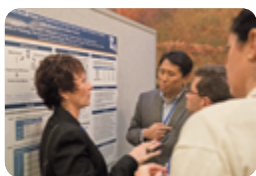# STATE OF THE SCIENCE REPORT

Highlights from the 21st Annual PCF Scientific Retreat

October 2014

Provided with the compliments of the Prostate Cancer Foundation

PROSTATE CANCER FOUNDATION

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Introduction

The Prostate Cancer Foundation (PCF) convened the 21st Annual PCF Scientific Retreat in Carlsbad, CA, on October 23-25, 2014. PCF's Annual Scientific Retreat brings together the world's top physicians, scientists and business leaders in an interactive environment enriched with a diverse and impactful agenda of scientific presentations, knowledge exchange, and collaborative forums and discussions. This event is considered the foremost prostate cancer conference in the world and one of PCF's primary societal contributions. Over the last two decades, the Scientific Retreat has successfully advanced our Foundation mission of eliminating prostate cancer as a health risk for all men and their families.

The 21st Annual Scientific Retreat featured the following:

- 50 presentations in the Plenary Session

- 166 poster presentations

- 20 different scientific disciplines related to prostate cancer biology presented and discussed

- 57% of speakers presented first-in-field, unpublished data at a PCF Scientific Retreat for the first time

- Attendance by 529 participants from 17 countries, including 223 PhDs, 172 MDs, 91 MD PhDs, 2 PharmDs, 2 DVM PhDs, 1 DMD, and 1 DO

- 117 academic institutions, 32 biopharmaceutical companies, 13 medical research foundations, and 6 other for-profit companies

- NIH, NCI, and Dept. of Defense research leaders

- Attendance by 121 PCF Young Investigators

- Attendance by 21 PCF Board of Director members, major donors, and special guests

The PCF "Global Research Enterprise" now extends to 19 countries and funds a robust research portfolio. Since 1993, PCF has awarded over $382 million in innovative prostate cancer research projects, led by an estimated 500+ prostate cancer researchers. This includes $33 million awarded to 153 PCF Young Investigators since 2007 and nearly $102 million to PCF Challenge Award teams since 2008.

We thank the supporters of the Retreat for their generous contributions: Sanofi-Aventis, Janssen, Millennium/Takeda, Astellas/Medivation, Genentech, Bayer, Bristol-Myers Squibb, GenomeDx and Genomic Health.

The 2014 State of the Science Report individually summarizes each presentation given at the Retreat to provide a synthetic overview of the scientific discipline and latest findings impacting prostate cancer research, diagnosis, prognosis or treatment. The goal of PCF in hosting this Retreat and disseminating this information is to translate these findings as rapidly as possible into clinical investigation. Toward that end, we hope this report will be useful to you and stimulate further dialogue, data exchange and inquisition. If you have specific questions, please contact Dr. Andrea Miyahira at amiyahira@pcf.org.

Yours sincerely,

Jonathan W. Simons, MD
President & CEO
David H. Koch Chair

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

Session 1: Healthcare Disparity in Prostate Cancer

What Can Big Data Tell Us About Racial Disparities in Prostate Cancer?

Paul Nguyen, MD
Harvard: Dana-Farber Cancer Institute

- African-American men have a 2.4-fold higher mortality from prostate cancer compared with Caucasians. At diagnosis, African-American men have a higher-grade disease and PSA levels, are younger, and have a greater incidence of metastatic disease across all age groups compared to Caucasians.

- Overall, African-American men have a 1.6-fold greater incidence rate of prostate cancer, but higher incidence alone does not fully account for the disparity in mortality rates.

- Dr. Paul Nguyen discussed how data from large-scale epidemiologic studies could be used to tease apart relative proportions of risk vis–à–vis the various social and biological factors that may contribute to the disparity in prostate cancer mortality rates between African-American and Caucasian men.

- Disparities between African-American and Caucasian men were identified in the chain of healthcare, including screening, diagnosis, staging, and treatment.

- The Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial randomized 77,500 men aged 55 to 74, to be screened vs. not screened by PSA and by digital rectal exam. The study subjects were followed for 13 years to determine the effects of screening on cancer-related mortality.

- African-American men represent 13.2% of the U.S. population, but were found to be underrepresented in screening trials. In the PLCO trial, only 4.4% of the study subjects were African-American. Whether decreased screening has a disproportionately adverse effect on African-American men needs to be addressed.

- In the PLCO trial, there was a lower rate of follow-up of African-American men found to have elevated PSA levels. African-American men with elevated PSA levels had a 45% lower rate of a repeat PSA or subsequent biopsy compared with Caucasian men. The time between diagnosis and treatment was increased in African-American men by an average of 4 days for African-American men with intermediate-risk disease and 9 days for African-American men with high risk disease.

- The Surveillance, Epidemiology, and End Results (SEER) – Medicare database is a database containing clinical, demographic and cause of death information for

cancer patients whose medical benefits are covered by the U.S. Medicare program.

- Analysis of the SEER database revealed that for African-American men, tumor staging and receipt of definitive therapy was performed less often, particularly in cases of high risk disease. More African-American men underwent observation, while fewer had radical prostatectomies or adjuvant androgen deprivation therapy (ADT) combined with external beam radiotherapy.

- The quality of treatment also tends to be lower for African-American men, who are more likely to receive radical prostatectomies at less experienced, low-volume hospitals, which have higher rates of complications including transfusion, length of stay and inpatient mortality.

- Income inequalities contribute to medical care disparities in the U.S. Of patients with below-average income, 39% do not see a doctor for medical issues because of cost. Having medical insurance reduces the disparity in treatment between African-American and Caucasian men.

- In equal access settings, disparities are reduced. In a 1989-2008 Center for Prostate Disease Research study on the military healthcare system, no differences were seen in prostate cancer survival rates for African-American vs. Caucasian men who chose active surveillance.

- Biological differences contribute to disparities. In breast cancer, the disparity in survival between African-American and Caucasian women is widening due to the development of drugs for ER+ and HER2+ breast cancer while African-American women have a disproportionately higher ER-/PR-/HER2- (triple negative) breast cancer phenotype, for which fewer life-prolonging agents are under development.

- New treatments for advanced prostate cancer have reduced mortality rates in Phase III clinical trials by approximately 21-37%. However, eliminating the social component of African-American disparities may have an even greater effect than any therapy and could reduce the risk of mortality from prostate cancer by as much as 44%.

- These results indicate that addressing system-based inequalities including income and access to healthcare, physician/provider-based biases, and patient-based preferences, beliefs, and behaviors can address disparities and reduce the mortality rate in African-American men from prostate cancer.

Breakthroughs Improving Prostate Cancer Survival

	Hazard Ratio for Death
Eliminating the Social Component of AA Survival Disparity	**0.56**
Enzalutamide	0.63
Abiraterone	0.65
Radium 223	0.70
Cabazitaxel	0.70
Sipuleucel-T	0.79
Docetaxel	0.79

Figure 1: New treatments for prostate cancer have reduced mortality rates in men by approximately 21-37% (Hazard Ratios of 0.79 – 0.63). However, eliminating the social component of African-American disparities may reduce the risk of mortality from prostate cancer for African-American men by 44% (Hazard Ratio of 0.56).

Biological and Social Determinants of Prostate Cancer Disparities

Timothy Rebbeck, PhD
University of Pennsylvania School of Medicine

- African-American men have a higher chance of dying from cancer compared with Caucasian men for a number of cancers including larynx, stomach, myeloma, oral cavity and pharynx, small intestine, liver, colon and rectum, esophagus, lung and bronchus, and pancreas. Prostate cancer tops this list of disparities, with African-American men being 2.4 times more likely to die from the disease than Caucasian men.

- Dr. Timothy Rebbeck discussed using socially-defined group memberships such as race or ethnicity to generate a framework as a starting point for understanding disparities in prostate cancer risk and outcomes.

- Self-identified race/ethnicity correlates with lifestyle and culture that may affect healthcare-seeking behavior or other behaviorally-associated risk factors. In addition, race/ethnicity also correlates with genetics and biological phenotype.

Both lifestyle-based and biology-based risk factors affect disease characteristics and patient outcome.

- About 140 loci in the genome have been identified as being associated with increased risk for prostate cancer. In African-American men, only about 30 of these loci were confirmed as being associated with prostate cancer risk. Novel susceptibility loci have also been identified in African-American men, some of which may also play a role in prostate cancer risk in other races.

- To understand how African-American men evolved to have genes that increase the risk for prostate cancer, the frequencies of genetic loci associated with prostate cancer were compared in populations of men of African descent from different places around the world.

- Three loci were identified as enriched in African-American men and may have been selected for because they confer other desirable traits. The genes in these regions are involved in skin pigmentation, BMI, height and lung function (PLRH), reproductive fitness (LMTK2), and susceptibility to African eye worm infections (PPP1R14A).

- Somatic (acquired) mutations were also compared in tumors of men of African-descent from different geographical locations and with Caucasian men to identify predictive markers that can stratify those who will benefit from active surveillance vs. definitive treatment. A number of genomic alterations previously identified in prostate tumors from Caucasians were found in tumors from African-American men, although several genes were differentially expressed between African-American men and Caucasians. How these genes increase or decrease risk in African-American men vs. Caucasians is being studied.

- Overall, patterns of inherited and acquired genomic alterations can be used to identify factors associated with the risk of aggressive prostate cancer in men of African descent. These studies will lead to a better understanding of how to diagnose and treat African-American men.
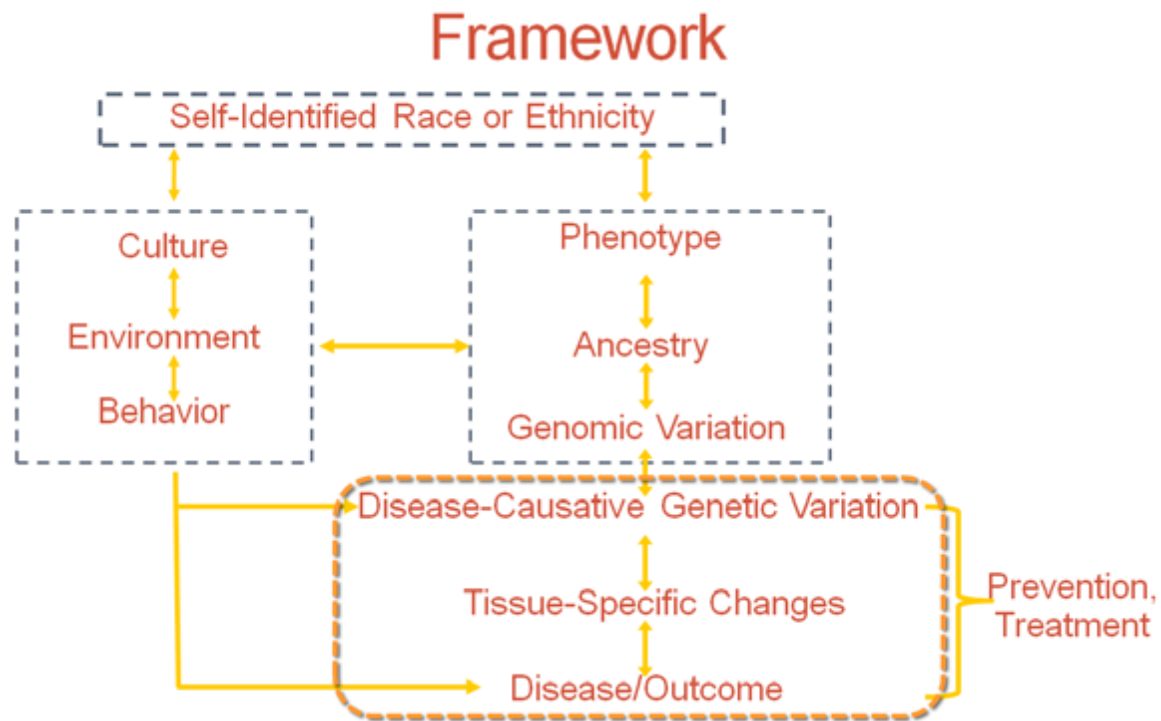
Framework

Figure 2: Dr. Rebbeck's framework to determine an individual's risk of prostate cancer. Patients are first grouped based on self-identified race/ethnicity which correlates with lifestyle-associated risk factors (culture, environment, and behavior). Race/ethnicity also correlates with biology-based risk factors (phenotype, ancestry, genomic variation). Both lifestyle-based and biology-based risk factors affect disease characteristics and patient outcome.

Obesity, Race and Prostate Cancer Risk

Alan Kristal, DrPH
Fred Hutchinson Cancer Research Center

- The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was a clinical trial in which healthy men were given selenium and/or vitamin E to determine if these dietary supplements could impact the development of prostate cancer. Participants were followed for at least five years during which they were assessed for changes in health status, prostate cancer and other endpoints. The power of this study is that it was very large and almost all men received prostate cancer screening annually.

- Dr. Alan Kristal discussed the use of data from 3,398 African-American and 22,673 non-Hispanic Caucasian men from this trial to evaluate the effects of race and obesity on prostate cancer incidence.

- Obesity substantially increased the risks of both low and high-grade prostate cancer risk in African-American men. In contrast, among Caucasian men—as

found in previous studies—obesity modestly reduced the risk of low-grade tumors, but modestly increased the risk of high-grade cancer.

- The increased risk of prostate cancer among African-American men (compared to Caucasian men) was approximately 28% among men of normal-weight (BMI <25). However, as BMI increased, so too did the excess cancer risk among African-American men, reaching 105% among men who were severely obese (BMI 35+).

- The mechanisms underlying these findings are unknown but the effects of obesity on inflammation, estrogen metabolism and insulin/insulin growth factor activity may differ in African-American compared to Caucasian men.

- One of the confusing aspects of prostate cancer risk is that it is lower among men with diabetes, yet obesity is the primary cause of diabetes. Teasing apart the biology underlying the effects of obesity and diabetes on prostate cancer risk may yield insights into the mechanisms driving the development of prostate cancer.

- Obesity and weight gain are associated with very small reductions in PSA levels. However, scientists disagree on whether or not this would affect prostate cancer detection.

- Overall, these studies suggest that obesity has a much stronger effect on prostate cancer risk in African-American compared to Caucasian men. They also suggest that weight loss may substantially reduce the disproportionate burden of prostate cancer among African-American men.
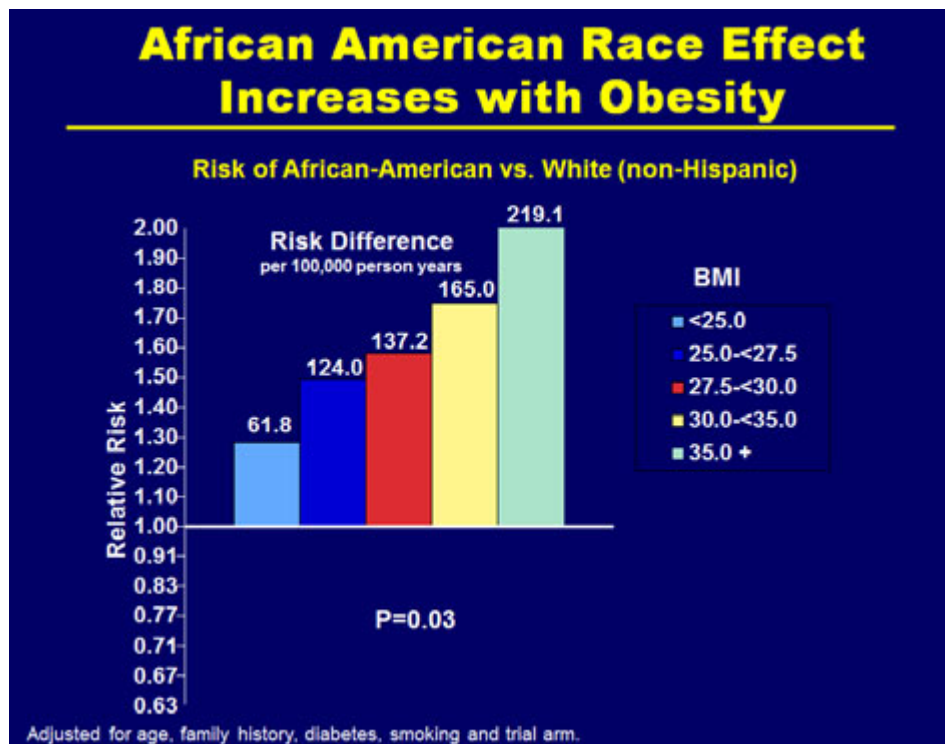

Figure 3: The relative risk of African-American men vs. Caucasian men for prostate cancer increases with increasing obesity (BMI), being up to 2-fold greater for African-American men in the highest BMI category (35.0+).

Genomics of African-American Prostate Cancer

Franklin Huang, MD, PhD
Harvard: Dana-Farber Cancer Institute

- African-American men have the highest incidence rate of prostate cancer. African-American men are younger, have more aggressive disease at the time of diagnosis, and have a 2.4-fold higher chance of mortality from prostate cancer vs. Caucasian men.

- Both socioeconomic and genetic factors contribute to this disparity.

- Dr. Franklin Huang discussed studies on molecular or genetic features that drive prostate cancer in African-American men vs. Caucasians.

- Tumors in different patients can arise from a multitude of different mutations, the relative importance of which may depend on the patient's genetic background (ethnicity). For instance, in lung cancer, mutations in the EGFR oncogene are found in 50% of East Asian vs. only 10-15% of Caucasian patients. Likewise, in colorectal cancer, mutations in the BRAF oncogene are found in tumors from 14% of Caucasian vs. 6% of African-American patients, and mutations in the KRAS oncogene are found in tumors from 21% of Caucasian vs. 37% of African-American patients.

- A common finding in prostate tumors is a genomic rearrangement in which the ERG oncogene is placed behind the TMPRSS2 promoter, leading to aberrantly high expression of ERG. ERG rearrangements are observed in prostate tumors from 42-50% of Caucasian patients compared with 24-31% of African-American patients.

- Only ~8% of the prostate cancer genomes that have been sequenced and made available in public domains are from patients of African-American descent. The identification of genes that drive prostate cancer will continue to increase as more samples and tumor types are studied.

- Dr. Huang performed the largest genomics study to date to identify somatic mutations, insertion/deletions and copy number alterations that are enriched for or found specifically in tumors from African-American patients. Sequencing of the protein-coding regions of DNA was performed on primary prostate tumor specimens from 109 untreated African-American men and results were compared with tissues from healthy regions of the prostate from the same patient.

- Several genes were identified as more frequently mutated in African-American prostate tumors compared with previous cohorts containing primarily Caucasian patients.

- Ongoing studies are being performed to validate these findings in a larger cohort of African-American patients.

- These studies may lead to new understandings of the biological mechanisms mediating the differences in prostate cancer risk in African-American vs. Caucasian men.

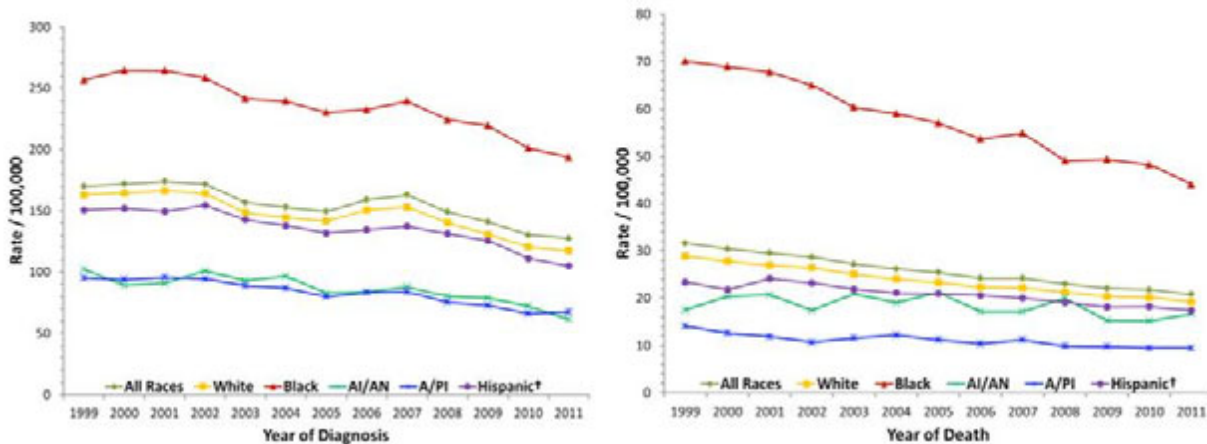## Prostate cancer incidence and death, in African-Americans

Figure 4: Prostate cancer incidence and death in African-American men.

SPECIAL LECTURE

Prostate Cancer Molecular Biomarker Development among African-American Compared to European-American Men

Isaac Powell, MD
Wayne State University School of Medicine

- African-American men have the highest incidence and mortality rates of prostate cancer compared with any other race or ethnicity. The incidence rate by ethnicity per 100,000 men is 223.9 for African-American men, 139.9 for Caucasians, 121.8 for Hispanics, 71.5 for American Indians, and 79.3 for Asian/Pacific Islanders. The mortality rate per 100,000 men is 48.9 for African-American men, 20.6 for Caucasians, 18.5 for Hispanics, 21.2 for American Indians, and 10.0 for Asian/Pacific Islanders.

- The rates of prostate cancer in populations of men of African descent living in different regions of the world are similar, indicating that genetic factors play a significant role. The varying percent of European ancestry found in African-

American populations from different regions of the U.S. may be helpful in parsing out genetic factors.

- Dr. Isaac Powell discussed studies on the biologic and genetic factors that contribute to the heterogeneity of prostate cancer between and within racial groups.

- Results from autopsy studies indicate that prostate cancer may initiate at the same age in African-American compared with Caucasian men but that the growth rate of prostate cancer is faster in African-American men. At younger ages, African-American and Caucasian men have similar prostate cancer incidence rates, tumor size, and Gleason grade. However with age, the frequency of prostate cancer and aggressive tumor features becomes increasingly pronounced among African-American men. Death from prostate cancer also becomes more frequent in African-American men compared with Caucasian men as age increases.

- Importantly, recurrence rates in African-American men in the lowest risk category are similar to those of Caucasians in the intermediate-risk category. Thus, active surveillance may not be the best option even for young African-American men due to faster growing disease and poorer patient follow-up.

- Genomic aberrations that may play a role in the increased prostate cancer aggressiveness in African-American men include a variant of the CYP3A4 gene and the 8q24 chromosome region.

- A study was performed to identify genes that are differentially expressed in prostate tumors from African-American vs. Caucasian men. Genes known for their involvement in hypertension and inflammation (IL-6, IL-8, IL-1) were expressed at higher levels in tumors from African-American men while other genes (ERG and ALOX15) were higher in tumors from Caucasians.

- TNF is a secreted protein with a major role in inflammation. Examination of the pathways and interactions between differentially expressed tumor genes found that TNF levels were similar between races, yet TNF was a hub linking two networks of interacting genes whose expression is opposite in tumors from African-American vs. Caucasian men. One network was higher in tumors from African-American men while the other was higher in tumors from Caucasians. Thus, TNF may play a role in racial differences in prostate cancer biology.

- IL-6 and IL-8 are also secreted inflammation-related proteins found in the tumor microenvironment. IL-6 and IL-8 are produced by tumor cells and can activate the androgen receptor (AR) and other oncogenic transcription factors including STAT3 and β-catenin in self or neighboring tumor cells.

- IL-8 has numerous functions including promoting angiogenesis, prostate cancer proliferation, and androgen independence. IL-8 levels were specifically increased in aggressive but not non-aggressive tumors from African-American men,

indicating the potential for this gene as a biomarker for predicting aggressive tumors in African-American men.

- Overexpression of ERG is considered an important biomarker of prostate cancer and diagnostic tests assessing ERG levels have been developed. However, because ERG expression was lower in prostate tumors from African-American men, it may have less utility as a diagnostic marker in this population.

