STATE OF THE SCIENCE REPORT

Highlights from the 18th Annual PCF Scientific Retreat

September 2011

Provided with the compliments of the Prostate Cancer Foundation

PROSTATE CANCER FOUNDATION

Table of Contents

Introduction 3

Session 1
Taxanes: Targeted Therapy in the 21st Century 5

Session 2
New Concepts in Stem Cell Biology 13

Session 3: Young Investigator #1 20

Special Lecture
The History of Development of Radium-223 24

Session 4
Genomics and Genetics of Prostate Cancer: What We Have Learned in the Last Year 26

Special Lecture
Prostate Cancer Targets the Hematopoietic Stem Cell Niche During Metastasis to Bone 34

Special Lecture
Improving Outcomes from Advanced Prostate Cancer 35

Special Lecture
Modeling Metastatic Prostate Cancer from Mouse to Man-Molecular Determinants of Therapeutic Response 38

Session 5: Panel Discussion
The New Era of Molecular Pathology 40

Session 7
Modulation of Therapeutic Response by Tumor Adaptation to Target Inhibition 42

Special Lecture
Prostate Cancer Medical Oncology Clinic in 2025 46

Session 8
PARP in Prostate Cancer 48

Session 9
Clinical and Biological Update: Status and Plans for Cabozantinib 53

Session 10
Bioinformatics for Discovery 58

Session 11: Young Investigator #2 60

2011 Program Agenda 68
PCF Funding 80

Introduction

For the eighteenth consecutive year, the Prostate Cancer Foundation brought together the world's top prostate cancer physicians and scientists in a collaborative forum to share new data and concepts. The 18th Annual PCF Scientific Retreat was the best meeting ever organized by PCF as measured by and the novelty of findings, breadth of attendees, the quality and topics of the presentations, and attendee and Board member feedback.

The overarching goal of all research discussed at the Retreat was to accelerate the end of death and suffering for men with prostate cancer. With a prime focus on scientific presentations, knowledge exchange and collaborative discussions, the Scientific Retreat featured the following:

- 46 scientific presentations and panels along with 51 poster presentations discussed 17 different scientific disciplines related to prostate cancer biology.
- 27 speakers (55%) presented first-in-field data at a PCF Scientific Retreat for the first time.
- Attendance by 350 participants representing 83 academic institutions, 30 biopharmaceutical companies and 7 medical research foundations from 11 countries.
- Attendance by 125 MDs, 108 PhDs, 3 ScDs, 4 PharmDs, 59 MD PhDs and 2 DMDs.
- Attendance by 47 Young Investigators who continue to prove themselves as a formidable force in forwarding innovative ideas and accelerating discovery.
- Attendance by12 PCF Board of Directors and 24 major donors attended the Scientific Retreat.
- A special panel discussion moderated by Mr. Michael Milken, and chaired by Dr. Francis Collins, Director of the NIH; Dr. Margaret Hamburg, Commissioner of the FDA; Dr. Leroy Hood, co-founder and President of the Institute of Systems Biology; Dr. Chris Viebacher, CEO, Sanofi-Aventis and President, PhRMA; and Dr. Elias Zerhouni, former Director of the NIH and advisor to the CEO of Sanofi-Aventis.

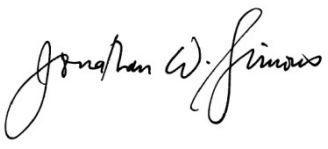
Focusing on prostate cancer patient-centric research, PCF's18 Provocative Questions for the 18th Annual PCF Scientific Retreat were:

1. What are the survival mechanisms in metastatic prostate cancer LRHR-, Abiraterone, MDV3100-resistant disease at patient relapse?
2. How does the androgen receptor signal in the absence of androgen?
3. What is therapeutically actionable against PIK3 <->AR "dual negative reciprocal feedback" in metastatic prostate cancer patients?
4. What mechanism causes "closed circle-daisy chains" of chromosomal fusions in men with lethal prostate cancers?
5. What are the primary resistance mechanisms and the attendant predictive diagnostics for each of the newly approved FDA agents for metastatic prostate cancer?
6. What is the mechanism of action for the bone-directed radiopharmaceutical, Rad223 that increases mCRPC patient survival?
7. What is the mechanism of survival improvement with infusions of re-engineered, patient-derived T-cells that increase survival without affecting tumor burden?

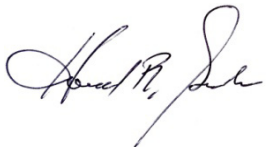
8. What are optimum host immunotherapy manipulations for patients with advanced prostate cancer?
9. What are the frequency rates of individual prostate cancer subtypes ('clonotypes') at diagnosis and relapse and can these results explain the disproportionate burden of PCa in African Americans and those with increased risk due to family history?
10. What are the mechanisms of bone pain resolution and vanished 99 Technetium uptake with "HGF-1-cMET-ness-multiple kinase inhibitor" treatment?
11. What are the prostate cancer-specific targets in circulating tumor cells (CTCs) that can be used for prostate cancer diagnosis and prognosis?
12. Based on newly approved therapies, how can we scientifically combine and sequence treatments and then move them up early into patients with lower metastatic tumor burdens?
13. Are there additional subtypes of prostate cancer yet undiscovered that predict clinical behavior, sensitivity and resistance to existing experimental and FDA-approved agents?
14. What initiates chromosomal fusions and epigenomic changes and how can these be prevented in the 20-40 year old prostate?
15. What are the actionable control points for the micro-environment, e.g. RANK-L, Src for progression of lethal clones?
16. What is the association of obesity and energy balance with lethal prostate cancer progression?
17. What are the metabolic determinants from exercise that confer a survival advantage in men with prostate cancer?
18. Does prostate cancer have a microorganism-induced initiation, propelled by infection and inflammation and if so, what are the microorganisms that drive PCa initiation?

This PCF 2011 State of the Science Report summarizes each presentation individually. The highlights of each session provide a brief overview of the scientific discipline and a summary of the latest findings that impact prostate cancer diagnosis, prognosis or treatment. PCF aims to translate these new findings, as rapidly as possible, into clinical investigation. Toward that end, we hope this report will be useful to you and will stimulate further dialogue, data exchange, and questioning. If you have specific questions, please contact Dr. Guneet Walia at gwalia@pcf.org.

