revealed that when *RB1* was deleted, N-MYC bound to approximately twice the number of genes. These additional genes included epigenetic regulators and neuroendocrine genes. These also included genes expressed in both NEPC subpopulations.
- Altogether, these studies suggest that N-MYC has different functions in different contexts. N-MYC acts to downregulate AR activity when *RB1* is present. When *RB1* is lost, N-MYC gains additional functions, including driving expression of neuron-lineage genes and progression to aggressive NEPC.
- The team is now studying whether any of the N-MYC regulated genes in NEPC may be promising as therapeutic targets.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/targeting-myc/>**

N-Myc induction and *RB1* loss is associated with poorer prognosis

**CRPC + NEPC Patient
N-Myc and *RB1* Status**

n = 76	<i>RB1</i> deletion YES	<i>RB1</i> deletion NO
N-Myc High	19	19
N-Myc Low	20	18



Himisha Beltran, MD

Figure: CRPC patients with high levels of N-MYC and *RB1*-deletion have the shortest survival times, compared to those with low N-MYC levels and/or intact *RB1*.

Small-Molecule MYC Inhibitors

Sarki Abdulkadir, MD, PhD
Northwestern University

- The MYC protein is one of the most important oncogenes in human cancer, driving the development and progression of ~70% of all cancers.
- MYC is a transcription factor, and together with its protein partner MAX, turns on all of the pathways necessary for cancer development and progression. MYC also functions to prevent anti-tumor immune responses.
- MYC would be an ideal target for cancer therapeutics. However, because of its unconventional and disorganized structure, MYC has proven difficult to target using standard drug development approaches. There are no approved direct MYC inhibitors.
- Dr. Sarki Abdulkadir discussed novel strategies for developing MYC inhibitors.
- A computer algorithm was used to estimate the ability of small molecules to bind to MYC, based on the profiles of ~30 compounds with validated MYC-binding capability. Using this algorithm, an “in silico” screen was performed to evaluate the structures of 35 million compounds and identify those with MYC-binding potential.

- Approximately 70 promising compounds were rapidly screened in laboratory experiments for MYC-binding, inhibition of MYC activities, pharmacokinetics, and toxicology properties. Chemistry was performed to create over 500 variations of the most promising compounds and determine if any had improved MYC-inhibitory and pharmacokinetic properties.
- ~85% of MYC-inhibitors that were highly active in laboratory assays were inactive in mouse tumor models. This is likely caused by unfavorable pharmacokinetics, poor tumor penetration, and other issues.
- Using this strategy, Dr. Abdulkadir generated a series of ~25 highly promising novel small molecule MYC-inhibitors. These were able to bind to MYC in cells, disrupt the interaction between MYC and MAX, inhibit MYC activity, and promote MYC degradation. These inhibitors had favorable pharmacokinetic properties, were effective in blocking tumor growth, and were tolerable, in mouse tumor models (**Figure**).
- These inhibitors also were effective against N-MYC, a MYC family protein which drives the development of neuroendocrine prostate cancer (NEPC).
- The MYC-inhibitors could also activate anti-tumor immune responses in mice. Treatment with MYC-inhibitors increased tumor infiltration with immune cells (T cells and NK cells). MYC-inhibitors also increased levels of the immune suppressive protein PD-L1.
- MYC-inhibitors were found to cause “immunogenic” tumor cell death (a form of cell death which activates immune responses). In laboratory assays, as tumor cells died following treatment with MYC-inhibitors, they upregulated several immune activating signals, including calreticulin, HMGB1, and ATP.
- These data suggest that synergy may be achieved by combining MYC-inhibitors with checkpoint immunotherapy. Indeed, synergy was observed in mouse tumor models treated with the MYC-inhibitor and the checkpoint immunotherapy anti-PD1.
- Overall, Dr. Abdulkadir and colleagues have developed novel MYC-inhibitors which exhibit potent activity in cell lines and in mouse models, have good pharmacology and tolerability in mice, and have synergy in combination with checkpoint immunotherapy.
- Ongoing preclinical work is being done in preparation for testing these inhibitors in clinical trials.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/targeting-myc/>**

MYCi361 inhibits MYC-driven Prostate Cancer in vivo

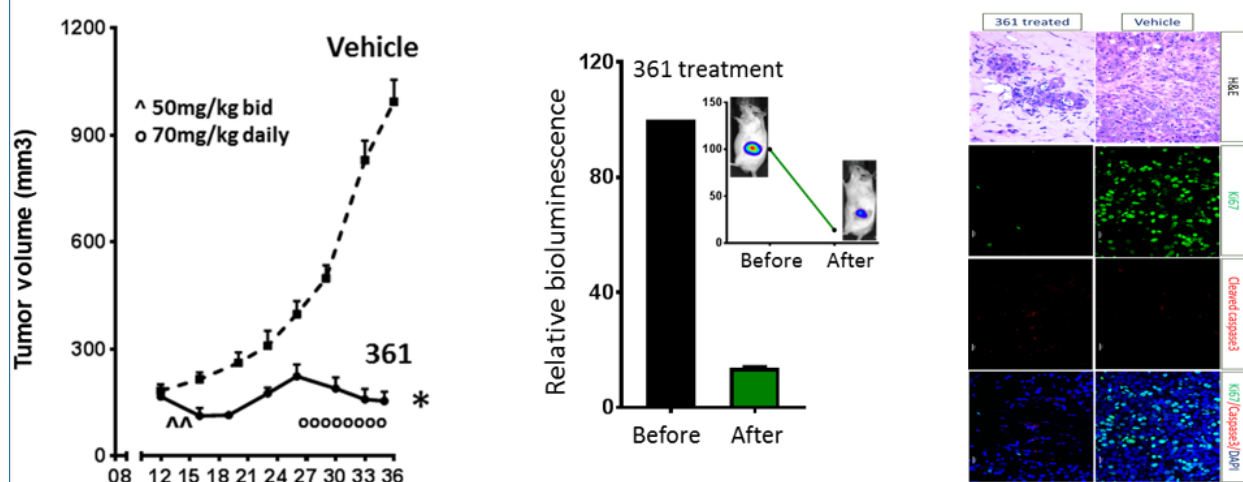


Figure: A novel small molecule MYC-inhibitor, MYCi361, was effective in blocking tumor growth in mouse tumor models. Left: The size of tumors treated with MYCi361 vs control (vehicle) was measured over time. Center: Tumor cells in this model expressed a luminescent protein that allowed quantitative visualization by molecular imaging. Right: Pathology examinations found fewer tumor cells (H&E), with lower cell division rates (Ki67), in tumors from mice treated with MYCi361 vs control.

SPECIAL LECTURE: Current Challenges in Treatment of Patients with Metastatic Prostate Cancer

Himisha Beltran, MD

Harvard: Dana-Farber Cancer Institute

- Prostate cancer affects millions of men worldwide. Despite advances in prostate cancer treatment, metastatic prostate cancer remains a leading cause of cancer deaths globally.
- In the U.S., prostate cancer is the second leading cause of cancer deaths in men, causing approximately 33,000 deaths each year.
- Recent exciting new progress in metastatic prostate cancer care includes the establishment of new standard of care therapies (androgen deprivation therapy (ADT) plus next generation AR-targeted therapies or docetaxel), advances in genomics, and advances in molecular imaging.

- There are now three FDA-approved precision medicines for metastatic CRPC (mCRPC) patients who have specific genomic alterations. Because of these approvals, tumor sequencing will become routine for many patients.
- Pembrolizumab is a checkpoint immunotherapy that has been approved for patients with metastatic solid tumors who have no other standard treatment options, and whose tumors have either mutations in mismatch repair (MMR) genes, microsatellite instability (MSI), or high tumor mutational burden (TMB-high).
- In 2020, two new precision medicines were FDA-approved for patients who have certain genomic alterations: the PARP-inhibitors olaparib and rucaparib.
- Olaparib is a PARP-inhibitor approved for mCRPC patients with germline (inherited) or somatic (tumor) mutations in certain DNA repair genes, who have previously been treated with second generation AR-targeted therapy.
- Rucaparib is a PARP-inhibitor approved for mCRPC patients with germline or somatic mutations in the DNA repair genes *BRCA1* and *BRCA2*, who have previously been treated with second generation AR-targeted therapy and taxane chemotherapy.
- These achievements have resulted in many more treatment choices for patients (**Figure**). Still, biomarkers are needed to identify the best treatment for each patient at each treatment decision.
- Clinical decisions that would benefit from biomarkers include the choice of AR pathway inhibitor vs. docetaxel for castrate sensitive prostate cancer, optimal sequencing of approved drugs for castration resistant prostate cancer (CRPC), patient selection for targeted therapies or immunotherapy, early detection of treatment resistance, and the design of rational combination therapies.
- Many precision medicines are being tested in clinical trials for patients with specific tumor mutations. These include treatments for patients with PTEN-loss (ipatasertib + abiraterone), CDK12-loss (immunotherapy), AKT mutations (AKT inhibitors), AR mutations or amplifications (taxanes vs. second generation AR-targeted therapy), loss of several tumor suppressor genes (platinum chemotherapy), and tumors with high PSMA expression (PSMA-targeted radionuclide therapy).
- Despite these advances, no cures have yet been established for patients with metastatic prostate cancer.
- A major challenge of developing effective precision medicines for prostate cancer is tumor heterogeneity. While there are a number of commonly occurring genomic alterations against which precision medicines are being developed, there are also many genomic alterations that are present in less than 5% of patients (a “long tail” of mutations). Little is yet known about the role these mutations play in driving disease progression and treatment resistance, and their potential as therapeutic targets or biomarkers. Additionally, little is known about the biology and clinical impact of co-occurring mutations and non-genomic drivers and resistance pathways.
- Exceptional responses – when patients experience deep and/or long-term tumor regression – remain rare, but offer opportunities for gaining insights into how to improve precision medicine for all patients.
- Dr. Beltran presented an example of a patient who exhibited an exceptional response to the checkpoint immunotherapy ipilimumab. The patient was an African American male who previously failed multiple lines of therapy including abiraterone, docetaxel, and PSMA-targeted radionuclide therapy. The patient was enrolled on a clinical trial for ipilimumab and thereafter experienced a dramatic drop in PSA levels and improvement in symptoms. The patient has gone for almost 2 years with no evidence of progression. Molecular analysis of the patient’s tumor revealed no genomic alterations in genes expected to cause sensitivity to

checkpoint immunotherapy (MMR, MSI or hyper-mutations), and no mutations in *AR*, *PTEN* or DNA repair genes. The patient did have an alteration in the WNT pathway and several other alterations of unknown significance.

- There are other, rare, patients who experience exceptional responses to checkpoint immunotherapies such as ipilimumab for yet unknown reasons. Recent studies suggest that immune system biomarkers such as high levels of T cells in tumors, may be able to identify patients who are more likely to respond to ipilimumab.
- Ongoing studies aim to better identify which patients will benefit from checkpoint immunotherapy, as well as to identify combination treatments to expand and improve the efficacy of these treatments in patients with prostate cancer.
- Dr. Beltran is leading a global “PCF N=1 Prostate Cancer Precision Medicine Working Group” to create a shared database to systematically report and study patients with exceptional responses to experimental and standard therapies (**Figure**).
- The working group has developed a multicenter N=1 natural history (observational) study, which will collect longitudinal clinical data on patients who have either a specific “long tail” genomic mutation, or have exhibited an exceptional response to certain treatments (ClinicalTrials.gov Identifier: NCT04706663). Clinical and genomic data from these patients will be housed in a database that is under development by the NCI. The study will also enable the collection of tumor and blood samples from patients for collaborative research.
- The goal of this study is to enable clinicians from many centers and around the globe to participate and contribute data on these categories of rare patients. This approach will enable greater numbers of such patients to be collectively studied, and will lead to a deeper understanding of the biology as well as insights into ways to improve and accelerate precision medicine for prostate cancer patients.
- The various types of genomic sequencing methods and ways to interpret the results represent another challenge in precision medicine for prostate cancer. Different genomic sequencing methods identify different types of genomic alterations, such as mutations within vs. outside of gene-coding regions, chromosomal alterations and gene amplifications and deletions. Technologies are now being developed to use liquid biopsies, which sequence tumor DNA present in patients’ blood, as a practical alternative to invasive tumor biopsies.
- The ways that genomic sequencing data is interpreted and reported back to physicians and patients is also highly variable. There is variability in calling different mutations as clinically significant, not significant or of unknown significance, in the ability to determine if a mutation is present vs. absent vs. not evaluated, in the ability to determine if a mutation is clonal vs. subclonal (present in all or only some of the tumor population) and the sensitivity and specificity of different technologies for detecting mutations.
- The variability of different tests ultimately results in variability of patient access to precision medicines. For instance, some tests are targeted and only look for mutations in the most commonly altered cancer genes, while others look at the whole exome or whole genome and are able to identify rare and unique alterations.
- Tumors are constantly evolving and developing new mutations in order to continue growing, metastasize to new tissues, evade the immune system, and resist therapies. Thus, when and what mutations to test for remain unclear. Whether precision medicines are best directed at early tumor mutations vs. those acquired later in disease progression such as treatment resistance mechanisms, also remains unclear. This impacts whether tumor sequencing can be done using primary tumor samples or requires more recent tumor or liquid biopsies.
- For instance, loss of the tumor suppressor gene *PTEN* is thought to be an early mutation in tumor development. In a phase 3 clinical trial evaluating the efficacy of ipatasertib +

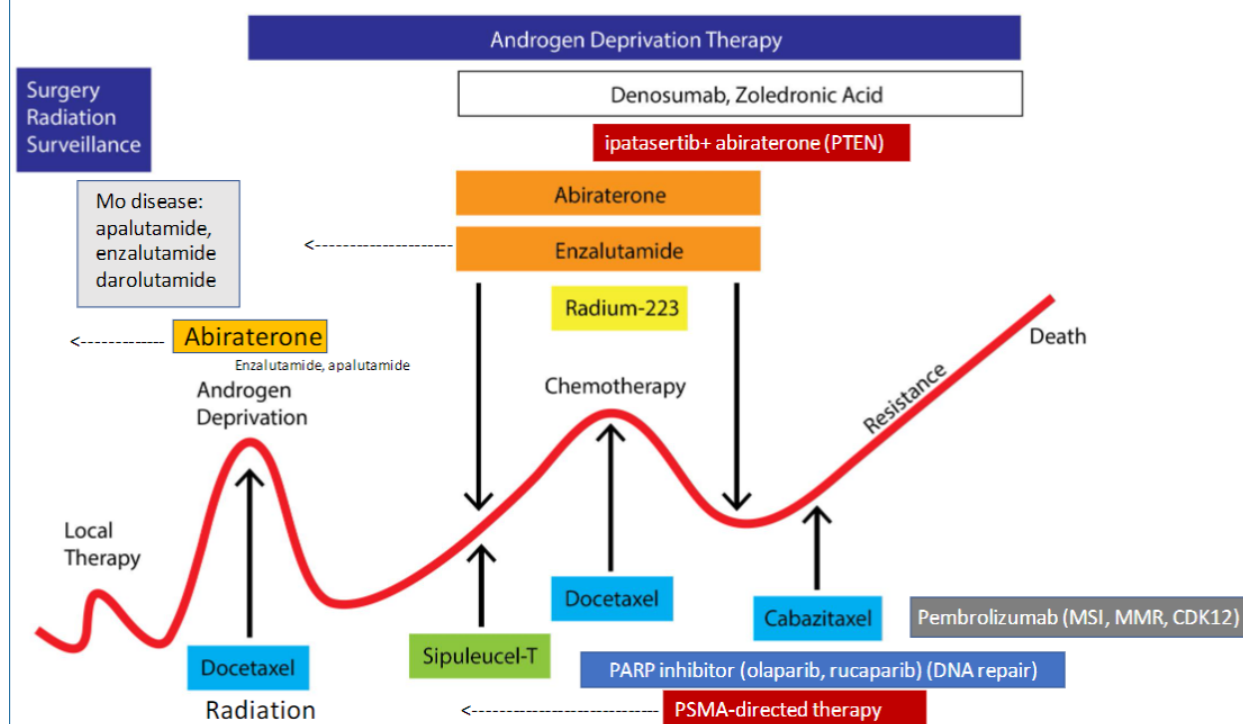
abiraterone in patients with *PTEN*-loss, different types of tests had similar sensitivity for identifying tumors with *PTEN*-loss.

- In contrast, loss of the RB1 tumor suppressor gene typically occurs later in disease progression. *RB1*-loss is thus more difficult to detect as it may not be present in all tumor cells. Furthermore, RB1 function can be lost by various mechanisms including genomic deletion, mutations that alter function, and by non-genomic mechanisms such as gene silencing. A test that uses either genomic sequencing or protein levels alone cannot evaluate RB1-loss by all of these various mechanisms.
- Another area of research important for precision medicine is the understanding of clonal drivers and sub-clonal selection. Dr. Beltran and team are using whole exome sequencing of tumor biopsies and circulating tumor DNA to evaluate the emergence of sub-clones and their role in treatment resistance.
- Non-genomic tumor features are also important for precision medicine and understanding whether and why patients do or don't respond to a specific therapy. These include gene expression levels, epigenetics, proteomics, metabolism, the tumor microenvironment, and immune responses. Use of these features as biomarkers is an important area of ongoing study.
- PSMA (prostate specific membrane antigen) is a protein that is often highly expressed on prostate cancer cells, and is the target of many new types of therapies that are being developed. Emerging drugs that target PSMA include radionuclide therapies, immunotherapies, and antibody-drug-conjugates. PSMA is also a biomarker, as it can be detected by a new type of highly sensitive prostate cancer PET imaging.
- The efficacy of PSMA-targeted drugs will likely be influenced both by the level and heterogeneity of PSMA expression, patient biology, and the mechanism of the drug. For instance, studies by Dr. Beltran and colleagues suggest that patients with *BRCA2*-alterations may be more sensitive to PSMA-targeted radionuclide therapy.
- Many drugs that target non-genomic alterations are under development. How to optimize patient selection for these drugs will be important.
- Molecular biomarkers identify not only actionable targets, but are important to study to understand and identify mechanisms of treatment resistance.
- In approximately 80% of CRPC patients, resistance to AR-targeted therapies is driven by mutations that amplify the AR pathway. Combining or sequencing abiraterone and enzalutamide has not been effective in these patients. New treatment strategies for CRPC are urgently needed.
- New treatment strategies include combination treatment strategies and new AR pathway inhibitors with alternative mechanisms of action.
- PROTACs are a novel class of drugs which cause degradation of the protein target. AR-targeted PROTACs have been promising in early clinical trials in CRPC, and development continues.
- Promising treatment combinations include AR-inhibitors plus treatments that target the PARP, PI3K/AKT, or EZH2 pathways. For instance, *PTEN*-deficient tumors may be more vulnerable to abiraterone + ipatasertib, which targets the PI3K/AKT pathway.
- Cabozantinib + the checkpoint immunotherapy atezolizumab is a promising combination strategy that targets tumor signaling pathways plus the immune system. In the recent COSMIC-021, this combination had a 33% overall response rate and an 80% disease control rate in CRPC patients.
- Approximately 15-20% of CRPC cases however, are not driven by AR, and include tumors that have been termed "AR-indifferent," "AR-independent," "AR-negative," "aggressive

variant,” and small cell/neuroendocrine prostate cancer (NEPC). These tumors may be more resistant to AR-targeted therapies than CRPC cases which remain driven by AR.