- These studies indicate that different genes and biological pathways contribute to the initiation and progression of prostate cancer in African-American men vs Caucasians.

- Inflammatory pathways in particular, appear to play a role in prostate cancer in African-American men. Therapies developed to target these pathways will likely exhibit differential efficacy in men of different racial groups.

- Ongoing studies will determine the mechanisms of how different biological pathways drive prostate tumors in men of different ancestry and identify race-specific biomarkers that predict aggressive disease.
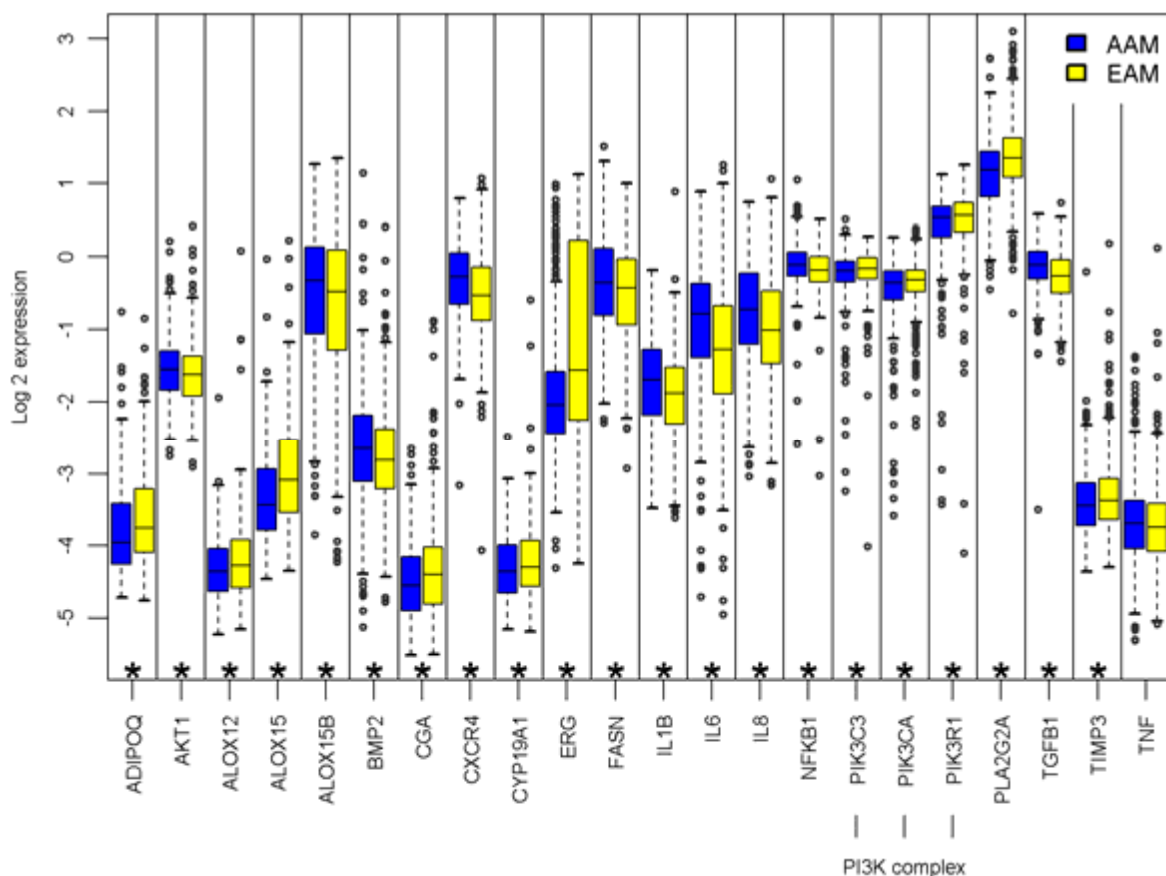

Figure 5: Boxplots of genes differentially expressed between tumors from African-American men (AAM) vs. European-American men (EAM). Asterisks at the bottom of the graph indicate statistically significant differences between races. Genes known for their involvement in hypertension and inflammation (IL-6, IL-8, IL-1) were expressed at higher levels in tumors from African-American men while other genes (ERG and ALOX15) were higher in tumors from European-American men. As TNF is a central hub in the network, it is included in the graph even though it is not differently expressed between races.

Session 3: AR-Splice Variants

AR-V7 and Treatment Resistance in Castrate-Resistant Prostate Cancer

Emmanuel Antonarakis, MD
John Hopkins University

- The androgen receptor (AR), which is a transcription factor, is the primary driver of prostate cancer and regulates the expression of genes required for prostate cell growth and survival.

- The AR protein is composed of 3 domains: The N-terminal domain (NTD), the DNA-binding domain (DBD), and the ligand-binding domain (LBD).

- To activate AR, androgen ligands (e.g. testosterone, dihydrotestosterone) bind to the LBD inducing a conformational change in AR. AR is then able to move from the cell's cytoplasm into the nucleus and induce gene expression via the DNA-binding and gene transcription functions of the DBD and NTD.

- Dr. Emmanuel Antonarakis discussed the role of AR splice variants in prostate cancer. AR-variants are alternate versions of AR which lack regions of the protein. Several AR-variants, including AR-V7, lack the LBD and do not need to bind androgens to become activated. These variants can continually induce expression of prostate cancer growth and survival genes in the absence of androgens.

- The AR-targeting therapies enzalutamide and abiraterone inhibit AR via the LBD. Enzalutamide binds directly to the LBD to inhibit AR signaling. Abiraterone targets the AR LBD indirectly by blocking synthesis of the androgens needed for LBD activation. Expression of AR-variants lacking the LBD may be a potential mechanism of prostate cancer resistance to enzalutamide and abiraterone.

- Dr. Antonarakis and colleagues hypothesized that detection of AR-V7 in circulating tumor cells (CTCs) from castrate-resistant prostate cancer (CRPC) patients would be associated with resistance to enzalutamide and abiraterone.

- Of 20 or more variants, AR-V7 is the most abundant and one of only 2-3 AR variants proven to be translated into a protein. The expression of AR-V7 was increased in CRPC cells by ~20-fold. For these reasons, Dr. Antonarakis decided to focus primarily on AR-V7 rather than other variants.

- In this study, CTCs were isolated from the blood of 62 prostate cancer patients prior to and during treatment with either enzalutamide or abiraterone (31 patients each).

- A custom blood-based test was developed to determine whether AR-V7 mRNA is expressed in the CTC samples. Therapeutic responses and clinical outcomes of patients that did vs. did not express AR-V7 were compared.

- Out of 62 patients, 27 of 44 (61%) that did not express AR-V7 (AR-V7-negative) responded to either therapy as assessed by a reduction in PSA levels by 50% or more. Conversely, only 1 of 18 AR-V7-positive patients had a reduction in PSA levels at any time point during therapy, and this PSA reduction did not cross the 50% threshold used to define a PSA response (i.e. the true PSA response rate in AR-V7-positive patients was 0%).

- Both progression-free survival and overall survival were also significantly worse in patients that were AR-V7-positive compared with patients who were AR-V7-negative.

- AR-V7 expression in CTCs was also compared before and during treatment and analyzed for gain or loss of AR-V7 expression during the course of therapy with enzalutamide or abiraterone.

- No patients whose CTCs expressed AR-V7 prior to treatment went on to lose expression, while 6 of 44 patients who were originally AR-V7-negative gained expression during the course of therapy. Patients who gained expression of AR-V7 (i.e. converted from AR-V7-negative to AR-V7-positive) had significantly worse progression-free survival and overall survival compared with patients who remained AR-V7-negative.

- There is also a potential rationale explaining why AR-V7 might be linked to chemotherapy resistance to taxanes. The AR-V7 protein lacks the hinge region which is adjacent to the LBD. The hinge region of AR binds to microtubules which transport AR into the nucleus of the cell.

- Taxanes such as docetaxel and cabazitaxel are the only chemotherapeutics with demonstrated efficacy in prostate cancer. Taxanes work by freezing and breaking microtubules and are thought to be effective against prostate cancer because AR is inhibited from being transported into the nucleus.

- Dr. Antonarakis has planned a prospective study to test whether AR-V7 confers resistance to docetaxel or cabazitaxel. Progression-free survival and overall survival of AR-V7-positive vs. AR-V7-negative CRPC patients will be compared in the context of taxane chemotherapy. The utility of AR-V7 as a predictive biomarker for drug response or resistance will be evaluated in the setting of taxane chemotherapy vs. AR-targeting therapy (abiraterone, enzalutamide). The preliminary results from this study will be presented at the 2015 Genitourinary Cancers Symposium.

- AR-V7 may also represent a new therapeutic target; it may be disrupted by new AR-targeting therapies such as the AR-degrading agent galeterone and bromodomain/BET-inhibitors which inhibit the DNA-binding and transcriptional activity of AR. Future clinical trials should test these hypotheses as they

represent promising therapies for enzalutamide and abiraterone-resistant patients.

- In summary, the expression of AR-V7 is associated with (and is likely to be a mechanism of) resistance to enzalutamide and abiraterone, but perhaps not to taxanes. Clinical tests will be developed to assess AR-V7 expression which should result in selection of patients that will benefit from abiraterone and enzalutamide. Reliable detection of AR-V7 from blood should also fuel the development of new drugs capable of inhibiting or degrading AR-V7 and switching off aberrant AR-variant-mediated signaling.
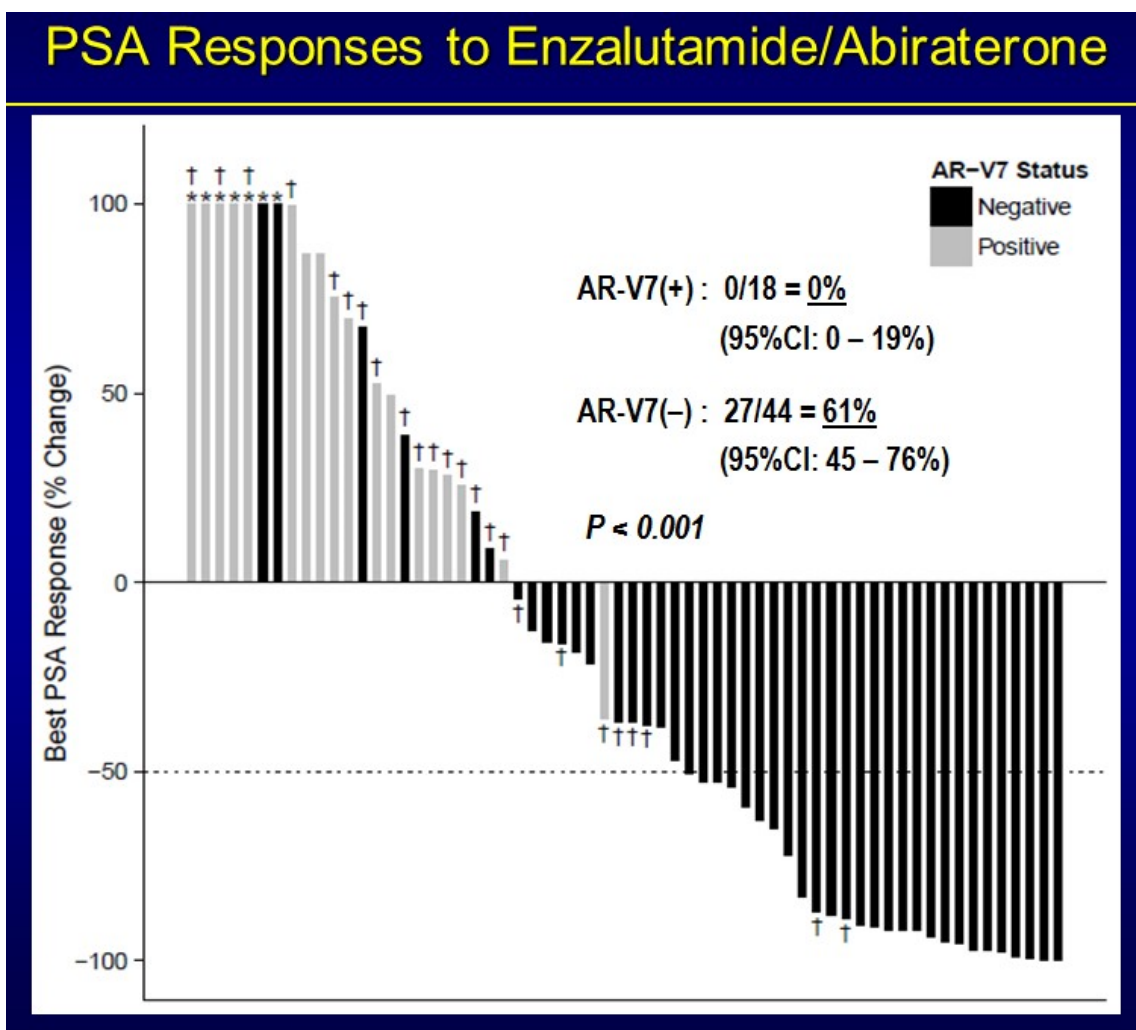

Figure 6: Waterfall plot depicting the best PSA responses (% change) in AR-V7-negative and AR-V7-positive CRPC patients being treated with abiraterone or enzalutamide. Out of 62 patients, 27 of 44 AR-V7-negative (-) patients had a reduction in PSA levels during therapy, while only 1 of 18 AR-V7-positive (+) patients had a reduction in PSA levels during therapy (although this did not cross the 50% threshold for defining a true PSA response). Asterisks (*) indicate a >100% increase in best PSA response. The dagger (†) indicates patients who had received the alternative AR-directed agent previously (i.e. enzalutamide-treated patients who had received prior abiraterone, or abiraterone-treated patients who had received prior enzalutamide).

Dynamics of AR Splice Variants' Nuclear Accumulation and Implications for Treatment Outcomes

Paraskevi Giannakakou, PhD
Weill Cornell Medical College, Meyer Cancer Center

- The androgen receptor (AR) is the primary driver of prostate cancer and causes growth, invasion and survival. Androgen deprivation therapy (ADT) is a primary treatment for prostate cancer. However, many tumors develop mechanisms of resistance to AR-targeted therapy and progress to lethal disease.

- Dr. Paraskevi Giannakakou discussed studies exploring mechanisms of CRPC resistance to taxanes (docetaxel and cabazitaxel), the only approved chemotherapies for the treatment of CRPC that have been shown to prolong survival.

- Taxanes act to freeze and stabilize microtubules, which are cytoskeletal filaments involved in trafficking within cells. AR is transported via microtubules into the cell nucleus in order to induce the expression of oncogenic growth and survival genes.

- AR nuclear transport and transcriptional activity is inhibited by taxanes as a result of disabling the microtubule transportation tracks.

- AR-variants which lack the ligand binding domain (LBD) of AR, including AR-V7 and AR-v567, do not require androgens to become activated. These variants are constitutively active and can be found in the nucleus of tumors from CRPC patients.

- The question of whether AR-variants play a role in resistance to taxanes was explored.

- AR-V7 but not AR-v567 lacks the hinge region of AR in addition to the LBD. The hinge region mediates binding to microtubules. Accordingly, AR- v567 but not AR-V7 could bind to microtubules.

- Treatment of cells with docetaxel inhibited nuclear translocation of AR-v567 but not AR-V7, demonstrating that the inability of AR-V7 to bind microtubules allows it to constitutively enter the nucleus in a microtubule-independent manner that is not affected by taxanes.

- In mice, the growth of tumors expressing AR-v567 but not AR-V7 was inhibited by taxane treatment.

- These results indicate that expression of AR-V7 but not AR- v567 by prostate tumors cell may confer taxane chemotherapy resistance.

- A clinical trial is being initiated to examine efficacy and mechanistic differences of clinical responses and resistance of mCRPC patients to two different taxane

therapies: docetaxel vs. cabazitaxel. The expression of full-length-AR and AR-variants will be examined in circulating tumor cells isolated from patient blood. It is hoped that knowing the AR-V7 status of a patient will aid in the selection of patients that will respond to these powerful chemotherapies.

- These clinical studies will validate whether AR-V7 is a mechanism of resistance to taxanes in addition to enzalutamide and abiraterone.

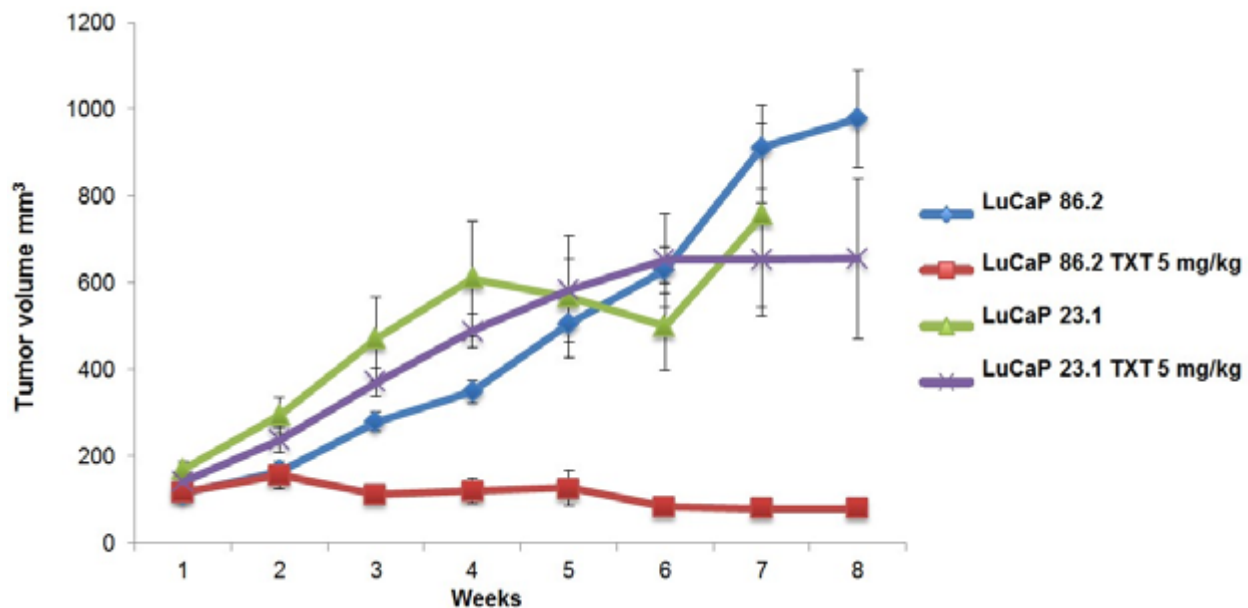- Drugs to inhibit AR-V7 are important current and future discovery efforts.

Figure 7: AR-v567 (expressed in LuCaP 23.1 cells) confers sensitivity, while AR-V7 (expressed in LuCaP 86.2 cells) confers resistance to Taxane treatment in mice.

SPECIAL LECTURE

Project DataSphere

Kald Abdallah, MD, PhD
Project DataSphere, LLC

- Dr. Kald Abdallah discussed the Project DataSphere® initiative: an independent, voluntary, non-profit organization developed to share, integrate, and analyze cancer clinical trial data.

- This initiative was conceived in 2011 by the CEO Roundtable on Cancer and its Life Sciences Consortium.

- Project DataSphere is gathering and housing raw de-identified patient data, data dictionaries, protocols and case report forms from the control arm of randomized Phase III clinical trials provided by academic and industry collaborators.

- The Project DataSphere website (www.projectdatasphere.org) was launched in April 2014. Anyone can apply for access to the website's data and analytical tools which were developed by the business analytics specialist SAS.

- At this time, there are 18 available comparative-arm datasets comprising data from almost 11,000 patients. Twelve of these datasets are from prostate cancer clinical trials. Additional data are being sought and collaborators will contribute some treatment arm datasets.

- The goals for analysis of these data include:
  - Identifying new prognostic factors
  - Identifying new patient subgroups and tumor subtypes
  - Enabling more robust interpretation of single arm Phase II trials ("virtual" control arm)
  - Establishing safety baselines for adverse events
  - Streamlining development of protocols and case report forms
  - Predicting outcomes such as treatment responses and adverse events

- In partnership with PCF, Sage Bionetworks, The DREAM Project, and several Universities, the Prostate Cancer Challenge was announced. This is a crowd-sourcing competition using curated Phase III prostate cancer datasets to address overall survival, treatment discontinuation, and disease aggressiveness.

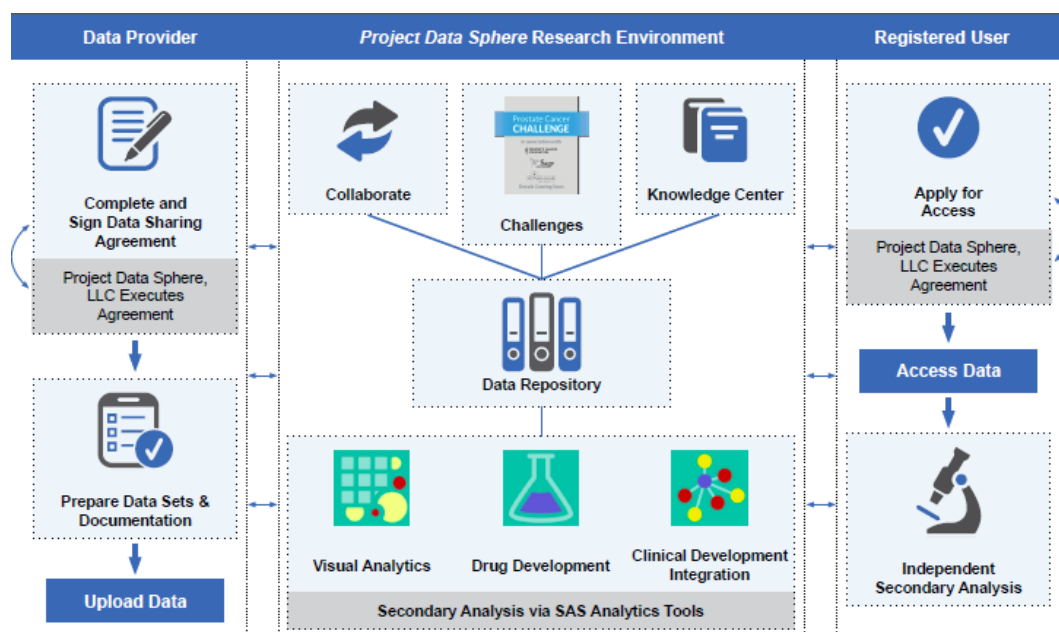- Please visit the website for more information: www.projectdatasphere.org.

Figure 8: Project DataSphere people, process and technology.

Session 4: Research Integrity and Standards for Scientific Reproducibility

Closing the Reproducibility Gap with Standards and Best Practices

Leonard Freedman, PhD
Global Biological Standards Institute

- Dr. Leonard Freedman discussed the importance of establishing biological standards for scientific reproducibility and the functions and goals of the Global Biological Standards Institute (GBSI).

- GBSI was formed to provide leadership in the establishment of global standards and best practices to accelerate the translation of research breakthroughs into life-saving therapies.

- The goals of GBSI include developing guides to create standards in an operationalized manner, issuing whitepapers and performing benchmark studies, creating task forces to address needs in key research areas, engaging policy advocacy groups, and sponsoring conferences and training programs to educate and advocate for the advancement of global biomedical best practices and standards.

- Irreproducibility of published preclinical research findings is an all too common problem. With an estimated prevalence exceeding 50%, the results from $28B/year spent on research in the U.S. alone are not reproducible. Irreproducible studies in the literature leads to wasted time and resources of investigators, loss of public trust, and significantly slows drug development by pharmaceutical companies.

- Academic and pharmaceutical investigations based on reproducible findings will benefit all who are invested. Academic scientists will make faster and better progress while funds from federal institutes, pharmaceutical companies, foundations and private funding sources will be better spent.