Yours sincerely,



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



Howard R. Soule, PhD
Chief Science Officer

Session 1

Taxanes: Targeted Therapy in the 21st Century

Introduction:

Microtubules are long polymeric chains that form an interconnected network inside the cell. They perform several critical cellular functions such as providing structural support (i.e. forming the cytoskeleton); participating in cell division and cellular trafficking etc. These tubular structures have an inherent polarity which allows the transmission of information in a directional manner, from the + end of a microtubule to the –end. These tubules are constantly assembled (polymerized) and dis-assembled (de-polymerized) in a normal cell to generate new microtubules or disassemble existing ones to provide raw material for laying out the new ones, respectively.

The opening session of the 18th Annual PCF Scientific Retreat reported latest findings on the action of a class of medications, called taxanes which bind microtubules and prevent their disassembly. Taxane action results in un-availability of building blocks for the formation of newer tubules causing arrested growth of the cancer cell, eventually leading to its death (apoptosis).

Major Points from Session 1:

- Androgen Receptor (AR) binds androgens and this androgen-AR complex translocates to the nucleus to activate genes. In metastatic castration-resistant prostate cancer (mCRPC), AR alone translocates to the nucleus and induces the expression of cancer-specific genes.
- This translocation of AR from the cytoplasm to the nucleus appears to be mediated by microtubules.
- Apart from affecting microtubule assembly/disassembly, taxanes inhibit prostate cancer cell growth by preventing Androgen Receptor (AR) translocation to the nucleus.
- As AR is sequestered in the cytoplasm and cannot activate genes in the nucleus, the levels of AR-transcriptionally controlled genes decrease e.g. PSA levels drop.
- Combination therapy employing taxanes and inhibitors of AR-microtubule interaction may hold potential in further reducing AR function in metastatic hormone-resistant prostate cancer.
- Circulating Tumor Cells (CTCs) may be useful to predict patients' clinical response/resistance to taxane therapy.

Michael Morris, MD

Memorial Sloan-Kettering Cancer Center

History of Taxane Development in Metastatic Prostate Cancer

Funded by the PCF-DoD Therapy Consortium

What this means for patients: Taxanes are the first line of chemotherapy for patients with metastatic prostate cancer no longer responding to testosterone-lowering agents. Their exact mechanisms of action are progressively being deciphered for better medication design, patient selection, and timing of use. The use of this class of medications prolongs life and can palliate pain in patients with advanced disease. Combinations with other classes of agents or the application of chemotherapy earlier in the disease course have the potential to amplify these benefits, and these strategies are currently being tested.

The first presentation of the Retreat, by Dr. Michael Morris, provided an overview of the use of taxanes in the treatment of advanced prostate cancer. Docetaxel (Taxotere) and Cabazitaxel (Jevtana) are derived from the European yew tree. Dr. Morris demonstrated a video on the dynamic and critical role of microtubules in cellular functioning. Taxanes inhibit the normal dynamic assembly and disassembly of microtubules, a critical building block of the cell's internal structural support system known as the "cytoskeleton." By inhibiting normal microtubule behavior, critical cellular functions are disrupted and the cancer cell dies. Early explorations of chemotherapy for prostate cancer focused on drug combinations that attacked the cytoskeleton, and ultimately on May 19, 2004, docetaxel was approved by the FDA for the treatment of hormone-refractory prostate cancer. Two independent, multi-centre Phase III clinical trials tested the effects of docetaxel-containing chemotherapy regimens against mitoxantrone, the standard chemotherapy for bone-pain at that time. . In the pivotal trial that defined the current standard regimen for first-line chemotherapy, patients receiving docetaxel and prednisone every three weeks had a 20% higher risk of living than those receiving mitoxantrone or docetaxel weekly. Docetaxel thus became the first line chemotherapeutic for the treatment of CRPC. Last year, cabazitaxel was approved by the FDA for the treatment of hormone-refractory prostate cancer patients who had progressive disease despite prior treatment with docetaxel. On an FDA mandate, currently a Phase III trial is open and accruing patients to compare docetaxel and cabazitaxel as first-line chemotherapy for CRPC.

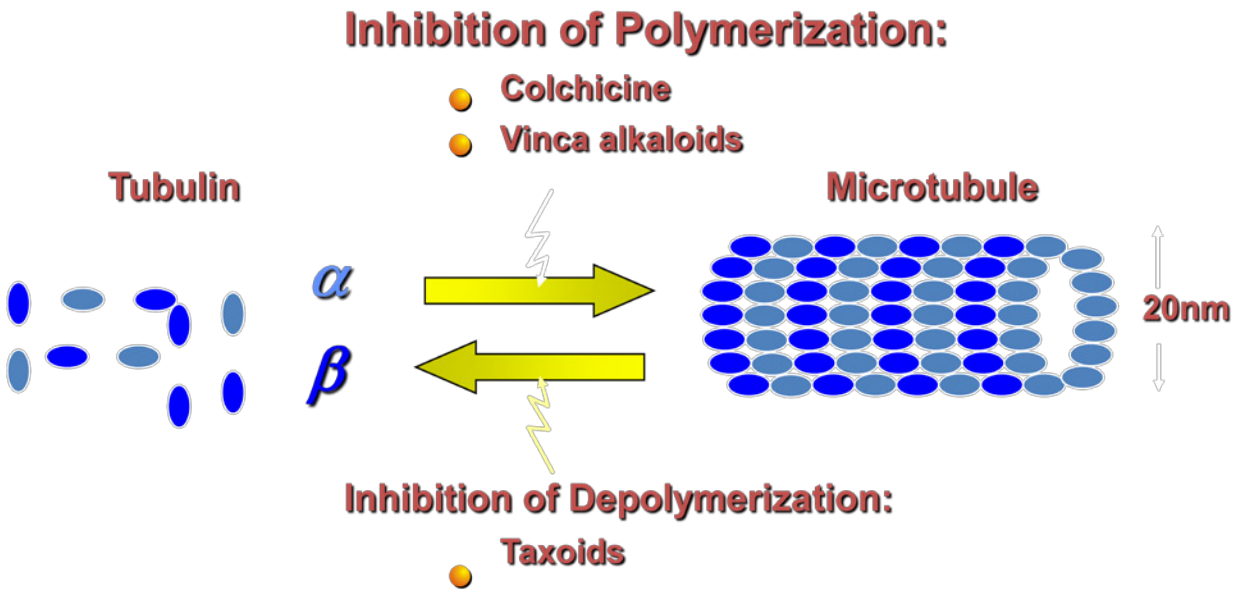


Figure 1: The mechanism of action of 'spindle poisons'. Colchicine and Vinca alkaloids prevent the polymerization of individual α and β tubulin monomers to microtubules. Taxanes inhibit microtubule depolymerization.