- These tumors may be identified by clinico-pathologic or molecular biomarkers. Biomarkers include loss of AR or PSA expression, aggressive clinical features including visceral bone metastases and low PSA, and molecular features such as combined (≥ 2) loss of the *TP53*, *RB1*, and *PTEN* tumor suppressor genes.
- Molecular features unique to NEPC include loss of all three tumor suppressor genes (*TP53*, *RB1*, and *PTEN*) or *RB1*-loss in combination with N-MYC overexpression. NEPC has also been found to lose expression of PSMA along with AR. PSMA-negative CRPC tumors are a highly aggressive disease subset with poor prognosis, that include NEPC.
- Dr. Beltran and colleagues have been developing circulating tumor DNA biomarkers to identify patients with NEPC. Epigenetic alterations serve as robust biomarkers to distinguish NEPC from typical prostate adenocarcinoma. This finding validates the critical role of epigenetic alterations in driving progression to NEPC by enabling prostate cells to lose prostate cell features and gain features of other cells such as stem, embryonic, and neuroendocrine cells.
- Proteins that are overexpressed in AR-independent CRPC and NEPC and may serve as potential therapeutic targets. These include DLL3, CEACAM-5, EZH2, LSD1, BRN2, and others. Treatments that target these proteins are being developed and tested in NEPC. Biomarkers to identify which patients may benefit from these therapies are also being developed.
- The Alliance Clinical Trials Cooperative Group is developing a novel prostate cancer umbrella trial. In this trial, CRPC patients will undergo genomic sequencing to identify “actionable” alterations. Patients with actionable alterations will be enrolled onto a treatment arm to receive a therapy hypothesized to be effective in tumors with such mutations. Patients without actionable alterations will receive physician’s choice of standard of care therapy.
- In 5-10 years, it is anticipated that there will be much progress made in precision medicine for prostate cancer patients. These include new and improved biomarker assessment of patients, new treatment strategies with novel mechanisms, and new treatment targets.
- Overall, it will take collaboration between clinicians, researchers, patients, and other stakeholders to accelerate precision medicine for individuals with prostate cancer. A collaborative approach will be particularly important for finding effective treatments for patients with rare tumor alterations.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/video/current-challenges-in-treatment-of-patients-with-metastatic-prostate-cancer/>

A CHANGING THERAPEUTIC LANDSCAPE



PCF Press:

Highlights from Day 1 and Look Forward at Day 2

**Karen Knudsen, PhD
Thomas Jefferson University**

Dr. Karen Knudsen highlighted the most important research and clinical findings from presentations given on Day 1 of the PCF Scientific Retreat Plenary Sessions, along with a preview of the topics to be discussed on Day 2.

The full presentation can be viewed here:

<https://www.pcf.org/scientific-retreat/video/highlights-from-day-1-and-look-forward-at-day-2/>

PANEL DISCUSSION: Prostate Cancer Disparities: Lessons from the COVID-19 Era

Moderator:

**Brandon Mahal, MD
University of Miami**

Panelists:

**Erin Kobetz, PhD, MPH (University of Miami)
Monica Baskin, PhD (University of Alabama at Birmingham)
Thomas Farrington (Prostate Health Education Network)
Randy Vince Jr., MD (University of Michigan)**

- Brandon Mahal moderated a panel discussion on prostate cancer disparities, with panelists, Dr. Erin Kobetz, Dr. Monica Baskin, Mr. Thomas Farrington, and Dr. Randy Vince Jr.
- African American men have significantly higher rates of prostate cancer incidence and mortality compared to White American men.

- The COVID-19 pandemic has also illuminated the severe health care disparities in the U.S., as racial and ethnic minority groups have been disproportionately affected by COVID-19, with significantly higher rates of cases and worse outcomes.
- The panel discussed underlying causes, effects, and solutions surrounding racial and ethnic health care disparities in prostate cancer care and COVID-19.
- The causes of prostate cancer disparities are complex and multifactorial. Many recent studies have demonstrated that healthcare access and equity are major contributors to disparities in prostate cancer mortality. Specifically, several studies have shown that in equal health care access settings such as the V.A., and clinical trials, Black men have similar or better prostate cancer outcomes compared to Caucasian men.
- Interwoven at all levels, is the longstanding impact of systemic and structural racism in the U.S., which has led to compounded social and economic disparities that ultimately impact physical and mental health.
- Studies have demonstrated that the effects of racism, such as poverty and chronic stress, have downstream biological effects. For instance, these stressors accelerate telomere shortening rates, which may accelerate the onset of age-related diseases, including cancer. Levels of cortisol, which contribute to obesity, diabetes, and chronic inflammation, are also increased by these same socio-economic stressors. Poverty has also been associated with increased rates of epigenetic changes. Whether the social and economic effects of systemic racism drive changes in biology that lead to higher incidence rates, lower age of onset, and more aggressive disease at diagnosis seen in Black men, is currently unknown, and more research is warranted.
- There is a deep distrust of the medical system by the Black community due to its history of racist and unethical actions, such as the 40-year long Tuskegee experiment, in which doctors purposefully withheld treatment from Black men infected with syphilis, even after a cure was developed, for the purpose of “studying” the natural history of the disease.
- There is also a disparity in the number of Black medical providers. Studies have demonstrated that Black patients prefer to see providers who share their culture, and outcomes for Black patients are better if seen by a Black provider. This difference in outcomes may result from racial biases by the providers and/or a more constructive patient-doctor relationship when the providers are also Black.
- Another contributor to disparities is poor access to adequate information in the Black community regarding prostate cancer screening, symptoms, and the variety of available treatments, as well as anxiety and fear surrounding cancer screening and treatment.
- There are also significant racial disparities seen in research: African Americans and other minority groups are significantly underrepresented in genomics studies, clinical trials, biomarker development, and other types of basic, translational, and clinical biomedical research studies. Research disparities will ultimately contribute to health care disparities, as understandings of disease biology, determinations of the efficacy and side effects of new treatments, the role of cancer screening, and patient management strategies have been understudied in minority populations.
- For instance, PSA screening benefits have been understudied in Black men, despite the fact that groups with higher incidence rates would likely have a higher benefit from screening. Thus, when the U.S. Preventative Services Task Force (USPSTF) recommended against routine PSA screening in 2012, this likely had a disproportionately ill effect on Black men. This recommendation has since been overturned in 2018 in favor of a recommendation that men aged 55-69 make individual decisions about PSA screening after having an informed discussion with their doctor about its risks and benefits.

- Solutions to medical disparities will require interventions at all levels of medicine, research, and society as a whole.
- In order to adequately address and overcome healthcare disparities, research and community outreach programs must be participatory and collaborative in design, at the same time including the voices of the communities impacted by disparities. This will enable research and outreach programs to address both scientifically and socially relevant issues and allow the Black community to feel they are partners in research instead of subjects being “researched on.”
- One model community outreach program at the University of Alabama at Birmingham focuses on utilizing community advisors. Local residents help develop and deliver messaging and education on prostate cancer screening, treatment, clinical trials, and information on how to obtain screening, medical care and other resources.
- Medical and research institutions must commit to improving their own community outreach to address education and awareness issues and begin rebuilding the trust of the medical establishment within the Black community.
- Medical and research institutions must make a deliberate effort to increase the representation of diverse populations in research and clinical trials.
- It is critical for researchers to recognize that there is tremendous ancestral heterogeneity among all races. In some instances, there exist more genetic differences within a specific race than between races. Diversity within groups must be acknowledged and accounted for in research to properly identify biological and other contributors to disparities correctly.
- During the COVID-19 pandemic, it has become even more imperative to establish a strong and effective line of communication between medical institutions and the communities they serve. Critical messages include the continuing importance of cancer screening and treatment, and how institutions are implementing measures to deliver cancer care safely. These messages must be delivered via traditional media, social media, and individuals doing “on-the-ground” outreach. Additionally, individuals engaged in community outreach need to be outfitted with the tools and resources to have socially distanced and virtual awareness events, including ensuring access to the internet.
- Research is ongoing to determine the national impact of the COVID-19 pandemic on cancer screening, care, outcomes, and clinical trial enrollment.
- Whether the pandemic will exacerbate prostate cancer disparities is also being investigated, including by delaying screening, diagnosis, and treatment. Because Black men are often diagnosed at a later disease stage than Caucasian men, delays in screening and early detection may likely become the biggest contributor to increased disparities.
- The ultimate goal is to establish health equity across all healthcare fields for people of all races, ethnicities, and backgrounds. Achieving this goal will require changes in research priorities and medical practices, education and outreach, new policies, and structural and societal changes at all levels.
- **The full panel discussion can be viewed here: <https://www.pcf.org/scientific-retreat/video/prostate-cancer-disparities/>**

Session 4: Late Breaking Clinical Data for Prostate Cancer Patients

Combinatorial Targeting of AR and AKT with Abiraterone and Ipatasertib for mCRPC with and without PTEN loss: The IPATential150 Phase 3 Trial

Johann de Bono, MD, PhD

The Institute of Cancer Research; Royal Marsden Hospital, London, UK

- PTEN is an important tumor suppressor gene that is lost in 40-50% of advanced prostate cancer cases. PTEN-loss is associated with poorer prognosis and outcomes, such as shorter time on treatment.
- Dr. Johann de Bono discussed a precision medicine clinical trial testing a new treatment combination in prostate cancer patients with PTEN-loss.
- PTEN functions by inactivating the AKT oncogene. Tumors with PTEN-loss have higher AKT activity. This results in increased metabolic reprogramming and increased infiltration of tumors with myeloid-derived suppressor cells (MDSCs), a type of immune cell that suppresses anti-tumor immune responses and may enhance tumor growth.
- The androgen receptor (AR), which is the major driver of prostate cancer and hence the target of many standard prostate cancer treatments, can also regulate the AKT and PTEN pathway.
- These data suggest that combining AR-targeting therapies (such as abiraterone) with AKT-targeting therapies may be effective in prostate cancer, particularly in patients with PTEN-loss, or who have AKT hyper-activation through other mechanisms.
- The randomized, double-blinded, phase 3 IPATential150 trial tested the efficacy and safety of abiraterone plus the AKT-inhibitor ipatasertib vs. abiraterone plus a placebo.
- Ipatasertib is an oral drug that can inhibit all 3 forms of AKT.
- A prior randomized phase 2 trial (A. MARTIN trial) had tested abiraterone combined with either placebo or ipatasertib in 253 patients with advanced or metastatic prostate cancer who had previously been treated with docetaxel chemotherapy. The primary endpoints of the trial were radiographic progression free survival (growth of tumors on scans) in the entire cohort and in the subset of patients with PTEN-loss.
- The trial found that the addition of ipatasertib significantly improved radiographic progression free survival only in patients with PTEN-loss.
- The global phase 3 IPATential150 trial tested abiraterone plus ipatasertib vs. abiraterone plus a placebo in 1,101 metastatic castration resistant prostate cancer (mCRPC) patients. Patients enrolled had symptomatic or mildly symptomatic mCRPC with no prior treatments in the mCRPC setting (prior docetaxel in the hormone-sensitive prostate cancer setting was allowed). The primary endpoints of this trial were radiographic progression free survival in the entire cohort and in the subset of patients with PTEN-loss.
- In this trial, the testing for PTEN-“loss” was different from the phase 2 trial. In this trial, PTEN protein levels were evaluated, with at least half the tumor cells having to lack PTEN to be called as “PTEN-loss.” In the phase 2 trial, PTEN-loss was determined by a different immunohistochemical assay utilizing a different antibody with tumors with an H-score of <10 (minimal staining) with this assay being deemed as having PTEN-loss.
- Of the 1,101 patients on the IPATential150 trial, 521 had PTEN-loss.

- A comparison of PTEN-loss determined by protein levels vs. by genomic sequencing in patients from the IPATential150 trial found that while many but not all tumors with genomically deleted PTEN also had PTEN protein loss, some but not all of the tumors with PTEN protein loss had lost PTEN at the genomic level. It remains to be determined which method for determining PTEN-loss is most precise, and most biologically and clinically relevant.
- Interestingly, correlative studies on tumor samples from this global trial revealed that patients from East Asia had a different distribution of tumor mutations compared with non-East Asian patients. Tumors from East Asian patients had significantly lower frequencies of mutations in *PTEN* (15% vs 31% of patients), *TMPRSS2*, and *TP53*, and significantly higher frequencies of mutations in *MYC*, *SPOP*, *BRCA2*, and *CDK12*, compared with non-East Asian patients. This finding is now being validated in other studies.
- *PTEN*-loss tended to co-occur with genetic alterations in *TP53* and *TMPRSS2*, and to be mutually exclusive from mutations in *SPOP* and *CDK12*.
- A preliminary analysis of the IPATential150 trial found that in patients with PTEN-loss, the addition of ipatasertib to abiraterone statistically significantly decreased risk of disease progression by 23% and improved median radiographic progression free survival by 2 months, vs. placebo (18.5 months vs. 16.5 months) (**Figure**). Median radiographic progression free survival was also statistically significantly improved with ipatasertib vs. placebo in patients with PTEN-loss as defined by genomic sequencing (19.1 months vs 14.2 months).
- In the total patient population, the addition of ipatasertib to abiraterone improved median radiographic progression free survival by 2.6 months vs. placebo (19.2 months vs 16.6 months) although this did not statistically meet the pre-defined significance level.
- Among patients with PTEN-loss, 19% experienced a complete response with ipatasertib + abiraterone vs. 6% of patients who received abiraterone plus placebo. Among all patients, 18% experienced a complete response with ipatasertib + abiraterone vs. 9% of patients who received abiraterone plus placebo.
- The addition of ipatasertib also increased PSA response rates and extended the time to PSA progression, in both patients with PTEN-loss and in all patients.
- The trial is not mature enough yet to evaluate the impact on overall survival or other secondary endpoints such as time to pain progression and time to initiation of cytotoxic chemotherapy.
- The rate and grade of side effects were higher among patients receiving ipatasertib + abiraterone vs. abiraterone plus placebo. Grade 3-4 side effects that were more prevalent among patients receiving ipatasertib + abiraterone included rash, diarrhea, hyperglycemia, increased liver enzymes, and dehydration.
- 21% of patients on the combination arm discontinued treatment, vs. 5% receiving abiraterone alone. Treatment discontinuations and dose reductions were primarily due to side effects including diarrhea, skin rash and hyperglycemia. It is possible that these side effects can be effectively managed with anti-diarrheal and anti-histamine medications.
- Altogether, this trial demonstrated that the addition of ipatasertib to abiraterone in mCRPC patients as a first-line treatment statistically significantly delayed radiographic progression in patients with PTEN-loss. Ipatasertib also statistically significantly improved overall response rates, PSA progression and PSA responses in these patients. Although this combination was associated with increased side effects, it is likely that these can be effectively managed with prophylactic medications.
- This demonstrates promise for this treatment combination as a novel precision medicine in patients with advanced prostate cancer and warrants additional study in further clinical trials.

- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/clinical-data-for-prostate-cancer-patients/>

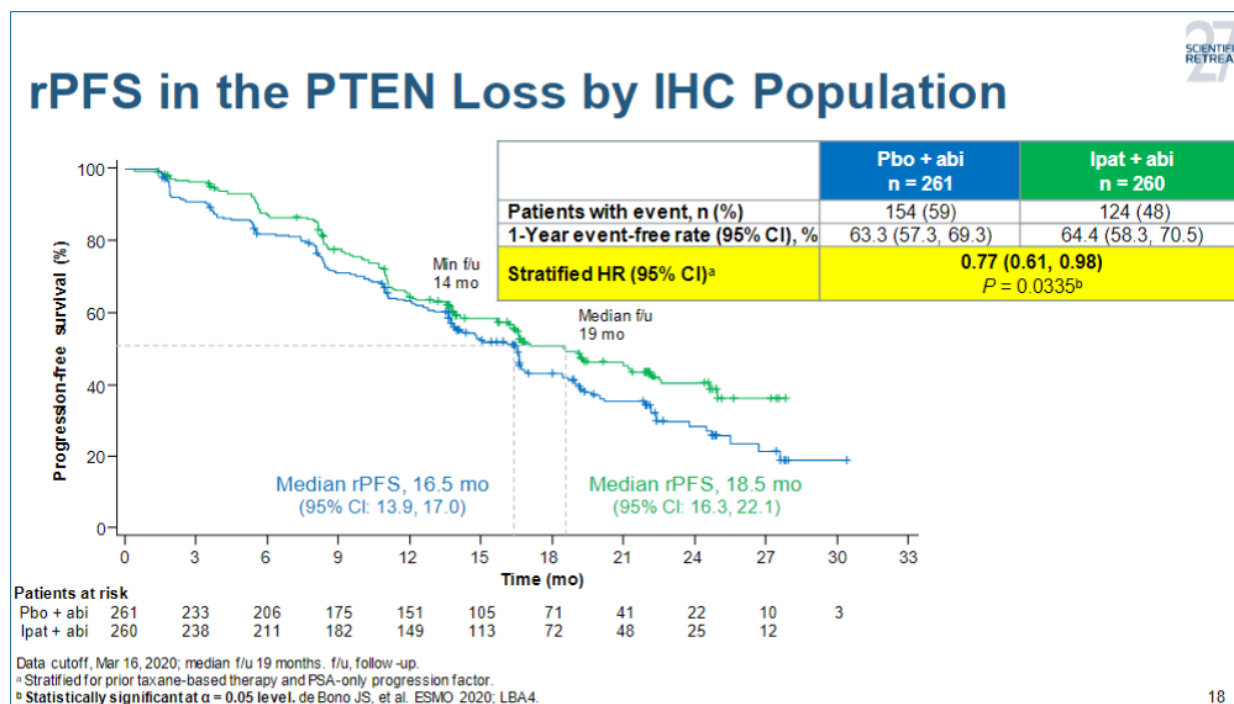


Figure: In patients with PTEN-loss, the addition of ipatasertib to abiraterone statistically significantly improved median radiographic progression free survival by 2 months vs. placebo (18.5 months vs 16.5 months).

Phase 1 Clinical Profile of AMG 160, a Half-Life Extended PSMA Bispecific T cell Engager (BiTE®) Immunotherapy for Patients with Metastatic Castration-Resistant Prostate Cancer

Matthew Rettig, MD

University of California, Los Angeles; VA Greater Los Angeles Healthcare System

- Immunotherapies, treatments that use a patient's own immune system to target and kill their tumor cells, are a highly promising class of cancer therapeutics that can induce long-term regressions and even cures in patients with tumor types such as melanoma and lung cancer. However, immunotherapies have only had limited efficacy in patients with prostate cancer and have yet to be optimized.
- T cells are a type of immune cell that can kill tumor cells if properly prompted. Activation of anti-tumor T cells is the goal of most cancer immunotherapies.

- Bispecific T cell Engagers (BiTE®) are a class of immunotherapy composed of two antibody fragments fused together: typically, one targets T cells, and the other targets tumor cells. This brings T cells into close contact with tumor cells, activating the T cell to kill tumor cells.
- PSMA (prostate specific membrane antigen) is a protein present at high levels on prostate cancer and is considered an ideal therapeutic target. Many PSMA-targeting treatments are being developed and tested for prostate cancer.
- Dr. Matthew Rettig discussed a phase 1 trial testing AMG 160, a BiTE® which targets T cells and PSMA. AMG 160 also has a modification that improves its time in circulation, enabling infusions to be given every two weeks.
- A previously developed PSMA-targeting BiTE® that lacked this modification required continual infusion.
- A phase 1 trial was conducted to test the safety and identify the optimal dose for AMG 160 in patients with metastatic castration resistant prostate cancer (mCRPC). These patients had already progressed on (or were ineligible for) AR-targeted therapies and taxane chemotherapy.
- Overall, 43 patients received at least 1 dose of AMG 160. 6 dose levels were tested.
- Treatment-related adverse events (TEAEs) were observed in 95% of patients, most being grades 1-2. There were no grade 5 (death) events, and none resulted in treatment discontinuation.
- TEAEs that occurred in at least 20% of patients (all grade) included cytokine release syndrome (90.7% of patients), fatigue (44.2%), vomiting (44.2%), nausea (39.5%), pyrexia (37.2%), headache (34.9%), diarrhea (32.6%), dry mouth (30.2%), rash (27.9%), hypophosphataemia (25.6%), hypotension (23.3%), chills (23.3%), dysgeusia (23.3%), and decreased appetite (20.9%).
- Grade 3 events that occurred included cytokine release syndrome (25.6% of patients), fatigue (2%), diarrhea (4.7%), rash (9.3%), hypophosphataemia (9.3%), and hypotension (11.6%).
- There were 3 reversible dose-limiting toxicities: two grade 2 rash events and one grade 3 gastrointestinal hemorrhage event. Eight patients (18.6%) experienced grade 4 laboratory abnormalities that were clinically non-significant.
- Cytokine release syndrome (CRS) is a systemic inflammatory response characterized by fever and multiple organ dysfunction that is often triggered by immunotherapies. In this trial, CRS was reversible, manageable, most severe in cycle 1, and was associated with fever, hypotension, transient transaminitis, nausea/vomiting and/or diarrhea. There were no grade 4 or 5 CRS events.
- CRS could be mitigated with a prophylactic strategy composed of dose priming (lower run-in dose before maintenance dose), dexamethasone premedication, and I.V. hydration. This strategy eliminated grade 3 CRS events and severe adverse events in a test cohort of 5 patients.
- AMG 160 appeared to have promising anti-tumor activity.
- PSA levels dropped in 68.6% of evaluable patients, and PSA reductions of ≥50% were observed in 34.3% of evaluable patients. Increased dose levels of AMG 160 were associated with better PSA responses.
- Circulating tumor cell (CTC) responses were observed in 23.1% of evaluable patients.
- Among 15 patients with disease measurable by scans, 3 (20%) experienced a partial response (tumor shrinkage) and 8 (53.3%) had stable disease.