- Many factors can lead to irreproducibility, however very little of it is due to outright fraud. The vast majority stems from variations, errors, and omissions in laboratory protocols, analysis of data, experimental design, and the reagents and assays used in different laboratories.

- Dr. Freedman advocated the development of "white paper" documents to define best practices and implement standards.

- Having formal processes to define standards will facilitate the establishment of best practices, reduce variance in study results, and improve the reproducibility and fidelity of academic and clinical research.

- Cell line authentication uses STR (short tandem repeat) analysis to validate the identity of the cell line being studied and identifies any microbial contaminants that may alter the results of assays.

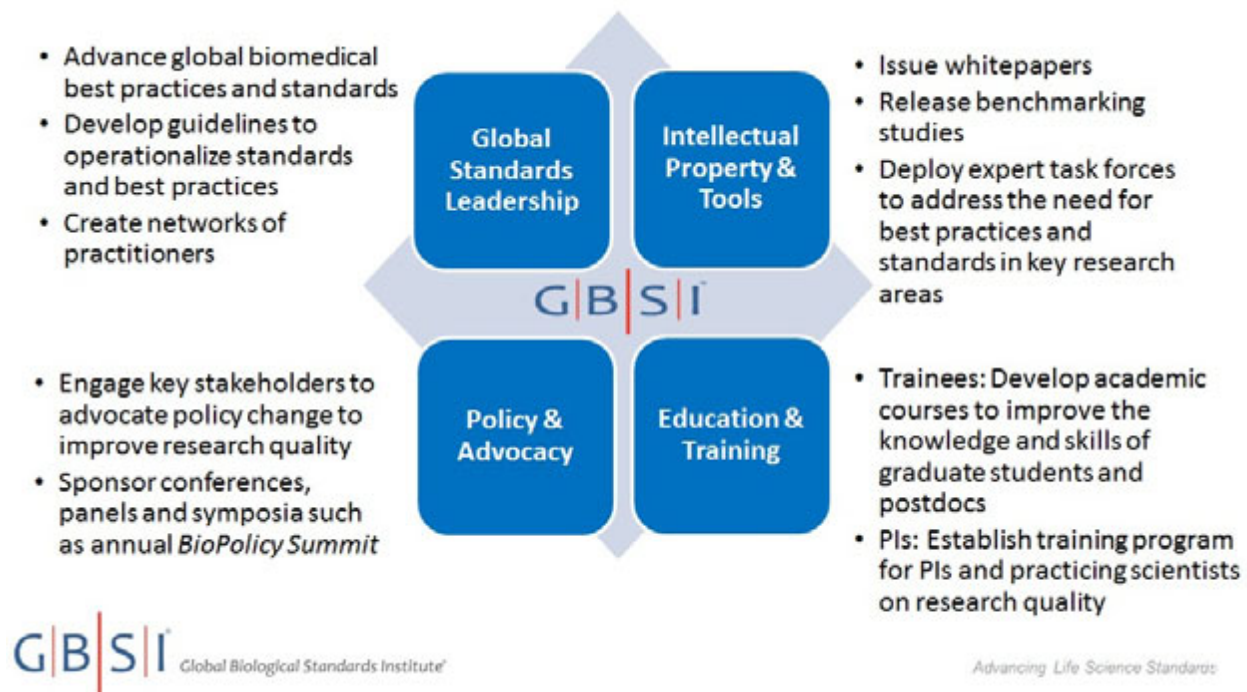- In 2014, PCF mandated annual cell line authentication for all PCF-funded research.

Figure 9: The goals of Global Biological Standards Institute (GBSI) include developing guides to create biological standards in an operationalized manner, issuing whitepapers and performing benchmark studies, creating taskforces to address needs in key research areas, engaging policy advocacy groups, and sponsoring conferences and training programs to educate and advocate for the advancement of global biomedical best practices and standards.

Improving Scientific Reproducibility

John P. A. Ioannidis, MD, DSc
Stanford University

- Scientific irreproducibility stems from many sources. These range from innocent mistakes and the use of bad reagents, to poorly executed experiments or data analysis, to outright fraud.

- Dr. John Ioannidis discussed research practices that could be adopted by scientists to improve the proportion of true research findings published in the scientific literature.

- The integrity of studies published by large consortiums has demonstrated that when teams of scientists collaborate to generate large scale datasets using agnostic platforms, standardized approaches and stringent analysis protocols, results can be improved from 99% nonreplicable to 99% replicable.

- The adoption of a new culture of scientific replication is encouraged. Replication can be done by the original team of investigators using multiple methods or stages of experimentation and analysis to validate their own findings. Alternatively, replication can be done by other investigators from the field with either agreeing or competing theories or hypotheses. For replication of *in silico* data analysis, even the public could be involved when the data is made openly accessible.

- Registration of clinical trial protocols, analysis plans, and their resulting datasets has been successful in making researchers aware of what trials have been done. Similar registration efforts could be applied to other types of studies such as animal research or epidemiological studies and informatics analyses done on large datasets that may or may not have been published. Levels of registration could extend from no registration on exploratory research, to the inclusion of datasets, protocols, analysis plans, raw data, and even live streaming of experiments where input from others could be received in real time. Knowledge of what databases are available would forward such efforts.

- Scientific journals should adopt publication policies that require the deposition of a study's datasets and full descriptions of materials and methods. Across the 50 highest-impact journals, varying policies exist for the deposition of different data types or methods and protocols. Unfortunately the percentage of the studies published in those journals which had deposited full datasets and methods was very low, often zero.

- Data sharing is ideal though politically complex. Each scientific field needs to examine the obstacles, allocation of credit, the understanding of data quality, and what the available data represent in order to implement and optimize data sharing.

- A study examining the prevalence of reanalysis of clinical trial raw data found only 37 reanalyses published, despite the availability of over a half-million clinical trials. Most reanalyses were done by the same authors. Alarmingly, in about one-third of these studies different conclusions were reached. This leads to concerns that if reanalysis was more common, many clinical trial results might be called into question along with the entire field of clinical practice.

- Limiting the influence of conflicted stakeholders and authors will likely have a large effect on the publication of reproducible studies. There should be transparency into conflicts of interest and questions should be raised over who should be a sponsor vs. an author on the publications of randomized trials, meta-analyses, cost-effectiveness analyses, guidelines, and other sensitive studies.

- Statistical analyses and methods could be improved by creating transparent and registered statistical analysis plans, improving the training and literacy of investigators in statistical methods, creating better study designs, standardizing features such as randomization and blinding of data being analyzed, and creating beneficial and adherent checklists for study design and conduct.

- Implementing reporting standards may improve data transparency and study designs. For instance, the international EQUATOR initiative includes multiple standards for the reporting of data from studies on local best practices in sustainable development.

- Developing an overlying hub for these activities will advance the collection, understanding and communication of experiences across different fields and promote policies with a demonstrated impact in changing the outcomes of various practices. The Meta-Research Innovation Center at Stanford (METRICS) is one such hub that was launched in 2014 for such efforts.

- Many of these practices will not change unless we reengineer the scientific reward system. A researcher's value is currently determined by their productivity which focuses on publications and obtaining grants. Optimal changes in the reward system would increase the value given to reproducibility of work, sharing of data and resources, and the translational impact of the research.

- Understanding and aligning the interests of stakeholders in science who are otherwise differentially concerned with results being publishable, fundable, translatable, or profitable would be ideal for improving the integrity of scientific publications.

- In conclusion, many practice changes may improve the efficiency of research and the credibility of the published literature.

- Research on the prevalence of problems and the efficacy vs. harms of practice changes will be key for implementing optimal research practices that improve the success, credibility and legacy of scientific research.

Box 1. Some Research Practices that May Help Increase the Proportion of True Research Findings

- Large-scale collaborative research
- Adoption of replication culture
- Registration (of studies, protocols, analysis codes, datasets, raw data, and results)
- Sharing (of data, protocols, materials, software, and other tools)
- Reproducibility practices
- Containment of conflicted sponsors and authors
- More appropriate statistical methods
- Standardization of definitions and analyses
- More stringent thresholds for claiming discoveries or "successes"
- Improvement of study design standards
- Improvements in peer review, reporting, and dissemination of research
- Better training of scientific workforce in methods and statistical literacy

Figure 10: Some research practices that may help increase the proportion of true research findings.

The Cancer Biology Reproducibility Project

Elizabeth Iorns, PhD
Science Exchange

- Dr. Elizabeth Iorns discussed the problem of scientific reproducibility and the Science Exchange as a mechanism for identifying reproducible or irreproducible study results.

- Reproducibly is the ability of a scientific study performed by one researcher or group to be reproduced in part or whole by independent researchers. This principle is the backbone of the scientific method.

- A survey on data reproducibility found that the inability to replicate published findings is prevalent and has been experienced by approximately 50% of researchers.

- Studies by pharmaceutical companies, government agencies, and foundations concerning reproducibility of preclinical drug target findings had even graver results. The Amyotrophic Lateral Sclerosis (ALS) Therapy Development Institute

re-tested findings on over 70 drugs from 221 studies but were unable to reproduce a single study. An NIH study could only reproduce 2 of 12 spinal cord injury studies. Bayer could only reproduce 14 of 67 published reports of cancer targets. Amgen could only reproduce 6 of 53 "landmark" oncology studies.

- Overall, an estimated 70% of scientific publications contain irreproducible results. Self-correction of the literature does not occur as hoped, as only 0.2% of the literature gets retracted, fewer than 30% of researchers report their negative findings, and only 14% of the literature includes negative results. It is believed that these rates should be much higher. Furthermore, incorrect findings are often perpetuated by being "validated" in subsequent studies by different groups. The Bayer study found that whether or not a finding had been reported in 10 vs. two publications had no impact on the likelihood of validating a drug target.

- No correlation was found between reproducibility and either the impact factor of the journal or the number of citations the publication received.

- Irreproducible results can be quickly identified by unsuccessful attempts to replicate published experimental procedures. An additional benefit of direct replication is that directly reproducible results also tend to validate when transferred to other models or systems, indicating that directly reproducible findings are robust. Incentivizing reproducible research results is difficult because the system rewards productivity and the number of publications and grants as opposed to the reproducibility of an investigator's research.

- The Science Exchange is a partnering service that engages independent labs from around the world to attempt the replication of experiments. The Science Exchange can be used by researchers to find an independent lab to validate their findings or by other stakeholders desiring to determine the validity of results from published papers of interest.

- The Science Exchange's replication protocols include statistical power calculations that estimate sample sizes needed for an 80% chance of detecting an effect. The independent labs selected to perform replication experiments are expert in the techniques being replicated, ensuring expert, rapid and cost-effective work. Labs that are part of the Science Exchange network are from over 400 research institutions, including 75 of the top 100 research universities in the U.S.

- The Science Exchange has partnered with the Center for Open Science and the Laura and John Arnold Foundation to initiate the Cancer Biology Reproducibility Project. The goal of this project is to independently replicate key experimental results from the 50 most highly cited cancer biology publications from 2010-2012 (excluding clinical trials, case studies, and sequencing publications). $1.3 million has been raised for this project.

- The phases of the Cancer Biology Reproducibility Project include:

  1. The key experiments are identified from each paper.

2. Protocols are drafted for each experiment, shared with the original authors for review and feedback, and peer reviewed through eLife.
3. Any necessary reagents are requested by Science Exchange from the original lab.
4. Each experiment is matched to and performed by an expert independent lab from the Science Exchange network.
5. Reproducibility of the experiments is determined and results are published in eLife for each paper attempted for replication.

- The goals of the Cancer Biology Reproducibility Project are to demonstrate the efficacy, cost-effectiveness and scalability of Science Exchange's method for determining reproducibility, to identify best practices for maximizing reproducibility, and to generate a dataset of high-impact replicated studies.

- Using the framework from the Cancer Biology Reproducibility Project, the Science Exchange will conduct a test of reproducibility of significant prostate cancer research findings through the Movember Foundation-PCF Scientific Reproducibility Initiative. PCF intends to test 3-4 significant findings for reproducibility in the next year.
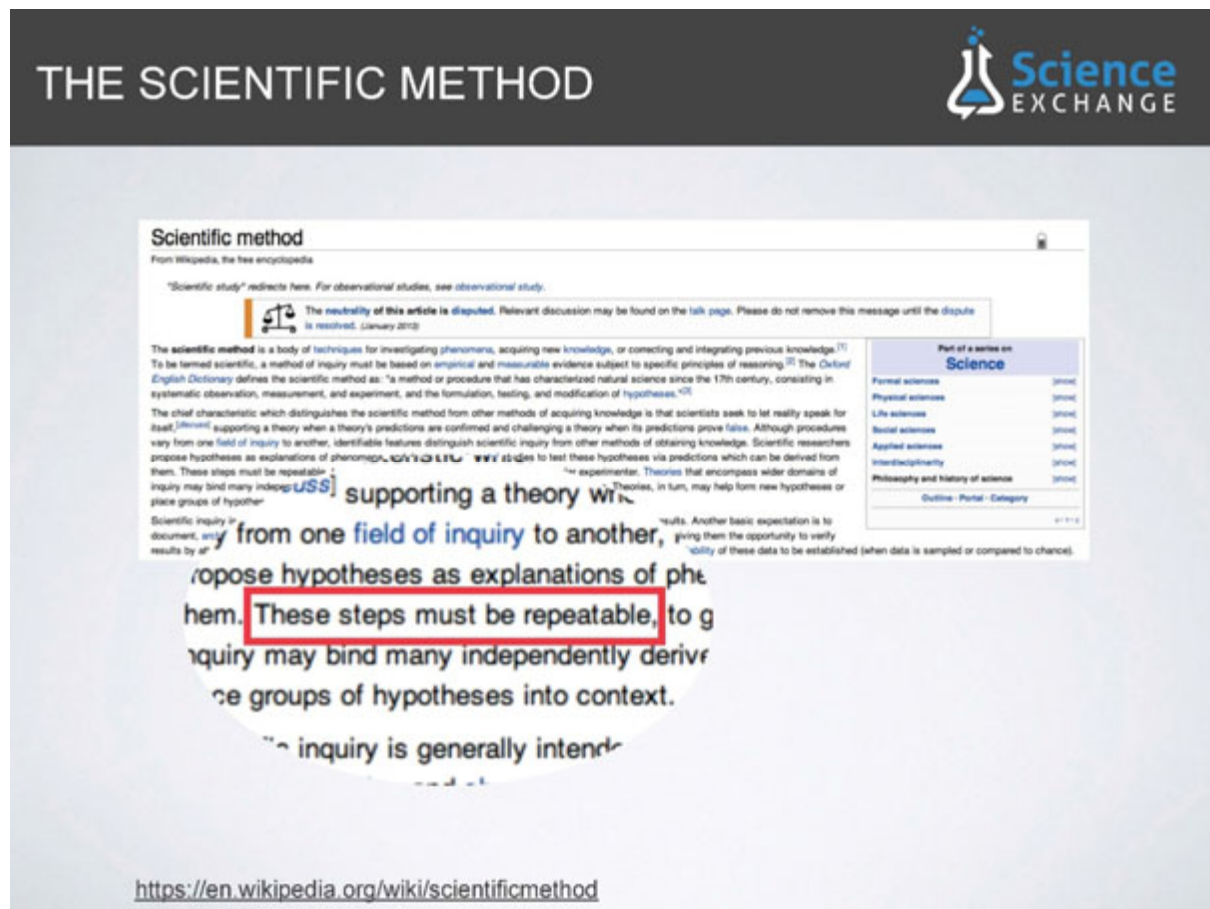

Figure 11: Reproducibly is the ability of a scientific study performed by one researcher or group to be reproduced in part or whole by independent researchers. This principle is the backbone of the scientific method.

Introducing the Movember Foundation-PCF Scientific Reproducibility Initiative

Howard Soule, PhD
Prostate Cancer Foundation

- Dr. Howard Soule introduced the "Movember Foundation-PCF Scientific Reproducibility Initiative," which PCF will launch in late 2014.

- The Movember Foundation has partnered with PCF to sponsor the replication of key prostate cancer research findings through the Science Exchange.

- An exhaustive literature search of high impact prostate cancer research papers was performed by Dr. Elizabeth Iorns of the Science Exchange, of which many have already been reproduced by the field (such as mutations in the androgen receptor in prostate cancer cells).

- Several highly impactful studies have been selected for examination of the reproducibility of their most critical findings by independent labs through the Science Exchange's partnering service.

- The Science Exchange will use the same process as established for the Cancer Biology Reproducibility Project, including informing and gaining cooperation for protocols and reagents from the original lab, replication of the experiments by an independent lab in the Science Exchange network, follow up with the original lab to attempt to solve any instances of irreproducibility, and publication of either positive or negative results in a scientific journal.

- This effort will enable the confirmation of potentially high-impact exploratory research results that can be effectively built upon for the acceleration of prostate cancer research.

Session 5: Bromodomains: Mechanisms and Therapeutic Targeting

Betting on BETs for Advanced Prostate Cancer Treatment

Irfan Asangani, PhD
University of Michigan Medical School

- The androgen receptor (AR) is the main driver of prostate cancer and the primary therapeutic target. Once activated by binding to androgen ligands, AR enters the nucleus of cells and binds to DNA, turning on the expression of genes required for the growth and survival of prostate cancer cells. New strategies for inhibiting AR may translate into powerful new therapies for prostate cancer patients, especially for patients resistant to all known androgen axis medications.

- Dr. Irfan Asangani discussed the discovery of a new protein family that interacts with AR and the therapeutic potential of inhibiting these proteins.

- BET bromodomains are a family of proteins with roles in the regulation of gene expression and the structure of chromosomes.

- BRD4 is a BET bromodomain protein that was found to interact with AR and promoted the ability of AR to turn on gene expression.

- The small molecule BET-inhibitor JQ1 specifically blocked cell growth and AR activity in prostate cancer cell lines that are dependent on AR, but not in those that do not express or rely on AR for survival. Several other BET-inhibitors have efficacy in inhibiting the gene expression activity of AR. Thus, BRD4 is required for the activity of AR, which can be blocked by BET-inhibitors.

- The N-terminal domains of AR and of BRD4 were identified as the regions where these proteins interact with one another.

- BET-inhibitors disabled the interaction between BRD4 and AR and disrupted the ability of both to assemble on DNA at "super-enhancer" regions. Super-enhancers are located in the regulatory regions of genes and contain many binding sites for transcription factors such as AR that induce gene expression.

- Enzalutamide is an AR-inhibitor that binds to AR and blocks its ability to become activated and enter the cell's nucleus.

- The efficacy of JQ1 was compared with enzalutamide. JQ1 was found to be a more potent inhibitor of AR-directed gene expression than enzalutamide in prostate cancer cell lines.

- These results indicate that BET-inhibitors have significant promise as a prostate cancer therapeutic by blocking an interaction between AR and BRD4 that is one requirement for AR activity.

- ETS proteins are another family of oncogenic transcription factors that are commonly overexpressed in prostate cancer cells.

- BRD4 was found to bind to many regions of DNA that ETS proteins regulate. BET-inhibitors blocked ETS proteins from binding to these DNA regions and blocked the oncogenic activity of ETS proteins.

- MYC is another oncogenic transcription factor involved in many different types of cancer.

- BET-inhibitors were found to block the expression of MYC and the growth of prostate cancer cells that express AR. These data indicate that AR turns on MYC expression in order to promote tumor cell growth and this function is blocked by BET-inhibitors. Interestingly, AR-inhibitors (enzalutamide and abiraterone) had the opposite effect and instead promoted MYC expression.

- In summary, BET-inhibitors have promise in treatment for prostate cancer by inhibiting three critical oncogenic transcription factors: AR, ETS, and MYC.

- At least 6 BET-inhibitors are in Phase I clinical trials for hematological and solid cancers including castrate-resistant prostate cancer (CRPC), and many more are in preclinical stages. Combining BET-inhibitors with therapies including AR-targeting medicines may also be a promising avenue of research.
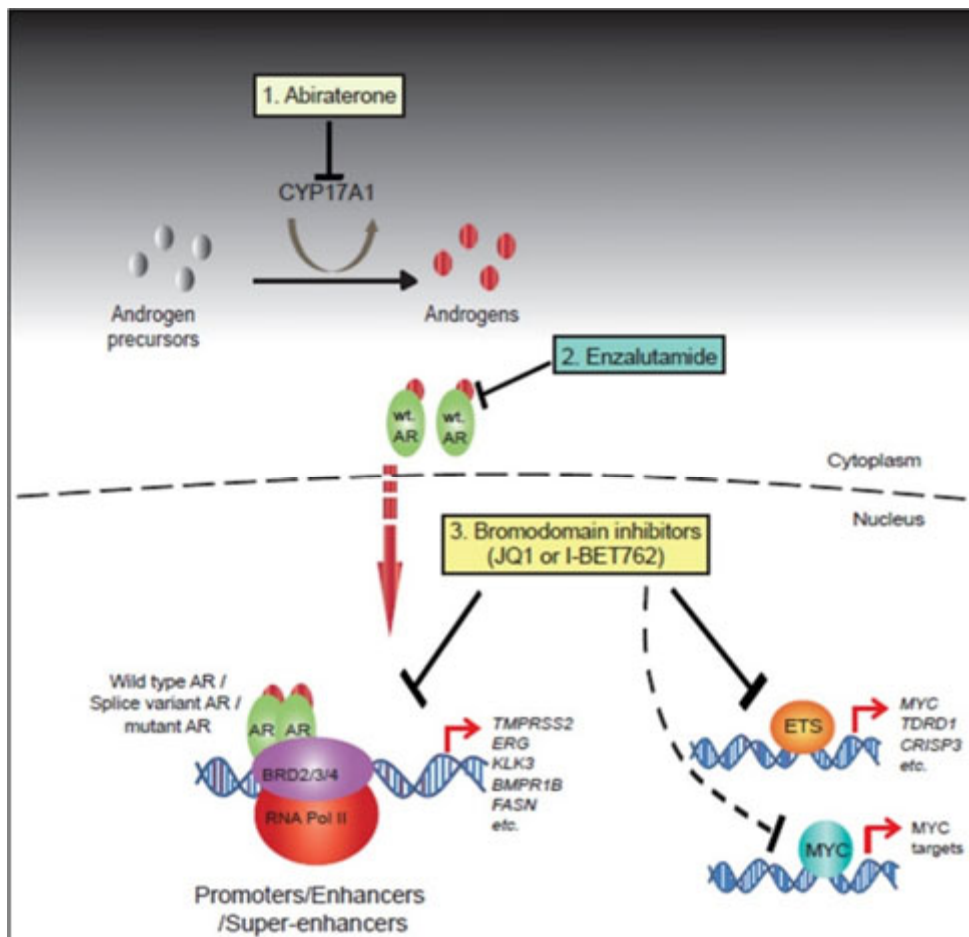

Figure 12: BET-inhibitors have promise in treatment for prostate cancer by inhibiting three critical oncogenic transcription factors: AR, ETS, and MYC.

SPECIAL LECTURE

Targeting PARP for the Treatment of Prostate Cancer

Johann de Bono, MD, PhD
Royal Marsden Hospital, UK

- Prostate cancer is genetically heterogeneous but currently patients are treated based on nonspecific standardized protocols. Treatments targeting the genetic alterations found in an individual's tumor will significantly improve patient outcome while reducing unnecessary morbidities.

- Dr. Johann de Bono presented results from clinical investigations of a PARP1-inhibitor (olaparib) in prostate cancer patients with tumors harboring mutations in DNA-damage repair genes.

- Mutations in DNA-damage repair genes are found in 15-35% of sporadic prostate cancer cases. These include loss of both chromosomal copies of BRCA2 and ATM.

- Inherited mutations in BRCA1/2 genes result in a poorer prostate cancer outcome.

- Loss of DNA-damage repair proteins can be advantageous to tumors by enabling acquisition of additional genomic alterations. However, cancer cells are forced to rely on other DNA-damage repair mechanisms to maintain sufficient genomic integrity for cell survival.