Dr. Morris summarized his presentation by raising three very important questions that should be addressed in the field:
1). WHO: it is important to identify the patients that are most suited for chemotherapeutic treatment;
2). WHEN: when in the treatment regimen, should chemotherapy be delivered
3). Combinations: What are the best chemotherapeutic combinations for the most effective therapy that avoid past pitfalls.

Natasha Kyprianou, PhD

University of Kentucky

Taxanes Export the Androgen Receptor: A Tale Beyond Microtubule Targeting

What this means for patients: Dr. Kyprianou's research has provided insight into the reasons for the failure of paclitaxel (taxol) as a chemotherapeutic agent for mCRPC. These results demonstrate a new mechanism of action for docetaxel, linking AR signaling and taxane chemotherapy in prostate cancer.

The male hormones, androgens drive the growth of prostate cancer cells, which is suppressed by androgen ablation therapy. Resistance to this therapy develops as cancer cells start overexpressing the androgen receptor (AR). To effect its function AR changes cellular localization, i.e. AR translocates from the cytoplasm to the nucleus to activate genes that promote cancer growth, invasion and metastatic behavior. Taxanes have been shown to be effective first line chemotherapeutics for the treatment of CRPC. However, a subset of prostate cancer patients develops resistance against this therapy

and the mechanism driving therapeutic resistance to taxanes remains unclear. Dr. Kyprianou's team studied the effect of taxane chemotherapy on androgens and the AR signaling axis. Their findings show that AR is transported to the nucleus via microtubules, AR interacting directly with the microtubule-building block, tubulin (Figure 2). Therefore, taxanes that affect microtubule organization interfere with AR nuclear localization and activity in human prostate tumors. As the AR is unable to reach the nucleus, it can no longer activate androgen-responsive genes responsible for cancer growth (e.g. PSA) and this is reflected in the decrease of PSA gene expression in human prostate tumors after treatment with docetaxel.

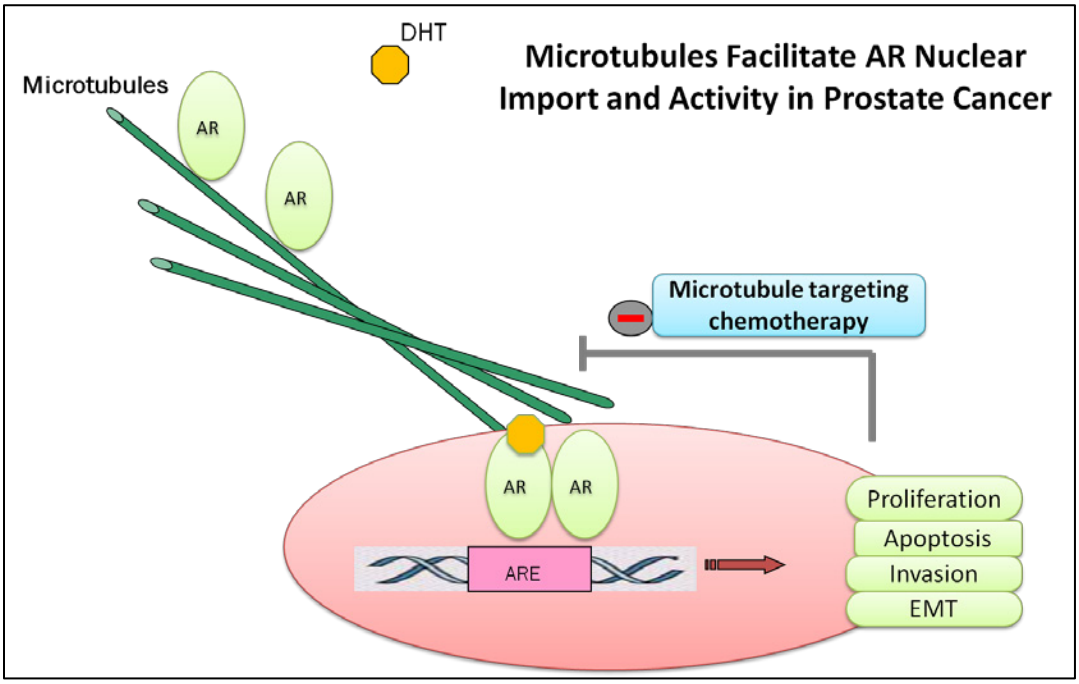


Figure 2: A model proposed by Dr. Kyprianou for the interaction of AR with microtubules. AR interacts with microtubules through its N-terminus and is transported to the nucleus, where it activates cancer-specific genes. Microtubule-targeting therapy targets this transport and can prevent the switching 'on' of pro-cancer genes.

Dr. Kyprianou also showed data that tubulin interacts with AR specifically at the latter's N-terminal domain, which serves as an 'engine' driving AR activity. Therefore, chemical inhibitors such as EPI-001 that specifically target the AR N-terminus can inhibit the AR-tubulin interaction, further preventing AR transport to the nucleus. This was reflected in the reduction of tumor volume when mice were treated with a combination of taxanes and EPI-001. Thus these exciting new findings attribute a new mechanism of action to taxanes and provide initial evidence for the use of taxanes in combination with EPI-001 for the treatment of metastatic treatment-resistant prostate cancer.

Paraskevi (Evi) Giannakakou, PhD

Weill Cornell Medical College

Using Circulating Tumor Cells to Dissect Mechanisms of Clinical Taxane Resistance

Funded by a PCF Special Challenge Award

What this means for patients: Circulating Tumor Cells (CTCs) from CRPC patients may be used to study and predict patients' clinical response/pre-existing resistance to taxane-based chemotherapy.