- Several long-term responses were observed, with 6 patients (14%) being on treatment for over 6 months at the time of this presentation. 44.2% of patients remained on AMG 160 at the time of data analysis.
- Several deep responses, in which patients experienced deep PSA reductions and significant tumor shrinkage on scans, were observed (**Figure**).
- Altogether, these results demonstrate that AMG 160 has a manageable safety profile as a monotherapy and had promising efficacy in a cohort of heavily pre-treated patients. Additional testing is warranted.
- This trial is now enrolling patients onto the expansion cohort (testing the identified optimal dose in more patients). The trial has also recently opened a second arm of the trial, which is testing AMG 160 in combination with the checkpoint immunotherapy pembrolizumab.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/video/clinical-data-for-prostate-cancer-patients/>

Examples of Deep Responses to AMG 160

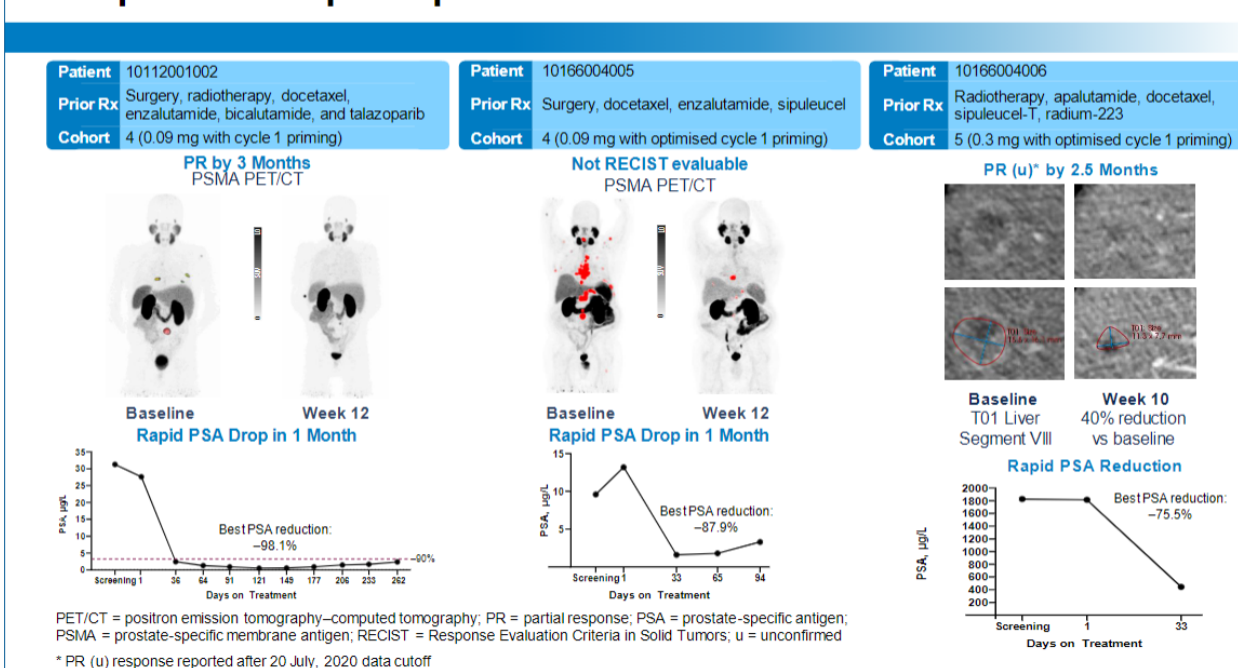


Figure: Examples of 3 patients who exhibited deep responses to AMG-160, including significant PSA reductions and tumor shrinkage on scans.

Phase 1 Study of AMG 509, a STEAP1 x CD3 T Cell-Recruiting XmAb® 2+1 Immune Therapy, in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC)

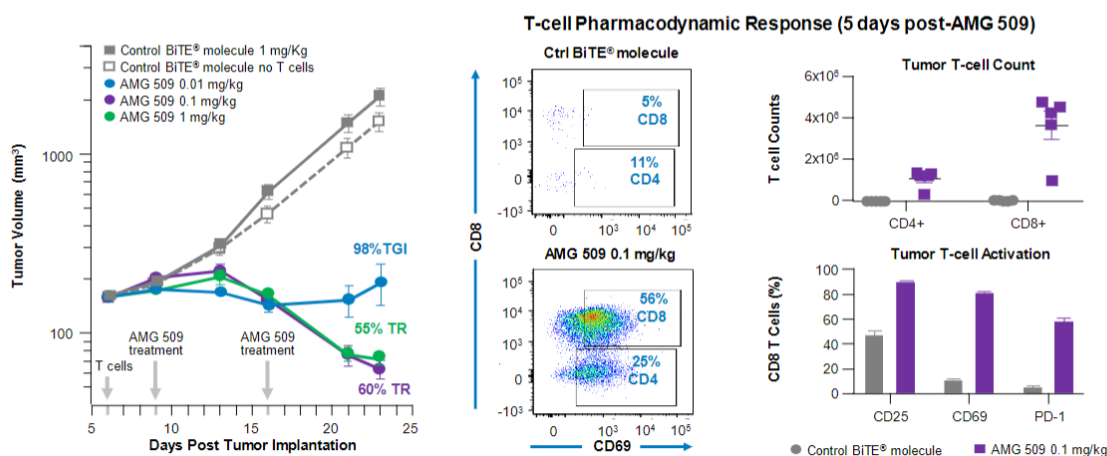
Wm. Kevin Kelly, DO

Sidney Kimmel Medical College at Thomas Jefferson University; Sidney Kimmel Cancer Center

- Metastatic castration resistant prostate cancer (mCRPC) remains an incurable disease state for which new treatments are urgently needed.
- Immunotherapies are treatments which activate a patient's own immune system to kill their tumor. Immunotherapy has been highly promising and effective in many cancer types, but has had only limited efficacy in prostate cancer to date. Optimizing immunotherapy for prostate cancer is a critical research priority.
- Bispecific T-cell Engagers (BiTE®) are a class of immunotherapy composed of two antibody fragments fused together: typically, one targets T cells, and the other targets tumor cells. This brings T cells into close contact with tumor cells, activating the T cell to kill tumor cells.
- STEAP1 (Six Transmembrane Epithelial Antigen of the Prostate 1) is a protein that is expressed at high levels on the surface of most advanced prostate cancer cases, including ~88% of mCRPC cases, and is considered a promising therapeutic target. STEAP1 is also expressed on ~84% of primary prostate cancer, though levels are lower than metastatic prostate cancer. STEAP1 is largely absent on normal cells.
- A STEAP1-targeted antibody drug conjugate (ADC) showed evidence of clinical activity in a prior phase 1 clinical trial.
- Dr. Wm. Kevin Kelly discussed the development of a STEAP1-targeting BiTE®, AMG 509, for prostate cancer.
- AMG 509 contains two identical STEAP1-targeting antibody fragments which bind STEAP1-expressing cells (such as prostate cancer), an anti-CD3 antibody fragment that binds T cells, and a non-targeting antibody domain that extends the circulation time of AMG 509.
- In preclinical studies, AMG 509 caused T cells to potently and selectively kill STEAP1-expressing prostate cancer and sarcoma cells.
- Treatment with AMG 509 activated T cells and caused significant tumor regression in mouse prostate cancer models (**Figure**). In this study, mice were given human prostate tumors and human T cells.
- A phase 1 clinical trial has been initiated to test safety and tolerability, and identify the optimal dose of AMG 509 in advanced mCRPC patients. Once the optimal dose is identified, this dose will be further tested in an expanded cohort of patients. Secondary objectives of the trial include determination of preliminary anti-tumor efficacy and characterizing the pharmacokinetics of AMG 509.
- The study is currently ongoing.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/clinical-data-for-prostate-cancer-patients/>**

AMG 509 Preclinical In Vivo Efficacy

- Regression of 22RV1^{STEAP1} Prostate xenograft model following AMG 509 treatment is accompanied by increased activation and level of T-cells mediated by Xmap & tumor engagement.



- Data on File. TGI, Tumor Growth Inhibition; TR, Tumor Regression.

Figure: In preclinical studies, treatment with AMG 509 caused significant tumor regression (left) and activated T cells (center, right) in mouse prostate cancer models. In this study, mice were given human prostate tumors and human T cells.

Human Costimulatory Bispecific Antibodies in Cancer Immunotherapy: Focus in Prostate Cancer

Dimitris Skokos, PhD
Regeneron Pharmaceuticals

Elizabeth Miller, MD
Regeneron Pharmaceuticals

- Cancer immunotherapies have demonstrated significant efficacy and even cures in patients with certain cancer types, including melanoma and lung cancer. However, such efficacy has only been seen in very limited numbers of prostate cancer patients thus far. Much research is now focused on the critical goal of optimizing immunotherapy for prostate cancer.
- The most effective cancer immunotherapies have largely been from two categories.
- Non-tumor targeted “checkpoint inhibitors,” are treatments that target immune-suppressive molecules (for example, CTLA4, PD1, PDL1) expressed by T cells, tumor cells, or other cell types. Checkpoint immunotherapies remove the “brakes” on the immune system, allowing robust activation of T cells. However, responses can vary widely by tumor type.

- Tumor-targeted cancer immunotherapies in contrast, include a component that directly targets tumor cells. These therapies include CAR T cells (patient T cells engineered to target tumor cells) and bi-specific antibody-based therapies, which simultaneously bind to both T cells and tumor cells in order to bring T cells into contact with and kill tumor cells. Tumor targets that are ideal for this approach include proteins which are highly expressed on cancer cells but are low or absent on normal cells. In prostate cancer, ideal targets include the PSMA protein.
- Both types of cancer immunotherapy categories can be potent, but have challenges including efficacy, durability, safety, and production time and costs.
- Dr. Dimitris Skokos and Dr. Elizabeth Miller discussed the development of a novel class of tumor-targeting bi-specific antibodies for prostate cancer.
- T cells are a primary effector immune cell type that when fully activated, can potently kill target cells. Proper activation of T cells requires two signals.
- “Signal 1” is detection of a “foreign” antigen on the target cell by the T (CD3/TCR complex) cell. This antigen can be a protein from a virus or bacteria that indicates infection, or a mutated or abnormally expressed protein in the case of cancer.
- “Signal 2” is a “co-stimulation” signal, which amplifies T cell activation only in the presence of signal 1. CD28 is one of the most potent and well-studied costimulatory receptors expressed on T cells.
- Dr. Skokos and Dr. Miller discussed two novel bi-specific antibody-based strategies that are being developed for cancer therapeutics. Both strategies include a bi-specific antibody that targets a tumor specific antigen (TSA) plus CD28 (TSAxCD28) on T cells to provide signal 2.
- One approach combines a checkpoint immunotherapy (anti-PD1) with a bi-specific antibody targeting a tumor specific antigen and CD28 (TSAxCD28). In this strategy, the bi-specific antibody would bridge T cells to cancer cells, thereby selectively activating T cells at the tumor site via the CD28 pathway, thus providing signal 2. The checkpoint immunotherapy can block negative signals and result in stronger signal 1 through recognition of the tumor antigens presented by the tumor cells (endogenous signal 1). This strategy has potential in settings where pre-existing anti-tumor immunity has been demonstrated or is likely, for instance patients who have had some response to checkpoint immunotherapy, which could be enhanced by a co-stimulatory bi-specific antibody.
- A second approach combines two different bi-specific antibodies. One targets a tumor specific antigen and CD3 on T cells to activate signal 1. The other targets a tumor antigen and CD28 on the T cell to provide signal 2. This combination therapy requires highly specific tumor antigens, and it may be effective in patients without pre-existing anti-tumor immunity. The bi-specific antibodies can also be targeted to two different tumor antigens, to increase specificity of targeting to tumor cells and limit toxicity. It may also be possible to combine this approach with checkpoint immunotherapy as part of a triple combination strategy.
- Bi-specific antibodies that target the prostate cancer-associated protein PSMA are being developed for these approaches.
- In preclinical studies in prostate cancer mouse models, treatment with a co-stimulatory bi-specific antibody (anti-PSMAxCD28) plus anti-PD1 was more effective than either treatment alone, in driving robust tumor regression and selectively activating tumor-infiltrating T cells, without evidence of systemic toxicity (**Figure**).
- Preclinical toxicology studies of anti-PSMAxCD28 plus anti-PD1 in cynomolgus monkeys demonstrated promising safety data. This is important as prior efforts by pharmaceutical

companies to develop therapeutic anti-CD28 antibodies resulted in severe cytokine release syndrome (CD28 superagonist antibody).

- A phase 1/2 trial has been initiated to test the bi-specific antibody REGN5678 (anti-PSMAxCD28) in combination with cemiplimab (anti-PD1) checkpoint immunotherapy in patients with metastatic castration resistant prostate cancer (mCRPC). This trial is evaluating safety and identifying active dose(s) of REGN5678 to be used in this combination.
- This study is ongoing and will provide valuable insights into the potential of this treatment combination for patients with mCRPC.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/video/clinical-data-for-prostate-cancer-patients/>

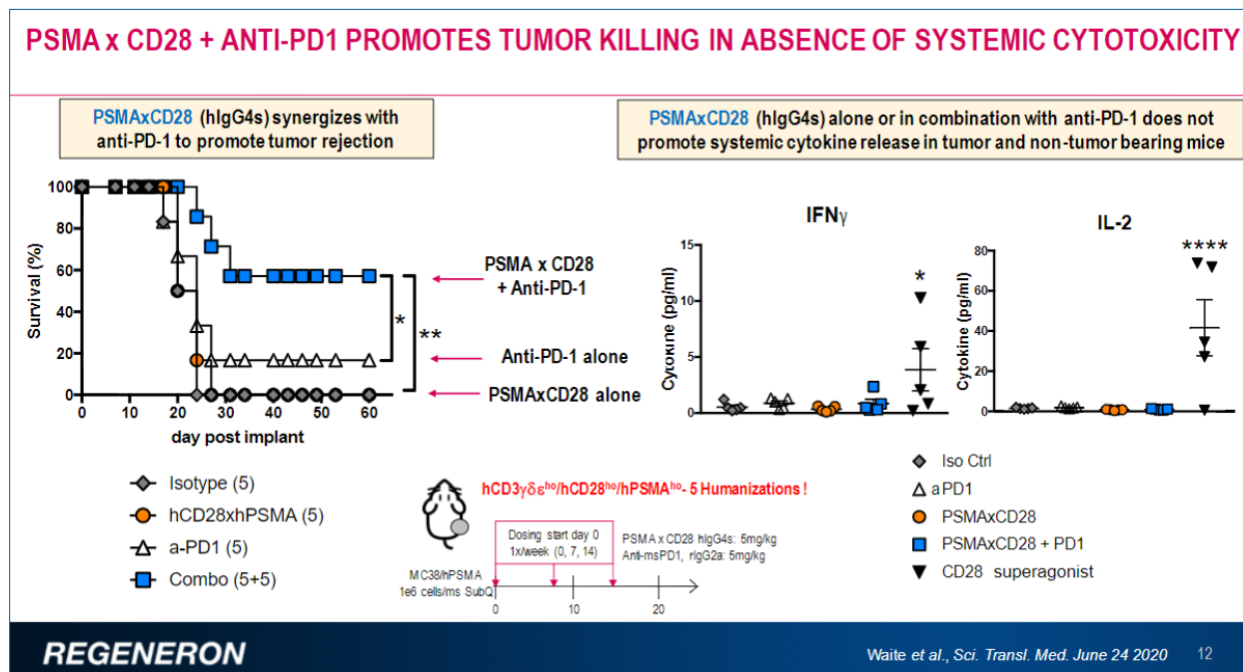


Figure: In preclinical studies in prostate cancer mouse models, treatment with the co-stimulatory bi-specific antibody (anti-PSMAxCD28) plus anti-PD1 was more effective than either treatment alone, in causing tumor regression (left) and activating T cells (right), without evidence of systemic toxicity.

Session 5: Microbiome and Cancer

The Plasticity of the Microbiome in Colorectal Cancer

Christian Jobin, PhD
University of Florida

- The microbiome is the complex community of microorganisms that live on the human host, including on our skin and mucosal surfaces such as the gastrointestinal tract.
- The microbiome plays an essential role in human biology, and we largely have a symbiotic relationship. Microbes aid in food digestion and metabolism, and help to train the immune system to recognize which microbes are good/harmless, and which are threats to our health. Good microbes also prevent colonization by bad microbes.
- However, microbiome alterations can play roles in many diseases, including metabolic disorders, autoimmune diseases, and cancer.
- In cancer, the microbiome can impact disease development, progression, anti-tumor immune responses, and the efficacy of different treatments.
- Dr. Christian Jobin discussed roles of the microbiome in colorectal cancer.
- In a normal healthy microbiome, microbes and human epithelial cells interact and exchange molecules such as nutrients, in a symbiotic fashion.
- Changes such as inflammation, diet, and medications alter the composition of the microbiome (microbiome dysbiosis), and can result in a cancer-promoting microbiome. This occurs when the microbiome includes microbes which produce carcinogenic molecules, such as colibactin, H₂S, and various toxins.
- Colibactin is a DNA-damaging enzyme produced by some bacteria that can drive development of colorectal cancer by causing genomic mutations in colon cells.
- Studies have found that bacteria carrying the Colibactin gene island were present in the microbiome of prostate cancer patients.
- Inflammation is a major driver of microbiome dysbiosis.
- Dr. Jobin and colleagues aimed to determine whether blocking inflammation may prevent colorectal cancer caused by microbiome dysbiosis.
- In mouse models of inflammation-driven colon cancer, treatment with an anti-inflammatory medication altered inflammation-driven microbiome changes and prevented colorectal cancer development (**Figure**).
- Mice that were not treated with the anti-inflammatory medication but instead received the gastrointestinal microbiome from mice that had been treated, were also resistant to the development of inflammation-driven colon cancer.
- Together, these studies demonstrate that preventing inflammation prevents the development of a carcinogenic microbiome, and that a healthy microbiome can prevent the development of inflammation-driven cancers.
- The potential for the microbiome as a treatment to improve responses to anti-cancer therapies, such as immunotherapies, is being tested in clinical trials, including for prostate cancer.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/video/microbiome-and-cancer/>

Anti-TNF treatment attenuates pks+ *E. coli*-induced tumorigenesis in DSS/*Apc*^{min/+} mice

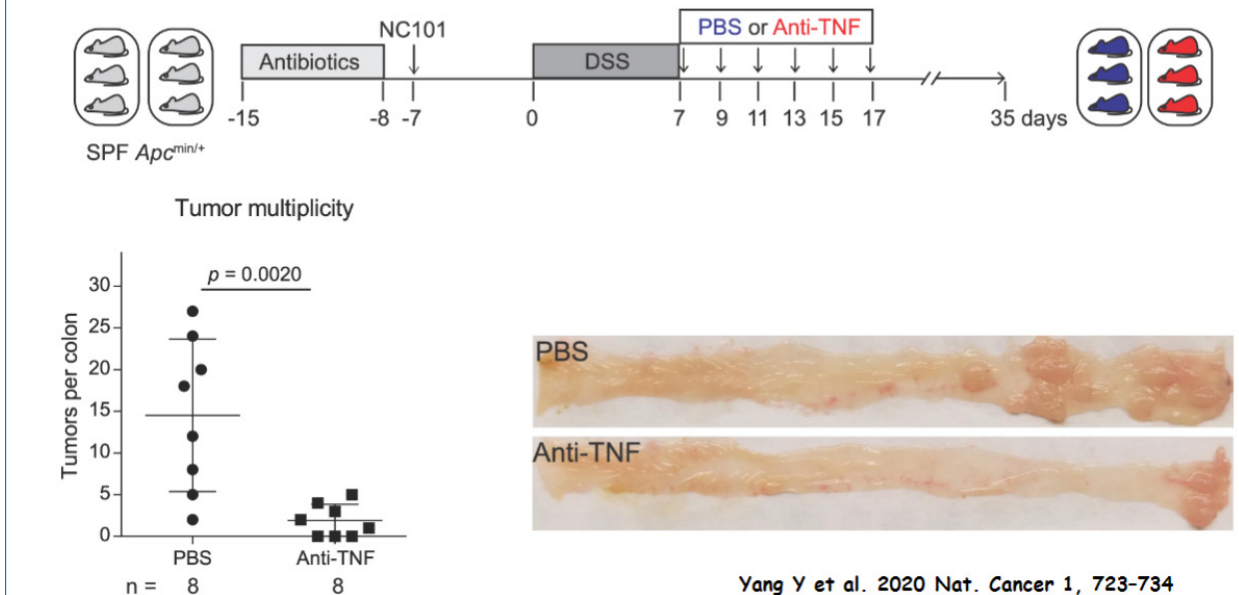


Figure: In mouse models of inflammation-driven colon cancer, treatment with an anti-inflammatory medication (anti-TNF) prevented colorectal cancer development.