- "Synthetic lethality" is the concept that potent and lethal synergy can be achieved by treatments that target two otherwise non-lethal events, such as two pathways that are required for cell survival, but compensate for one-another when only one is lost.

- PARP1 is a DNA-damage repair protein that functions in multiple DNA-repair mechanisms. Targeting PARP1 in tumors that have mutations in other DNA-damage repair pathways can induce cancer cell death by synthetic lethality.

- Clinical studies have found that cancer cells that have lost both alleles of BRCA1 or BRCA2 have increased sensitivity to PARP-inhibitors and platinum chemotherapy which also acts to inhibit PARP1. Tumor cells can develop resistance to PARP-inhibitors and platinum by regaining BRCA function.

- Other DNA-damage repair genes that exhibit synthetic lethality with PARP-inhibitors when lost or mutated have been identified in screening studies. These include: ATM, ATR, CHEK1/2, PALB2, RAD51D, FANCA, FANCD, CDK5, MAPK12, PLK3, PNKP, STK22c, STK36, CDK12, PPP2R2A, and STAG2.

- A number of PARP-inhibiting compounds are being tested in clinical trials for various cancers. PARP1 inhibitors such as olaparib are well tolerated as single

agents and potently synergize with DNA-damaging cytotoxic agents and radiation therapy.

- In clinical trials, breast, ovarian and prostate cancer patients carrying inherited mutations in BRCA genes specifically exhibited durable responses to PARP-inhibitors.

- Dr. de Bono led the investigator-initiated Phase II TO-PARP trial to test olaparib in metastatic castrate-resistant prostate cancer (mCRPC) patients. The TO-PARP trial has a unique adaptive design which advances through several stages. The first clinical trial is ongoing and is testing olaparib efficacy in mCRPC patients and identifying biomarkers that predict responses to the agent. In a subsequent randomized clinical trial planned for 2015, patients with somatic mutations in DNA damage repair genes will be selectively treated.

- To identify biomarkers of olaparib response, pre- and post-treatment tumor biopsies and circulating tumor DNA were examined for genomic alterations in DNA-damage repair genes and other genes. Tumor tissues were also assessed for the extent of DNA-damage.

- Out of 30 evaluable patients, 10 (33%) showed a response to olaparib, as measured by a reduction in PSA levels at 12 weeks post-treatment. Several impressive and durable objective radiologic responses lasting more than six months were observed.

- Genomic analysis of the tumors from these patients revealed that some of the responders had lost both copies of the DNA repair genes BRCA2 and ATM. No associations were observed between responses and loss of the tumor suppressor PTEN or genomic translocations that cause overexpression of the ERG oncogene.

- These studies indicate that PARP-inhibitors have clinical activity against sporadic tumors harboring mutations in DNA-damage repair genes, which are present in up to a third of prostate cancer patients. Routine assessment for alterations in these genes, particularly BRCA2 and ATM, will identify patients likely to benefit from treatment with PARP-inhibitors and allow more precise care of prostate cancer patients.
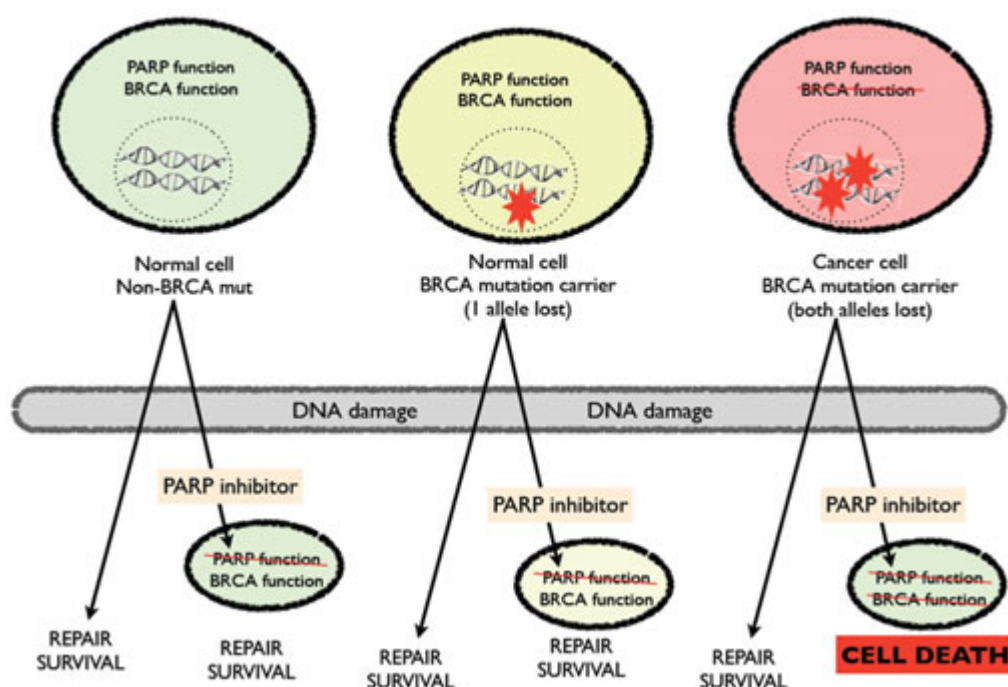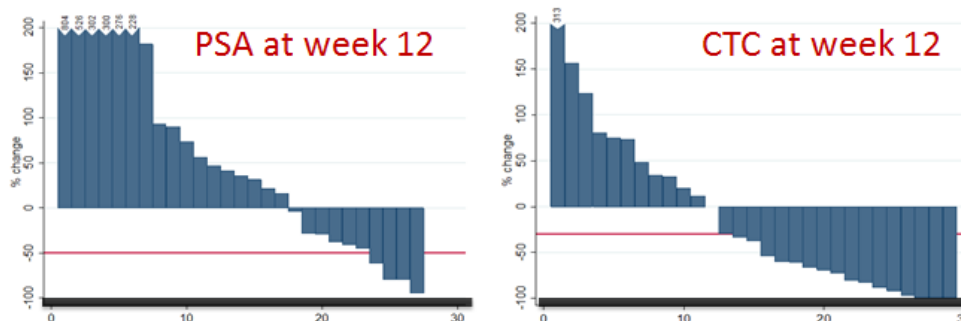
Figure 13: The concept of synthetic lethality pertaining to PARP and BRCA. In the absence of one (either inhibition of PARP or loss of both copies of the BRCA gene), the other will compensate and maintain cell survival when DNA is damaged. However, when both PARP is inhibited and both copies of BRCA are lost, cells cannot survive DNA damage.

Figure 14: Results from the Phase II TO-PARP trial testing olaparib in metastatic castrate-resistant prostate cancer (mCRPC) patients. Out of 30 evaluable patients, 10 (33%) showed a response to olaparib as measured by a reduction in PSA levels at 12 weeks post-treatment.

Session 6: Immunology of the Tumor Microenvironment

T-cell Exclusion as a Dominant Means of Immune Suppression in Pancreatic Ductal Adenocarcinoma

Douglas Fearon, PhD
University of Cambridge, UK

- The immune system has the remarkable capacity to recognize and kill tumor cells. However, as cancers progress, tumor cells develop mechanisms to turn off or evade the immune system in order to survive.

- Immunotherapies have generated deep and durable responses that may be curative in a subset of patients with melanoma and other tumors. However, minimal efficacy has been observed in prostate and pancreatic cancer patients. Determining the mechanisms that tumors use to limit the immune system is critical for developing more effective immunotherapeutic strategies.

- Dr. Douglas Fearon discussed a dominant mechanism of immune suppression that was discovered in pancreatic tumors.

- T-cells are a primary immune cell type that seek out and kill tumor cells. T-cells become activated and target tumor cells by recognizing antigens expressed by tumor cells. The prevalence of T-cell infiltration into tumors has significant prognostic value in colorectal and ovarian cancers.

- The KPC mouse is a genetically engineered pancreatic tumor model where pancreas cells can be specifically induced to lose the p53 tumor suppressor gene and express an oncogenic mutant version of the KRAS gene, which leads to the development of pancreatic ductal adenocarcinoma.

- KPC mice have populations of T-cells that recognize pancreatic tumor cells. However, T-cells are not observed infiltrating tumors and tumors are resistant to T-cell checkpoint-inhibitor immunotherapies. This indicates that tumors may be suppressing the immune system by mechanisms that are not reversible by T-cell-activating therapies.

- Histological examination of tumors identified the presence of a population of reactive cancer-associated fibroblast (CAF) cells in the tumor microenvironment that express the FAP protein. This cell type is associated with the wound-healing response, a condition which promotes an alternate immune program that is oppressive to anti-tumor immune responses.

- To determine the role of CAFs, a genetically engineered mouse model was generated in which cells that express the FAP gene (CAFs) will die following the administration of diphtheria toxin (FAP-DTR mice). Lewis lung carcinoma cells

were grown as tumors in these mice. Tumors grew robustly under normal conditions but when diphtheria toxin was administered to deplete CAFs, T-cells prevented further growth.

- FAP-DTR mice were crossed with KPC mice to examine the role of CAFs in pancreatic tumors. Depletion of CAFs in these mice also allowed T-cells to limit the growth of pancreatic tumors.

- Results from this model system indicate that CAFs are important in preventing T-cells from limiting tumor growth.

- Furthermore, depletion of CAFs synergized with the T-cell checkpoint-inhibitor immunotherapy anti-PD-L1. Therefore, the tumor-promoting functions of CAFs appear to be related to exclusion of T-cells from the tumor.

- CAFs were found to express CXCL12, a molecule that is secreted from the cell. CXCL12 was observed coating the outside of tumor cells and corresponded with the absence of T-cells in the tumor.

- CXCL12 can bind to CXCR4, a receptor located on the surface of cells including T-cells.

- AMD3100 is an inhibitor of CXCR4 that blocks the interaction with CXCL12.

- When KPC mice were implanted with an osmotic pump that continually administers AMD3100, T-cells infiltrated into pancreatic tumors and the growth of tumors was arrested.

- AMD3100 treatment synergized with anti-PD-L1 in inhibiting tumor growth and was dependent on the presence of T-cells. Following this treatment, almost no cancer cells remained in the tissue.

- In summary, the immune response against pancreatic cancer is inhibited by tumor-infiltrating CAFs that secrete CXCL12. CXCL12 then coats the exterior of tumor cells and inhibits tumor-killing T-cells from infiltrating the tumor.

- CXCL12 is also observed in human colorectal and ovarian cancers indicating that similar mechanisms may block anti-tumor immune responses in those cancer types.

- Targeting CAF cells, CXCL12, or CXCR4, alone or in combination with immunotherapies, is a promising therapeutic strategy and may significantly extend the lives of patients.

Figure 15: AMD3100 blocking of CXCR4: immune control of pancreatic ductal adenocarcinoma (PDA) and sensitivity to αPD-L1. A) Treatment of KPC mice with AMD3100 inhibited the growth of tumors (orange line vs. black line for untreated PBS control). The anti-tumor effects in mice treated with AMD3100 required T cells, as tumors grew faster if mice were administered antibodies that deplete T-cells (αCD4/CD8) but not a control antibody (isotype IgG). B) Inhibition of tumor growth by AMD3100 treatment in KPC mice synergized with the immune checkpoint inhibitor αPD-L1 but not αCTLA-4. Figure from Feig *et al*., *Proc Natl Acad Sci U S A*. 2013 Dec 10;110(50):20212-7.

Session 7: Department of Defense Prostate Cancer Research Program (PCRP) Special Presentations

Rare Germline Copy Number Variants and Prostate Cancer Risk among Mexican-American Men

Donna Lehman, PhD
University of Texas Health Science Center at San Antonio

- The risk of developing prostate cancer can be affected by lifestyle and genetic factors.

- Dr. Donna Lehman discussed the association between genetic markers called copy number variants (CNV) and prostate cancer risk among Mexican-American men.

- The San Antonio Biomarkers of Risk for Prostate Cancer (SABOR) study is a longitudinal cohort study that follows prostate cancer incidence and outcomes in men from various ethnic and racial backgrounds in southern Texas. Subjects undergo annual PSA testing and digital rectal exam (DRE) screening. Prostate biopsies are performed in the case of abnormal PSA or DRE results.

- The patients enrolled since 2001 are made up of 49.6% non-Hispanic Caucasians, 13.3% African-Americans, and 36.1% Mexican-Americans (Hispanic-Caucasians).

- Within the Mexican-American population, the 209 men who developed prostate cancer were compared with 769 controls.

- Copy number variants (CNV) are sections of DNA ranging in size from 1 to several million base pairs that are either lost or replicated in the genome, resulting in individuals having 0 to >2 copies.

- Characteristics of CNVs include deletions, duplications, and more complex gain or loss of the DNA region. These changes can lead to disruption of normal function of genes nearby.

- CNVs were identified by sequencing the germline genomes of Mexican-American prostate cancer patients and controls. 462 CNVs were identified in at least two individuals using bioinformatics tools and were examined for association with prostate cancer risk in this cohort. 215 of these CNV regions overlapped with genes and 10 overlapped with microRNAs. Many previously unidentified CNVs were discovered.

- Two rare CNVs found to be associated with altered risk were replicated in larger datasets.

- A CNV in the10q21.31locus which is near the PTEN tumor suppressor gene (57bp away from the 2nd exon of PTEN) was associated with increased risk of prostate cancer in Mexican-American men but not Caucasian men.

- A CNV in the 8q24 locus was associated with decreased risk of prostate cancer in Mexican-American men. The nearest tumor-associated gene found was MYC, located ~7Mb away. Other nearby genes included NDRG1, ST3GAL1, ZFAT, and a long-noncoding RNA gene. It is unclear if any of these genes is associated with altered prostate cancer risk.

- In summary, while common CNVs do not appear to be associated with increased risk of prostate cancer incidence and/or progression, this study identified two rare CNVs (8q24 and 10q21.31) associated with prostate cancer risk in Mexican-American men only.

- CNVs and other genetic risk factors associated with prostate cancer risk may be specific to ethnicity and might be used to identify genes that contribute to prostate cancer in a race-specific manner.
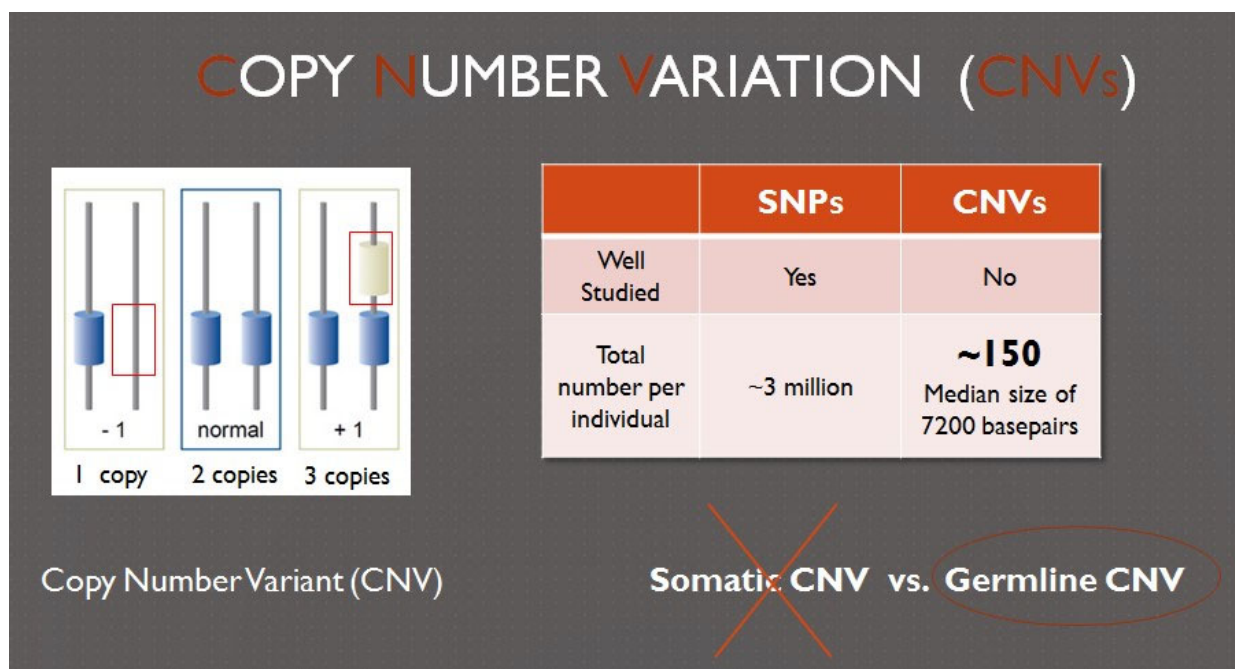

Figure 16: Copy number variants (CNV) are sections of DNA with a median length of 7200bp that can be either lost or replicated in the genome, resulting in individuals having 0 to >2 copies. CNVs are poorly studied compared to single nucleotide polymorphisms (SNPs) and number far less, being in the range of hundreds as opposed to millions.

Development, Validation and Dissemination of an Integrated Risk Prediction Model and Decision Aid to Discern Aggressive vs. Indolent Prostate Cancer

June Chan, ScD
University of California, San Francisco

- Prostate cancer screening in the United States male population is performed by PSA testing. Since the initiation of wide-spread PSA screening in the early 1990s, age-adjusted mortality for prostate cancer has fallen by ~30%, although it is controversial whether PSA screening caused this reduction in mortality.

- Active surveillance is recommended for some men with low risk prostate cancer. However, current classification schemes cannot sufficiently distinguish indolent from aggressive disease, biopsies provide an incomplete sampling of the tumor, many tumors are pathologically upgraded after surgery and there is incomplete understanding about the relationship between prostate cancer risk and morbidity. This causes anxiety for patients and clinicians and results in a significant number of low risk patients being over-treated with surgery and radiation. Thus, the reduction in prostate cancer mortality has been at the cost of overtreatment of many patients.

- Dr. June Chan discussed the development of a novel integrated risk prediction model which incorporates clinical, lifestyle, tumor genomic, and germline genomic variables in order to create tools that better inform men with early stage localized prostate cancer about their risk of harboring more aggressive prostate cancer.

- Ultimately these tools aim to improve management of low risk patients by reducing over-treatment and anxiety while improving decision making quality and satisfaction with care.

- Towards the goal of building this model, the initial prognostic value of combinations of clinical parameters was assessed. A base risk-prediction model was created that incorporates 5 clinical parameters: PSA levels at diagnosis, age at diagnosis, percentage of biopsy specimens that contain tumor tissue, prostate size, and race.

- Next, other data were added to determine their value in predicting whether a patient will be upgraded or upstaged from low risk to higher risk disease following radical prostatectomy.

- Early results from examination of 1,269 patients have found that the accuracy of the base risk-prediction model in predicting upstaging following radical prostatectomy was not improved by adding data about whether the patient had even been a smoker.

- While patient BMI may play a biological role in prostate cancer progression, BMI was only borderline associated with upgrading or upstaging and did not improve the accuracy of the risk-prediction model beyond the 5 base clinical parameters.

- In a second part of this work, UCSF researchers will work with patient advocates to develop and pilot a web portal and health coach decision support intervention program at UCSF and affiliated hospitals. A randomized clinical trial will test the effects of this intervention program vs. usual care on patients' decision making quality, satisfaction, anxiety, uncertainty, and choices in the management of their care.
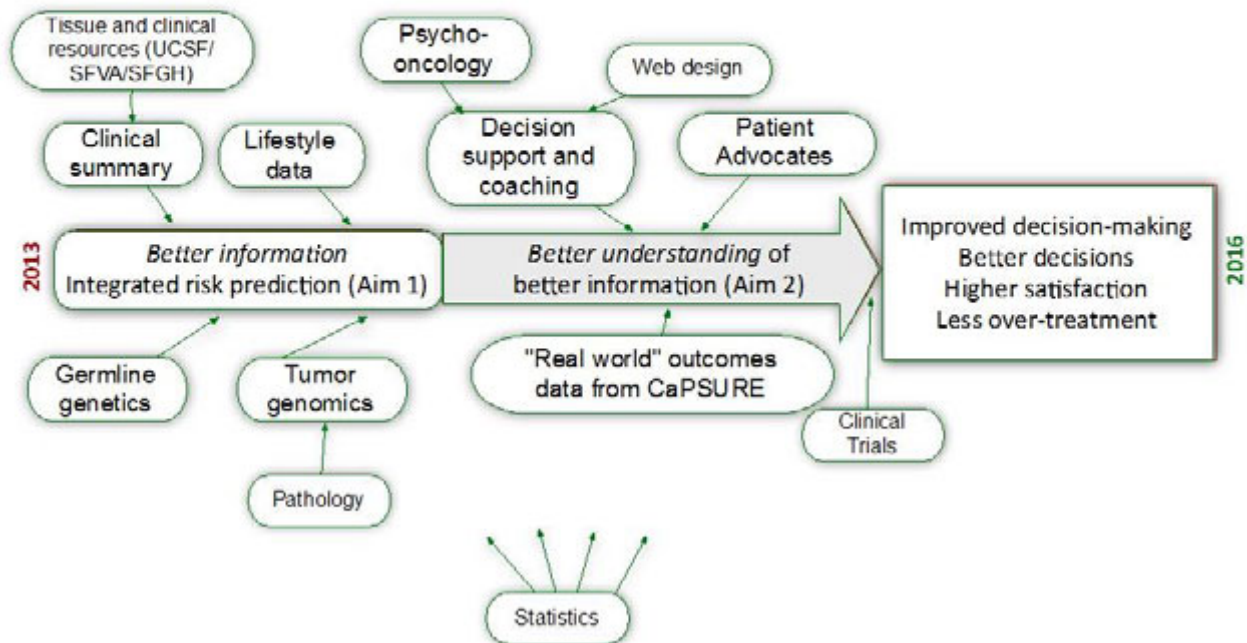
Figure 17: This project is developing a novel integrated risk prediction model that incorporates clinical, lifestyle, tumor genomic, and germline genomic variables. In addition, UCSF researchers will work with patient advocates to develop and pilot a web portal and health coach decision support intervention program. Clinical trials will compare the effects of the intervention program to usual care on patients' decision making quality, satisfaction, anxiety, uncertainty, and choices in the management of their care. These tools aim to improve management of low risk patients by reducing over-treatment and anxiety while improving decision-making quality and satisfaction with care.

Session 8: Progress Reports from the PCF Dream Teams

The West Coast Prostate Cancer Dream Team: Targeting Adaptive Responses in Abiraterone and Enzalutamide Refractory mCRPC

Eric Small, MD
University of California, San Francisco

- In 2012, PCF along with Movember and Stand Up to Cancer awarded $10 Million in funding to two prostate cancer research "Dream Teams".

- The "West Coast" Dream Team is an international alliance between research groups at UCSF, UCLA, UC Davis, UC Santa Cruz, Oregon Health & Science University (OHSU), and the Vancouver Prostate Centre/University of British Columbia.

- Dr. Eric Small, the leader of the West Coast Dream Team presented their recent findings.

- The goal of this team is to discover molecular pathways that confer prostate cancer resistance to abiraterone and enzalutamide, two potent anti-androgen therapies prescribed to metastatic castrate-resistant prostate cancer (mCRPC) patients.

- The strategy of the West Coast Dream Team study starts with accrual of mCRPC patients who have either progressed on abiraterone or enzalutamide, exhibit an aggressive phenotype, or are on a Dream Team clinical trial. Current accrual for these studies is ongoing at multiple sites that are a part of this Team. Approximately 150 of a planned 300 patients have undergone a biopsy of a metastatic site.

- Abiraterone acts by blocking an enzyme involved in androgen synthesis, thereby depleting the level of androgens that can activate the androgen receptor (AR), the primary driver of prostate cancer. Enzalutamide acts by binding to the ligand-binding domain of AR, blocking it from being activated by androgens.

- Adaptations in cancer cells that allow persistent AR signaling or other emerging pathways have been implicated in the development of resistance to abiraterone and/or enzalutamide. Prostate cancer samples are being assessed for these alterations.