The medications, taxanes, impair microtubule disassembly, thereby critically impacting the transportation of cellular cargo. Findings by Dr. Giannakakou's team further confirmed the results observed by Dr. Kyprianou, that Androgen Receptor (AR) uses cellular microtubules for its transport into the nucleus. These findings also re-iterate that taxanes inhibit AR-induced activation of cancer-specific genes, because these microtubule-stabilizing chemotherapeutics cause the sequestration of AR in the cytoplasm. This team at WCMC showed that AR interacts with the microtubule motor-protein, dynein for its transport along the microtubules. However, in contrast to the results from University of Kentucky, these findings demonstrate that the other end of AR (i.e its C-terminal domain) is essential for its interaction with the microtubules. The most important, translationally significant finding of this work was the fact that taxanes inhibit AR nuclear translocation in CTCs isolated from CRPC patients' blood. This taxane-induced blockade to nuclear accumulation of the AR in patient-derived CTCs predicts patients' clinical responses to taxane chemotherapy in metastatic prostate cancer.

Patients express several variants of AR. Dr. Giannakakou's results show that some of these variants depend on microtubules for their transport to the nucleus (microtubule-dependent) while some do not (microtubule-independent). Therefore, patients with the microtubule-independent variants will not benefit from taxane chemotherapy; while on the other hand, patients with the microtubule-dependent ones are highly sensitive to taxane therapy. In collaboration with Drs. David Nanus, Steven Plymate and Brian KirbyDr of Cornell University, Giannakakou has developed a system that can identify AR variants and their cellular localization in patients. This system employs a PSMA-based microfluidic Geometrically Enhanced Differential Immunocapture (GEDI) device (Figure 3). The information from this system can then inform potential response to taxane chemotherapy. Thus the ability to isolate and study single CTCs from patients can predict clinical response/resistance to taxanes.

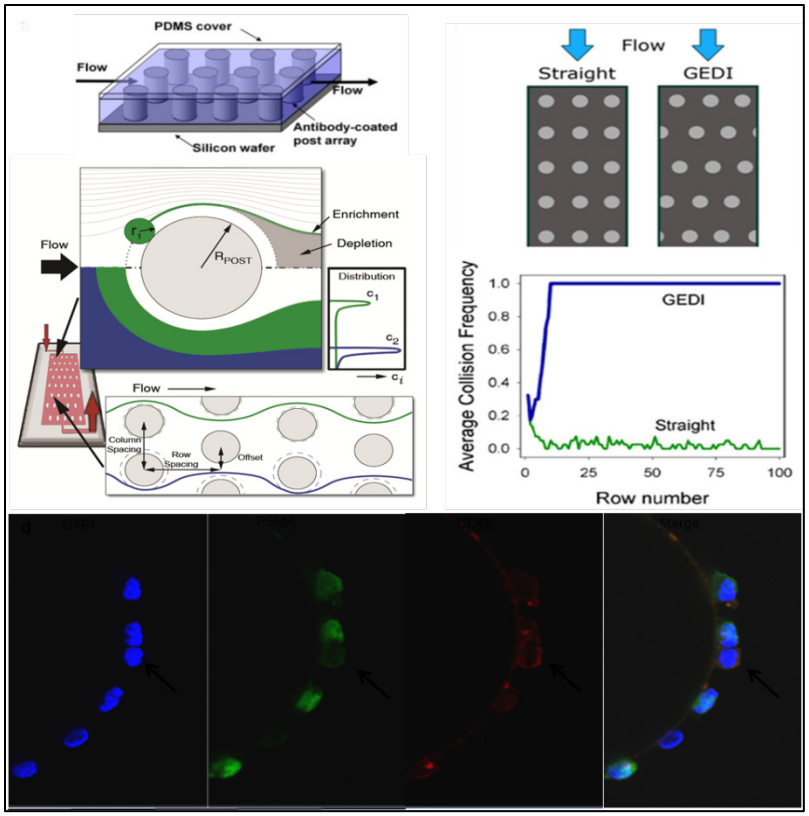


Figure 3: A schematic of the Genetically Enhanced Differential Immunocapture (GEDI) microdevice and its implementation. The top panel shows particle trajectories through a microfluidic obstacle array. The lower panel is an assortment of confocal microscopic images of cells captured on the GEDI device and stained for DAPI (blue, PSMA (green) and CD465 (red). Note that the cells are caught because they have PSMA on their surfaces.

Martin Gleave, MD

The Vancouver Prostate Centre

Role of Clusterin in Stress Response, Autophagy and Taxane Resistance

Funded by a PCF-Safeway Challenge Award

What this means for patients: Clusterin, that plays a cancer cell protective role in hormone resistance, is a new therapeutic target for advanced prostate cancer. Its inhibitor, OGX-011, holds immense potential as a chemotherapeutic for delaying CRPC progression.

Prostate cancer patients tend to develop resistance against treatment and the development of CRPC is attributed to re-activation of the androgen receptor (AR) signaling axis and alternative growth factor pathways that spur the growth of cancer cells. Cancer cells respond to therapy by switching on stress-response genes which aid tumor cell survival and treatment resistance. One such protein is clusterin (CLU), which

is activated in response to various treatment stressors such as androgen ablation; treatment with MDV3100, microtubule inhibitors such as taxanes etc. Dr. Martin Gleave's group at the Vancouver Prostate Centre is studying the role of clusterin in treatment-resistance as well as treatment modalities that inhibit its activity. In his presentation at the PCF Retreat, Dr. Gleave elaborated on his results of the role of clusterin in cancer cell resistance to taxane chemotherapy. His experiments demonstrate that upon treatment of cancer cells with the taxane, paclitaxel, another protein called YB-1 is activated. YB1 then induces CLU activity, preventing treatment-induced cell death, thereby facilitating taxane-resistance. CLU also facilitates the quick elimination of toxic protein aggregates from the cell by the process of autophagy. Thus CLU plays a cyto-protective role in cancer cells, conferring cell survival against a broad spectrum of treatments (Figure 4).