Host-Microbiome Interactions in Human Cancer

Ran Blekhman, PhD
University of Minnesota

- The microbiome is the community of microorganisms that live on the surfaces of humans, including on the skin and in the gut.
- The microbiome plays an important role in many normal human biological processes, such as food digestion and metabolism.
- A dysfunctional microbiome is associated with certain diseases, including obesity and metabolic disorders, inflammatory diseases, and cancer.
- Many studies have been done to evaluate the relationship between human genetics and disease. These studies have identified heritable genetic factors that modify risk for various diseases and disorders. However, little is known about the relationship between human genetic variation and the microbiome in disease development.
- Dr. Ran Blekhman discussed studies on interactions between host genetics and the microbiome, in order to better understand the basis of complex diseases.

- The gut microbiome was found to vary based on host genetics. In one study, an artificial intelligence algorithm was able to predict host ethnicity based on gut microbiome composition alone. A study in twins identified several microbes whose presence in the gut depend on heritable factors.
- A genome-wide association study (GWAS) identified several host genetic regions that strongly correlated with the composition of the microbiome. For example, genetic variation in the LCT gene, which determines lactose tolerance, was associated with the abundance of a bacteria that digests lactose (*bifidobacterium*) in the gut.
- Dr. Blekhman and colleagues performed a study to evaluate host-microbiome interactions in colon cancer. This study compared colon cancer patients' normal and tumor genomic profiles, and the composition of the microbiome in the tumor vs. the normal region of their colon. A more diverse microbiome was found in tumor vs normal colon areas, with many changes in abundance of various species of bacteria.
- A microbiome profile was identified that could predict colorectal cancer stage (stage 1/2 vs stage 3/4), with 80% specificity and 85% accuracy.
- The microbiome profile could also predict the presence of certain tumor driving mutations, including mutations in the tumor suppressor gene APC. APC mutations are the primary driver of colorectal cancer. The microbiome profile was also a strong predictor of alterations in tumor driver pathways including the MAPK, WNT, p53 and ErbB1 pathways.
- This data was used to generate a map of the tumor-microbiome interaction network **(Figure)**. This allows visualization of how strongly different tumor pathways are linked to different microbiome species.
- Dr. Blekhman's team has created several open-access bioinformatics tools to study the relationships between host genomics and the microbiome.
- These studies demonstrate that there is an overall association between microbiome composition and the tumor mutational landscape, and that certain tumor mutations can alter microbiome composition.
- It will be critical to understand the role of this relationship in cancer development and progression, and whether and how the microbiome can be targeted as a cancer therapeutic strategy.
- **This presentation can be viewed in full here:** <https://www.pcf.org/scientific-retreat/video/microbiome-and-cancer/>

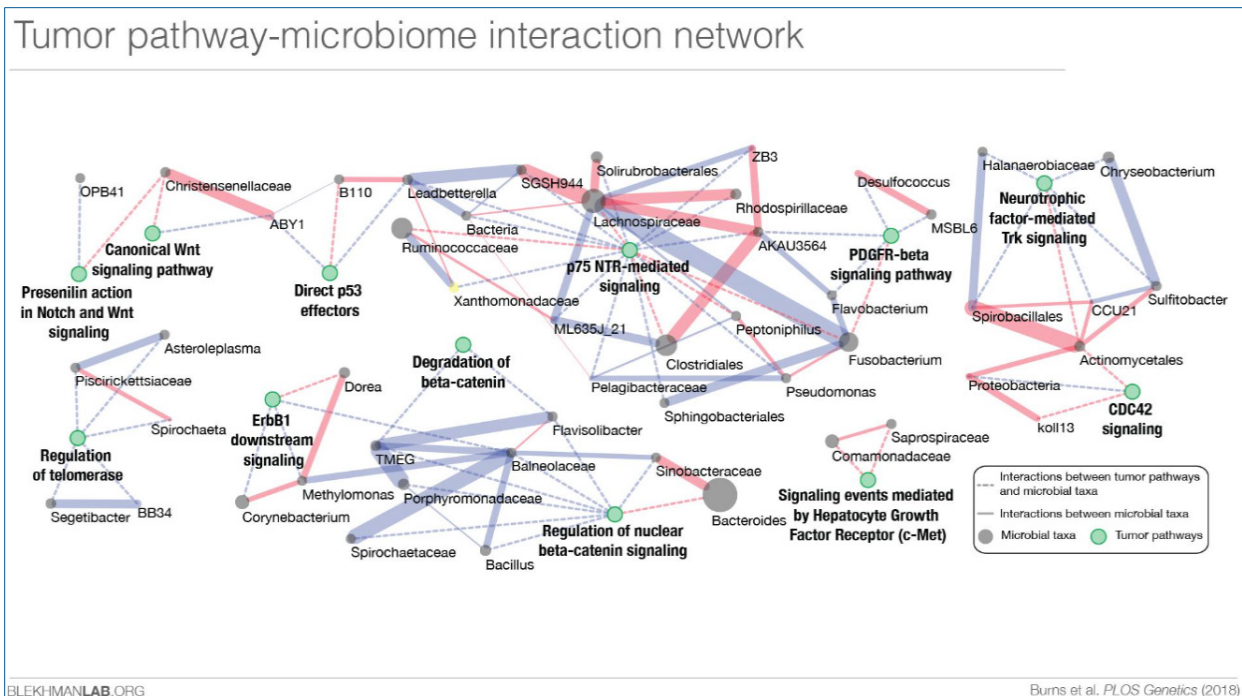


Figure: A map of the tumor-microbiome interaction network in colorectal cancer patients. This map demonstrates the strength of interactions between different tumor-driver pathways and gut microbiome species.

Gut Microbiota and Cancer Immunotherapy

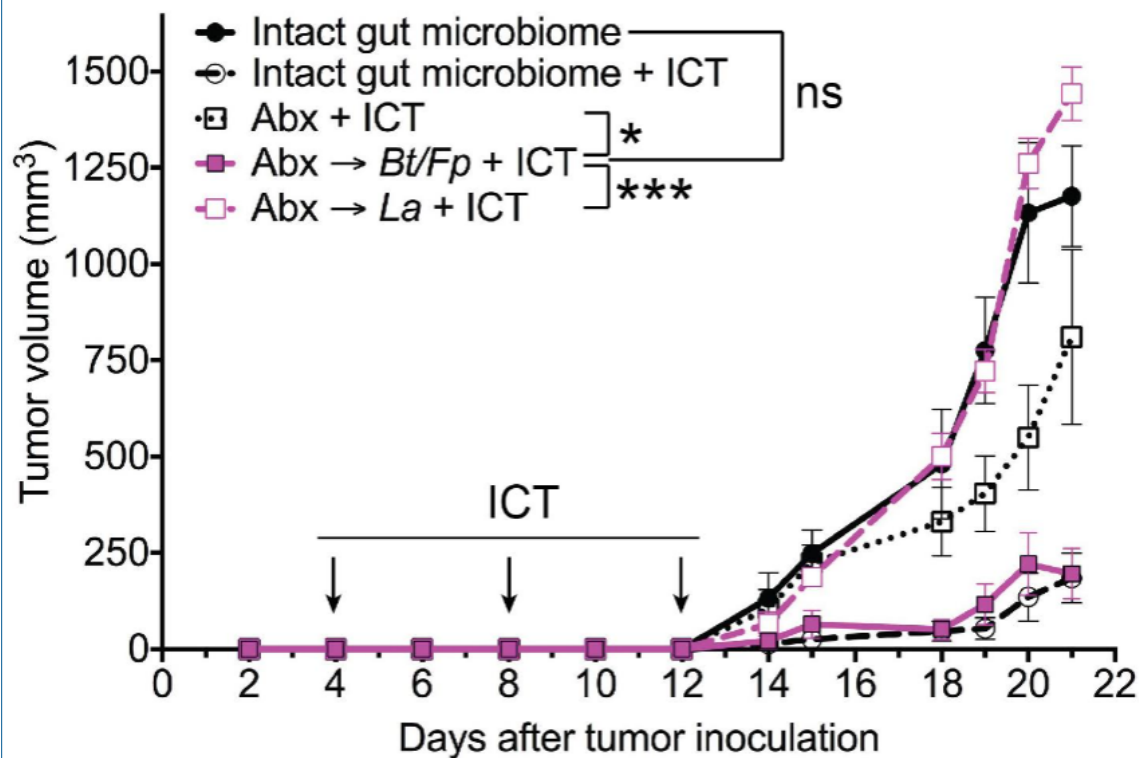
Andrew Y. Koh, MD

University of Texas Southwestern Medical Center

- The microbiome is the community of microorganisms that live on skin, the gastrointestinal tract and other mucosal surfaces of humans.
- The microbiome has a largely symbiotic relationship with the human host, including playing a critical role in processes such as digestion and metabolism. The microbiome also plays a role in “immune education” – teaching the immune system how to recognize and appropriately respond to good and bad microbes.
- Dysfunctions in the microbiome have roles in driving diseases, such as cancer.
- Interestingly, the microbiome may play a critical role in the efficacy of cancer immunotherapy. Preclinical studies have found that cancer immunotherapies were ineffective in cancer-bearing mice that had been treated with antibiotics or had been raised in a sterile, germ-free environment.
- Dr. Andrew Koh discussed studies to evaluate the role of the gut microbiome in regulating responses to cancer immunotherapy.

- Checkpoint immunotherapy is a class of immunotherapy that is highly effective in some patients with certain types of cancers including melanoma.
- Dr. Koh and colleagues performed a study to profile the gut microbiome from melanoma patients who were responding vs. not responding to treatment with checkpoint immunotherapy. The presence and absence of specific gut microbes were found to be associated with responses to checkpoint immunotherapy. Two bacteria species, *F. prausnitzii* and *B. theta*, which were present in responders and absent in non-responders were focused on for additional studies.
- To determine if *F. prausnitzii* and *B. theta* could promote responses to checkpoint immunotherapy, mice with melanoma were treated with antibiotics, then given a probiotic regimen containing *F. prausnitzii* and *B. theta* in combination with checkpoint immunotherapy (**Figure**). Tumor regression only occurred in mice treated with checkpoint immunotherapy that had either an intact microbiome or had received *F. prausnitzii* and *B. theta* probiotics (**Figure**). In contrast, checkpoint immunotherapy had no efficacy in mice that had been treated with antibiotics and were given either no probiotics or *Lactobacillus*, a common over-the-counter probiotic (**Figure**).
- To study the mechanisms of immune cell modulation by gut microbes, immune cells were profiled from these mice. In mice with an intact gut microbiome, treatment with checkpoint immunotherapy caused downregulation of PD1 on T cells (the target of the immunotherapy) and tumor infiltration by immune cells; these immune responses did not occur in mice that had been treated with antibiotics.
- Mice genetically engineered to lack lymph nodes also did not have responses to checkpoint immunotherapy. Treatment efficacy also required live probiotics to be given (not heat-killed). Mesenteric lymph nodes (lymph nodes adjacent to the gut) were the most important type of lymph nodes for optimal responses to checkpoint immunotherapy.
- Interestingly, in these mouse models, checkpoint immunotherapy promoted entry of live gut microbes into mesenteric and other lymph nodes, the spleen, and the tumor.
- Altogether, these studies suggest that checkpoint immunotherapy causes gut microbes to enter immune tissues such as lymph nodes, and stimulate immune activation necessary for the development of effective anti-tumor immune responses.
- Additional studies into how the microbiome can be modulated to improve the efficacy of immunotherapies and other treatments for cancer patients is highly warranted.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/microbiome-and-cancer/>**

Precision Probiotic Therapy (*B. theta*, *F. prausnitzii*) Augments ICT Efficacy in Mice (n=8) with Melanoma



AY Koh, unpublished observation

Figure: The ability of checkpoint immunotherapy (ICT) to prevent tumor growth in mice requires an intact gut microbiome or a probiotic regimen of *B. theta* and *F. prausnitzii* (*Bt/Fp*) after treatment with antibiotics (Abx). Checkpoint immunotherapy had no efficacy in mice that had been treated with antibiotics (Abx) and were given either no probiotics or *Lactobacillus* (*La*).

SPECIAL LECTURE: STATE OF THE SCIENCE 2020

Jonathan W. Simons, MD
President and CEO
Prostate Cancer Foundation

This presentation can be viewed in full here:

<https://www.pcf.org/scientific-retreat/video/state-of-the-science/>

SPECIAL LECTURE: VA-PCF Collaboration: Streamlined Genetic Sequencing in Veterans for Improved Clinical Care and Research Opportunities

Julie Graff, MD
VA Portland Health Care System

- In 2016, the Prostate Cancer Foundation (PCF) and the United States Department of Veterans Affairs (VA) announced a partnership to ensure that Veterans with prostate cancer receive the best possible care and outcomes. As part of this announcement, PCF pledged \$50 million to support the PCF Veterans Health Initiative to expand prostate cancer precision oncology research in the VA, and 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.
- Dr. Julie Graff discussed achievements, ongoing studies, and future goals of the PCF Veterans Health Initiative.
- Since 2018, PCF has funded the establishment of 13 VA hospitals as “PCF-VA Centers of Excellence” in Chicago, IL, Los Angeles, CA, San Francisco, CA, Tampa and Bay Pines, FL, Seattle, WA, Ann Arbor, MI, Manhattan, NY, the Bronx, NY, Washington DC, Durham, NC, Philadelphia, PA, Portland, OR, and Boston, MA. An additional 8 unfunded PCF-VA Centers of Excellence have been initiated in Atlanta, Baltimore, Dallas, Denver, Houston, Minneapolis, Phoenix, and Salt Lake City.
- PCF-VA Centers of Excellence share the mission of delivering best-in-class precision oncology treatment and care for prostate cancer patients. These centers are committed to offering genomic sequencing to all patients, opening precision-oncology and other prostate cancer clinical trials, and training VA physician-scientists in optimal delivery of precision oncology care and research.
- Within this initiative is the VA/PCF Precision Oncology Program for Cancer of the Prostate (POPCAP) program. The POPCAP program aims to implement precision medicine for U.S. Veterans with prostate cancer across a network of VA centers that have the capacity to facilitate genomic sequencing and clinical trials.
- All patients undergo genomic sequencing for germline (inherited) and/or somatic (tumor) mutations, and treatment decisions are made based on sequencing results. This includes selection of standard of care treatment, enrollment onto precision medicine clinical trials, or off-label use of FDA-approved drugs for patients found to have targetable mutations. POPCAP is led by Dr. Bruce Montgomery (University of Washington; VA Puget Sound) and Dr. Matthew Rettig (University of California, Los Angeles; VA Greater Los Angeles Healthcare System).
- POPCAP includes a series of prostate cancer precision medicine clinical trials within the VA and programs for the establishment of a precision medicine infrastructure, including tumor genomics capabilities, a biorepository, programs to recruit and train VA physician-scientists, and a data core.
- VA-MAPP is large biorepository effort within POPCAP that includes a data core to identify cases, a biorepository of patient samples, an infrastructure arm to perform and analyze genomic sequencing and histopathology on patient samples, and a collaborative research arm to study and share data and patient samples for research purposes. This program is led

by Dr. Rettig and Dr. Isla Garraway (University of California, Los Angeles; VA Greater Los Angeles Healthcare System).

- NACHO (Next Generation Sequencing Ascertainment for Choosing Oncology Treatment) is a new program within VA-MAPP to develop a centralized precision medicine infrastructure in the VA. This includes protocols for identifying patients nationally who may benefit from precision medicine, obtaining patient samples for sequencing (including fresh biopsies or archival samples), ordering genomic testing, and delivering sequencing results and treatment recommendations back to the treating physician.
- Approximately 12% of patients with metastatic prostate cancer carry a heritable genetic alteration that caused their cancer. A pilot POPCAP program led by Dr. Montgomery is aiming to establish a more efficient system for providing germline sequencing and genetic counseling to Veterans with metastatic prostate cancer to identify patients with heritable cancer risk genes, nationally. In this program, genetic counseling is provided to patients found to carry a heritable cancer risk gene, as opposed to pre-testing genetic counseling.
- A Virtual Clinical Trials program, led by Dr. Montgomery, is being established as a centralized infrastructure for enrolling VA patients onto VA clinical trials, nationally. The goal is to enable patients to be enrolled in clinical trials that were not available at their VA center, either by rapidly opening the trial at the VA center, or providing funds for the patient to travel to receive care at a center that is participating in the trial. This program will include coordinators that communicate with doctors and patients via telephone/teleconference, and a central IRB (the regulatory committee which oversees clinical trials and patient research).
- PATCH is a precision medicine umbrella trial being developed by Dr. Graff, in which patients who undergo genomic sequencing can be assigned to one of several treatment arms if their tumor contains specific mutations.
- CHOMP is a phase 2 trial led by Dr. Rettig, to test checkpoint immunotherapy in metastatic prostate cancer patients whose tumors have a mismatch repair gene (MMR) deficiency or loss/inactivation of both alleles of the *CDK12* gene. Both of these are thought to make tumors more susceptible to immunotherapy.
- Cobra is a randomized trial led by Dr. Montgomery, testing the PARP-inhibitor olaparib followed by carboplatin chemotherapy vs. carboplatin followed by olaparib in mCRPC patients who have a germline or somatic mutation in certain DNA repair genes.
- AMPLITUDE is a randomized trial testing abiraterone/prednisone alone vs. in combination with the PARP-inhibitor niraparib, in metastatic hormone-sensitive prostate cancer patients who have a germline or somatic mutation in certain DNA repair genes. This is an industry sponsored trial where the VA is represented in the advisory committee. It will open an exciting trial to Veterans as well as help develop investigators within the VA.
- To date, PCF has provided an estimated \$49.2 million in funding commitments to advance our Veterans Health Initiative. This includes \$32.5 million to support 13 Centers of Excellence, \$11.5 million to 12 team science “Valor” Challenge Awards, \$4.7 million to support 21 PCF-VA Young Investigators, and \$200,000 to two PCF Pilot Awards.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/va-pcf-collaboration/>**