- Needle biopsies from metastatic tumors are obtained. Samples collected thus far include biopsies from nearly 150 metastatic sites: about half are from bone, a quarter from lymph nodes, and a quarter from liver. A biopsy success rate of about 75% has been achieved.

- Each biopsy undergoes clinical assessment which can be reported to patients, as well as discovery (research) evaluation. Clinical assessments reported to patients are undertaken at a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory at OHSU, where clinical-grade genomic sequencing is performed as well as tumor histology, AR copy number analysis, and analysis for a specified set of mutations. Half of the tissue is sent to UCSF where laser-capture microdissection is used to discretely isolate tumor cells from tissue on which deep genomic sequencing is performed.

- The goal of this process is to discover dysregulated pathways that associate with tumor subtypes, treatment resistance, or responses to novel treatments. This knowledge will support precision medicine treatment strategies where patients are matched with the therapies most likely to benefit them.

- An aggressive "non-adenocarcinoma" tumor phenotype that is intermediate in morphology between classical adenocarcinoma and small cell carcinoma phenotypes has been observed in tumor biopsies from treatment-resistant patients.

- Compared with adenocarcinoma, the non-adenocarcinoma subtype is highly lethal with a significantly shorter overall survival time.

- Morphologically and clinically, these tumor subtypes are distinct. Analyses are being performed to determine if these subtypes are also genomically distinct.

- A 50-gene signature was discovered that was 96% accurate in differentiating adenocarcinoma from non-adenocarcinoma tumors with neuronal features.

- Amplification of the AR gene is one mechanism of resistance to abiraterone or enzalutamide. Examination of 76 advanced mCRPC patients found that AR was amplified in 58% of tumors.

- AR amplification was observed in 82% of patients who had not yet received abiraterone or enzalutamide, but was significantly less in patients who had resistance to abiraterone or enzalutamide.

- Rates of AR amplification were similar across metastatic tumors from different sites and were present in 54% of bone metastases, 61% of lymph node metastases, and 67% of liver metastases. AR amplification was also similar in adenocarcinoma vs. non-adenocarcinoma (neuronal) tumor subtypes, being present in 59% and 57% of tumors, respectively.

- AR amplification status may inform if patients will respond to subsequent treatment with abiraterone or enzalutamide. This hypothesis is being tested in Dream Team clinical trials.

- Patients are continuing to be accrued to this study and analyses are ongoing. These studies will lead to the identification of new therapeutic targets and will yield information that can direct the selection of therapies most likely to benefit patients.
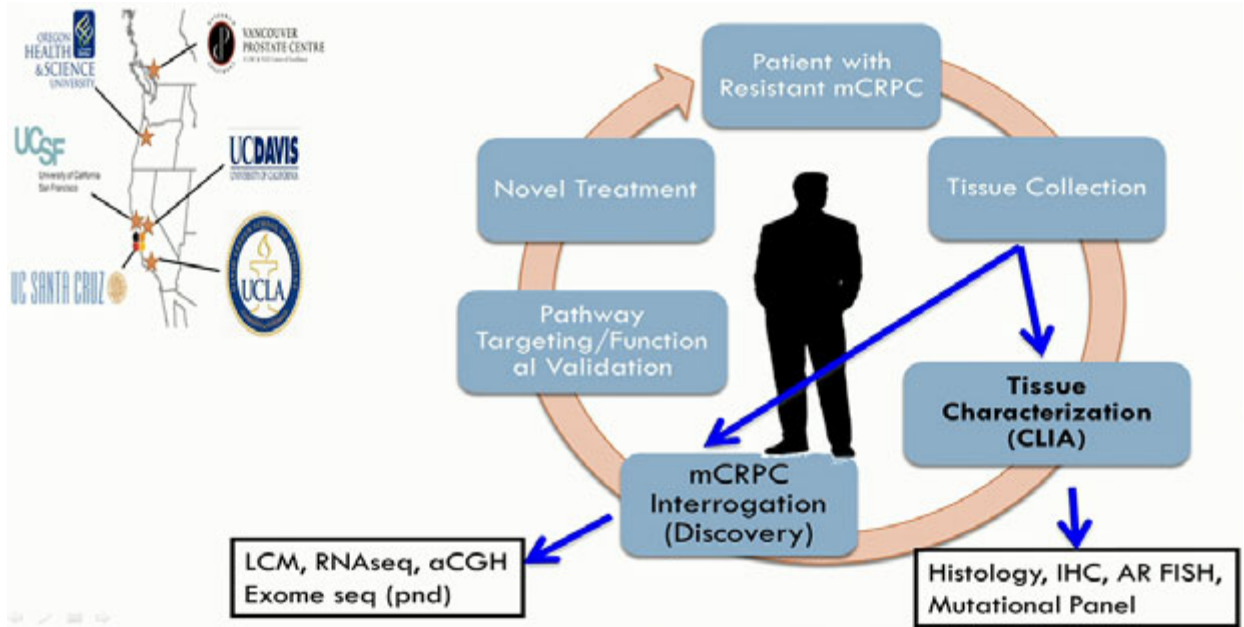
Figure 18: Left: The alliance of West Coast Dream Team institutions. Right: West Coast Dream Team study design.

Session 9: Prostate Cancer Models and Molecular Pharmacology

HOXB13-Driven MYC Expression and PTEN Loss Yield Genomic Instability and Lethal Metastatic Prostate Cancer

Charles Bieberich, PhD
University of Maryland, Baltimore County

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

- Cancer develops and progresses due to genomic instability that promotes the acquisition of genetic alterations, which confer uncontrolled growth and the capability to metastasize and grow in other body sites.

- Different types of genomic alterations are associated with different cancer types. Prostate cancers commonly have somatic copy number alterations and rearrangements, in which genomic regions containing oncogenic factors are multiplied or regions containing tumor suppressor genes are lost. The overall number of these changes is associated with a tumor's aggressiveness.

- In prostate cancer, deletions of chromosome 10q23 containing the tumor suppressor gene PTEN and amplification of chromosome 8q24 containing the MYC oncogene commonly occur and are associated with aggressiveness.

- Models examining PTEN-loss or MYC-amplification individually show that these alterations confer early signs of malignancy but do not progress to metastatic disease. However, the presence of both alterations together is associated with progressive metastatic disease and a high risk of prostate cancer-specific mortality.

- Dr. Charles Bieberich and Dr. Angelo De Marzo discussed results of studies on the combined effects of PTEN-loss and MYC-amplification in prostate cancer biology. They hypothesized that prostate luminal cells with both alterations will develop into aggressive tumors with genomic instability and metastatic potential.

- MYC is a global transcription factor that regulates the expression of approximately 15% of all genes. Gene programs regulated by MYC include cell cycle progression, metabolism, ribosome biogenesis, protein synthesis and mitochondrial biogenesis and function.

- MYC is a known oncogene that is overexpressed in many tumor types mostly due to translocations of genomic regions and gene amplification. In prostate cancer, MYC-amplification occurs late in disease in a subset of patients, indicating a role in prostate cancer progression in the context of other alterations.

- MYC levels can be visualized using quantitative image analysis of tissues. In prostate atrophy cases, MYC is expressed at normal levels but overexpressed beginning in the earliest disease stage of prostatic intraepithelial neoplasia (PIN) as well as in adenocarcinomas and metastases.

- PTEN is a tumor suppressor gene that is lost in many types of cancer and is associated with prostate cancer aggressiveness and mortality. PTEN is usually lost due to deletion of the genomic region containing the PTEN gene during disease progression.

- A genetically engineered mouse model was developed in which MYC is selectively overexpressed in prostate cells (HOXB13/MYC mice). HOXB13/MYC mice developed PIN lesions and progressed to aggressive micro-invasive carcinomas. No metastases or prostate-cancer mortality occurred in HOXB13/MYC mice.

- A second genetically engineered mouse model was developed in which the PTEN gene can be deleted from both chromosomes specifically in prostate cells (HOXB13/PTEN $^{FL/FL}$ mice).

- Finally, HOXB13/MYC mice were crossed with HOXB13/PTEN $^{FL/FL}$ mice to generate HOXB13/MYC/ PTEN$^{FL/FL}$ mice in which overexpression of MYC and deletion of PTEN can co-occur specifically in prostate cells.

- These mice developed PIN lesions that resemble human PIN by 8 weeks of age. Progression to invasive lesions was observed by 12 weeks of age and in these lesions, focal deletion of PTEN was observed. By 16 weeks, adenocarcinomas had developed which exhibited very high expression levels of MYC and complete loss of PTEN.

- By 20-28 weeks of age, 100% of mice developed lymph node metastases, 60% developed liver metastases and 50% developed lung metastases. Only one bone metastasis was observed in more than 40 mice that have been examined thus far.

- All HOXB13/MYC/ PTEN$^{FL/FL}$ mice died by 30 weeks of age while no mice died if only one copy of the PTEN gene could be lost.

- Examination of the prostate cancer genomes from these mice revealed a significant amount of genetic instability in which many genomic regions were deleted or amplified.

- One effect of MYC is to drive the activity of RNA polymerase I, an enzyme that directs transcription of the RNA molecules needed to create ribosomes, the protein synthesis factories of the cell. Cell growth depends on the rate of protein synthesis and this may be one important oncogenic function of MYC.

- To test the role of RNA polymerase I in MYC-driven prostate cancer biology, HOXB13/MYC/ PTEN$^{FL/FL}$ mice were treated with BMH-21, an inhibitor of RNA polymerase I. Overall, a profound therapeutic effect was observed, warranting

continued study of RNA polymerase I-inhibitors in the treatment of prostate cancer.

- In summary, MYC-overexpression and PTEN-deletion in prostate luminal cells synergize to promote the development of aggressive metastatic prostate cancer.

- The majority of mouse models of prostate cancer fail to recapitulate the biology of human prostate cancers. However, prostate tumors that arose in HOXB13/MYC/ PTEN$^{FL/FL}$ mice structurally and phenotypically resembled high grade human prostate cancer, indicating this model may have high utility for studying human prostate cancer biology.

- Finally, disease progression driven by MYC-overexpression and PTEN-deletion may occur through genomic instability in which many regions of the genome are deleted or amplified.
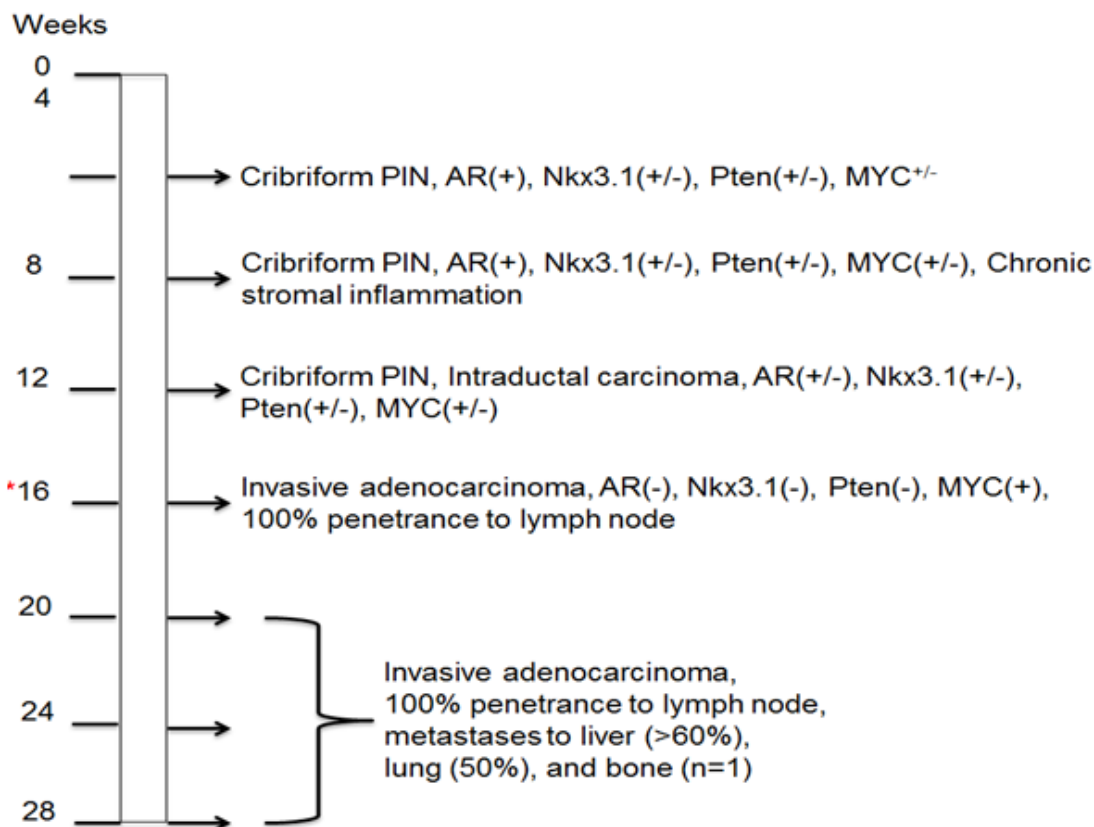

Figure 19: Major histological and immunohistochemical findings in HOXB13/MYC/ PTEN$^{FL/FL}$ male mice over time (weeks of age). Figure from Hubbard G, *et al*., 2014, *Manuscript in Process*.

SPECIAL LECTURE

Transitioning from a Prognostic to a Predictive Model of Therapy Allocation

Christopher Logothetis, MD
University of Texas MD Anderson Cancer Center

- Dr. Christopher Logothetis discussed applying clinical observations to a predictive model of prostate cancer progression in order to understand how to best leverage advances in prostate cancer therapies for curative intent.
- In this model, prostate cancer is viewed as a series of vicious spirals in which each turn represents the gain of an oncogenic mutation. The distance between each turn represents how fast tumors advance through these spirals as they transform and adapt for survival.
- Earlier in the spiral, disease is less likely to adapt to therapy, thus patients are more likely to be treatment-responsive.
- The androgen receptor (AR) is the primary driver of prostate cancer growth and survival and is activated by androgens including testosterone and dihydrotestosterone (DHT). Very early in the course of prostate cancer, tumors are androgen-dependent and suppressed by androgen-inhibition (1).
- Next, tumors progress through oncogenic phases that shift dependency from androgens supplied by distant endocrine organs to self-supply of persistent androgen signals via various mechanisms (2).
- Later, more complex biology arises in which pathways involved in interactions between prostate cancer and bone cells are turned on and promote bone metastases (3).
- Ultimately, the tumor's genetic instability will promote continued gain of oncogenic alterations and the emergence of aggressive tumors with an altered cell cycle that require aggressive cytotoxic therapy (4).
- If correct, this model predicts that earlier therapy will be more efficacious while later therapy will be more palliative as disease becomes increasingly complex and harder to subdue.

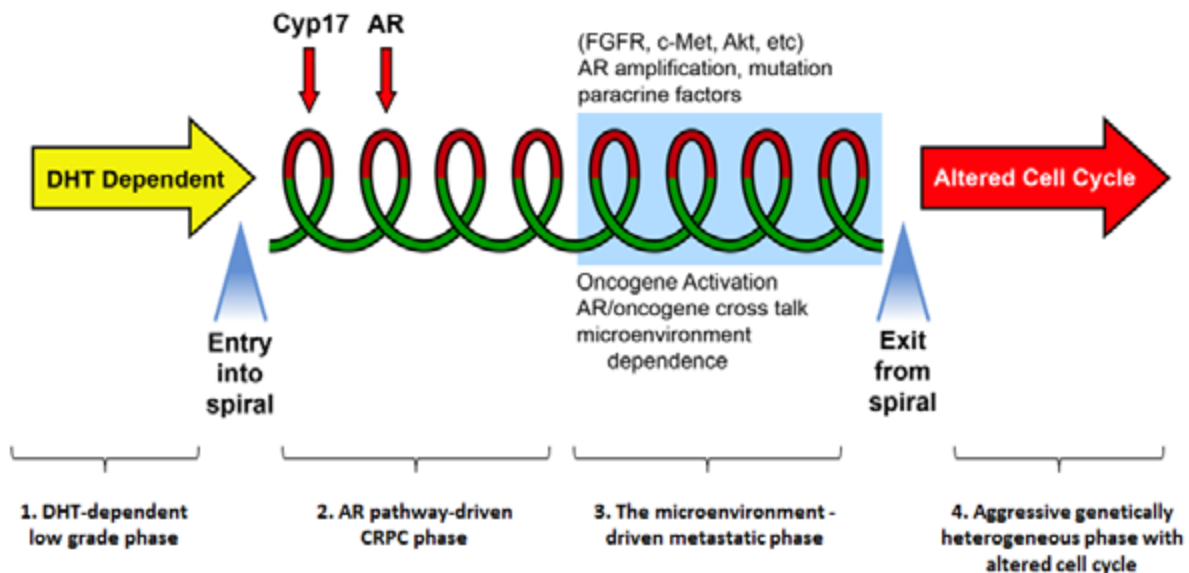# Model for Reclassification of Prostate Cancer

Figure 20: Model for reclassification of prostate cancer in which each turn represents the gain of an oncogenic mutation. (1) Very early tumors are androgen-dependent and suppressed by androgen-deprivation therapy (ADT). (2) Next, tumors gain resistance to ADT via mutations that supply persistent androgen receptor (AR) signals. (3) Later, pathways involved in interactions between prostate cancer cells and bone cells are turned on and promote bone metastases. (4) Ultimately, aggressive tumors with an altered cell cycle emerge.

The AR-pathway Driven CRPC Phase (2)

- When tumors enter the spiral phase of this model, they have developed resistance to androgen deprivation therapy (ADT) and are considered "castrate-resistant" prostate cancers (CRPC).

- However CRPC tumors can still be driven by persistent AR-signaling. CRPC tumors can have increased copy numbers of the AR gene and increased AR expression levels as mechanisms of adapting to maintain AR activity in the androgen-deprived environment.

- Instead of viewing the CRPC state as "AR-therapy resistant," amplification of the AR pathway suggests the importance of AR biology in these tumors and predicts that patients are likely to benefit from more intensive AR-targeting therapies such as abiraterone or enzalutamide or the combination of the two.

- Results from clinical trials found a similar frequency of CRPC patient responses to enzalutamide and abiraterone, both inducing > 50% PSA declines in 45-50% of patients, and >90% PSA declines in 16-20% of patients.

- Combining enzalutamide and abiraterone increased response rates to 75% of patients showing >50% PSA declines, and to 45% of patients showing >90% PSA declines. Examination of progression-free survival also indicated that a

greater proportion of patients benefited from the combination than either drug alone. These studies suggest that in some men, an initial multi-pronged assault against the AR pathway produces more significant clinical responses. Randomized trials need to be performed to confirm these promising results.

- Enzalutamide and abiraterone have non-overlapping mechanisms of action in blocking the AR pathway. Various mechanisms may confer resistance to one but not the other therapy. For instance, tumors can gain resistance to abiraterone by producing their own androgens. These patients may benefit from enzalutamide. It is important to determine which patients will benefit from different AR-targeting therapies.

- AR is composed of three domains: an N-terminal domain, a DNA-binding domain, and a C-terminal ligand binding domain (LBD). Normally, androgens need to bind to the LBD in order for AR to become activated and enter the nucleus of the cell where it turns on the expression of growth and survival genes.

- Prostate cancer cells can express shorter, variant forms of AR that lack the LBD and are constitutively active even in the absence of meaningful concentrations of androgens. These AR-variants may function independently of androgen levels or may "cooperate" with other hormones in the presence of minute concentration of androgens and are resistant to androgen depletion by ADT or the androgen-synthesis inhibitor, abiraterone. The LBD is also the region of AR that enzalutamide directly targets to prevent AR activity. Thus, variants lacking the LBD are unperturbed by enzalutamide. Expression of AR-V7, the most commonly observed AR-variant, was found to predict resistance to both enzalutamide and abiraterone.

- A Phase III clinical trial was designed to determine if initial tumor biopsy characteristics, such as the expression of AR variants, could predict the response of CRPC patients to abiraterone. Biopsy specimens were examined for ratios of variant vs. full length AR, levels of AR in the nucleus, and the presence of the androgen synthesis enzyme CYP17. The combination of all three markers more precisely segregated responders from resistant patients indicating significant promise for these biomarkers in stratifying CRPC patients who will benefit from abiraterone therapy.

- In a study to identify potential markers of response or resistance to high intensity AR-inhibition therapy (enzalutamide + abiraterone + LHRH agonist), tumors from patients treated with this regimen were examined for expression levels of variant vs. full length AR, CYP17, and the prostate-tumor suppressor gene NKX3.1. Tumors demonstrating primary treatment-resistance had high ratios of variant vs. full length AR, providing further evidence that AR-variants render tumors resistant to AR-targeting therapy.

- AR variants lacking the LBD are thus a major mechanism of prostate cancer cross-resistance to multiple AR-targeting therapies, against which new therapies are critically needed.

- Overall, predictive markers can now stratify ~60% of CRPC patients as likely to be either highly responsive to AR-targeting therapy or exhibit upfront resistance.

- An important clinical question is whether earlier treatment of patients with therapies currently used for late-stage patients will have a more profound effect than later treatment, when tumors have already become more complex and likely to adapt.

- In a clinical trial, the efficacy of LHRH agonists alone vs. LHRH + abiraterone prior to prostatectomy was tested. Metastatic recurrences were significantly reduced in the abiraterone-arm, indicating there may be a clinical benefit of earlier abiraterone therapy.

- An aggressive AR-independent tumor subtype that expresses neuro-developmental markers can emerge in CRPC patients as a resistance mechanism to treatment with abiraterone or enzalutamide. A concern is that earlier treatment with these stronger AR-suppression therapies will provoke the earlier emergence of this lethal disease phenotype.

- To address this question, gene expression was analyzed in tumors treated with LHRH agonists vs. LHRH agonists + abiraterone. Neuro-developmental marker expression was higher in tumors from patients in the LHRH agonist arm vs. LHRH agonist + abiraterone.

- Thus, a therapeutic strategy of earlier and stronger AR suppression may prevent the formation of the neuro-developmental tumor phenotype as earlier tumors with fewer heterogeneous genomic alterations will be less likely to develop resistance mechanisms.

- The glucocorticoid receptor (GR) is a transcription factor related to AR that is able to turn on expression of many of the same prostate cancer growth and survival genes.

- A gain in GR expression and activity is a potential tumor resistance mechanism to AR-targeting therapy.

- GR expression was higher in tumors from patients treated with LHRH agonist + abiraterone vs. the LHRH agonist alone, indicating an importance for the GR pathway in abiraterone-treated patients that should be studied further.

- Understanding the mechanisms that drive tumor recurrence is critical for developing and applying curative therapeutic strategies. If recurrent tumors that express PSA (driven by AR) reflect the biology of the primary tumor instead of metastases, then earlier treatment for a finite time with maximal AR-ablation therapy may be curative in a subset of patients. This would be particularly important, as 90% of patients who eventually die from prostate cancer initially present with localized disease and their response to AR-ablation therapy could be predicted from the initial primary tumor biopsy. A clinical trial testing this concept is ongoing.

The Microenvironment-driven Metastatic Phase (3)

- As tumors progress and become more biologically complex, they hijack bone developmental pathways such as the FGF/FGFR pathway to provide signals between tumor cells and bone cells that promote bone metastases.

- In a clinical trial testing dovitinib, an inhibitor of FGFR1, a striking regression of bone metastases were observed in ~30% of patients. This demonstrates that blocking bone cell supply of FGFR signals to tumor cells blocks the growth of bone metastases.

- Radium-223 is a bone-targeting radiotherapy for prostate cancer patients with bone metastases.

- The clinical effects of Radium-223 treatment are consistent with targeting of the bone microenvironment as opposed to tumor cells because PSA does not appreciatively decline while bone metabolism markers (alkaline phosphatase) decrease and patients live longer.