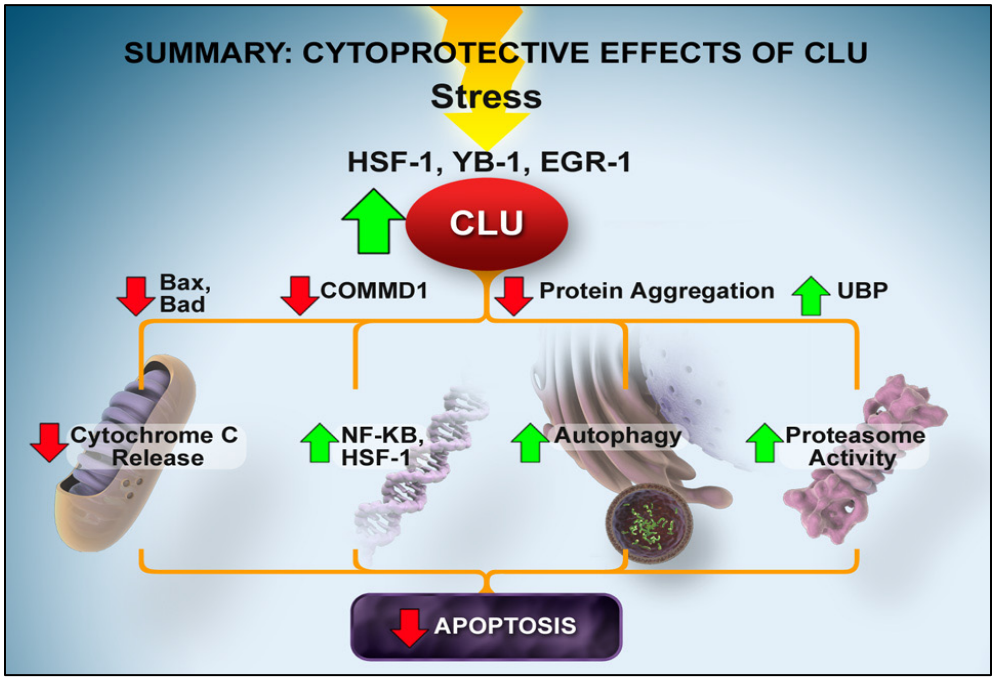


Figure 4: The stress-induced, cytoprotective protein, Clusterin (CLU) plays a critical role in cancer cell resistance to taxane therapy. Through its multiple effects it prevents treatment-induced cancer cell death.

This group at the Vancouver Prostate Centre tested custirsen (OGX-011), a CLU inhibitor, both as a first line therapy in CRPC patients as well as a treatment modality in post-chemo CRPC patients. OGX-011 in combination with taxotere, prolonged median overall survival by 6.9 months when used as a first line treatment in CRPC patients. In the second trial, when OGX-011 was administered to CRPC patients as a second-line therapy, this medication restores patients' sensitivity to docetaxel. Interestingly, OGX-011 synergistically also sensitizes castrate-resistant prostate cancer tumors to the medication MDV3100. Thus, the use of clusterin-inhibitor OGX-011 holds promise in

CRPC combination therapy both as first- and second-line therapies. A global Phase III trial to test the benefit of OGX-011 is currently open and accruing.

Ahmed Ashour Ahmed, MD, PhD
University of Oxford, England
Targeting Signaling Pathways to Circumvent Taxane Resistance

What this means for patients: Ovarian cancer research may have a lot to teach prostate cancer research as both diseases have sensitivity to taxane chemotherapy. Taxanes increase the stability of microtubules in the cell. Dr. Ahmed proposes that therapeutically modulating microtubule stability will increase the response of cancer patients to paclitaxel.

Dr. Ahmed from Oxford University started his PCF presentation by presenting the fact that mortality due to ovarian cancer has remarkably remained stable since 1971, with ovarian cancer mortality rates showing only a 10% decline in the period 1997-2007, as against a 33% decrease in breast cancer deaths. Initially the medication, carboplatin, was used to treat ovarian cancer. The addition of the taxane chemotherapeutic, paclitaxel to carboplatin chemotherapy has improved survival of advanced ovarian cancer patients; however, the response rate to this therapy is only 40%. Therefore, it is important to understand the mechanisms of patient response to primary therapy with taxanes to develop novel combinations of these medications with other agents. As discussed above, paclitaxel binds microtubules and prevents their disassembly, making building blocks for new microtubule synthesis unavailable. This mechanism arrests the growth of cancer cells and leads to cell death.

Dr. Ahmed's team identified a protein called TGFBI (Transforming Growth Factor Beta Induced) that sensitizes cancer cells to taxane treatment. They noted that ovarian cancers that lack TGFBI are uniquely resistant to single-agent paclitaxel therapy. TGFBI, when present, to integrins on the cancer cell surface and this sends signals to promote the assembly of microtubules inside the cell to make them available for taxane binding. The number of available microtubules in turn determines the effectiveness of treatment with taxanes, greater microtubule availability leading to higher taxane-induced cancer cell death. Dr. Ahmed's team therefore hypothesized that perturbing cell signaling pathways that increase the number of available microtubules, will result in increased response to paclitaxel, affording greater cancer cell death (Figure 5).

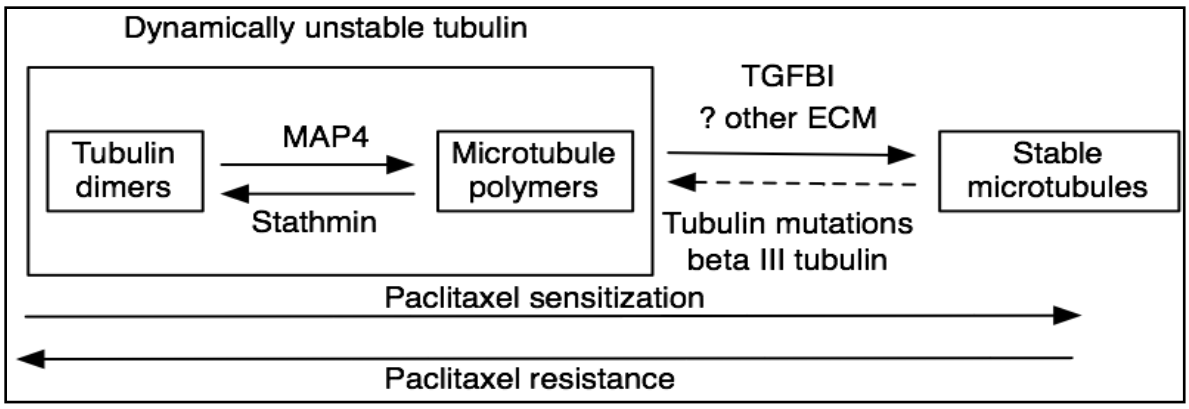


Figure 5: The mechanisms of paclitaxel sensitization and resistance.