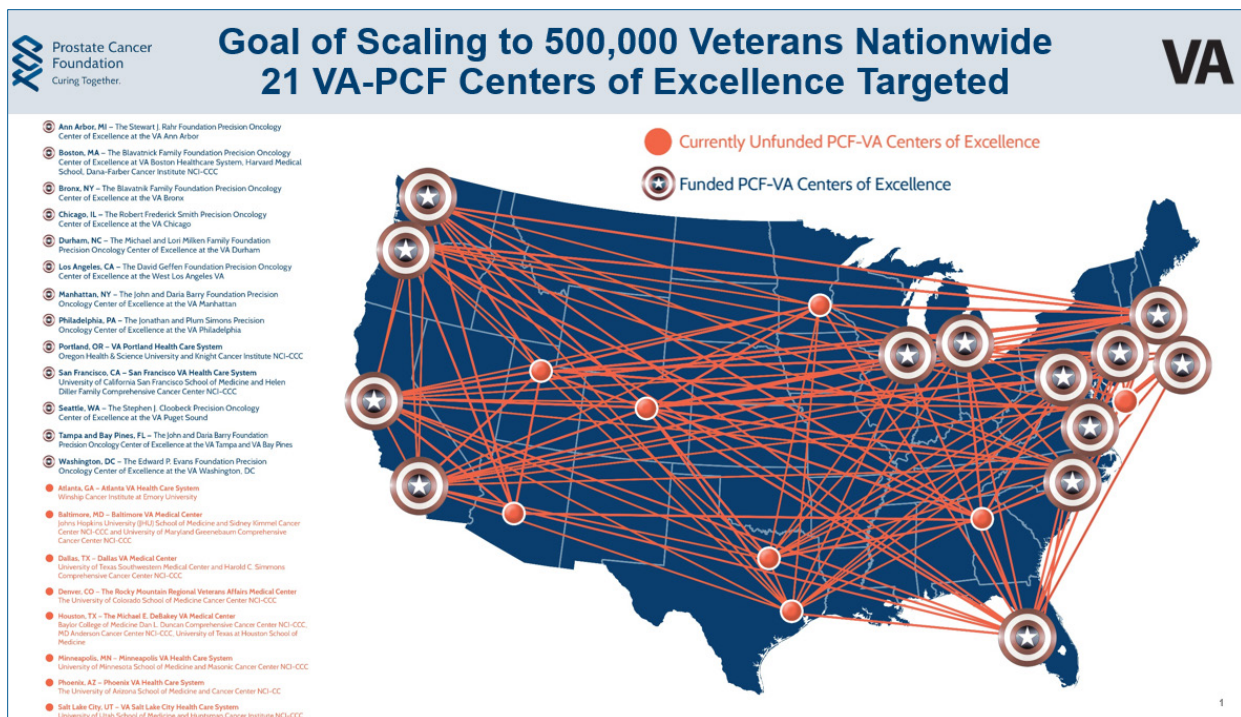


Figure: Since 2018, PCF has funded the establishment of 13 VA hospitals as “PCF-VA Centers of Excellence” in Chicago, IL, Los Angeles, CA, San Francisco, CA, Tampa and Bay Pines, FL, Seattle, WA, Ann Arbor, MI, Manhattan, NY, the Bronx, NY, Washington DC, Durham, NC, Philadelphia, PA, Portland, OR, and Boston, MA. An additional 8 unfunded PCF-VA Centers of Excellence have been initiated in Atlanta, Baltimore, Dallas, Denver, Houston, Minneapolis, Phoenix, and Salt Lake City.

SPECIAL LECTURE: A Polygenic Risk Score for Predicting Prostate Cancer in Men of African Descent

Christopher Haiman, ScD
Center for Genetic Epidemiology and Norris Comprehensive Cancer Center,
University of Southern California

- African American men have a 70% higher incidence rate of prostate cancer than Caucasian American men, and approximately double the mortality rate.
- The factors that contribute to prostate cancer disparities are complex, and may include healthcare inequities and other socio-economic factors, as well as differences in biology.
- Understanding and eliminating prostate cancer disparities in African American men is an important and urgent need.
- Dr. Christopher Haiman discussed studies to investigate and identify hereditary genetic factors that increase risk of developing prostate cancer, with a focus on men of African ancestry.

- Prior studies have identified prostate cancer risk alleles that occur more frequently in African American men.
- In one study, 7 independent risk alleles in 3 regions on the chromosome 8q24 region were identified, all of which were more common in men with African ancestry compared to men with European, Hispanic, and Asian ancestry. Moreover, the presence of all 7 risk alleles increased prostate cancer risk by 68% in African American men vs. by 32% in White men.
- The African Ancestry Prostate Cancer Consortium is a global consortium initiated in 2007. This consortium has collectively completed 32 genome wide association studies (GWAS) on 12,000 prostate cancer cases and 12,000 controls from all 7 continents. These studies have identified 5 prostate cancer risk alleles that occur in 2-10% of men with African ancestry but are absent in other ancestral populations, and each increase risk for prostate cancer by 1.2 to 2.2-fold. The affected genes include *IRS2*, *ZNF652*, and *CHEK2*.
- The chromosome 8q24 region remains the most important hereditary prostate cancer risk region. Altogether, 15 independent risk variants have been identified in 8q24. One of these variants, rs72725854, has only been observed in men of African ancestry. 11% of African American men carry at least one rs72725854 allele, which conveys a 2-fold increased risk for prostate cancer. This allele is estimated to account for ~10% of the familial risk for prostate cancer in African Americans. This suggests that this allele should be included in prostate cancer genetic testing for men with African ancestry.
- The PRACTICAL Consortium is a large international GWAS study to identify prostate cancer risk genes. This study includes genetic data from 237,380 individuals, roughly half of whom have prostate cancer and half of whom are controls. Most individuals are of European ancestry (~76%), ~9% are of African ancestry, ~11.6% are Asian, and ~3.4% are Hispanic/Latino.
- Overall, PRACTICAL has identified 269 hereditary prostate cancer risk variants, which collectively explain ~ 40% of familial risk for prostate cancer.
- A polygenic risk score (PRS) was developed to estimate an individual's risk for prostate cancer based on these 269 genetic variants. Individuals with the highest PRS score (top 10%) had the highest risk for prostate cancer. The PRS was best at predicting risk in men with European ancestry, and had lower performance in other ancestral populations.
- The PRS score was better at predicting prostate cancer risk in men aged ≤55 vs. men >55. This likely reflects the fact that individuals who develop prostate cancer at a younger age are more likely to have hereditary prostate cancer.
- The PRS was not able to predict whether a patient's prostate cancer would be aggressive or non-aggressive.
- However, ~50% of all prostate cancer cases occurred within the 20% of individuals with highest PRS scores. This suggests that the PRS could be used to identify individuals at highest risk for prostate cancer, who should consider more intensive prostate cancer screening.
- PRS scores were on average ~2-fold higher in the overall population of men of African ancestry compared to men of European ancestry. Thus, the PRS score suggests a stronger hereditary risk for prostate cancer in individuals of African ancestry.
- The PRS could also estimate an individual's lifetime risk of prostate cancer (**Figure**). Men in the top 10% of PRS scores had a prostate cancer lifetime risk of 40-60%.
- Ongoing studies are aiming to create an improved PRS score with better performance in more diverse populations, particularly in individuals of African ancestry. To do this, the consortium is enrolling more patients and controls, with a focus on non-Europeans, who will undergo genomic profiling.

- Another major ongoing effort led by Dr. Haiman, is the RESPOND study. RESPOND is a nationwide study to understand the biological, social, and other factors driving prostate cancer disparities in African American men. This study has a goal of recruiting 10,000 African American men with prostate cancer through cancer registries in 8 states. This effort is supported by a Robert F. Smith – PCF Challenge Award.
- Overall, these studies demonstrate that the PRS score is able to identify individuals with increased lifetime risk for prostate cancer, although it remains to be improved for non-European populations.
- How best to use the PRS in the clinic remains to be determined. Possible uses include incorporating the PRS into genetic testing for men with a family history of prostate cancer, and identifying individuals who are at higher vs lower risk, which could inform risk-stratified prostate cancer screening. Further studies, including a prospective, multiethnic risk-screening trial, are needed.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/polygenic-risk-score/>**

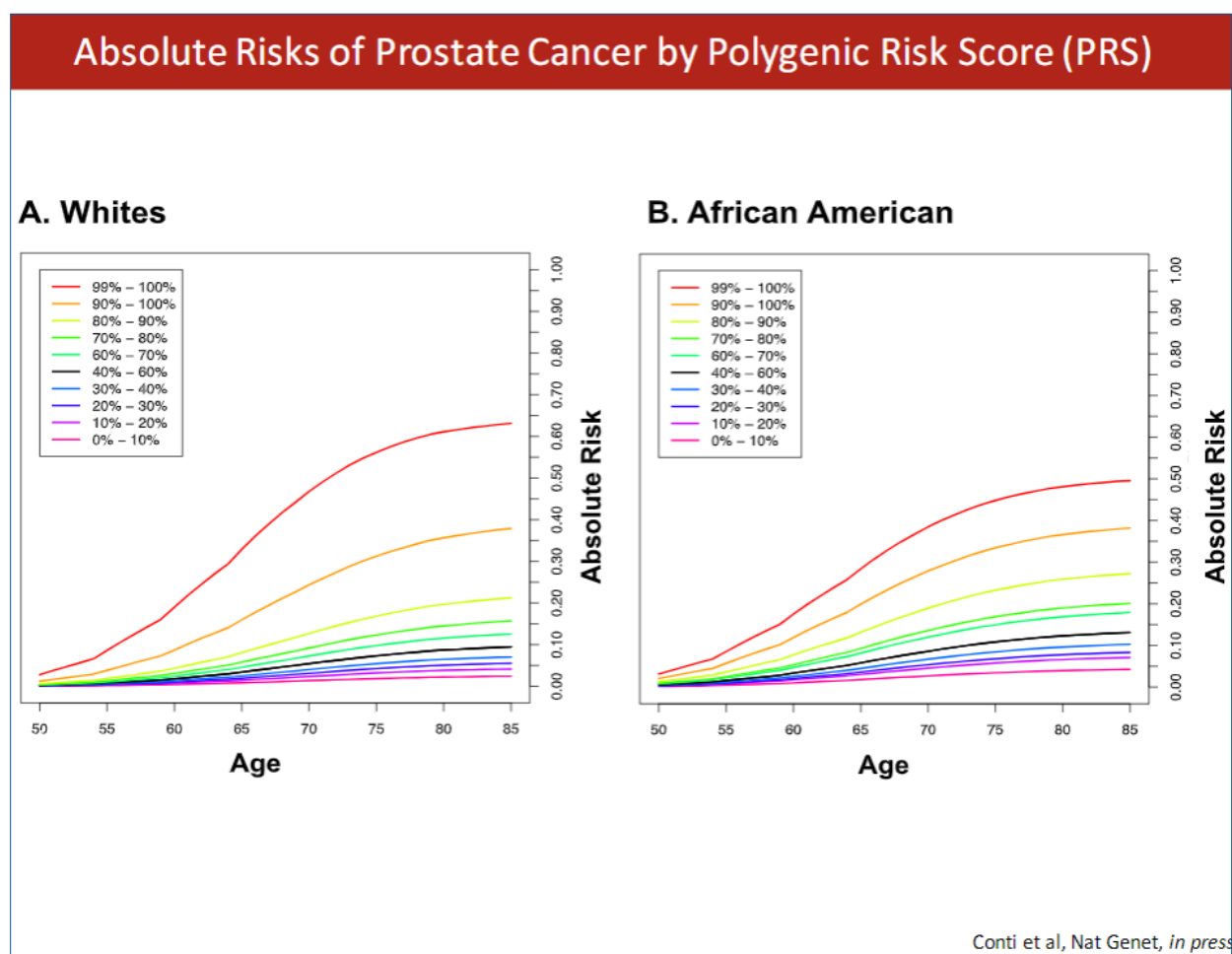


Figure: Estimation of lifetime risk of prostate cancer using the prostate cancer polygenic risk score (PRS) in White men (left) and African American men (right). Men with a higher PRS (top 1% in red, top 10% in orange) had the highest lifetime risk of prostate cancer.

Session 6: Advances for Immunotherapy in Prostate Cancer

Clinical Development of PSCA-Targeted CAR T Cells for Advanced Prostate Cancer

Tanya Dorff, MD
City of Hope

- Chimeric antigen receptor (CAR) T cells are a type of personalized cancer immunotherapy in which a patient's own immune cells are genetically engineered to target and kill their tumor cells. CAR T cells have been highly effective and are approved for patients with certain types of leukemia and lymphoma. This has inspired research into developing CAR T cells for the treatment of other cancer types, including prostate cancer.
- CAR T cells work via a genetically engineered CAR gene that recognizes a protein target on the tumor cell and then triggers the T cell to become activated and kill the target cell. For CAR T cells to be safe and effective, the protein they are engineered to recognize must be present at high levels on cancer cells and absent from or present only at very low levels on non-cancer cells.
- Prostate cancer-associated proteins that have promise as CAR T cell targets include PSMA, PSCA, and STEAP-1.
- Dr. Tanya Dorff discussed progress on the development of a PSCA-targeting CAR T cell treatment for prostate cancer.
- PSCA (prostate stem cell antigen) is expressed on the surface of ~80% of primary prostate cancer cases and ~90% of metastatic prostate tumors. PSCA has limited expression on normal tissues, including the bladder and gastric lining. PSCA is also expressed on gastric, pancreatic and bladder cancers, so a PSCA-targeted CAR T cell may be effective in those cancers.
- Whether PSCA expression is regulated by the androgen receptor (AR) or affected by hormonal therapy is unclear. If there is an effect, this may impact optimal treatment timing and treatment sequencing.
- Led by Dr. Saul Priceman, the team generated a series of PSCA-targeting CAR genes for testing in preclinical studies. These constructs differed in their 3D structure and how they provide an activation signal to the T cell.
- An optimal PSCA-targeting CAR gene was identified, which utilized the T cell activation domain from the 4-1BB protein, and caused robust T cell activation with minimal T cell exhaustion. This CAR T cell ("PSCA-BBζ") achieved greater complete remissions and survival in mice with prostate cancer than the other constructs, and was selected for further clinical development.
- Optimal activity of CAR T cells in mice required preconditioning with a lympho-depleting chemotherapy prior to receiving CAR T cells, a treatment to clear out some immune cells from the bone marrow to create space for the CAR T cells to reside. Whether preconditioning is necessary for the efficacy of CAR T cells in patients with solid tumors is unknown but it may create changes in the tumor that make it more visible to the T cells.
- A phase 1 clinical trial was initiated to test the safety and identify the optimal dosage of the PSCA-BBζ CAR T cell product in patients with PSCA-expressing metastatic castration

resistant prostate cancer (mCRPC). Some patients will undergo lympho-depleting chemotherapy prior to receiving CAR T cells.

- Generation of the CAR T cell product requires patients to first undergo apheresis, a process to harvest immune cells from the blood. The immune cells are grown in the laboratory under conditions that will greatly expand the number of T cells. T cells are then uploaded with the CAR gene, and a certain number are reinfused into patients, while the rest are frozen and stored for possible later doses.
- Patients on this trial underwent a pre-treatment and post-treatment metastatic biopsy, in order to confirm their cancer expresses PSCA, and to study how the treatment changes tumor and immune biology.
- This trial was still actively recruiting and treating patients at the time of this presentation.
- Dr. Dorff presented the experience of one patient on the trial who had a promising response. This patient had extensive metastatic disease and had failed many prior treatments including novel AR-targeted therapy, chemotherapy combinations, sipuleucel-T, pembrolizumab, and PSMA-targeted radionuclide therapy (¹⁷⁷Lu-PSMA).
- Within 28 days after receiving PSCA CAR T cells (with lympho-depleting preconditioning therapy), the patient experienced a significant reduction in PSA levels and shrinking of metastases in the bones and soft tissues (**Figure**).
- Examination of tumor biopsy samples from this patient found PSCA was expressed before and after treatment. This is important because if PSCA expression is lost, the tumor would likely stop responding to treatment.
- Current standard imaging technologies (CT and bone scans) have poor resolution of prostate cancer metastases in bones. For instance, on CT scans it is hard to tell the difference between a growing tumor and scars left behind from healing tumors.
- Dr. Dorff and colleagues are investigating MRI as an improved method to quantify responses of bone metastases to this treatment. Preliminary studies demonstrated MRI could visualize shrinking bone metastases after PSCA CAR T cell treatment. The potential for PSMA PET imaging to measure treatment responses will also be studied.
- Dr. Dorff and team are also performing correlative studies using samples from patients on this trial to see how tumor cells in the circulation (circulating tumor cells) and bone marrow change after PSCA CAR T cell treatment. In the patient case presented, numbers of tumor cells in blood and marrow decreased after treatment.
- The team is currently developing assays to evaluate PSCA CAR T cells from blood samples, and PSCA expression on circulating tumor cells, so these can be easily measured in patients during treatment.
- Toxicities experienced by the patient presented included cytokine release syndrome which resolved with tocilizumab treatment, hemorrhagic cystitis (bladder inflammation with hemorrhage) which required a transfusion, and delayed gastric emptying.
- Whether lympho-depleting preconditioning therapy is necessary for this treatment is being investigated as a part of the trial. An evaluation of the first 6 patients on the trial found a much higher number of PSCA CAR T cells persisted in blood in the 3 patients who received lympho-depleting preconditioning therapy vs. in the 3 patients who did not.
- The trial is continuing to enroll and treat patients. Questions that remain to be addressed include evaluation of optimal dose of CAR T cells, how long PSCA CAR T cells persist in patients, whether multiple doses should be given, mechanisms of treatment responses vs. treatment failures, and other approaches for improving efficacy and reducing toxicities.
- CAR T cells against other prostate cancer targets are also being developed by this team and others. Ultimately, a combination therapy consisting of CAR T cells with two or more

different targets may be necessary to achieve complete and durable remissions in patients with prostate cancer.

- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/immunotherapy-in-prostate-cancer/>.

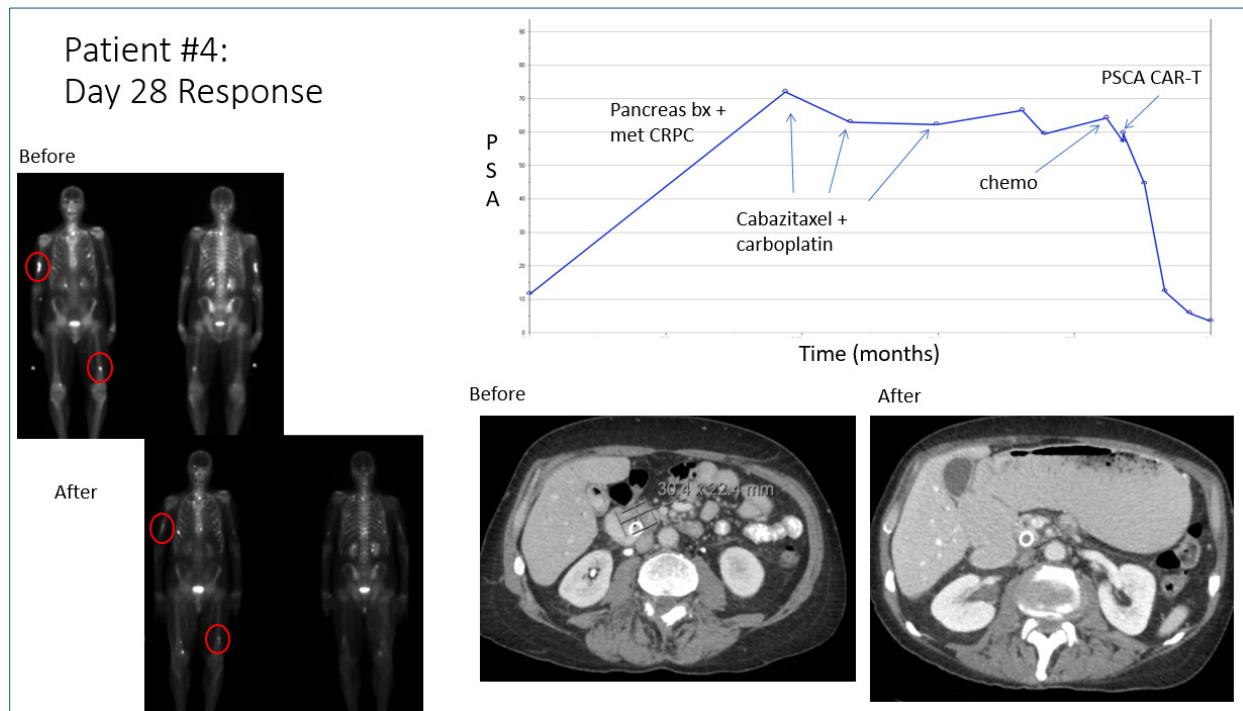


Figure: Responses in one patient, 28 days after receiving PSCA CAR T cells (with lympho-depleting preconditioning therapy). The patient experienced a significant reduction in PSA levels (top right) and shrinking of metastases in the bones (left) and soft tissues (bottom).