- A clinical trial has been initiated that will take serial bone marrow biopsies from patients treated with Radium-223 in order to identify biomarkers that correlate with bone metabolism markers and clinical outcome. These biomarkers represent potential therapeutic targets for treatment of bone metastases.

- Circulating tumor cells (CTCs) and CTCs that circulate in clusters initiate new metastases. Clusters of CTCs are particularly prevalent in bone marrow. Studies are being performed to identify factors that promote CTC clusters and determine whether these factors promote bone metastases.

Aggressive Genetically Heterogeneous Phase with Altered Cell Cycle (4)

- In the latest stage of prostate cancer progression, emergent lethal tumors have an altered cell cycle which can confer sensitivity to chemotherapy. These tumors are highly heterogeneous and can have morphological features of small cell carcinoma.

- Clinical trials testing serial chemotherapy treatment of highly advanced tumors found that 90% of patients respond to chemotherapy though for relatively short time periods.

- A subset of small cell carcinomas exhibiting loss of the tumor suppressor gene RB, altered expression of the tumor suppressor protein p53, and an altered cell cycle were identified. These patients should be considered for treatment with chemotherapy.

- A clinical trial is testing whether patients with advanced small cell carcinoma phenotypes will be particularly responsive to combination chemotherapies.

Checkpoint Blockade Immunotherapy

- Immunotherapy is emerging as an effective treatment for subsets of patients with various solid tumors. Anti-CTLA4 (ipilimumab) is a "checkpoint blockade" immunotherapy that turns off signals that inhibit immune cells from targeting and killing tumor cells.

- In rare instances, prostate cancer patients have exhibited profound responses to ipilimumab. However in a subset analysis of patients who meet favorable response criteria for other immunotherapies (those without liver metastases or elevated lactate dehydrogenase levels) it is apparent that ipilimumab significantly delays progression without appreciable effects on disease regression.

- A clinical trial was initiated to test the combined effects of ipilimumab + LHRH agonists prior to prostatectomy. An increase in expression levels of immune suppressive molecules PD-1 and PD-L1 was observed when ipilimumab was combined with LHRH agonists but not with LHRH agonists alone. This indicates that adaptation to ipilimumab involves upregulation of immune-inhibiting pathways. Clinical trials combining inhibitors of PD-1/PD-L1 with ipilimumab in prostate cancer patients are being initiated.

- Overall, immunotherapy with checkpoint inhibitors that block negative regulatory immune cell pathways (CTLA4, PD-1, PD-L1) have an organ-specific effect and might exhibit therapeutic synergy if combined with AR-targeting therapies. Identifying the most effective therapeutic combinations and the best time during the disease course to administer immunotherapies is critical.

- Currently the treatment protocol of clinicians is to wait and treat patients later to reduce the negative effects of overtreatment.

- These studies support a new conceptual view of how best to treat prostate cancer patients to prevent the emergence of lethal disease and lead to cures: earlier, with stronger therapies, and implementing biomarkers to match patients with the therapies most likely to benefit them.

- Ongoing clinical trials are validating these hypotheses.

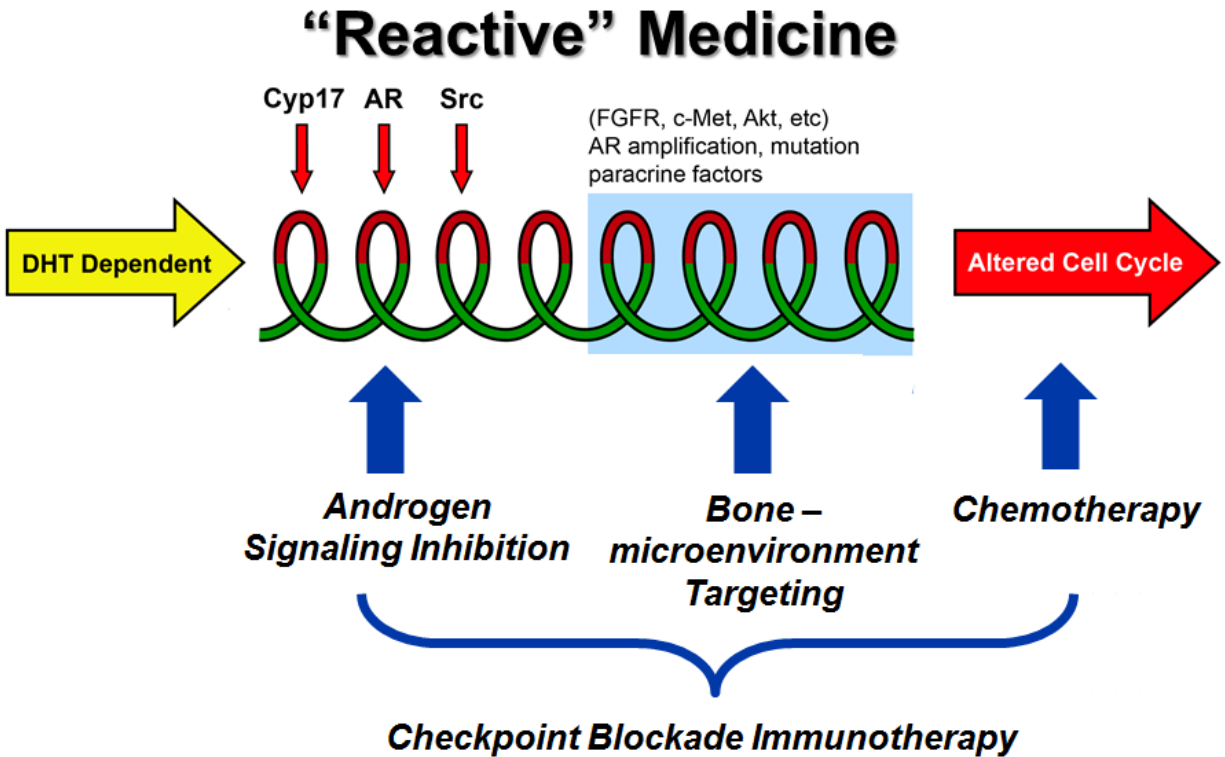**Figure 21**: This model provides a new conceptual view of how best to treat prostate cancer patients: earlier, more complete androgen-signaling inhibition during the AR pathway-driven CRPC phase, bone microenvironment targeting during bone metastatic phases, and chemotherapy once tumors with an altered cell cycle emerge. Checkpoint blockade immunotherapy may be beneficial at various times during the disease course.

Session 10: Bioinformatics

canSAR Integrative Data for Cancer Drug Discovery

Bissan Al-Lazikani, PhD
The Institute of Cancer Research, UK

- Dr. Bissan Al-Lazikani introduced canSAR, an integrative computational database created at the Institute of Cancer Research in the UK for identifying and characterizing novel targets for drug discovery.

- A subset of proteins within the human proteome is disease-causing, while another partially overlapping subset of proteins can be modified by an agent or compound and are therefore considered "druggable." This overlap is the target space for therapeutic drug discovery.

- The goal of canSAR is to create a systematic, objective approach that takes large scale cancer gene information and identifies drug targets.

- Over 1 billion experimental data points are integrated into the canSAR database. These include information from over 1000 cell lines and variants, over 1 million bioactive small molecules, clinical disease data, and the human proteome. Data include cancer and other disease-specific mutations, gene expression levels, chemical screening results, 3D structure, protein binding sites, interaction networks, cell line and tissue characterization, chemical properties of compounds, clinical information on drug responses, and clinical data such as survival and stage.

- The database is designed for queries into information about potential drug targets. A target synopsis can be automatically obtained which includes gene expression data, data on copy number variation and mutations identified in various tumor types, whether the target has been included in any RNAi studies, a druggability assessment, a 3D structure analysis and maps of sites that can be bound by inhibitors, data from chemical screening studies, and a chemically and biologically annotated cellular interaction network.

- canSAR can also analyze lists of cancer genes from a study and use the information in the database to generate ranked lists of genes ideal as novel targets and for repurposing drugs that are known to be effective against other targets.

- Queries can also be made into what is known about a compound or drug candidate and what is known about a cancer cell line.

- In the evaluation of canSAR study results, it was observed that when the cellular interaction network of cancer genes is plotted, predicted druggable or actionable

proteins can be found all over the network. However, targets of approved cancer drugs always clustered in highly-interconnected sub-networks that are non-overlapping and only occupy some areas of the network.

- This suggests that when choosing drug combinations for therapy, if drugs are chosen that target overlapping/interconnected areas of the network, while some synergy may be obtained, the generation of resistance to both drugs via the same mechanisms is highly likely. However, if drugs that interact with non-overlapping areas of the network are combined, stronger synergy may be achieved while making resistance more difficult.

- To address unmet therapeutic needs in various cancers and avoid acquired drug-resistance, mechanistically distinct targets with different cellular interaction networks and different liabilities need to be identified.

- In a study that used canSAR to examine 479 driver genes listed in the Cancer Gene Census, 123 druggable candidate targets were identified. Of these, 25 were approved drug targets, 86 were targets known to have active compounds, and 103 were targets predicted as druggable, 46 of which were novel targets not yet explored in drug discovery studies.

- A large number of unexplored potential targets have yet to be drugged.

- In the near future, data from patients stratified by genetic backgrounds or diseases can be used to identify novel druggable cancer driver genes and mechanistically distinct drugs. This will enable advancements in personalized medicine strategies that treat individual patients according to their specific tumor characteristics.

- canSAR is freely available and is used by over 50,000 unique visitors worldwide from both academia and industry. Visit canSAR at: www.cansar.icr.ac.uk
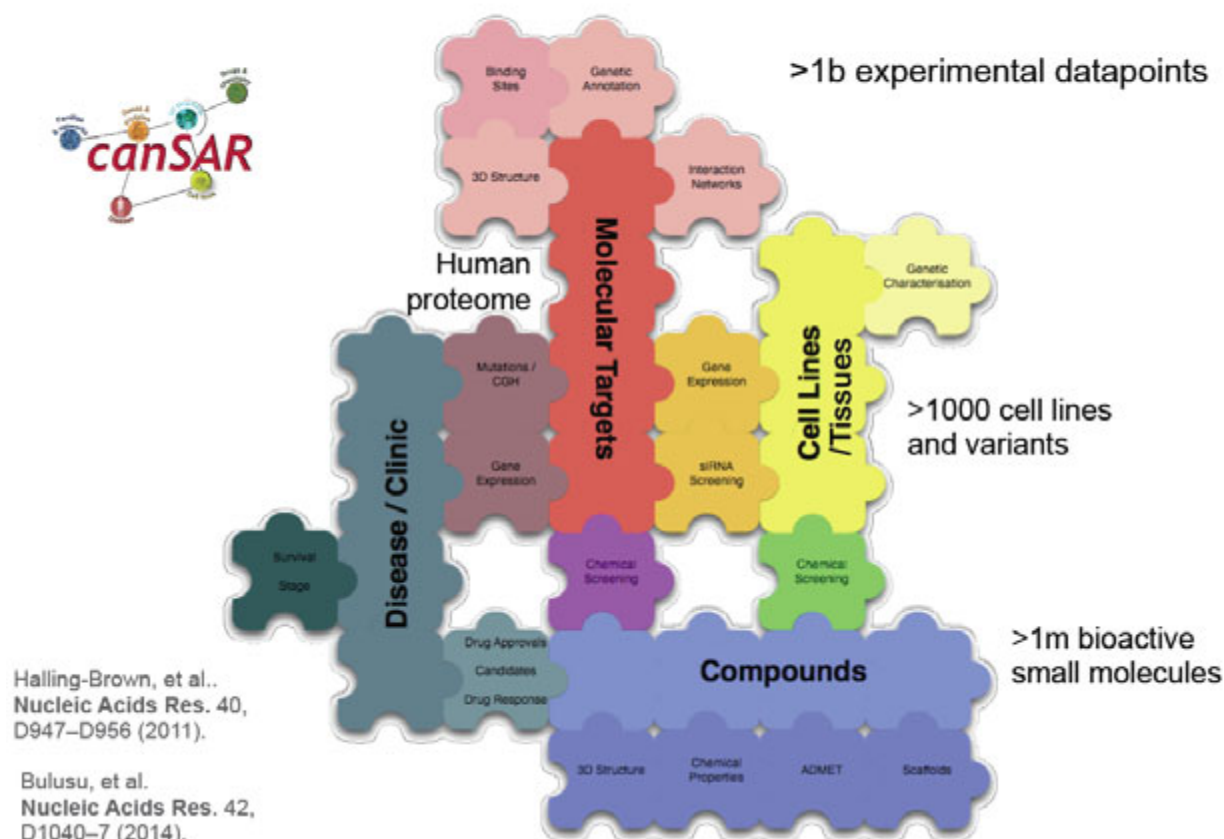
Figure 22: The types of experimental data points that are integrated into the canSAR database.

The cBioPortal for Cancer Genomics

Nikolaus Schultz, PhD
Memorial Sloan-Kettering Cancer Center

- Dr. Nikolaus Schultz discussed and demonstrated the use of the cBioPortal for Cancer Genomics, an online interactive tool for visualizing cancer genomics data.

- The cBioPortal was originally created to convert genomic data from The Cancer Genome Atlas (TCGA) into knowledge that can be accessible and understandable by biologists and clinicians. The cBioPortal presents data including mutations, copy number changes, methylation states, gene fusions, and mRNA expression changes in a fast, intuitive, and interactive visual interface.

- The cBioPortal database includes TCGA data, data from published studies, private data and data from the Sanger Institute's Catalogue of Somatic Mutations in Cancer (COSMIC) database, the PharmGKB pharmacogenomics database, the Pathway Commons collection of biological pathways, and clinical trials information from www.clincialtrials.gov

- The cBioPortal query uses a simple 4-step interface. Selections are made regarding the desired cancer study, genomic profiles, the patient/case set, and the genes to be analyzed.

- A summary is delivered for each gene which includes the overall alteration frequency and a visualization of individual alterations across the cohort. This allows viewing of overlapping or mutually exclusive genetic alterations across a cohort. Visualization can be customized to incorporate patient clinical parameters such as age and tumor grade.

- The position of mutations along a gene can be viewed for all patients from a given study set, cancer type, or all included in the database.

- Individual patients can be selected to view genetic alterations, clinical data, and de-identified pathology reports with images of histology slides.

- Serial samples from prostate cancer patients can be viewed against their treatment timelines to identify mutations that arise during the course of treatment.

- Several additional options exist for using cBioPortal to examine prostate cancer data. Permission for controlled access can be obtained to examine datasets from the International PCF-Stand Up to Cancer Dream Team, the University of Washington, and organoid data from the lab of Dr. Yu Chen. Alternatively, cBioPortal can be locally installed at any user's institution and uploaded with private datasets.

- Following data analysis, the results can be stored in cBioPortal and made openly available following publication of results.

- cBioPortal is open access and publicly available at www.cbioportal.org
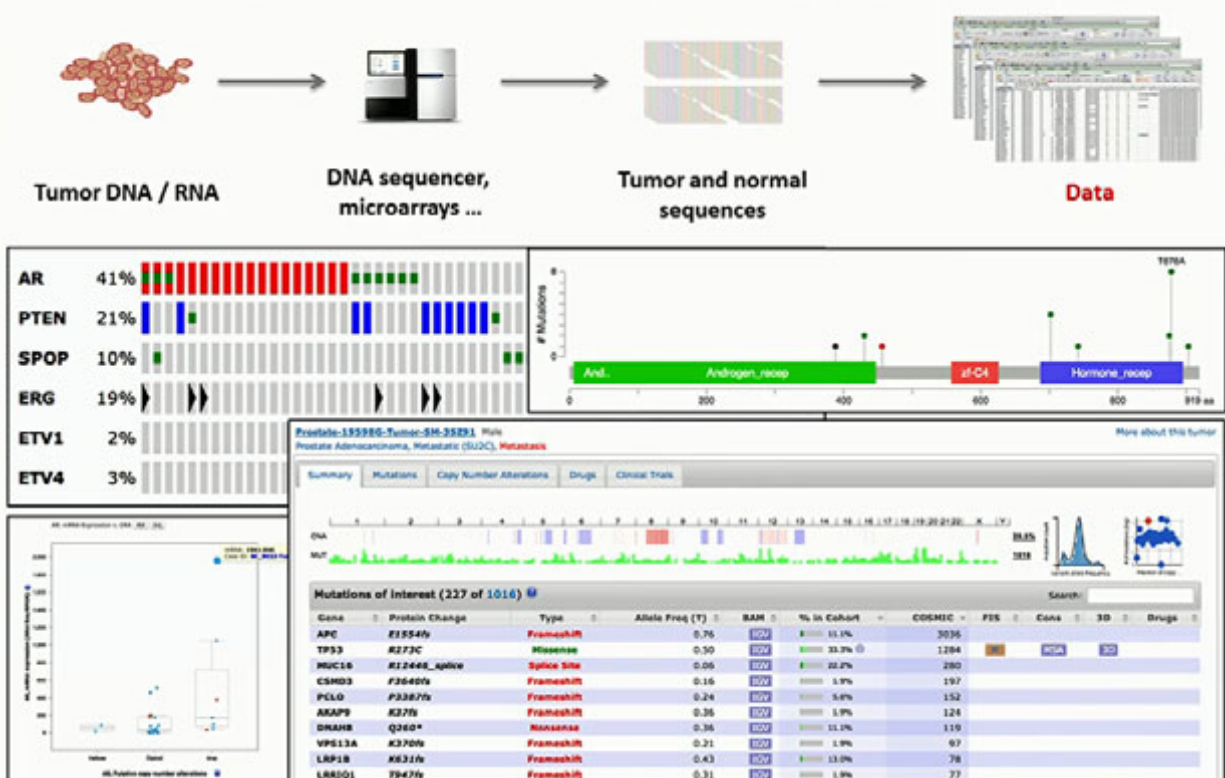
Figure 23: cBioportal converts genomic data obtained from sequencing tumor DNA or RNA into accessible and understandable knowledge. Multiple types of information can be visualized including a summary of overall frequency and individual alterations present for genes of interest across a cohort, the position of all mutations along a gene for patients from a given study set, gene expression in different sets of patients, and lists of mutations in a selected individual.

Session 11: Adipose Tissue, Inflammation and Obesity

Lipogenic Prostate Cancers

Massimo Loda, MD
Harvard: Dana-Farber Cancer Institute

- Metabolic syndrome is an abnormal metabolic condition that is diagnosed based on having elevated fasting blood glucose levels and two of the following: abdominal obesity, hypertension, and/or abnormal lipid levels in the blood. Metabolic syndrome increases risk for diabetes and heart disease.

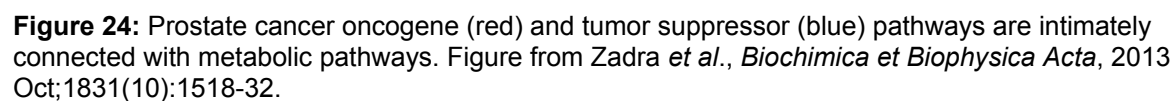- Several studies have found that the risk of death from prostate cancer is disproportionately high in patients with metabolic syndrome and obesity. This suggests that alterations in the body's metabolism are associated with progression of prostate cancer.

- Dr. Massimo Loda discussed mechanisms that link metabolic syndrome and obesity to prostate cancer.

- AMP-activated protein kinase (AMPK) is an enzyme that plays a master role in metabolism by sensing energy levels within the cell.

- Inactivation of AMPK is associated with metabolic syndrome. Increased expression and/or activity of enzymes that are inhibited by AMPK have been observed in prostate cancer.

- In mouse models lacking one copy of the tumor suppressor gene PTEN, treatment with drugs that activate AMPK reduced prostate cancer incidence and delayed onset.

- AMPK activation caused death of prostate cancer cells primarily by inhibiting lipogenesis and synergized with therapies that target the androgen receptor (AR), the primary driver of prostate cancer cell growth and survival.

- These findings indicate that therapies that activate AMPK or target select metabolic enzymes/pathways may have a therapeutic effect for prostate cancer.

- Profiling of metabolites from prostate tumors and assessment of the associated metabolic pathways resulted in the identification of a tight linkage between metabolism and prostate cancer oncogenes and tumor suppressors.

- A study was performed to determine whether alterations in metabolism are different in cancers driven by various oncogenes. Human prostate cells engineered to express either MYC or the AKT1 oncogenes, tumors from genetically engineered MYC and AKT mouse tumor models, and tumor tissues

from human prostate tumors that express either the MYC or AKT pathways were profiled for metabolites.

- AKT-driven tumors were found to be glycolytic, which is the metabolic breakdown of glucose and sugars.

- MYC-driven tumors were found to be lipogenic, where glucose and other molecules are synthesized into lipids. Lipogenesis metabolites that were high in MYC-driven tumors included sarcosine, arachidonic acid, oleic acid and docosahexaenoic acid.

- Metabolic enzymes such as fatty acid synthase were differentially expressed in prostate tumors vs. normal prostate tissue and in MYC vs. AKT-driven tumors. The glycolytic enzyme, Hexokinase 2, was high in AKT-driven tumors, while the glutamine metabolism enzyme, glutaminase, was high in MYC-driven tumors.

- Overall, these studies demonstrate that metabolism is altered in prostate cancer cells and different metabolic abnormalities are associated with different oncogenic pathways. Tumors arising in the context of the metabolic syndrome and MYC or FASN-driven tumors may be lipogenic and targeted by AMPK activators and/or inhibitors of lipogenic enzymes.

- Enzymes involved in these metabolic pathways may represent novel targets for the treatment of prostate tumors driven by specific oncogenes.

- Profiling of metabolites and metabolic pathways in tissue or serum may be useful for identifying different tumor subtypes or for monitoring disease progression.

- These studies have recently been published in *Cancer Research* and *EMBO Molecular Medicine*.

Figure 24: Prostate cancer oncogene (red) and tumor suppressor (blue) pathways are intimately connected with metabolic pathways. Figure from Zadra *et al*., *Biochimica et Biophysica Acta*, 2013 Oct;1831(10):1518-32.

SPECIAL LECTURE

ICECaP: Intermediate Clinical Endpoints for Treatment of High-Risk Prostate Cancer – Update

Christopher Sweeney, MBBS
Harvard: Dana-Farber Cancer Institute

- Every year ~230,000 men in the U.S. are diagnosed with prostate cancer.

- At diagnosis, ~95% of patients (~220,000) have localized prostate cancer, of which ~75% are cured by surgery or radiation therapy or do not require therapy and the other ~25% relapse. Of treated patients who relapse, ~20% (17,000) progress to lethal metastatic disease, while the remaining ~80% have a more indolent relapse at an older age and eventually die of other causes.

- Approximately 5% of patients (~10,000) diagnosed with prostate cancer initially present with incurable metastatic disease.

- This accounts for nearly all of the 29,000 U.S. men that die every year from prostate cancer.

- The ~17,000 patients that die every year after initially being treated for localized disease represent a major population to target for reducing the mortality of prostate cancer. A potential strategy is earlier systemic medical treatment with therapies that are effective against highly resistant CRPC to eradicate initial hormone-sensitive micrometastatic disease.

- Many patients who relapse have a relatively long and slow course of disease progression. Clinical trials use overall survival as the primary endpoint to measure the efficacy of treatments. This makes clinical investigation of new treatments for patients with localized, high risk prostate cancer difficult and expensive and therefore unattractive for trial sponsors.

- Dr. Christopher Sweeney discussed ICECaP (Intermediate Clinical Endpoints for Treatment of High Risk Prostate Cancer), a PCF-funded initiative with industry partners to discover intermediate registrational clinical endpoints (ICEs) that correlate to survival.

- This would attract therapeutic development into the early disease setting where cure might be possible for a subset of patients.

- ICEs have been accepted as surrogates for overall survival in breast and colon cancer adjuvant clinical trials.

- Men who present with higher-grade disease and are younger with a longer life expectancy are more likely to die from prostate cancer. These men represent a subgroup to focus studies on for identification of ICEs for curative intent therapy.