They tested their hypothesis by analyzing microtubules in >2 million single cells by depleting 799 individual microtubule modulators (kinases). This screen revealed novel, druggable modulators of microtubule stability and therefore, paclitaxel response. Dr. Ahmed and his team are currently validating the therapeutic potential of these targets in in a variety of cancer cell types including ovary and prostate.

Session 2

New Concepts in Stem Cell Biology

Introduction:
Cancer is a stem cell disease. Stem cells are cells that have infinite self-renewal capabilities and can also develop into diverse specialized cell types, e.g. depending on the stimulation they receive, embryonic stem cells can form more than 200 cell types. Cancer stem cells are thought to be treatment-resistant cells that re-populate a tumor after therapy.

Prostate cancer is heterogeneous in cellular morphology, proliferative capabilities, underlying genetic alterations as well as response/resistance to therapy. The underlying mechanisms that generate tumor heterogeneity still remain unknown. One of the chief questions that remains unanswered until recently is whether different cancer subtypes in a patient arise from distinct 'cells of origin' or whether all subtypes are progeny of the same original cell, having diverged along distinct paths. It is important to note that the cell of origin, i.e. the normal cell that acquires the first cancer-promoting genetic alteration (and therefore, the cancer-initiating cell), is distinct from the cancer stem cell, i.e. the cellular subset within the tumor that uniquely sustains malignant growth (the cancer-propagating cell).

As prostate cancer spreads from its primary site in the prostate to distant sites in bone and soft tissue, the tumor cells acquire new properties that allow them to move out of

the surrounding tissue, into the blood vessels and eventually extravasate (leak) out of the blood vessels. Targeting these circulating tumor cells in transit is proposed as an effective therapeutic modicum. Therefore, understanding the properties of these circulating tumor cells is an important area of prostate cancer biology.

Major Points from Session 2:

- Dr. Owen Witte from UCLA has developed a human prostate cancer regeneration system where normal human prostate cells are transformed with oncogenes and then re-constituted beneath the renal capsule of an immunodeficient mouse. These cells form malignant glands and are indistinguishable from prostate cancer biopsies from patients. This system can be used for the systematic examination of cancer-promoting genes and their consequent effects in cancer progression.
- Activated Androgen Receptor (AR) + Src kinases cause highly malignant prostate glands in the model described above.
- Src kinases are important new therapeutic targets for prostate cancer and clinical trials of the Src kinase-inhibitor, dasatinib are currently underway to evaluate its effectiveness in PCa treatment.
- Contrary to expectation, basal cells (and not luminal cells) of the prostatic tissue form the cancer 'cells of origin'.
- The same 'cell of origin' can give rise to multiple tumor subsets depending on factors such as its microenvironment, the kind of genetic alterations it undergoes etc.
- Cancer cells undergo metastases by a process known as Epithelial-Mesenchymal Transitions (EMT) and Mesenchymal-Epithelial Transitions (MET), properties found uniquely only in embryonic stem cells and lost in a healthy adult.
- Tumor cells in circulation present properties of both EMT/MET and stem-ness and these properties can be therapeutically targeted to potentially prevent cancer metastasis.
- Quantifying circulating tumor cells in patients' blood holds potential for monitoring their response to treatment.

Owen Witte, MD

University of California, Los Angeles

Defining Prostate Cancer Therapeutic Targets in Non-Mutated Cellular Pathways

Funded by a PCF Challenge Award

What this means for patients: Dr. Witte has developed a human prostate regeneration model system. His findings validate Src kinases as therapeutic targets for the treatment of CRPC. Initial findings from his group show that the medication, dasatinib, might be effective in a subset of CRPC patients.

Genes and their proteins that are mutated or modified in cancer are at times not easily therapeutically targetable. Dr. Witte began his presentation by stating that there is a

need to identify cancer cell signaling components and pathways that are not mutated and therefore amenable to therapeutic intervention. Dr. Witte and colleagues observed that a type of proteins called tyrosine kinases are usually over-active in several CRPC patients. They also noted that tyrosine kinases are not mutated in prostate cancer and are therefore a good drug target. Dr. Witte and his team studied one such family of tyrosine kinases, the Src kinases in detail. Src kinases regulate several cell signaling pathways critical for cancer cell survival, proliferation, invasion, migration and angiogenesis (Figure 6). Several cancers show an enhanced activity of Src kinases; however no mutations have been identified in these proteins.

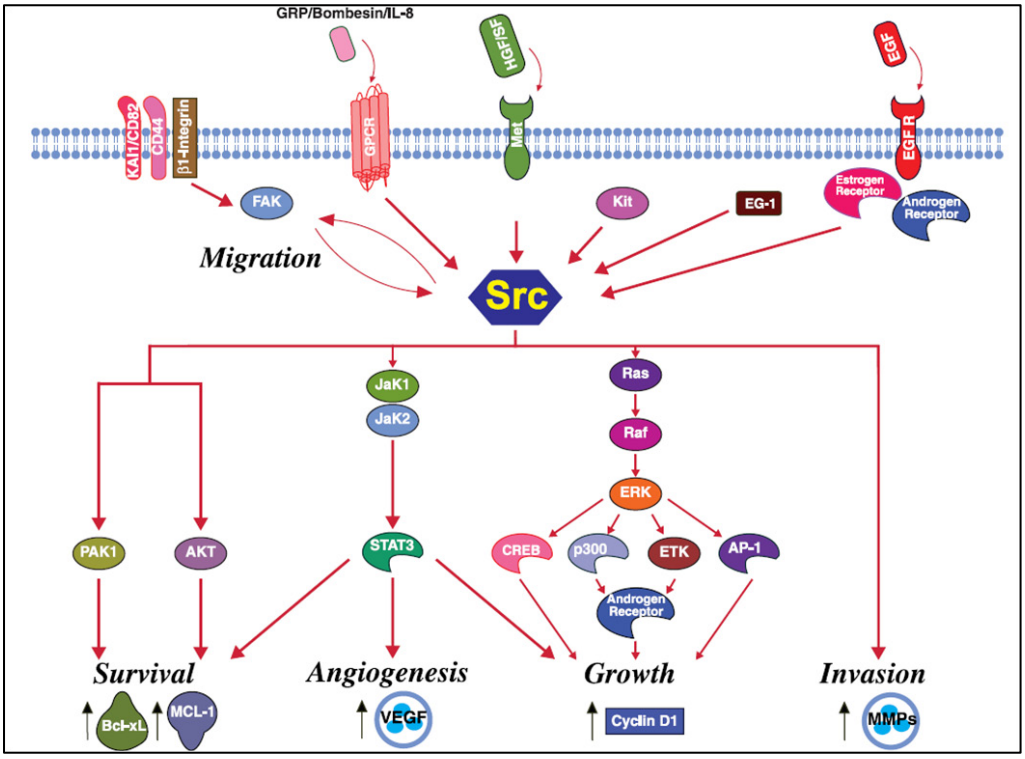


Figure 6: The multiple roles played by Src kinase in the cell. This member of the tyrosine kinase family of enzymes integrates several cell signaling pathways, regulating multiple aspects of cellular physiology such as survival, angiogenesis, growth, invasion etc.