Co-expression of a Novel TGF β R Dominant Negative Receptor to Enhance PSMA Chimeric Antigen Receptor Therapy in the Treatment of Castrate Resistant Prostate Cancer Patients

Naomi Haas, MD
University of Pennsylvania

- CAR T cells are a type of personalized immunotherapy in which a patient's own immune cells are genetically engineered to recognize and kill tumor cells. This treatment has been highly effective in some leukemias and lymphomas and is now being developed for prostate and other cancers.

- PSMA is a protein that is present at high levels on the surface of most prostate cancer cells and low or absent on normal cells. PSMA is considered one of the most promising targets for prostate cancer therapies, including immunotherapies.
- Dr. Naomi Haas discussed the development of PSMA-targeting CAR T cells for the treatment of prostate cancer.
- Prostate cancer typically has a highly immune-suppressive tumor microenvironment, which limits anti-tumor immune responses. This has represented a major challenge in the development of effective immunotherapies in this cancer type.
- To overcome this challenge, the PSMA-CAR T cells developed by Haas and colleagues also express a receptor to avoid immune suppressive signals. This receptor, TGFβRdn, prevents negative signals from the immuno-suppressive TGFβ protein, and should enhance the activity of the CAR T cells.
- In preclinical studies in mouse prostate cancer models, the addition of TGFβRdn to PSMA-CAR T cells significantly increased their activity, overall numbers, long-term persistence, and anti-tumor efficacy (**Figure**).
- A phase 1 trial was initiated to test safety, feasibility and potential clinical efficacy of PSMA/TGFβRdn-CAR T cells for the treatment of metastatic castration resistant prostate cancer (mCRPC). To be eligible for the trial, at least 10% of a patient's tumor cells had to express PSMA. Patients also must previously have been treated with a second-generation anti-androgen therapy.
- The trial also evaluated safety and efficacy of the treatment with and without a lympho-depleting preconditioning therapy. This preconditioning therapy, which depletes normal immune cells, is hypothesized to increase the numbers and activity of CAR T cells by creating more space for them in immune tissues such as bone marrow.
- Thus far, 4 cohorts of patients (for a total of 10 patients) have been treated on the trial with different doses of CAR T cells, with and without lympho-depleting therapy.
- The maximum tolerable dose was determined to be 30 million PSMA/TGFβRdn-CAR T cells with lympho-depleting therapy. The 3 patients treated at this dose level all experienced grade 3 toxicities (syndrome of inappropriate antidiuretic hormone secretion (SIADH), cytokine release syndrome, and hypoxia), but no grade 4 or 5 toxicities.
- A single patient was treated at the higher dose level of 300 million PSMA/TGFβRdn-CAR T cells with lympho-depleting therapy, and experienced grade 5 toxicity (death) as a result of prolonged multi-organ failure and sepsis.
- Correlative studies using patient samples are being done to evaluate the levels of CAR T cells and cytokines in patient blood over time. Cytokines are proteins produced by immune cells and indicate immune activities related to efficacy as well as toxicities. Cytokine levels increased with CAR T dose and were highest in patients who received lympho-depleting therapy.
- Of the ten patients treated, 6 experienced reductions in PSA levels, including all 3 patients treated with the maximum tolerable dose. Changes in tumor burden using imaging are still being determined.
- Overall, these results demonstrate that treatment of mCRPC with PSMA/TGFβRdn-CAR T cells is feasible and safe at the current (maximum tolerable) dose level. Responses appear to be dose-dependent and enhanced with the addition of lympho-depleting therapy.
- This trial is still accruing and treating more patients. Patients with other tumor types that express PSMA are also being accrued to this trial.
- A phase 1/2 trial testing serial doses of PSMA/TGFβRdn-CAR T cells is also ongoing.

- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/immunotherapy-in-prostate-cancer/>

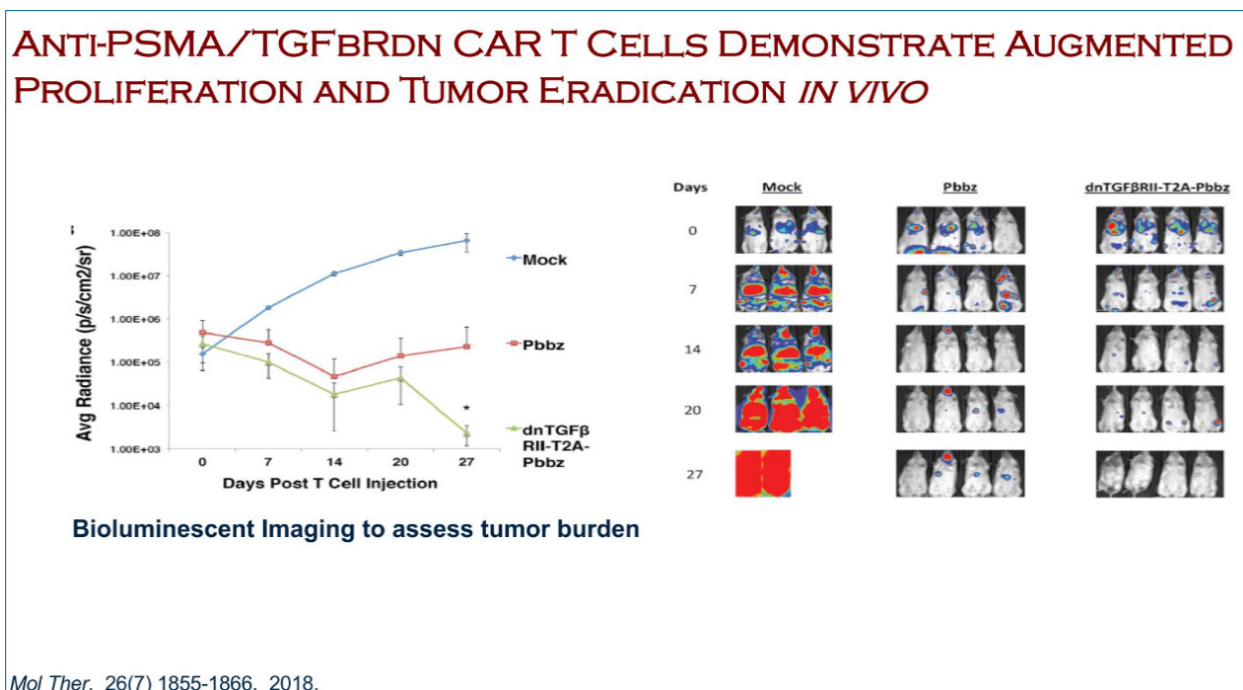


Figure: In preclinical studies in mouse prostate cancer models, PSMA/TGF β Rdn-CAR T cells had better anti-tumor efficacy than PSMA-CAR T cells without TGF β Rdn. Figures demonstrate tumor burden over time by molecular imaging, quantitatively (left) and visually (right), in mice that received no CAR T cells (mock), PSMA-CAR T cells without TGF β Rdn (Pbbz), and PSMA/TGF β Rdn-CAR T cells (dnTGF β RII-T2A-Pbbz).

Development of a First-in-Class Shared Neo-Antigen Vaccine for the Treatment of Prostate Cancer

M. Alejandro Sepulveda, PhD
Janssen Research & Development, LLC

- Anti-cancer vaccines are a strategy to instruct the immune system to attack cancer cells, as either a preventive or therapeutic treatment.
- While there are early studies suggesting promise for this approach in the treatment of prostate cancer, other than Provenge[®], no other vaccine candidates have yet demonstrated efficacy in stage 3 clinical trials. Indeed, recently, PROSTVAC, a vaccine against the prostate cancer protein PSA, which had shown promising early clinical data in phase 2 trials, failed in a phase 3 trial in metastatic castration-resistant prostate cancer (mCRPC).

- Antigens targeted by anti-cancer vaccines could include either normal proteins that are expressed at high levels on cancer cells but at low levels on normal cells, or mutated proteins that are expressed only by cancer cells. However, it is rare for the same protein mutation to be found in multiple prostate cancer patients, so targeting mutated proteins would require personalized vaccine development. Thus, most approaches have focused on targeting normal cancer-associated proteins, so that many patients can receive the same vaccine (“off-the-shelf”). Unfortunately, this approach is difficult because the immune system is also inherently trained to be tolerant to normal proteins in order to avoid auto-immunity. Identifying normal cancer-associated antigens that are not subject to immune tolerance is a challenge.
- Dr. Alejandro Sepulveda discussed a novel approach to develop an off-the-shelf prostate cancer vaccine which targets a common RNA-transcriptional instability that the Janssen team detected in prostate cancer patients.
- Dr. Sepulveda and colleagues hypothesized that prostate cancer antigens common to many patients could be identified by looking not only for protein changes caused by actual DNA mutations, but by looking for protein changes that result from mistakes in RNA production, such as inclusion of introns (regions between gene segments that are supposed to be excluded from the final mRNA), inclusion of cryptic exons (gene segments that are usually excluded in normal cells), and other alterations that result in an out-of-frame code which changes the protein sequence. These RNA processing-based changes would not be detectable by sequencing DNA from tumors, but instead would only be found by deep sequencing of mRNA.
- Altered mRNA that change the protein sequence are termed “neo-ORFs” (neo-open reading frames). The altered proteins resulting from neo-ORFs are termed “neo-antigens.”
- A computational study was done to look for common neo-ORFs in prostate cancer (caused by either DNA mutations or RNA processing alterations). RNA and DNA sequencing data from ~550 prostate cancer patients was evaluated for neo-ORFs present in at least 10% of the cohort, but that were not found in higher than 1% of normal tissue samples from a database of over 6,000 samples. Levels of the neo-ORF RNA also had to be at least 2-times higher in tumors than in the normal prostate mRNA.
- ~100 neo-ORFs were predicted by this analysis. In a validation study, 99% of the predicted neo-ORFs were confirmed to be present in an independent prostate cancer RNA sample set, and 85% were confirmed as full-length transcripts. Indeed, many were present in most patients at high frequencies (**Colored boxes in Figure**).
- Bioinformatic studies suggested that ~50% of patients would have at least 20 predicted neo-ORFs expressed in their tumors which can be presented by their own HLAs (immune molecules that activate T cells against antigens).
- Next, studies were performed to validate that the candidate neo-ORFs identified in the RNA analysis resulted in the expression of neo-antigens (as actual proteins) in prostate cancer cells. Mass spectrometry studies which evaluate protein sequences have confirmed the presence of 13 of 41 thus far.
- The team also found that of 23 prostate cancer neo-antigens tested, 21 were confirmed to effectively stimulate an immune response in healthy donor T cells. Indeed, from a cohort of 10 donors, all of them were able to generate immune responses against at least one neo-antigen, and 7 donors recognized 6 or more antigens.
- Dr. Sepulveda and the Janssen team estimate that a successful vaccine would need to contain 30-40 of these neo-antigens for maximum coverage of patients (for an off-the-shelf vaccine).

- With these neo-antigens at hand, the Janssen team is now focused on utilizing virus vectors as a vaccine platform. In this strategy, the genes for the neo-antigens are encoded in a replication-deficient adenovirus vector for the priming vaccination shot, and in a replication-deficient Vaccinia virus vector for the booster shot. This approach has been used successfully for the Janssen European Union-approved Ebola vaccine, which generates high levels of T cell immune responses that last for at least 1 year.
- Studies also suggest that anti-cancer vaccines will be more efficacious if combined with checkpoint immunotherapy, a type of treatment that blocks negative immune signals and enables much more potent immune responses to develop. This combination strategy will be tested for this vaccine.
- Altogether, this study demonstrates that there are a large number of common neo-antigens present in the tumors of prostate cancer patients, which are generated largely by RNA processing alterations. These neo-antigens are highly immunogenic and thus are promising candidates for the development of an off-the-shelf therapeutic vaccine for the treatment of prostate cancer.
- Work is ongoing to develop a candidate vaccine product that can be tested in clinical trials. Because immunotherapies are presumed to be most effective in low-burden disease, a possible target patient population could be in prostate cancer patients that have early metastatic or biochemically recurrent disease although other patient segments are also being considered.
- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/immunotherapy-in-prostate-cancer/>

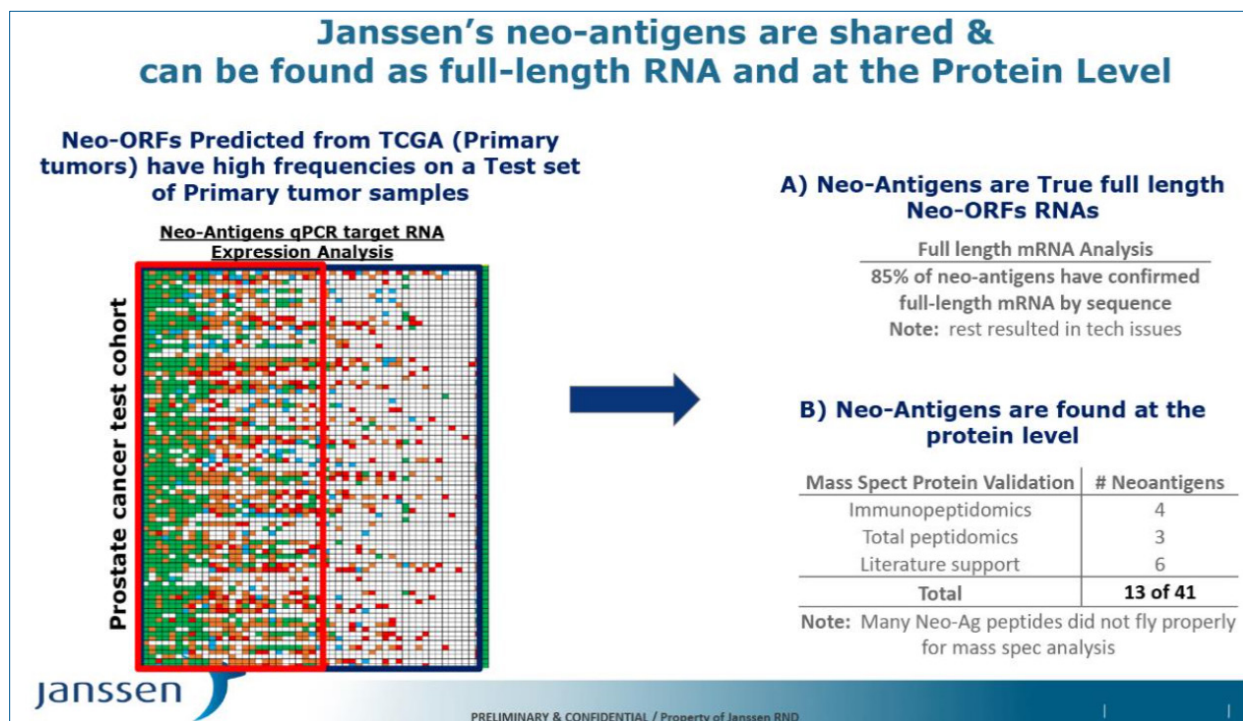


Figure: Left: RNA expression analysis of neo-ORFs demonstrated that many were present in most patients. Right top: Results from validation studies found that 85% of the predicted neo-ORFs were confirmed as full length RNA sequences. Right bottom: Early studies confirmed the expression (as actual proteins) of 13 of 41 predicted neo-ORFs.

Session 7: Recent Advances in Antibody-Drug Conjugates for the Treatment of Cancer

Novel Approaches to Development of Antibody-Drug Conjugates for the Treatment of Cancer

Yuuri Hashimoto, PhD
Daichi Sankyo Co., Ltd.

- Antibody drug conjugates (ADC) are an emerging class of therapies that consist of a tumor-targeting antibody connected to a chemotherapeutic drug. ADCs have been approved for the treatment of cancers including leukemia, multiple myeloma, and breast cancer. Several ADCs are being developed for prostate cancer.
- Dr. Yuuri Hashimoto discussed several ADCs that are being developed for various cancer types.
- The ADC technology discussed by Dr. Hashimoto, “DXd-ADCs,” consist of a tumor-targeting antibody connected via a stable cleavable linker to ~8 DXd chemotherapy molecules. DXd is a topoisomerase 1 inhibitor that is a more potent derivative of the chemotherapy drug irinotecan.
- DXd-ADCs work by first binding to tumor cells targeted by the antibody. The ADC is then taken into the cell, where lysosomal enzymes cleave the linker and release the DXd chemotherapy molecules, which then kill the cell.
- DS-8201 (Trastuzumab deruxtecan) is a HER2-targeting DXd-ADC being developed for HER2-expressing breast and other cancers. The HER2-targeting antibody used for this agent is based on trastuzumab, a therapeutic antibody used for the treatment of HER2-positive breast cancer.
- In preclinical studies, DS-8201 demonstrated favorable pharmacokinetic properties including being highly stable in the plasma with negligible release of the DXd chemotherapy molecules into the circulation. In mouse tumor models, DS-8201 demonstrated promising efficacy against HER2-positive breast and other cancer types as well as breast cancers derived from patients that had developed resistance to Trastuzumab emtansine. Trastuzumab emtansine is a HER2-targeting ADC that is FDA-approved for HER2-positive breast cancer.
- A phase 2 clinical trial was conducted to test 5.4 mg/kg DS-8201 in patients with HER2-positive metastatic or unresectable breast cancer, who previously failed treatment with Trastuzumab emtansine. Overall, confirmed responses ($\geq 30\%$ reduction in tumor size from baseline) were observed in 112 of 184 (61%) of patients, with 11 experiencing a complete response. The median time to tumor progression for patients on the trial was 16.4 months. The median overall survival time has not yet been reached.
- Treatment-emergent adverse effects that occurred in $>15\%$ of patients (any grade) included nausea, fatigue, alopecia, vomiting, constipation, decreased white blood cells and anemia, decreased appetite, headache, and cough. Of special interest was interstitial lung disease, which occurred in 13.6% of patients, including 4 (2.2%) who died from this side effect. An active monitoring program has been established for this side effect.
- Based on the positive results from this clinical trial, the FDA approved DS-8201 for HER2-positive breast cancer in December, 2019.