- Potential ICEs include PSA nadir (the absolute lowest level that PSA falls to) after radiotherapy, time to PSA nadir after radiotherapy, biochemical plus objective progression-free survival, and objective measures of progression-free survival such as radiological, loco-regional, and death.

- Relevant ICEs will probably be surrogates that predict metastasis-free survival and prostate cancer-specific survival.

- To identify ICEs that predict the effect of a treatment on overall survival, data from randomized controlled clinical trials for treatments of localized prostate cancer have been collected and are being analyzed using specialized statistical methods.

- At the present time, agreements to share data on 28,389 patients from 43 randomized controlled clinical trials have been attained and more are pending. Data has been attained for 14,848 patients from 19 trials and analysis is ongoing.

- In addition, a health-economic analysis of these data is being performed to assess cost savings to patients and society for the prevention of prostate cancer progression. This could also be a registrational endpoint in the era of healthcare cost containment.
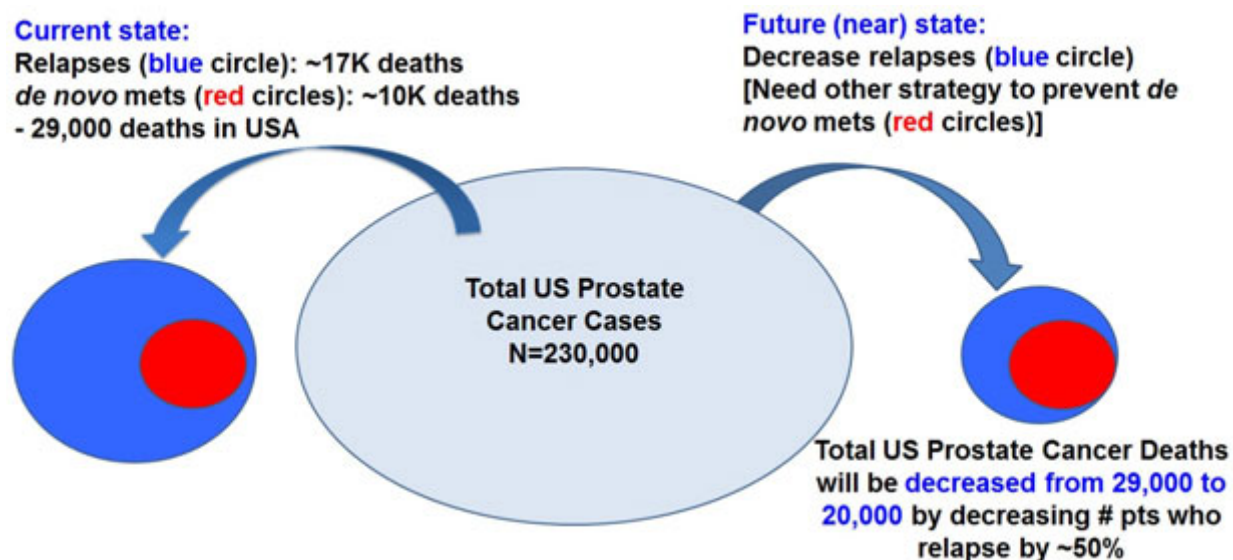

Current state:
Relapses (blue circle): ~17K deaths
de novo mets (red circles): ~10K deaths
- 29,000 deaths in USA

Future (near) state:
Decrease relapses (blue circle)
[Need other strategy to prevent *de novo* mets (red circles)]

Total US Prostate Cancer Cases
N=230,000

Total US Prostate Cancer Deaths will be **decreased from 29,000 to 20,000** by decreasing # pts who relapse by ~50%

Figure 25: Currently, 230,000 men in the U.S. are diagnosed with prostate cancer every year. Of these, ~17,000 deaths are from patients who present with localized prostate cancer but go on to progress to lethal metastatic disease. Approximately 10,000 deaths are patients initially diagnosed (*de novo*) with metastatic disease. This comes to nearly all of the 29,000 U.S. men that die every year from prostate cancer. The 17,000 patients that die every year after initially being treated for localized disease represent a major population to target for reducing the mortality rate from prostate cancer in the future.

Session 12: Mechanisms and Targeting of DNA-Damage Repair

Non-Coding Modulators of DNA Repair: PCAT1 as a Regulator of Homologous Recombination in Prostate Cancer

Felix Feng, MD
University of Michigan

- Recent investigations of the organization of the human genome have revealed a large number of RNA molecules that are not translated into proteins. These noncoding RNA genes outnumber protein-coding genes by more than 30-fold.

- Noncoding RNA genes include ribosomal RNA, inhibitory RNA (RNAi), small nuclear RNA, and long non-coding RNA (lncRNA).

- Dr. Felix Feng discussed the roles of various lncRNAs in regulating prostate cancer.

- RNA molecules from 82 prostate cancer cases and 20 benign prostate tissues were sequenced. The results identified 106 lncRNAs expressed exclusively in prostate cancer tissue.

- The most abundant prostate cancer lncRNA is PCAT1.

- PCAT1 regulates the expression of hundreds of genes and notably represses the expression of BRCA2. Human prostate cancer specimens with higher levels of PCAT1 had lower levels of BRCA2.

- BRCA2 is a DNA damage-repair gene that functions in homologous recombination—a mechanism that repairs DNA broken on both strands. PCAT1 was found to repress homologous recombination likely by down-regulating BRCA2.

- BRCA-deficient tumor cells become reliant on other DNA-damage repair proteins such as PARP1 to survive following DNA damage, and are highly sensitive to therapies that inhibit PARP1.

- PCAT1 overexpression sensitized prostate cancer cells to death following treatment with the PARP1-inhibitor olaparib and knockdown of PCAT1 caused resistance to olaparib. In mice, overexpression of PCAT1 in tumor cells significantly enhanced tumor growth which was blocked by olaparib.

- PCAT1 was found to bind to a region of the BRCA2 mRNA molecule that is also the binding site of HUR, a protein that stabilizes mRNA. By competing with HUR, PCAT1 disrupts the stability of BRCA2 mRNA, causing BRCA2 mRNA to be more rapidly degraded and consequentially lowering the amount of BRCA2 protein in cells.

- In another series of studies, tumor specimens from radical prostatectomies were examined for the expression of genes that can be used as prognostic biomarkers.

- The lncRNA SChLAP1 was identified as the most abundant gene expressed in tumors from patients who progressed to metastatic disease. SChLAP1 expression was a stronger predictor of metastatic progression than other clinical findings. These results were validated across four cohorts totaling 1,008 prostate cancer cases.

- SChLAP1 is being developed into a clinical prognostic test for prostate cancer progression to potentially lethal disease.

- These results show that certain lncRNAs play a role in prostate cancer growth and progression and may be useful as biomarkers that predict clinical outcome or sensitivity to therapies.

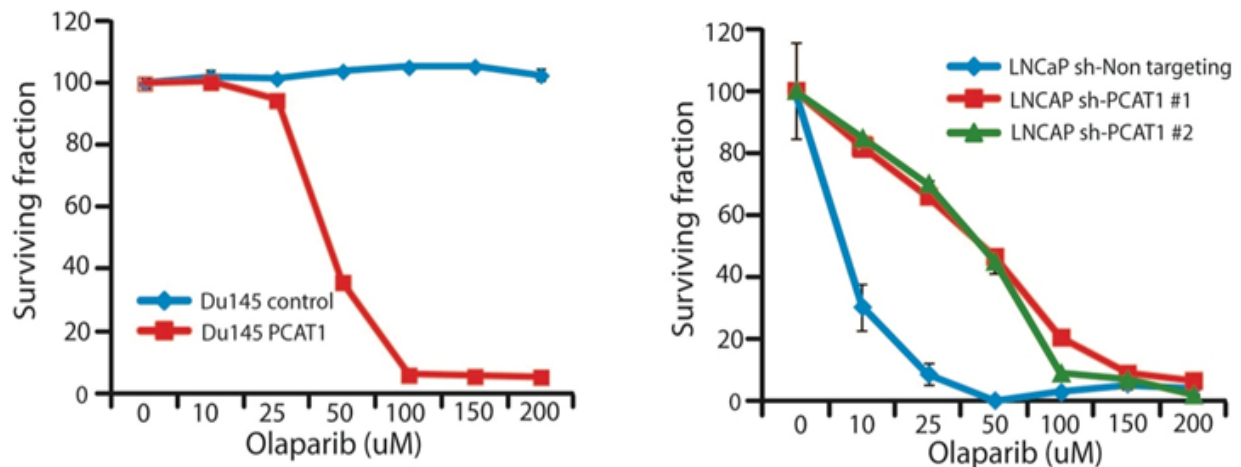**Figure 26**: PCAT-1 expression sensitizes prostate cancer cells to PARP inhibitors. Left: PCAT1 overexpression sensitized DU145 prostate cancer cells to death following treatment with the PARP1-inhibitor olaparib. Right: knockdown of PCAT1 (sh-PCAT1#1, #2) in LNCAP prostate cancer cells promoted resistance to olaparib compared to control (sh-Non targeting). Figure from Prensner *et al., Cancer Research,* 2014 Mar 15;74(6):1651-60.

Neo-Adjuvant Castration Improves Radiotherapy by Impairing DNA Repair

Thomas Helleday, PhD
Karolinska Institutet, Sweden

- Dr. Thomas Helleday discussed therapeutic strategies to target DNA-damage repair pathways for the treatment of prostate cancer.

- Clinical trials have demonstrated that combining androgen deprivation therapy (ADT) with radiotherapy (RT) for the treatment of high risk prostate cancer patients significantly prolongs survival compared with RT alone.

- RT induces significant levels of DNA damage in cells. Cancer cells already have high levels of endogenous DNA damage and have often lost proteins that function in DNA damage-repair. Treatment with RT leads to cancer cell death by damaging DNA beyond a point of rescue. DNA damage caused by RT may play a role in therapeutic synergy observed with ADT.

- Surgical castration was found to severely reduce prostate tumor levels of Ku70. Ku70 is a catalytic subunit of the DNA-PK enzyme, which repairs DNA following RT.

- PSA expression is driven by the androgen receptor (AR) pathway, the target of hormonal therapy (ADT or castration). After castration, levels of PSA dropped at a similar rate as Ku70, suggesting that changes in levels of PSA can be correlated to changes in levels of Ku70.

- Efficacy of RT is reduced if administered without hormonal therapy in part due to activation of Ku70 and the associated increase in DNA damage-repair.

- Multiple DNA damage-repair pathways exist and can act as back-up mechanisms to rescue cells from DNA-damage induced cell death when one DNA damage-repair pathway is lost.

- PARP1 is an enzyme in one such pathway and was found to be up-regulated following castration or castration + RT. Inhibition of PARP may synergize with hormonal therapy + RT.

- Precision cancer therapy is the treatment of patients based on the unique biology of their tumor. However, treatments tend not to be curative, likely because tumor cells within individual patients are heterogeneous and do not all harbor the same targetable aberrations.

- The ideal cancer therapy would be efficacious in the setting of cancer heterogeneity and would be curative. Possible therapeutic targets that meet these criteria are enzymes that block the normal cell survival mechanisms that repair damaged DNA.

- MTH1 is an enzyme that blocks oxidized DNA bases from being incorporated into the growing DNA strand during DNA replication. Cancer cells have persistently

high levels of damaged DNA bases due to high levels of DNA-damaging reactive oxygen species (ROS), indicating the MTH1 pathway is more essential for the survival of cancer cells than normal cells.

- Mice genetically engineered to lack the MTH1 gene grow and survive normally demonstrating that MTH1 is not essential for normal cell growth and survival.
- MTH1 activity was required for cancer cell survival following DNA damage and for the growth of tumors in mice.
- Several MTH1-inhibitors were developed that target the enzymatic pocket of MTH1.
- Administration of MTH1-inhibitors resulted in DNA damage, blocked DNA-damage repair, and induced cancer cell death *in vitro*, but did not kill normal cells.
- MTH1-inhibitors also blocked the growth of a variety of tumor cell types in mice including a multi-drug resistant melanoma tumor, without causing notable toxicity.
- MTH1-inhibitors are orally available and might have anti-cancer synergy when co-administered with chemotherapy, hormonal therapy, or certain targeted therapies.
- MTH1 inhibitors developed in the Helleday lab are freely available to investigators around the world to study mechanisms of action and efficacy against different cancer types.

Figure 27: MTH1 is required for tumor growth. Tumor cells were genetically engineered to express doxycycline-inducible inhibitory RNA molecules that target MTH1 (MTH1 shRNA) or a non-targeting control (NT shRNA). Tumor cells were grown in mice and treated with or without doxycycline (+/- dox) to induce expression of the inhibitory MTH1 shRNA which turns off expression of MTH1. Turning off MTH1 in tumors (MTH1 shRNA + dox) prohibited tumor growth (left) and prolonged survival of mice (right). Figure from: Gad *et al.*, *Nature,* 2014 Apr 10;508(7495):215-21.

Session 13: Prostate Cancer Dormancy

Prostate Cancer Dormancy: Setting the Stage

Colm Morrissey, PhD
University of Washington

- A subset of prostate cancer patients with undetectable PSA levels more than 5 years after radical prostatectomy still relapse. Gleason grade, growth of tumor cells in regions surrounding the prostate (extracapsular extension), and seminal vesicle invasion are all indicators of patients with high risk for relapse within 5 years.

- Disseminated tumor cells (DTCs) reside in a dormant state in metastatic sites such as the bone marrow for some patients following local therapy.

- Dr. Colm Morrissey discussed characteristics of DTCs from prostate cancer patients and the mechanisms that contribute to prostate cancer cell dormancy.

- Cells lacking the immune cell marker CD45, but expressing the epithelial cell marker EpCAM (EpCAM$^+$CD45$^-$ cells), are thought to be DTCs. Such cells were isolated from the bone marrow of prostate cancer patients and characterized by their gene expression signatures.

- EpCAM$^+$CD45$^-$ cells from patients possessed three gene expression signatures: (1) erythroid progenitor cells (red blood cell-like precursor cells), (2) prostate cancer cells, or (3) both of these genotypes.

- The prostate cancer or erythroid identity of these cells was validated by analysis of the presence or absence of genomic aberrations in the copy number of genes, a status indicative of cancer cells but not normal erythroid cells.

- This suggests that some EpCAM$^+$CD45$^-$ cells found in the bone marrow of patients are prostate cancer DTCs while others are related to red blood cell precursors.

- Prostate cancer cells that reside in the bone marrow of patients with no evidence of disease (NED) are likely to be dormant DTCs.

- To identify molecular pathways associated with DTC dormancy, individual EpCAM$^+$CD45$^-$ cells isolated from bone marrow with confirmed cancer cell gene expression patterns (DTCs) were compared in NED and advanced disease prostate cancer patients.

- When patients were classified by DTC gene expression patterns, three subtypes emerged: NED patients and two subtypes of advanced disease patients.

- The p38 pathway was found to be the most differentially expressed pathway when comparing NED patients with one advanced disease patient subtype. The p38 and ERK pathways were the most differentially expressed pathways when comparing NED patients with the other advanced disease patient subtype.

- Overall, dormancy-associated genes regulated by the p38 signaling pathway were more highly activated in DTCs from NED patients compared with advanced disease patients.

- This suggests that the p38 pathway may play a role in tumor cell dormancy by suppressing cell proliferation.
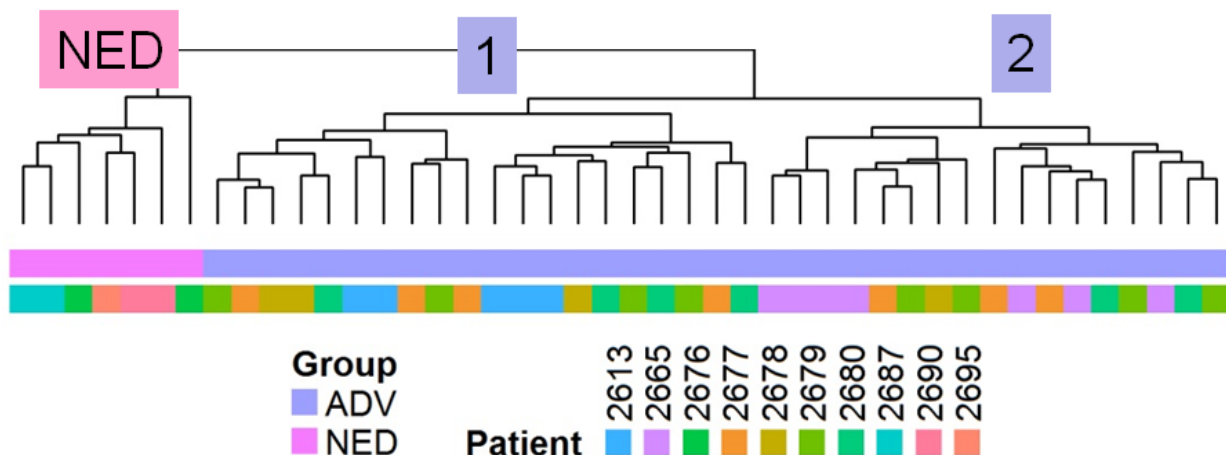

Figure 28: Cluster analysis of the top 50 upregulated and 50 downregulated genes in DTCs segregates patients into 3 groups: patients who exhibited no evidence of disease (NED), and two subtypes of advanced disease (ADV) patients.

Role of the Bone Microenvironment in Modulating the Dormancy of Prostate Cancer Cells

Kenneth Pienta, MD
Johns Hopkins University

- Every year, approximately 40,000 U.S. men who initially presented with localized prostate cancer and had been treated with surgery or radiation therapy later present with incurable metastatic disease.

- Of men receiving radical prostatectomy, 56% exhibit early disseminated tumor cells (DTCs) in pre-surgery bone marrow biopsies, and 30% exhibit a biochemical (PSA) recurrence within ten years. Of patients who recur, 40% will develop metastatic disease.

- Metastatic recurrences occur primarily in the bone and can occur after many years with no evidence of disease. This suggests that dormant DTCs had been residing in the bone marrow.

- Dr. Kenneth Pienta discussed how the bone marrow microenvironment regulates prostate cancer cell dormancy.

- Dormant prostate cancer cells in bone behave like hematopoietic stem cells (HSCs) and ultimately parasitize the identical niche in bone marrow.

- Once prostate cancer cells occupy the HSC niche, the tumor response to docetaxel chemotherapy is greatly reduced.

- Dormancy is a state of minimal physical and metabolic activity for the purpose of conserving energy and is often controlled by the environment.

- Mechanisms that regulate tumor cell dormancy are unclear. Dormant tumor cells may be in a state of minimal proliferation, may lack signals that allow them to develop blood vessels required for tumor growth, or may be repressed by the immune system.

- Experiments in which mice were injected with tumor cells and monitored for the development of bone metastases led to observations that metastases developed in the forelimb bones (humerus) of only 7% of mice while 33% developed metastases in hind limb bones (femur).

- Compared with the mouse femur, the bone marrow microenvironment of the humerus was found to express high levels of the Growth Arrest Specific-6 (GAS6) protein. GAS6 is expressed by growth-arrested cells and osteoblasts in the bone marrow and inhibits the proliferation of HSCs. Inhibition of proliferation by GAS6 may be another mechanism by which prostate cancer cells mimic HSCs.

- GAS6 is a secreted protein that interacts with 3 known receptors: Axl, Tyro3, and Mer TK which are expressed only on certain cells under certain conditions.

- GAS6 was found to inhibit the proliferation of prostate cancer cells, block expression of proliferation genes, and limit tumor growth in the bones of mice.

- The GAS6 receptors, Axl, Tyro3, and Mer TK are expressed on different cells and have different functions when stimulated by GAS6. Axl stimulation by GAS6 turns off cell growth while Tyro3 stimulation by GAS6 promotes proliferation.

- A mouse tumor metastasis model was created in which tumor cells are implanted under the skin, allowed to grow for 3 weeks, and then surgically removed. Tumor cells that have disseminated from the tumor remain dormant in the bone for 6-12 months before frank bone metastases can be observed.

- Primary tumors and metastases expressed Tyro3 but not Axl and were proliferative, while dormant DTCs expressed Axl but not Tyro3.

- GAS6 signaling therefore appears to regulate prostate cancer cell proliferation depending on whether the cells express Axl or Tyro3.

- The bone marrow microenvironment is thought to protect prostate cancer cells from therapy. When prostate cancer cells were grown with bone-forming cells called osteoblasts, they were protected from docetaxel chemotherapy. Osteoblasts without GAS6 lost the ability to protect prostate cancer cells from docetaxel. Chemotherapy is more toxic to dividing cells and GAS6-Axl signaling likely protects prostate cancer cells from chemotherapy by maintaining them in a dormant state.

- Incubation of prostate cancer cells with osteoblasts increased the proportion of prostate cancer cells with a stem cell-like phenotype. Osteoblasts that lacked GAS6 lost some of this ability. Higher numbers of stem cell-like cancer cells were also observed in the bones of mice that expressed GAS6 compared with mice genetically engineered to lack GAS6.

- These studies demonstrate that DTCs reside in the bone marrow niche by mimicking HSCs and express GAS6 receptors to regulate dormancy vs. proliferation.

- Dr. Pienta and his collaborators Drs. Taichman and Shiozawa are currently studying methods to get DTCs out of the protective bone marrow niche so they can be targeted by drugs as a therapeutic strategy for prostate cancer patients.
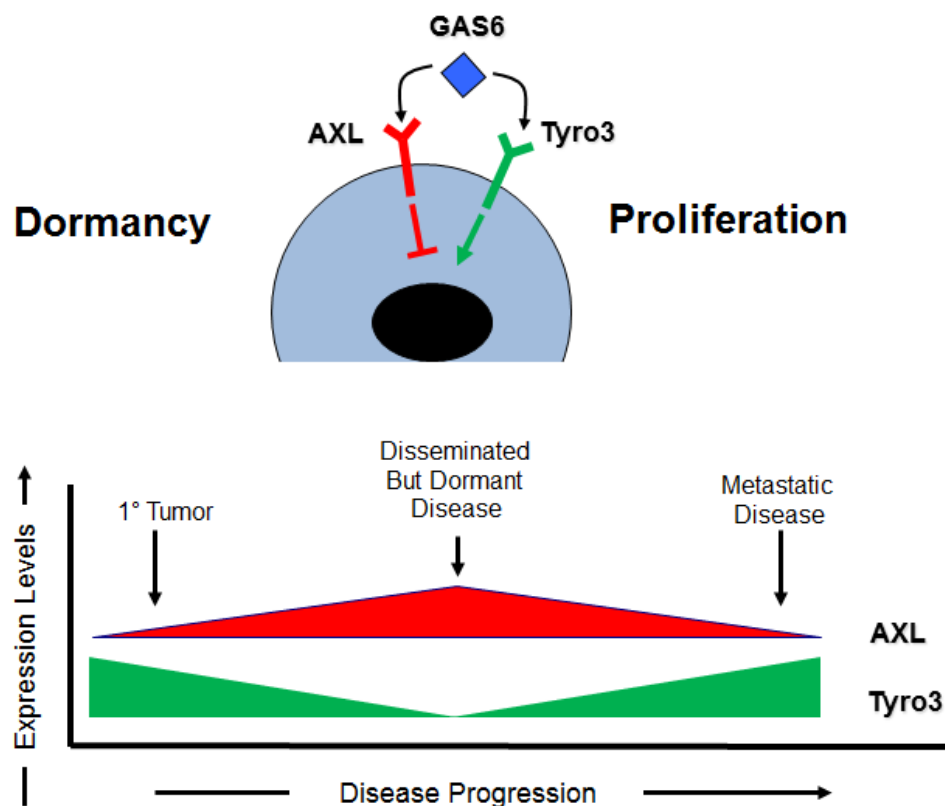

Figure 29: GAS6 Signaling Regulates DTC Proliferation. The GAS6 receptors, Axl and Tyro3, have different functions when stimulated by GAS6. Axl stimulation by GAS6 turns off cell growth while Tyro3 stimulation by GAS6 promotes proliferation. Primary tumors and metastases express Tyro3 but not Axl and are proliferative, while dormant DTCs express Axl but not Tyro3.