Dr. Witte has established a human prostate regeneration system in his laboratory at UCLA, in which prostate tumor tissue can be regenerated *in vivo* by combining dissociated prostate cells and engrafting these cells into immunodeficient mice (Figure 7). This system can efficiently report the effects of cancer-specific genes on the initiation and progression of prostate cancer, allowing a chronologic investigation of prostate cancer progression.

Dr. Witte used this system to evaluate the role of Src kinases in prostate cancer. These experimental results established that enhanced activity of both Src kinase and AR

induces invasive carcinoma with EMT and prostate cancer progression. Therefore, these results provide solid grounds for therapeutically targeting Src kinase in the subset of CRPC patients presenting elevated Src kinase levels. Dr. Witte and his team tested the effects of the small molecule inhibitor, dasatinib, in tumors that over-express Src kinase and noted that dasatinib inhibits invasive carcinoma induced by Src kinase. Dasatinib is an established inhibitor of tyrosine kinases and past Phase I/II studies of CRPC patients treated with a combination of dasatinib and docetaxel have shown a reduction in the size and/or number of existing bone lesions.

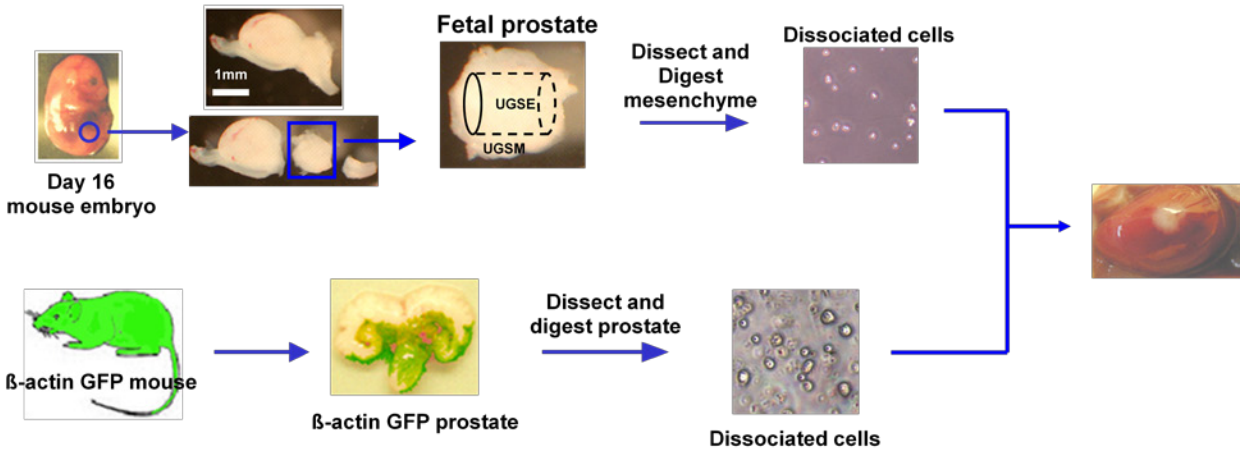


Figure 7: The prostate regeneration system developed by Dr. Owen Witte and his team at UCLA.

Dr. Witte and his team at UCLA are currently evaluating the effects of dasatinib, a Src kinase inhibitor, on the subset of prostate cancers that present with activated Src kinase levels.

Andrew Goldstein, PhD
University of California, Los Angeles
Late-Breaking Research on Prostate Stem Cells
Funded by a PCF-Young Investigator Award

What this means for patients: Dr. Goldstein is working on identifying underlying factors that determine tumor development and response to therapy.

Prostate cancer is a heterogeneous disease reflected by the fact that patients present with a range of tumors each with distinct genetic alterations, Gleason scores and varied responses to therapy. These heterogeneous tumor cells may arise either from different starting cells (each with a distinct molecular signature) or from a common 'cell of origin' that has originally acquired the first genetic hit and has over time given rise to different daughter cells while accumulating multiple other mutations in its journey towards a tumor. The identification of these 'cells of origin' is critical because this will allow better

prediction of tumor behavior; earlier detection of potential malignancies and crucial design of preventive therapies for individuals at high risk of developing aggressive forms of cancer.

In his doctoral work in Dr. Owen Witte's laboratory at UCLA, Dr. Goldstein identified prostate basal cells as one cell-type of origin of human prostate cancer. His results showed that upon activation of cancer-specific genes like AR, AKT and ERG, these human prostate basal cells can initiate Prostatic Intraepithelial Neoplasia (PIN)-like lesions and luminal adenocarcinoma. Dr. Goldstein examined the response of the same starting cell population, upon stimulation with a different combination of cancer genes (Myc and AKT). These experiments showed that the (Myc+AKT)-activated cells gave rise to a variety of rapidly-proliferating tumors that contained cells of different kinds such as luminal, neuroendocrine cancers as well as squamous cell types.

These findings demonstrate that factors such as the microenvironment of a cancer cell of origin and the genetic alterations it acquires are important for determining the fate of its daughter cells and thereby the kinds of tumors it develops into. These results from Dr. Goldstein's research demonstrate that heterogeneous subsets of prostate cancer can arise from cells within the same defined population, as illustrated in Figure 8 below.