- U3-1402 (Patritumab deruxtecan) is a HER3-targeted ADC that is being developed for HER3-expressing solid tumors. U3-1402 also uses DXd-ADC technology, carrying ~8 DXd molecules connected through a cleavable linker.
- In preclinical studies, U3-1402 demonstrated highly promising and specific efficacy against HER3-positive tumor models. U3-1402 was also effective in patient-derived erlotinib-resistant lung cancer tumor models. Erlotinib is an EGFR-tyrosine kinase inhibitor (EGFR-TKI) that is used for the treatment of EGFR-mutated non-small cell lung cancer (NSCLC).
- A phase 1 trial testing U3-1402 in patients with EGFR-mutated NSCLC, who previously failed treatment with EGFR-TKI, had promising results. Development of this treatment continues.
- TROP2 is expressed in prostate, breast, lung, and other cancers and may be a promising therapeutic target. DS-1062 is a TROP2-targeted ADC under development. DS-1062 carries four DXd chemotherapy molecules via a cleavable linker (**Figure**).
- In preclinical mouse tumor models, DS-1062 effectively blocked the growth of TROP2-expressing tumors (**Figure**).
- An ongoing phase 1 trial is testing DS-1062 in TROP2-positive lung cancer patients, and early results appear promising. A clinical trial to test DS-1062 in other tumor types including prostate cancer is under consideration.
- Several other DXd-ADCs are in preclinical and clinical development for various cancer types.
- **This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/recent-advances/>**

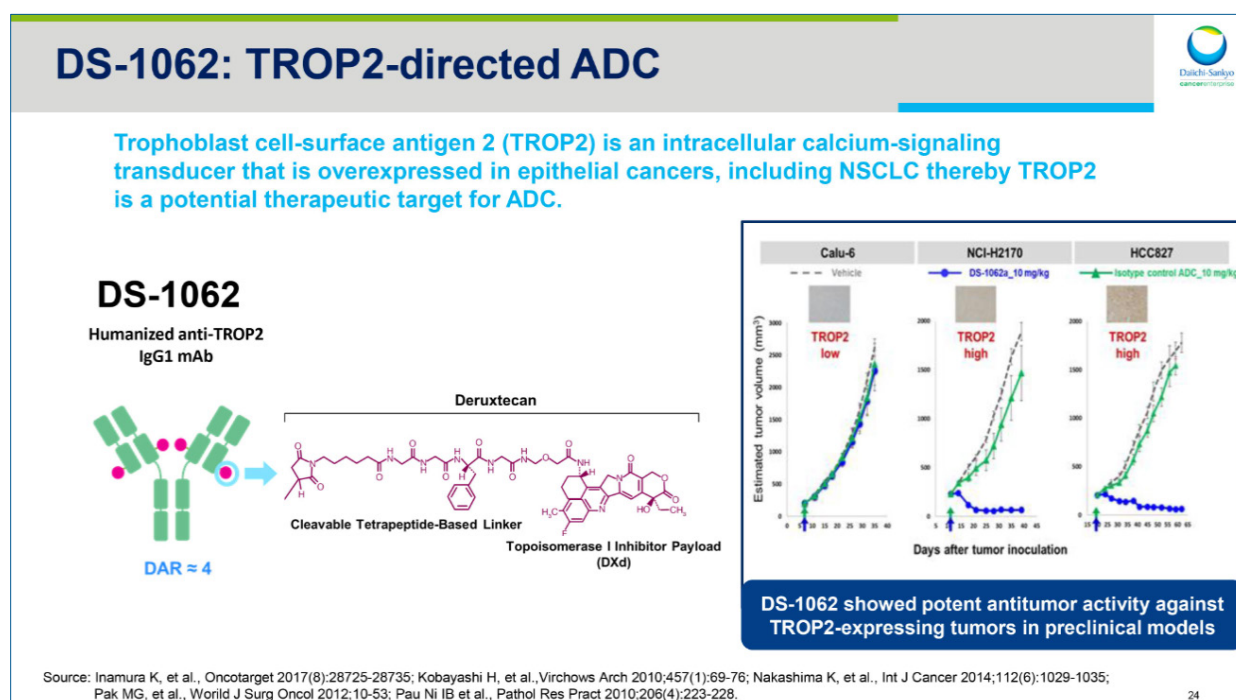


Figure: Left: DS-1062 is a TROP2-targeted ADC that carries four DXd chemotherapy molecules via a cleavable linker. Right: In preclinical mouse models, the TROP2-targeted ADC DS-1062 effectively blocked the growth of TROP2-expressing tumors.

PSMA Antibody Targeted Amanitin Conjugate (PSMA-ATAC): Introducing a Novel Mode of Action into Prostate Cancer Therapy

George Badescu, PhD
Heidelberg Pharma AG

- Antibody-drug conjugates (ADCs) are a new class of cancer treatments consisting of a tumor-targeting antibody attached to a chemotherapy agent.
- Amanitin is a novel toxin that works by inhibiting RNA polymerase II, the enzyme responsible for mRNA synthesis. This is a completely new mode of action for a chemotherapy. Amanitin is the only currently known inhibitor of RNA polymerase II.
- Unlike traditional chemotherapies which target aspects of rapidly dividing cells, inhibiting RNA polymerase II with amanitin kills both proliferating and dormant cells. Thus, amanitin may be able to overcome treatment resistance and tumor dormancy, which are common modes by which tumors evade therapy.
- Dr. George Badescu discussed a novel ADC technology that delivers amanitin as the toxic payload to tumor cells, termed “antibody targeted amanitin conjugates” (ATAC).
- In this technology, amanitin is attached to a tumor-targeting antibody via a cleavable linker. Upon binding to the target tumor cell, the ADC is taken into the cell, where the linker is cleaved and amanitin is released, killing the cell. If amanitin is given alone, without being attached to an antibody, it is not taken into cells and does not kill them.
- Cells typically express very low amounts of RNA polymerase II in the order of 1,000s of proteins, as compared to other proteins that are present by the millions in each cell. Thus, only a small number of amanitin molecules need to enter cells to inhibit enough RNA polymerase II to kill the cell. ATACs are effective even in cells that express very low levels of the antibody target.
- *TP53* is a critical tumor suppressor gene that is frequently deleted in cancer. RNA polymerase II is encoded in the genome very near to *TP53* (in chromosome 17p), and is often co-deleted with *TP53*.
- Dr. Badescu and colleagues demonstrated that tumors which have deleted one copy of RNA polymerase II may be exceptionally sensitive to amanitin. Thus, 17p deletion, which is seen in 20-80% of different tumor types, may be a biomarker for higher sensitivity to ATACs.
- In preclinical studies, ATACs were confirmed to be more effective, and required lower doses, in tumors with 17p deletion.
- Several ATACs are being developed for various cancer types.
- A HER2-targeting ATAC is under development for breast cancer. In preclinical studies, the HER2-ATAC was highly effective, even in tumors that had developed resistance to other HER2-targeting treatments.
- Prostate cancer is a slowly dividing cancer type, and thus may be a good match with ATAC therapies. In addition, ~60% of metastatic castration resistant prostate cancer (mCRPC) cases have 17p deletion.
- A PSMA-targeting ATAC is under development for prostate cancer. PSMA is a protein that is highly and specifically expressed on the surface of most prostate cancer cells, and is a promising therapeutic target. Many classes of PSMA-targeting cancer therapies are being developed.
- In preclinical studies in mouse models, complete regression of prostate tumors occurred after a single dose of PSMA-ATAC (**Figure**).

- These studies suggest PSMA-ATAC may have strong efficacy in mCRPC. Development of this ATAC is ongoing.
- This presentation can be viewed in full here: <https://www.pcf.org/scientific-retreat/video/recent-advances/>

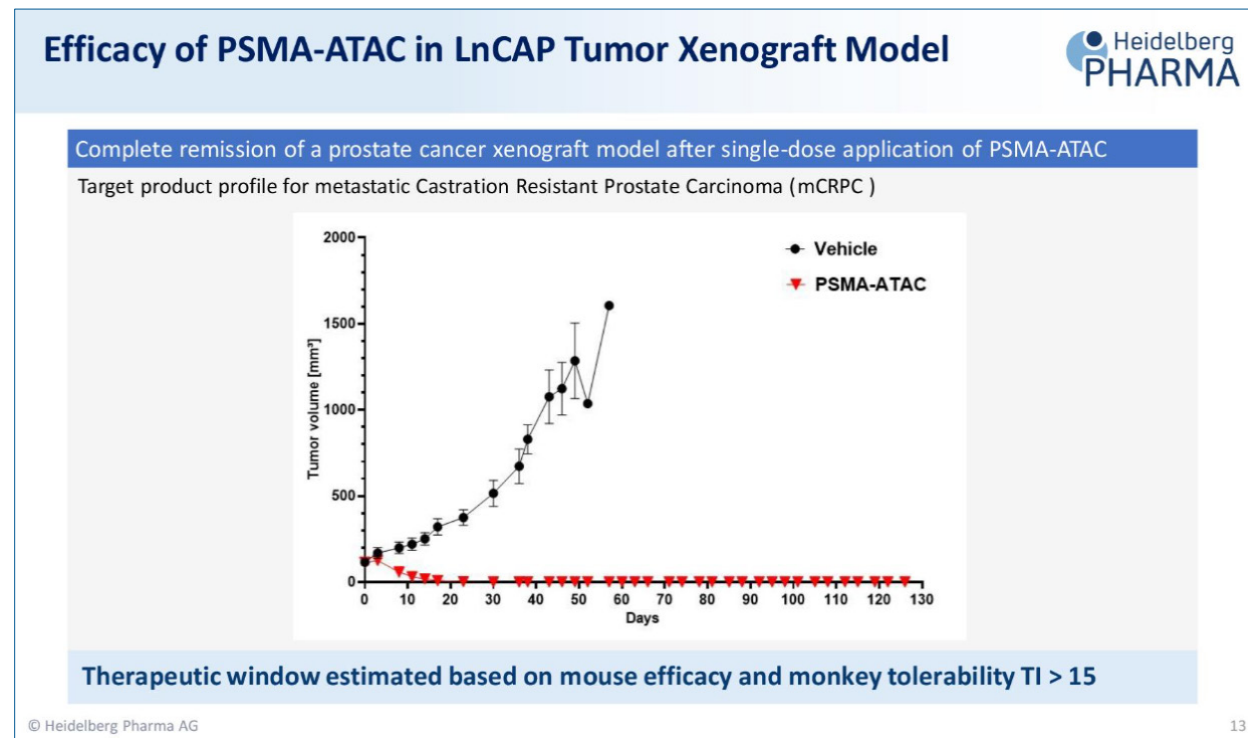


Figure: In preclinical studies in mouse models, complete regression of prostate tumors occurred after a single dose of PSMA-ATAC.



APPENDIX I:

27th ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT

PCF WOMEN IN SCIENCE FORUM

OCTOBER 20, 2020

PROGRAM AGENDA



Prostate Cancer Foundation Women in Science Forum

PCF Women in Science Forum

Tuesday, October 20, 2020

***All times in U.S. PDT**

Organizers: **Himisha Beltran, MD** (Harvard: Dana-Farber Cancer Institute), **Lorelei Mucci, ScD** (Harvard T.H. Chan School of Public Health), **Karen Knudsen, MBA, PhD** (Thomas Jefferson University), **Amina Zoubeydi, PhD** (Vancouver Prostate Centre), **Ayesha Shafi, PhD** (Thomas Jefferson University), **Sarah Amend, PhD** (Johns Hopkins University), **Susan Halabi, PhD** (Duke University), **Claire Fletcher, PhD** (Imperial College London), **Andrea Miyahira, PhD** (Prostate Cancer Foundation), **Howard Soule, PhD** (Prostate Cancer Foundation).

Overview: This is a half-day networking event in support of women in science in conjunction with the 27th Annual PCF Scientific Retreat. This fifth annual event is open to all individuals attending the PCF Scientific Retreat, both junior and senior and regardless of gender across all disciplines of science and people interested in this topic. The goals are to build teams and solve scientific problems through dialogue and social events. This will ensure a strong pipeline of women prostate cancer researchers, and will identify opportunities for further training, mentoring and synergy of a stellar network of women in science.

Welcome, Introductions and Vision

7:00 AM – 7:05 AM

Himisha Beltran, MD

Harvard: Dana-Farber Cancer Institute

Lorelei Mucci, ScD

Harvard T.H. Chan School of Public Health

Session 1: Keynote 1: Run Your Own Race, Always Remembering to Plant the Seeds of Triumph

7:05 AM – 7:50 AM

Introduction by Lorelei Mucci, ScD (Harvard T.H. Chan School of Public Health)

Dara Richardson-Heron, MD

Chief Patient Officer, Pfizer Inc.

Live Question and Answer

Moderators: Lorelei Mucci, ScD (Harvard T.H. Chan School of Public Health)

Alicia Morgans, MD (Northwestern University)

7:50 AM – 7:55 AM *Please Return to the Virtual Lobby to Join the Next Session*

Session 2: Keynote II: Adaptive Platform Trials: Scalable from Breast Cancer to COVID

7:55 AM – 8:45 AM

Introduction by Himisha Beltran, MD (Harvard: Dana-Farber Cancer Institute)

Laura Esserman, MD, MBA

Professor, Departments of Surgery and Radiology, University of California, San Francisco; Director, UCSF Breast Care Center; Co-Leader, Breast Oncology Program, UCSF Helen Diller Family Comprehensive Cancer Center; Alfred A. de Lorimier Endowed Chair in General Surgery

Live Question and Answer

Moderators: Susan Halabi, PhD (Duke University)

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

8:45 AM – 8:50 AM *Please Return to the Virtual Lobby to Join the Next Session*

Session 3: Panel Discussion: Diversity & Inclusion in Cancer Research Leadership

8:50 AM – 10:15 AM

Moderator:

Karen Knudsen, MBA, PhD

Executive Vice President of Oncology Services, Jefferson Health Enterprise Director, Sidney Kimmel Cancer Center, Thomas Jefferson University

Panelists:

Laurie Glimcher, MD

President and CEO, Dana-Farber Cancer Institute; Director, Dana-Farber/Harvard Cancer Center; The Richard and Susan Smith Professor of Medicine at Harvard Medical School

Elena Martinez, PhD

Sam M. Walton Endowed Chair for Cancer Research and Professor, Department of Family Medicine and Public Health; Associate Director, Population Sciences, Disparities and Community Engagement; UC San Diego Moores Cancer Center, University of California, San Diego

Charlene Le Fauve, PhD

Senior Advisor to the Chief Officer for Scientific Workforce Diversity, National Institutes of Health



Prostate Cancer Foundation
Women in Science Forum

Robert A. Winn, MD

Director, Virginia Commonwealth University (VCU) Massey Cancer Center; Senior Associate Dean for Cancer Innovation, VCU School of Medicine; Professor, Division of Pulmonary Disease and Critical Care Medicine, Virginia Commonwealth University

Panel Discussion followed by Live Question and Answer

10:15 AM – 10:45 AM **BREAK**

Please Return to the Virtual Lobby to Join the Next Session

Session 4: The Effects of the Pandemic on High School STEM Students

10:45 AM - 11:25 AM

Introduction by Brandon Mahal, MD (University of Miami)

Elisabeth Heath, MD (Karmanos Cancer Institute, Wayne State University)

Brandon Contreras

Teacher, Dominguez High School

Giselle Quiroz

Sheila Gallardo

Jenise Hurtado

Jessica Craig

Elizabeth Trujillo

Students, Dominguez High School

Musical Performance: "Rise Up"

Xochilt Marquez

Dominguez High School

Introduced by Brandon Contreras

Live Question and Answer

Moderators: Brandon Mahal, MD (University of Miami)

Elisabeth Heath, MD (Karmanos Cancer Institute, Wayne State University)

11:25 AM – 11:30 AM *Please Return to the Virtual Lobby to Join the Next Session*



Session 5: PCF Women in Science "Above and Beyond" Award Presentation and Keynote Lecture

11:30 AM – 12:00 PM

Introduction and Award Presentation

Amina Zoubeidi, PhD (Vancouver Prostate Centre)

Susan Halabi, PhD (Duke University)

Beside Every Great Woman are Other Great Women

Rachel Ramoni, DMD, ScD

Veterans Health Administration

Live Question and Answer

Moderators: Amina Zoubeidi, PhD (Vancouver Prostate Centre)

Susan Halabi, PhD (Duke University)

Session 6: Closing Remarks and Introduction to Breakout Networking Session

12:00 PM – 12:05 PM

Sarah Amend, PhD (Johns Hopkins University)

Claire Fletcher, PhD (Imperial College London)

Ayesha Shafi, PhD (Thomas Jefferson University)

12:05 PM – 12:15 PM *Please Return to the Virtual Lobby to Enter Breakout Networking Rooms*

Session 7: Breakout Networking Session: Collaborative Research Team Building

12:15 PM – 1:45 PM

This event **requires RSVP** and is an opportunity for attendees to lead or join a new prostate cancer research team with the goal of applying for a team science award/program grant such as a PCF Challenge Award, in the next 1-2 years.

Attendees participating in this event will have received an email from amiyahira@pcf.org with information on their team and breakout networking room number assignment.

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

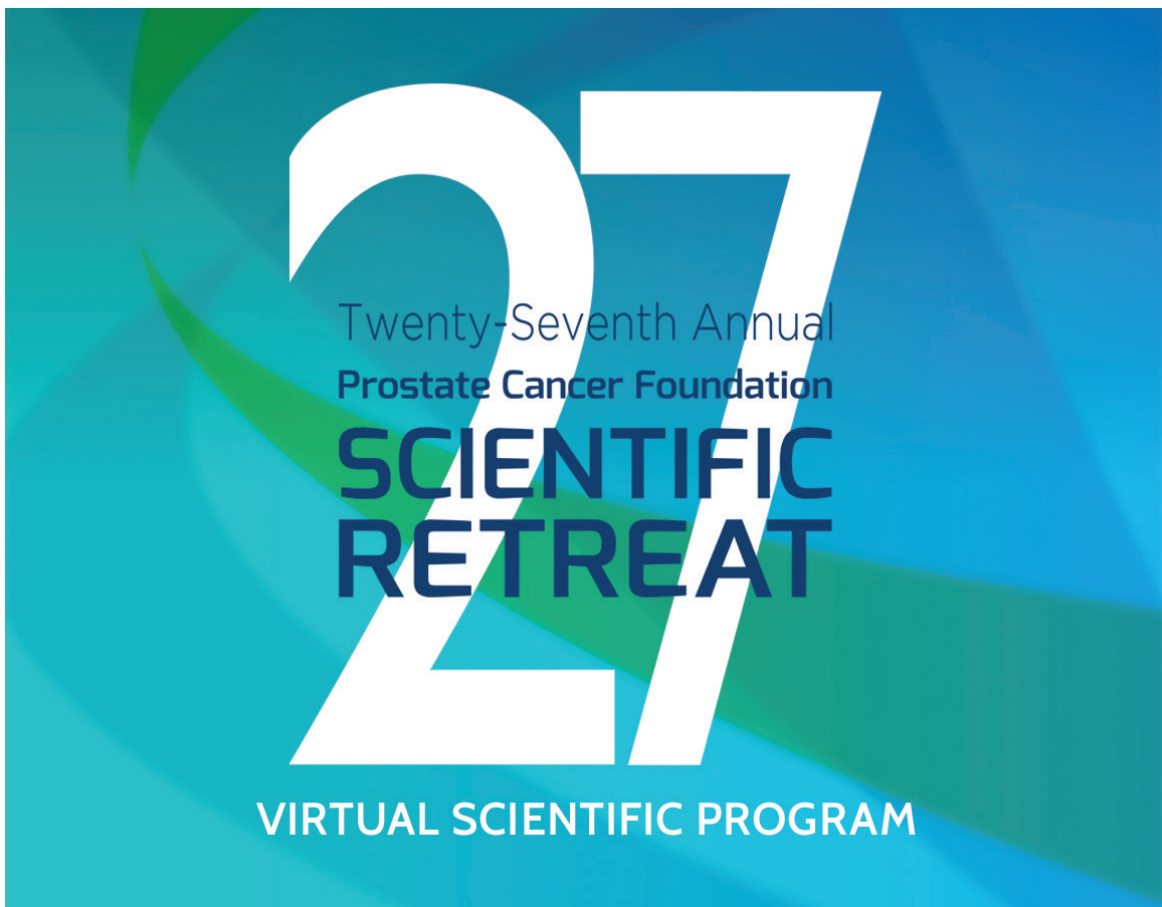


We deeply thank our Retreat supporters for providing funding for this educational initiative.