Therapeutically Targeting Dormant Tumor Cells

Ann Chambers, PhD
University of Western Ontario, Canada

- Cancer cells can exist in a dormant, non-dividing state in patients for years before causing late disease recurrence.

- Dr. Ann Chambers discussed an experimental system that can be used in the development of therapies that target dormant tumor cells.

- In assays that measure cell division, cells are loaded with imageable substances that are equally divided between daughter cells upon each cell division. Cells that retain their imageable molecules are likely to be non-dividing dormant cells.

- In a breast cancer brain metastasis model, breast cancer cells that express green florescence protein (GFP) are labeled with imageable iron oxide particles that are divided between daughter cells upon division and are detectable by magnetic resonance imaging (MRI). These cells are injected into mouse hearts, whereafter they travel throughout the body via the arterial system and form metastases, particularly in the brain. A custom single-cell MRI technology was developed that allows visualization of single dormant tumor cells retaining iron oxide particles as signal voids in the MRI image. Tumors can be detected using MRI hyper-intensity signals in mice and can be identified in histology by GFP florescence.

- Using this model, single dormant breast cancer cells can be seen localizing in the brain, many of which disappear over time, but a subset eventually progress and form growing brain metastases.

- The development of therapies that can target dormant tumor cells and monitoring methods that can identify patients harboring dormant tumor cells is critical for preventing lethal metastatic recurrences and curing patients.

In vivo MRI to Monitor Fate of Breast Cancer Metastases in Mouse Brain – 4D metastasis assay
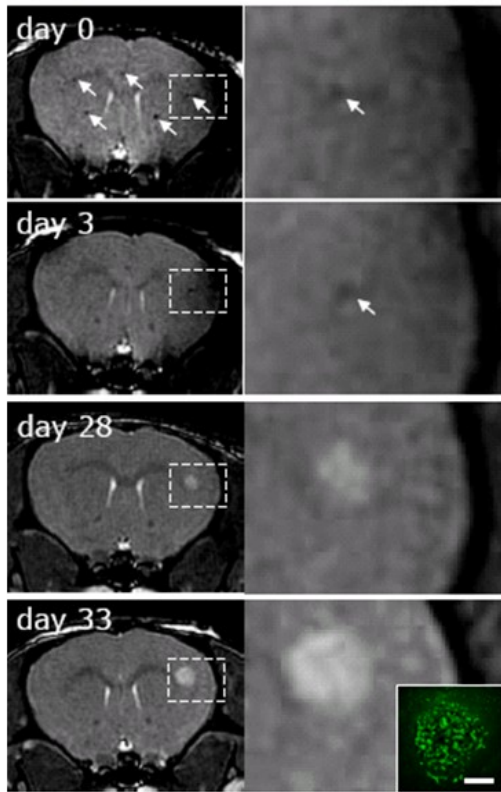
MDA-MB-231BR human breast cancer cells (GFP)

Iron-loaded before injection (MPIO)

Intracardiac injection in mice

MRI every 1 - 4 days – whole brain

Clinical 1.5 T MR scanner with custom mouse coil – FIESTA pulse sequence

Single cells = MR signal voids (dark)

Metastases = MR hyperintensity (light) and GFP on histology

Heyn C et al., Magnetic Resonance in Medicine 56: 1001-1010, 2006

Figure 30: In a breast cancer brain metastasis model, MDA-MB-231BR breast cancer cells that express green florescence protein (GFP) are labeled with iron oxide particles. These cells are injected into mice and take residence in body sites including the brain. A custom single-cell magnetic resonance imaging (MRI) technology visualizes single dormant tumor cells retaining iron oxide particles as signal voids in the MRI image (indicated by arrows in top 2 panels). Tumors can be detected using MRI hyper-intensity signals (bright spots in bottom two panels) and can be identified in histology by GFP florescence (green image inset in bottom right panel). Figure from Heyn *et al., Magn Reson Med*. 2006 Nov;56(5):1001-10.

APPENDIX:

21ST ANNUAL PROSTATE CANCER FOUNDATION SCIENTIFIC RETREAT
OCTOBER 23-25, 2014

PROGRAM AGENDA
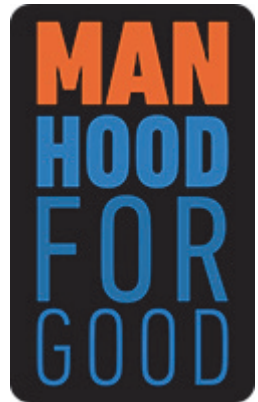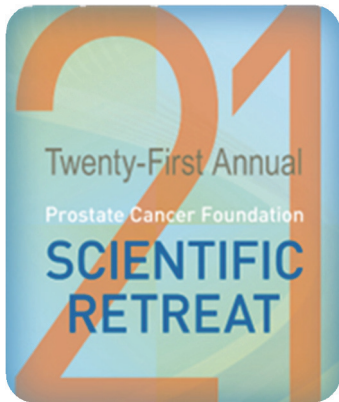
21ˢᵗ Annual Prostate Cancer Foundation Scientific Retreat

October 23 - 25, 2014

La Costa Resort
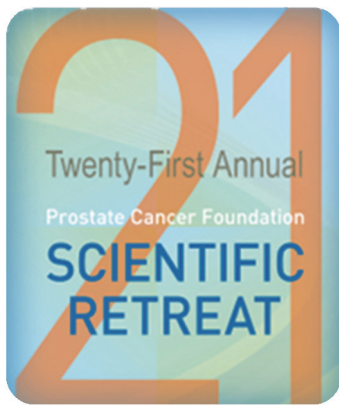### Carlsbad, California

AGENDA

Thursday, October 23, 2014

GENERAL SESSIONS
Location: Costa Del Sol Ballroom

Welcome and Introduction
2:00 PM - 2:10 PM

> **Howard Soule, PhD**
> Prostate Cancer Foundation

Special Awards Presentation
2:10 PM - 2:20 PM

> **Howard Soule, PhD**
> Prostate Cancer Foundation

Session 1: Health Care Disparity in Prostate Cancer
2:20 PM - 3:40 PM

> **Moderator: Paul Nguyen, MD**
> Harvard: Dana-Farber Cancer Institute

2:20 PM - 2:35 PM	***What Can Big Data Tell Us About Racial Disparities in Prostate Cancer?*** **Paul Nguyen, MD** Harvard: Dana-Farber Cancer Institute
2:35 PM - 2:40 PM	**Discussion**
2:40 PM - 2:55 PM	***Biological and Social Determinants of Prostate Cancer Disparities*** **Timothy Rebbeck, PhD** University of Pennsylvania School of Medicine
2:55 PM - 3:00 PM	**Discussion**
3:00 PM - 3:15 PM	***Obesity, Race and Prostate Cancer Risk*** **Alan Kristal, DrPH** Fred Hutchinson Cancer Research Center
3:15 PM - 3:20 PM	**Discussion**

3:20 PM - 3:35 PM   *Genomics of African American Prostate Cancer*
Franklin Huang, MD, PhD
Harvard: Dana-Farber Cancer Institute

3:35 PM - 3:40 PM   **Discussion**

SPECIAL LECTURE 1
3:40 PM - 4:05 PM

Prostate Cancer Molecular Biomarker Development Among African American Compared to European American Men

Isaac Powell, MD
Wayne State University School of Medicine

Introduced by Elisabeth Heath, MD
Wayne State University School of Medicine, Karmanos Cancer Institute

4:05 PM - 4:10 PM
Discussion

Session 2: Global Research in Cleveland
4:10 PM - 5:10 PM

    Moderator: Eric Klein, MD
    Cleveland Clinic

4:10 PM - 4:25 PM   *An Actionable Predictive Marker of Castration Resistance*
Nima Sharifi, MD
Cleveland Clinic

4:25 PM - 4:30 PM   **Discussion**

4:30 PM - 4:45 PM   *How Unphosphorylated STATs Drive Resistance to DNA Damage in Prostate Cancer*
Hyeon Joo Cheon, PhD
Cleveland Clinic

4:45 PM - 4:50 PM   **Discussion**

4:50 PM - 5:05 PM   *The Harrington Project*
Jonathan Stamler, MD
Case Western Reserve University

5:05 PM - 5:10 PM   **Discussion**

Session 3: AR-Splice Variants
5:10 PM - 6:10 PM

Moderators:
Stephen Plymate, MD
University of Washington
Paraskevi Giannakakou, PhD
Weill Cornell Medical College, Meyer Cancer Center

5:10 PM - 5:25 PM   ***AR-V7 and Treatment Resistance in Castrate Resistant Prostate Cancer***
Emmanuel Antonarakis, MD
John Hopkins University
Jun Luo, PhD
Johns Hopkins University

5:25 PM - 5:30 PM   **Discussion**

5:30 PM - 5:45 PM   ***Dynamics of AR Splice Variants' Nuclear Accumulation and Implications for Treatment Outcomes***
Paraskevi Giannakakou, PhD
Weill Cornell Medical College, Meyer Cancer Center

5:45 PM - 5:50 PM   **Discussion**

5:50 PM - 6:05 PM   ***Isoform Specific Actions of the AR-V7 Splice Variant***
Nancy Weigel, PhD
Baylor College of Medicine

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

SPECIAL LECTURE 2
6:10 PM - 6:25 PM

Project DataSphere

Kald Abdallah, MD, PhD
Project Data Sphere, LLC

Introduced by Howard Soule, PhD
Prostate Cancer Foundation

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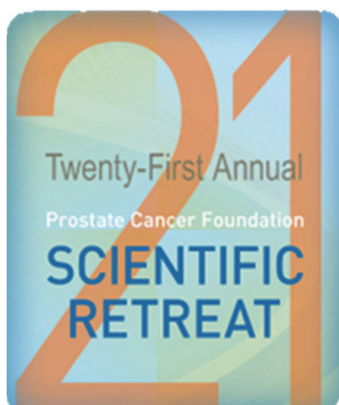**Discussion**

Dinner
7:15 PM - 8:45 PM

Poster Session and Dessert
8:45 PM - 11:00 PM

Dinner Location: Costa Del Sol Terrace
Poster Session and Dessert Location: Costa Del Sol ABC

AGENDA

Friday, October 24, 2014

6:30 AM - 7:30 AM   *Breakfast*
                        Location: Costa Del Sol Terrace

7:30 AM - 7:45 AM   **Move to Session 4**

GENERAL SESSIONS
Location: Costa Del Sol Ballroom

Session 4: Research Integrity and Standards for Scientific Reproducibility
7:45 AM - 8:45 AM

Moderator: Howard Soule, PhD
Prostate Cancer Foundation

7:45 AM - 8:00 AM   ***Closing the Reproducibility Gap with Standards and Best Practices***
                    Leonard Freedman, PhD
                    Global Biological Standards Institute

8:00 AM - 8:05 AM   **Discussion**

8:05 AM - 8:20 AM   ***Improving Scientific Reproducibility***
                    John Ioannidis, MD
                    Stanford University

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

8:25 AM - 8:40 AM   ***The Cancer Biology Reproducibility Project***
                    Elizabeth Iorns, PhD
                    Science Exchange

8:40 AM - 8:45 AM   ***Introducing the Movember Foundation-PCF Scientific Reproducibility Initiative***
                    Howard Soule, PhD
                    Prostate Cancer Foundation

Session 5: Bromodomains: Mechanisms and Therapeutic Targeting
8:45 AM - 9:35 AM

Moderator: Arul Chinnaiyan, MD, PhD
University of Michigan Medical School

8:45 AM - 9:10 AM   *Clinical Translation of Bromodomain Inhibition*
James Bradner, MD
Harvard Medical School, Harvard: Dana-Farber Cancer Institute

9:10 AM - 9:15 AM   **Discussion**

9:15 AM - 9:30 AM   *Betting on BETs for Advanced Prostate Cancer Treatment*
Irfan Asangani, PhD
University of Michigan Medical School

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

SPECIAL LECTURE 3
9:35 AM - 10:05 AM

Targeting PARP for the Treatment of Prostate Cancer

Johann de Bono, MD, PhD
Royal Marsden Hospital, UK

Introduced by Gerhardt Attard, MD, PhD
Royal Marsden Hospital, UK

10:05 AM - 10:10 AM
Discussion

SPECIAL LECTURE 4
10:10 AM – 10:40 AM

State of the Science 2014

Jonathan Simons, MD
Prostate Cancer Foundation

Introduced by Howard Soule, PhD
Prostate Cancer Foundation

10:40 AM - 10:45 AM
Discussion

KEYNOTE ADDRESS
10:45 AM - 11:45 AM

Two Decades of Progress

Mike Milken
The Milken Institute

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

Lunch
12:00 PM - 1:00 PM

Location: Costa Del Sol Terrace

1:00 PM - 1:15 PM   **Move to Session 6**

Location: Costa Del Sol Ballroom

Session 6: Immunology of the Tumor Microenvironment
1:15 PM - 2:15 PM
    Moderator: Sumit Subudhi, MD, PhD
    University of Texas MD Anderson Cancer Center

1:15 PM - 1:30 PM   ***Cabozantinib Works as a "Myeloid Switch" to Reverse the Immunosuppressive Tumor Microenvironment: Implications for Combination Therapy in Advanced Prostate Cancer***
    Akash Patnaik, MD, PhD, MMSc
    Beth Israel Deaconess Medical Center, Harvard Medical School
1:30 PM - 1:35 PM   **Discussion**

1:35 PM - 1:50 PM   ***Anti-CTLA-4 Immunotherapy in Prostate Cancer***
    Sumit Subudhi, MD, PhD
    University of Texas MD Anderson Cancer Center
1:50 PM - 1:55 PM   **Discussion**

1:55 PM - 2:10 PM   ***T cell Exclusion as a Dominant Means of Immune Suppression in Pancreatic Ductal Adenocarcinoma***
Douglas Fearon, PhD
University of Cambridge, UK

2:10 PM - 2:15 PM   **Discussion**

SPECIAL LECTURE 5
2:15 PM - 2:45 PM

***Cancer Immunoediting and its Application
to Personalized Cancer Immunotherapy***

Robert Schreiber, PhD
Washington University School of Medicine

Introduced by William Redmond, PhD
Earle A. Chiles Research Institute

2:45 PM - 2:50 PM
Discussion

Session 7: DoD PCRP Special Presentations
2:50 PM - 3:50 PM

    Moderator: Melissa Cunningham, PhD
Prostate Cancer Research Program, Congressionally Directed Medical Research Programs, Department of Defense

2:50 PM - 3:05 PM   ***Rare Germline Copy Number Variants and Prostate Cancer Risk Among Mexican American Men***
Donna Lehman, PhD
University of Texas, Health Science Center at San Antonio

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

3:10 PM - 3:25 PM   ***The Limitations of the Use of Human Tissues in Research***
William Grizzle, MD, PhD
University of Alabama at Birmingham

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

3:30 PM - 3:45 PM   ***Development, Validation and Dissemination of an Integrated Risk Prediction Model and Decision Aid to Discern Aggressive versus Indolent Prostate Cancer***
June Chan, ScD
University of California, San Francisco

3:45 PM - 3:50 PM   **Discussion**

SPECIAL LECTURE 6
3:50 PM - 4:20 PM

Is the Next Generation Prostate Cancer Test a Combination of Genetic and Protein Markers?   Preliminary Results from the STHLM3 Study

Henrik Grönberg, MD, PhD
Karolinska Institutet, Sweden

Introduced by Lorelei Mucci, ScD
Harvard School of Public Health

4:20 PM - 4:25 PM
Discussion

Session 8: Progress Reports from the PCF Dream Teams
4:25 PM - 4:55 PM

          Moderator: Howard Soule, PhD
          Prostate Cancer Foundation

4:25 PM - 4:35 PM   **_The West Coast Prostate Cancer Dream Team: Targeting Adaptive Responses in Abiraterone and Enzalutamide Refractory mCRPC_**
                        Eric Small, MD
                        University of California, San Francisco
4:35 PM - 4:40 PM   **Discussion**

4:40 PM - 4:50 PM   **_International SU2C-PCF Prostate Dream Team: Precision Therapy of Advanced Prostate Cancer_**
                        Arul Chinnaiyan, MD, PhD
                        University of Michigan Medical School
4:50 PM - 4:55 PM   **Discussion**

Session 9: Prostate Cancer Models and Molecular Pharmacology
4:55 PM - 5:35 PM

          Moderator: Kenneth Pienta, MD
          Johns Hopkins University

4:55 PM - 5:10 PM   **_Engineering Metastasis and the Hope for Curing Prostate Cancer_**
                        Lloyd Trotman, PhD
                        Cold Spring Harbor Laboratory

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

5:15 PM - 5:30 PM   ***HOXB13-Driven MYC Expression and PTEN Loss Yield Genomic Instability and Lethal Metastatic Prostate Cancer***
Charles Bieberich, PhD
University of Maryland, Baltimore County
Angelo De Marzo, MD, PhD
The Johns Hopkins University School of Medicine

5:30 PM - 5:35 PM   **Discussion**

SPECIAL LECTURE 7
5:35 PM - 5:50 PM

Transitioning from a Prognostic to a Predictive Model of Therapy Allocation

Christopher Logothetis, MD
University of Texas MD Anderson Cancer Center

Introduced by Jonathan Simons, MD
Prostate Cancer Foundation

5:50 PM - 5:55 PM
Discussion

Session 10: Bioinformatics
5:55 PM - 6:35 PM

    Moderator: Nikolaus Schultz, PhD
Memorial Sloan-Kettering Cancer Center

5:55 PM - 6:10 PM   ***canSAR Integrative Data for Cancer Drug Discovery***
Bissan Al-Lazikani, PhD
The Institute of Cancer Research, UK

6:10 PM - 6:15 PM   **Discussion**

6:15 PM - 6:30 PM   ***The cBioPortal for Cancer Genomics***
Nikolaus Schultz, PhD
Memorial Sloan-Kettering Cancer Center

6:30 PM - 6:35 PM   **Discussion**

Dinner, Awards and Entertainment
7:15 PM - 10:00 PM

Location: Terrace Lawn

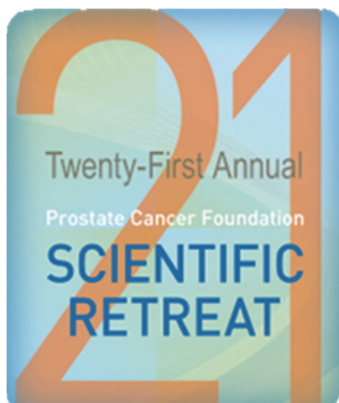**2014 PCF Young Investigator Awards**

2013 Movember-PCF Immunotherapy Challenge Awards

2014 Movember-PCF Challenge Awards

2014 Safeway-PCF Challenge Awards

AGENDA

Saturday, October 25, 2014

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

Location: Costa Del Sol Terrace

7:45 AM - 8:00 AM   **Move to Session 11**

GENERAL SESSIONS
Location: Costa Del Sol Ballroom

Session 11: Adipose Tissue, Inflammation and Obesity
8:00 AM - 8:40 AM

Moderator: Andrew Dannenberg, MD
Weill Cornell Medical College, Meyer Cancer Center

8:00 AM - 8:15 AM   ***Obesity, White Adipose Inflammation and Prostate Cancer***
Andrew Dannenberg, MD
Weill Cornell Medical College, Meyer Cancer Center

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

8:20 AM - 8:35 AM   ***Lipogenic Prostate Cancers***
Massimo Loda, MD
Harvard: Dana-Farber Cancer Institute

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

SPECIAL LECTURE 8
8:40 AM - 8:55 AM

Movember Global Action Plan Progress Report

Colleen Nelson, PhD
Queensland University of Technology, Australia

Introduced by Paul Villanti
Movember Foundation

8:55 AM - 9:00 AM
Discussion

SPECIAL LECTURE 9
9:00 AM - 9:15 AM

*ICECaP: Intermediate Clinical Endpoints for
Treatment of High Risk Prostate Cancer – Update*

Christopher Sweeney, MBBS
Harvard: Dana-Farber Cancer Institute

Introduced by Philip Kantoff, MD
Harvard: Dana-Farber Cancer Institute

9:15 AM - 9:20 AM
Discussion

Session 12: Mechanisms and Targeting of DNA-Damage Repair
9:20 AM - 10:40 AM

          Moderator: Karen Knudsen, PhD
          Thomas Jefferson University, Kimmel Cancer Center

9:20 AM - 9:35 AM   *Targeting Hormone-DNA Repair Crosstalk: Mechanisms and Therapeutic Implications*
          Karen Knudsen, PhD
          Thomas Jefferson University, Kimmel Cancer Center
9:35 AM - 9:40 AM   **Discussion**

9:40 AM - 9:55 AM   *Non-Coding Modulators of DNA Repair: PCAT1 as a Regulator of Homologous Recombination in Prostate Cancer*
          Felix Feng, MD
          University of Michigan
9:55 AM - 10:00 AM   **Discussion**

10:00 AM - 10:15 AM *Neo-Adjuvant Castration Improves Radiotherapy by Impairing DNA Repair*
          Thomas Helleday, PhD
          Karolinska Institutet, Sweden
10:15 AM - 10:20 AM **Discussion**

10:20 AM - 10:35 AM *Translational Development of CC-115, a Small Molecule Inhibitor of Tor Kinase and DNA-PK, in Prostate Cancer*
          Kristen Hege, MD
          Celgene
10:35 AM - 10:40 AM **Discussion**

Session 13: Prostate Cancer Dormancy
10:40 AM - 12:10 PM

          Moderators:
          Lorelei Mucci, ScD
          Harvard School of Public Health
          Steven Balk, MD, PhD
          Harvard: Beth Israel Deaconess Medical Center

10:40 AM - 10:45 AM *Prostate Cancer Dormancy Overview*
          Steven Balk, MD, PhD
          Harvard: Beth Israel Deaconess Medical Center

10:45 AM - 11:00 AM ***Prostate Cancer Dormancy; Setting the Stage***
Colm Morrissey, PhD
University of Washington

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

11:05 AM - 11:20 AM ***Role of the Bone Microenvironment in Modulating the Dormancy of Prostate Cancer Cells***
Kenneth Pienta, MD
Johns Hopkins University

11:20 AM - 11:25 AM **Discussion**

11:25 AM - 11:40 AM ***Therapeutically Targeting Dormant Tumor Cells***
Ann Chambers, PhD
University of Western Ontario, Canada

11:45 AM - 11:50 AM **Discussion**

11:50 AM - 12:05 PM ***Hijacking the Tumor Microenvironment: Lessons from Breast Cancer***
Sandra McAllister, PhD
Harvard: Brigham and Women's Hospital, Harvard Medical School

12:05 PM - 12:10 PM **Discussion**

Meeting Adjourned

The Prostate Cancer Foundation thanks the sponsors of the Retreat for their generous support.

Program Committee:

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

Andrea Miyahira, PhD (Prostate Cancer Foundation)
Jonathan Simons, MD (Prostate Cancer Foundation, Ex Officio)
Paul Nguyen, MD (Harvard: Dana-Farber Cancer Institute)
Eric Klein, MD (Cleveland Clinic)
Stephen Plymate, MD (University of Washington)
Paraskevi Giannakakou, PhD (Weill Cornell Medical College, Meyer Cancer Center)
Arul Chinnaiyan, MD, PhD (University of Michigan Medical School)
Sumit Subudhi, MD, PhD (University of Texas MD Anderson Cancer Center)
Kenneth Pienta, MD (Johns Hopkins University)
Nikolaus Schultz, PhD (Memorial Sloan-Kettering Cancer Center)
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Karen Knudsen, PhD (Thomas Jefferson University, Kimmel Cancer Center)
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