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APPENDIX II:

27th ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT

PCF YOUNG INVESTIGATOR FORUM

OCTOBER 21, 2020

PROGRAM AGENDA

AGENDA

YOUNG INVESTIGATOR FORUM

Wednesday, October 21, 2020

*All times in U.S. PDT

Welcome & Introduction

7:00 AM - 7:05 AM

Howard Soule, PhD

Prostate Cancer Foundation

Andrea Miyahira, PhD

Prostate Cancer Foundation

Session 1: Panel Discussion: Maintaining Research Productivity in the COVID Era: Perspectives from the YI Spectrum

7:05 AM - 8:25 AM

Moderators: Sarah Amend, PhD

Johns Hopkins University

Ayesha Shafi, PhD

Thomas Jefferson University

Panelists: Wassim Abida, MD, PhD

Memorial Sloan Kettering Cancer Center

Claire Fletcher, PhD

Imperial College London, UK

Salma Kaochar, PhD

Baylor College of Medicine

Kosj Yamoah, MD, PhD

Moffitt Cancer Center

Live Question & Answer

8:25 AM - 8:30 AM

Please Return to the Virtual Lobby to Join the Next Session



Session 2: Cancer Research and Career Development during a Pandemic: Challenges, Lessons, Strategies and Opportunities

8:30 AM - 9:05 AM

Ross Levine, MD

Memorial Sloan Kettering Cancer Center

*Introduced by Howard Soule, PhD
Prostate Cancer Foundation*

Live Question & Answer

Moderators: Howard Soule, PhD & Andrea Miyahira, PhD

Session 3: The PCF-ONE (PCF-One-on-one Networking & Engagement) Initiative

9:05 AM - 9:10 AM

Ayesha Shafi, PhD

Thomas Jefferson University

Sarah Amend, PhD

Johns Hopkins University

*Introduced by Andrea Miyahira, PhD
Prostate Cancer Foundation*

9:10 AM - 9:15 AM *Please Return to the Virtual Lobby to Join the Next Session*

Session 4: The Transition Path from Trainee to Faculty

9:15 AM - 10:05 AM

Tanya Stoyanova, PhD

Stanford University

*Introduced by Howard Soule, PhD
Prostate Cancer Foundation*

Live Question and Answer

Moderators: Howard Soule, PhD & Andrea Miyahira, PhD

10:05 AM - 10:10 AM *Please Return to the Virtual Lobby to Join the Next Session*



Session 5: Navigating Research and Careers in Challenging Times
10:10 AM - 10:58 AM

Dinah Singer, PhD
National Cancer Institute

Introduced by William Dahut, MD
National Cancer Institute

Live Question and Answer
Moderators: Howard Soule, PhD & Andrea Miyahira, PhD

Session 6: Closing Remarks and Introduction to Speed Networking Session
10:58 AM – 11:00 AM

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

11:00 AM - 11:30 AM **BREAK**
Please Return to the Virtual Lobby to Enter Speed Networking Rooms

Session 7: PCF Young Investigator Speed Networking
11:30 AM - 12:45 PM

Speed Networking

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

Attendees participating in this event will have received an email from amiyahira@pcf.org with information on their speed networking room number assignment.

11:30 AM – 11:55 AM **Speed Networking Session # 1**

11:55 AM - 12:20 PM **Speed Networking Session # 2**

12:20 PM - 12:45 PM **Speed Networking Session # 3**

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



Program Committee:

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

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

Sarah Amend, PhD (Johns Hopkins University)

Ayesha Shafi, PhD (Thomas Jefferson University)

Tanya Stoyanova, PhD (Stanford University)

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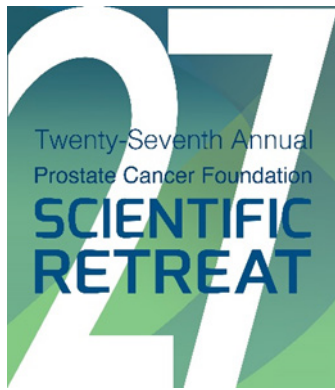
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APPENDIX III:

27th ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT OCTOBER 22-23, 2020

PROGRAM AGENDA



AGENDA

Thursday, October 22, 2020
***All times in U.S. PDT**

VIRTUAL POSTER SESSION

Starting on Tuesday October 20, 2020, 12:01 AM U.S. PDT

GENERAL SESSIONS

Welcome and Opening Remarks

7:00 AM - 7:05 AM

Howard Soule, PhD
Prostate Cancer Foundation

Session 1: Prostate Cancer, Androgens and COVID-19

7:05 AM - 8:05 AM

Moderator: Nima Sharifi, MD
Cleveland Clinic

Introduction

Nima Sharifi, MD
Cleveland Clinic

Regulation and Targeting of SARS-CoV-2 Entry Factors ACE2 and TMPRSS2 in Human Airway Epithelial Cell Subtypes

Arul Chinnaiyan, MD, PhD
University of Michigan; Michigan Center for Translational Pathology

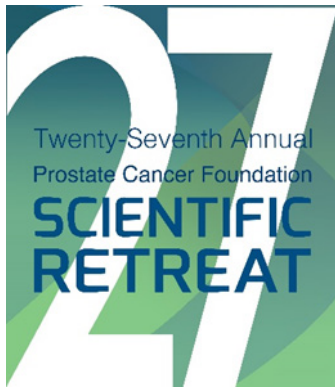
Randomized Clinical Trial of Camostat vs. Placebo in COVID-19 Outpatients

Joseph Vinetz, MD
Yale University

Hormonal Intervention for the Treatment of Veterans with COVID-19 Requiring Hospitalization (HITCH)

Matthew Rettig, MD
University of California, Los Angeles; VA Greater Los Angeles Healthcare System

Live Session Discussion



Thursday, October 22, 2020

8:05 AM - 8:10 AM Please Return to the Virtual Lobby to Join the Next Session

Session 2: Circulating DNA Methylation Biomarkers for Diagnosis, Prognosis and Treatment Selection

8:10 AM - 9:10 AM

Moderator: Gerhardt Attard, MD, PhD
University College London Cancer Institute, UK

Introduction

Gerhardt Attard, MD, PhD
University College London Cancer Institute, UK

Using 5-hydroxymethylcytosine Sequencing to Interrogate Biological Drivers of Advanced Prostate Cancer

Martin Sjöström, MD, PhD
University of California, San Francisco

Opportunities for Tracking the Prostate Cancer Methylome in Plasma

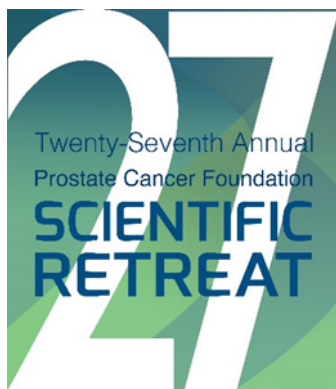
Gerhardt Attard, MD, PhD
University College London Cancer Institute, UK

Circulating Methylation Biomarkers for Neuroendocrine Prostate Cancer Differentiation

Francesca Demichelis, PhD
University of Trento, Italy

Live Session Discussion

9:10 AM - 9:15 AM Please Return to the Virtual Lobby to Join the Next Session



Thursday, October 22, 2020

SPECIAL LECTURE

9:15 AM - 9:38 AM

***Dual Functions of SPOP and ERG Dictate
Androgen Therapy Responses in Prostate Cancer***

Jean-Philippe Theurillat, MD

Institute of Oncology Research, Switzerland

*Introduced by Prof. Mark Rubin, MD
University of Bern, Switzerland*

Live Discussion

Moderators: Howard Soule, PhD & Andrea Miyahira, PhD

SPECIAL LECTURE

9:38 AM - 9:53 AM

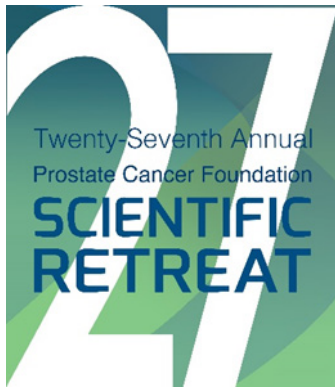
***A Community Resource of Genetically-Engineered Mouse Models that Recapitulate the
Phenotypic Spectrum of Prostate Cancer***

Cory Abate-Shen, PhD

Columbia University Irving Medical Center

Live Discussion

Moderators: Howard Soule, PhD & Andrea Miyahira, PhD



Thursday, October 22, 2020

SPECIAL LECTURE

9:53 AM - 10:15 AM

The Genomic Evolution of Prostate Cancer

Paul Boutros, PhD, MBA

University of California, Los Angeles

Introduced by Howard Soule, PhD

Prostate Cancer Foundation

Live Discussion

Moderators: Howard Soule, PhD & Andrea Miyahira, PhD

10:15 AM - 11:55 AM BREAK

Please Return to the Virtual Lobby to Join the Next Session

DEBATE:

Prostate Cancer Genomic Classifiers; Are We Ready for Prime Time?

11:55 AM - 12:40 PM

Moderators:

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

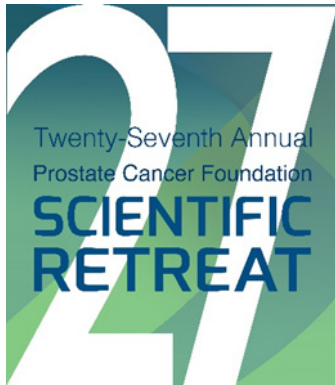
Rana McKay, MD (University of California, San Diego)

Speakers:

Pro: Daniel Spratt, MD (University of Michigan)

Con: Daniel Lin, MD (University of Washington)

Live Discussion



Thursday, October 22, 2020

12:40 PM - 12:45 PM Please Return to the Virtual Lobby to Join the Next Session

Session 3: Targeting MYC, the Emperor of Oncoproteins

12:45 PM - 2:00 PM

Moderator: Sarki Abdulkadir, MD, PhD
Northwestern University

Introduction
Sarki Abdulkadir, MD, PhD
Northwestern University

MYC and the Tumor Immune Microenvironment
Dean Felsher, MD, PhD
Stanford University

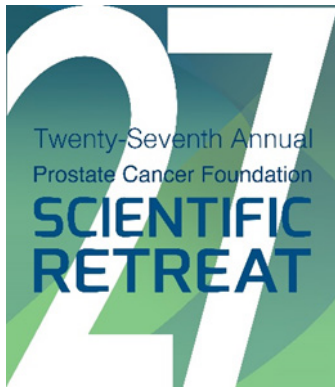
Advances in MYC Therapeutic Targeting in Cancer
Rosalie Sears, PhD
Oregon Health & Science University

N-Myc as a Driver of Lineage Plasticity in Advanced Prostate Cancer
David Rickman, PhD
Weill Cornell Medicine

Small-Molecule MYC Inhibitors
Sarki Abdulkadir, MD, PhD
Northwestern University

Live Session Discussion

2:00 PM - 2:05 PM Please Return to the Virtual Lobby to Join the Next Session



Thursday, October 22, 2020

SPECIAL LECTURE

2:05 PM - 2:35 PM

Current Challenges in Treatment of Patients with Metastatic Prostate Cancer

Himisha Beltran, MD

Harvard: Dana Farber Cancer Institute

Introduced by Rana McKay, MD

University of California, San Diego

Live Discussion

Moderators: Howard Soule, PhD & Andrea Miyahira, PhD

PCF Press:

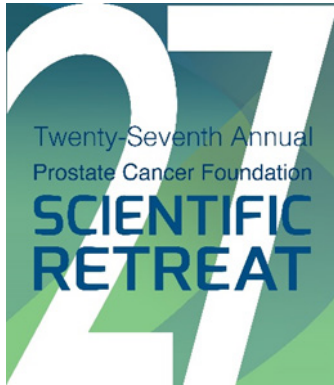
Highlights from Day 1 and Look Forward at Day 2

2:35 PM - 2:45 PM

Karen Knudsen, PhD

Thomas Jefferson University

END DAY ONE



Friday, October 23, 2020

PANEL DISCUSSION:

Prostate Cancer Disparities: Lessons from the COVID-19 Era

7:00 AM – 8:00 AM

Moderator: Brandon Mahal, MD

University of Miami

Panelists:

Erin Kobetz, PhD, MPH (University of Miami)

Monica Baskin, PhD (University of Alabama at Birmingham)

Thomas Farrington (Prostate Health Education Network)

Randy Vince Jr., MD (University of Michigan)

Introduced by Howard Soule, PhD

Prostate Cancer Foundation

Live Discussion

8:00 AM - 8:05 AM *Please Return to the Virtual Lobby to Join the Next Session*

Session 4: Late Breaking Clinical Data for Prostate Cancer Patients

8:05 AM - 9:20 AM

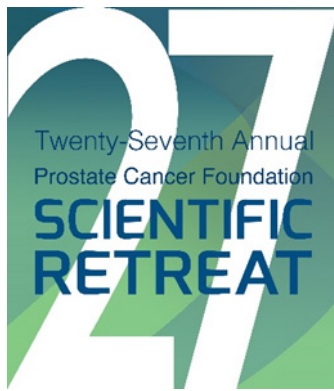
Moderators: Howard Soule, PhD

Prostate Cancer Foundation

Introduction

Howard Soule, PhD

Prostate Cancer Foundation



Friday, October 23, 2020

Combinatorial Targeting of AR and AKT with Abiraterone and Ipatasertib for mCRPC with and without PTEN loss: The Ipatential150 Phase 3 Trial

Johann de Bono, MD, PhD

The Institute of Cancer Research; Royal Marsden Hospital, London, UK

Phase 1 Clinical Profile of AMG 160, a Half-Life Extended PSMA Bispecific T-cell Engager (BiTE®) Immunotherapy for Patients with Metastatic Castration-Resistant Prostate Cancer

Matthew Rettig, MD

University of California, Los Angeles; VA Greater Los Angeles Healthcare System

Phase 1 Study of AMG 509, a STEAP1 x CD3 T Cell–Recruiting XmAb® 2+1 Immune Therapy, in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Wm. Kevin Kelly, DO

Sidney Kimmel Medical College at Thomas Jefferson University; Sidney Kimmel Cancer Center

Human Costimulatory Bispecific Antibodies in Cancer Immunotherapy: Focus in Prostate Cancer

Dimitris Skokos, PhD

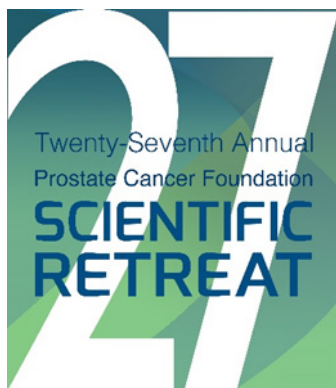
Regeneron Pharmaceuticals

Elizabeth Miller, MD

Regeneron Pharmaceuticals

Live Session Discussion

9:20 AM - 9:25 AM Please Return to the Virtual Lobby to Join the Next Session



Friday, October 23, 2020

Session 5: Microbiome and Cancer

9:25 AM - 10:25 AM

Moderator: Ellen Filvaroff, PhD

Bristol Myers Squibb

Introduction

Ellen Filvaroff, PhD

Bristol Myers Squibb

The Plasticity of the Microbiome in Colorectal Cancer

Christian Jobin, PhD

University of Florida

Host-Microbiome Interactions in Human Cancer

Ran Blekhman, PhD

University of Minnesota

Gut Microbiota and Cancer Immunotherapy

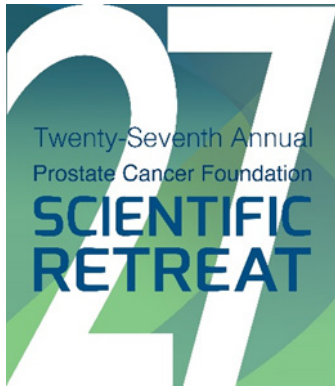
Andrew Y. Koh, MD

University of Texas Southwestern Medical Center

Live Session Discussion

10:25 AM - 10:55 AM BREAK

Please Return to the Virtual Lobby to Join the Next Session



Friday, October 23, 2020

SPECIAL LECTURE

10:55 AM - 11:30 AM

State of the Science 2020

Jonathan W. Simons, MD

Prostate Cancer Foundation

Introduced by Howard Soule, PhD

Prostate Cancer Foundation

11:30 AM - 11:35 AM *Please Return to the Virtual Lobby to Join the Next Session*

SPECIAL LECTURE

11:35 AM - 11:50 AM

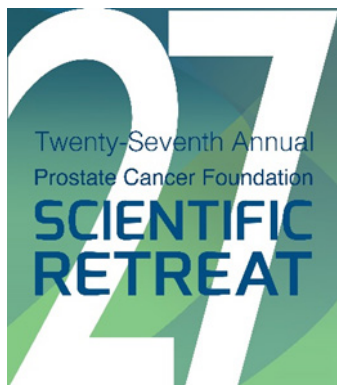
VA-PCF Collaboration: Streamlined Genetic Sequencing in Veterans for Improved Clinical Care and Research Opportunities

Julie Graff, MD

VA Portland Health Care System

Introduced by Rebecca Levine

Prostate Cancer Foundation



Friday, October 23, 2020

SPECIAL LECTURE

11:50 AM - 12:15 PM

A Polygenic Risk Score for Predicting Prostate Cancer in Men of African Descent

Christopher Haiman, ScD

Center for Genetic Epidemiology and Norris Comprehensive Cancer Center,
University of Southern California

Introduced by Howard Soule, PhD

Prostate Cancer Foundation

Live Discussion

Moderators: Howard Soule, PhD & Andrea Miyahira, PhD

12:15 PM - 12:20 PM Please Return to the Virtual Lobby to Join the Next Session

Session 6: Advances for Immunotherapy in Prostate Cancer

12:20 PM - 1:15 PM

Moderators: Howard Soule, PhD

Andrea Miyahira, PhD

Prostate Cancer Foundation

Introduction

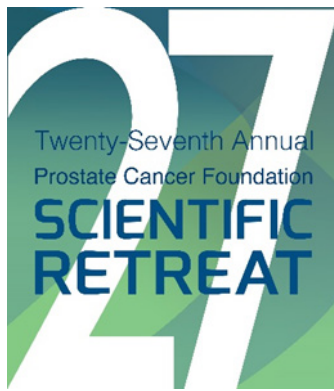
Howard Soule, PhD

Prostate Cancer Foundation

Clinical Development of PSCA-Targeted CAR T Cells for Advanced Prostate Cancer

Tanya Dorff, MD

City of Hope



Friday, October 23, 2020

Co-expression of a Novel TGF β R Dominant Negative Receptor to Enhance PSMA Chimeric Antigen Receptor Therapy in the Treatment of Castrate Resistant Prostate Cancer Patients

Naomi Haas, MD

University of Pennsylvania

Development of a First-in-Class Shared Neo-Antigen Vaccine for the Treatment of Prostate Cancer

M. Alejandro Sepulveda, PhD

Janssen Research & Development, LLC

Live Discussion

1:15 PM - 1:20 PM Please Return to the Virtual Lobby to Join the Next Session

Session 7: Recent Advances in Antibody-Drug Conjugates for the Treatment of Cancer

1:20 PM - 2:30 PM

Moderator: Marco Gottardis, PhD

Janssen Research & Development, LLC

Introduction

Marco Gottardis, PhD

Janssen Research & Development, LLC

Antibody Drug Conjugates: From Early Stage Research to Clinically Approved Drugs

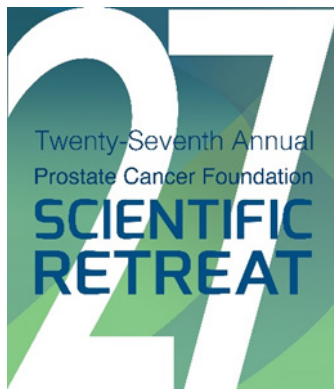
Peter Senter, PhD

Seattle Genetics

Novel Approaches to Development of Antibody-Drug Conjugates for the Treatment of Cancer

Yuuri Hashimoto, PhD

Daiichi Sankyo Co., Ltd.



Friday, October 23, 2020

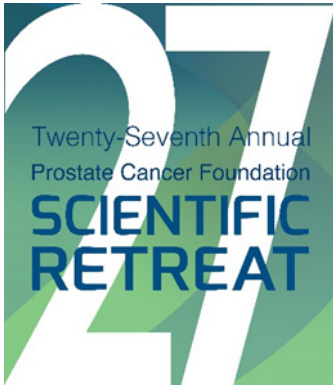
***PSMA Antibody Targeted Amanitin Conjugate (PSMA-ATAC):
Introducing a Novel Mode of Action into Prostate Cancer Therapy***
George Badescu, PhD
Heidelberg Pharma AG

Live Session Discussion

Closing Remarks
2:30 PM - 2:35 PM

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

**END DAY TWO
MEETING ADJOURNED**



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)

Sarki Abdulkadir, MD, PhD (Northwestern University)

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

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

Ellen Filvaroff, PhD (Bristol Myers Squibb)

Marco Gottardis, PhD (Janssen Pharmaceuticals)

Brandon Mahal, MD (University of Miami)

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

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