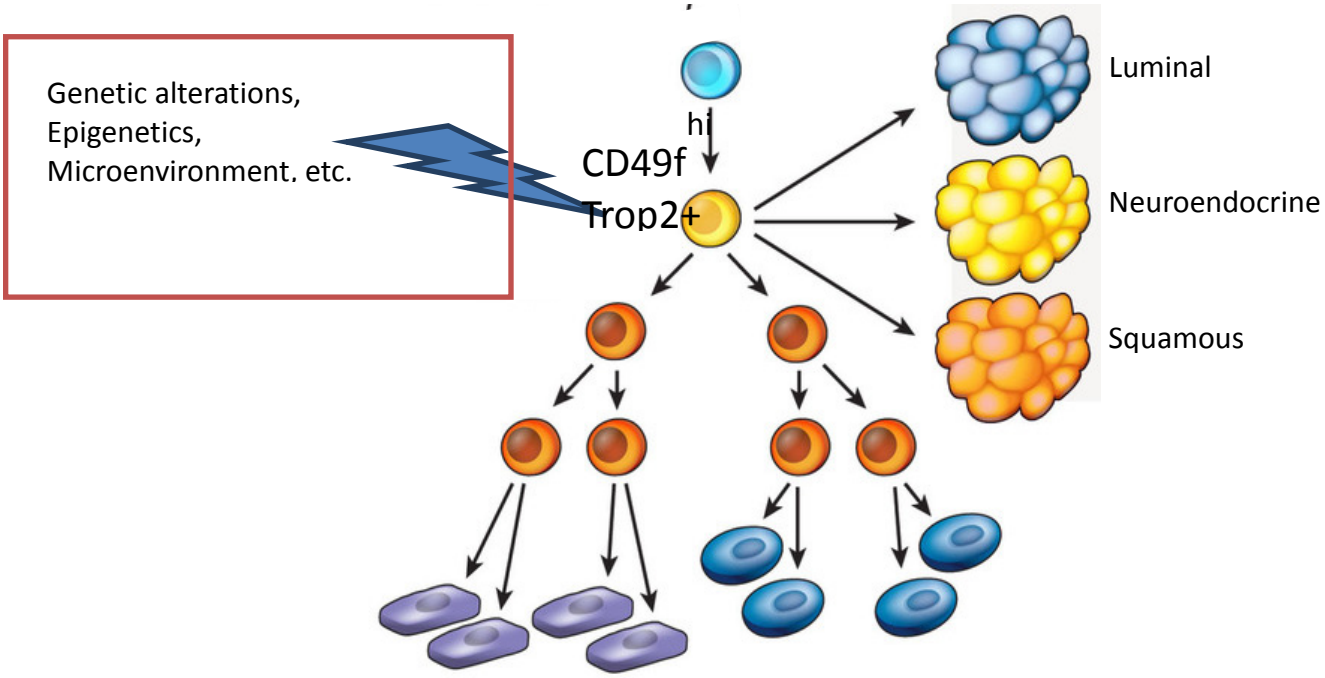


Figure 8: Distinct tumor populations can arise from target cells of the same population, depending on the genetic alterations they acquire, their microenvironment, etc.

Dr. Goldstein is currently testing his model to study the progression of these tumor types to castration resistance. He is also currently testing if these tumors are

transplantable into secondary recipients and can therefore initiate cancer. His work will eventually define the factors that determine tumor phenotype, aggressiveness as well as response to therapy.

Andrew Armstrong, MD, MSc

Duke University

Epithelial Plasticity and Stemness in Circulating Tumor Cells from Men with Metastatic Prostate Cancer

Funded by the Georgen Foundation-PCF Young Investigator Award

What this means for patients: Dr. Armstrong has identified unique properties of cancer cells in blood circulation, which are in the process of metastasizing to distant prostate sites. His results have two major implications; one, circulating tumor cells can be used as a diagnostic tool to study the metastatic process and two, these unique characteristics can be exploited to treat prostate cancer in hopes of preventing of metastasis.

During the initiation and metastatic progression of prostate cancer, cells acquire properties that allow them to transition between two different states, the epithelial and mesenchymal states. This property is found early during the development of a normal embryo and is lost in a healthy adult. It is interesting to note that cancer cells acquire this stem cell-like property which helps these rogue cells to invade surrounding tissue and metastasize (Figure 9).

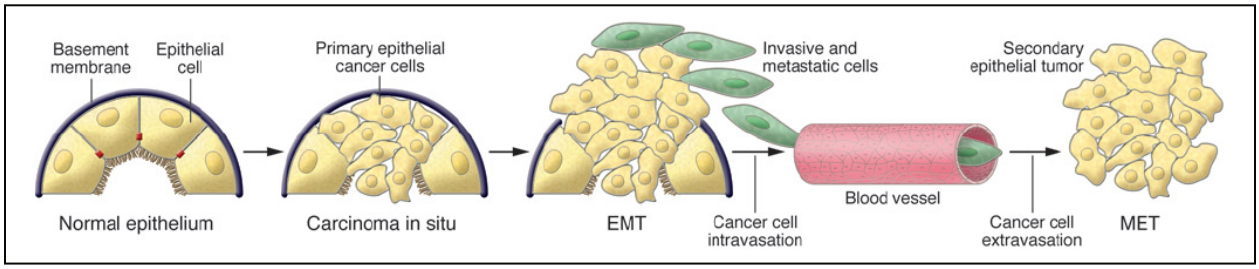


Figure 9: The establishment of metastatic cancerous lesions involves EMT and MET transitions in cancer cells. While in circulation, tumor cells express both epithelial as well as mesenchymal properties and can be therapeutically targeted.

Dr. Armstrong demonstrated this Epithelial-to-Mesenchymal Transitions (EMT) and the reverse, Mesenchymal-to-Epithelial Transitions (MET) in tumor cells that circulate in the blood of prostate cancer and breast cancer patients, providing evidence for a mechanism related to metastasis (Figure 10). He showed that EMT occurs when primary tumor cells acquire the capability to invade surrounding tissues and metastasize to distant sites. As illustrated in Figure 9 above, MET occurs when these circulating tumor cells move out of blood vessels and settle at a new site to initiate a secondary tumor. Dr. Armstrong's experiments demonstrate that these circulating tumor cells

(CTCs) with epithelial, mesenchymal as well as stem-cell like properties occur at a very high frequency in prostate cancer patients. These findings suggest that targeting these cancer stem-like cells would be an effective therapy to prevent cancer spread. Molecules associated with EMT and MET could be new therapeutic targets to attenuate prostate cancer metastasis. It is also important to develop improved CTC isolation technologies as studying CTCs will allow therapeutic target identification as well as help monitor patients' response to treatment.

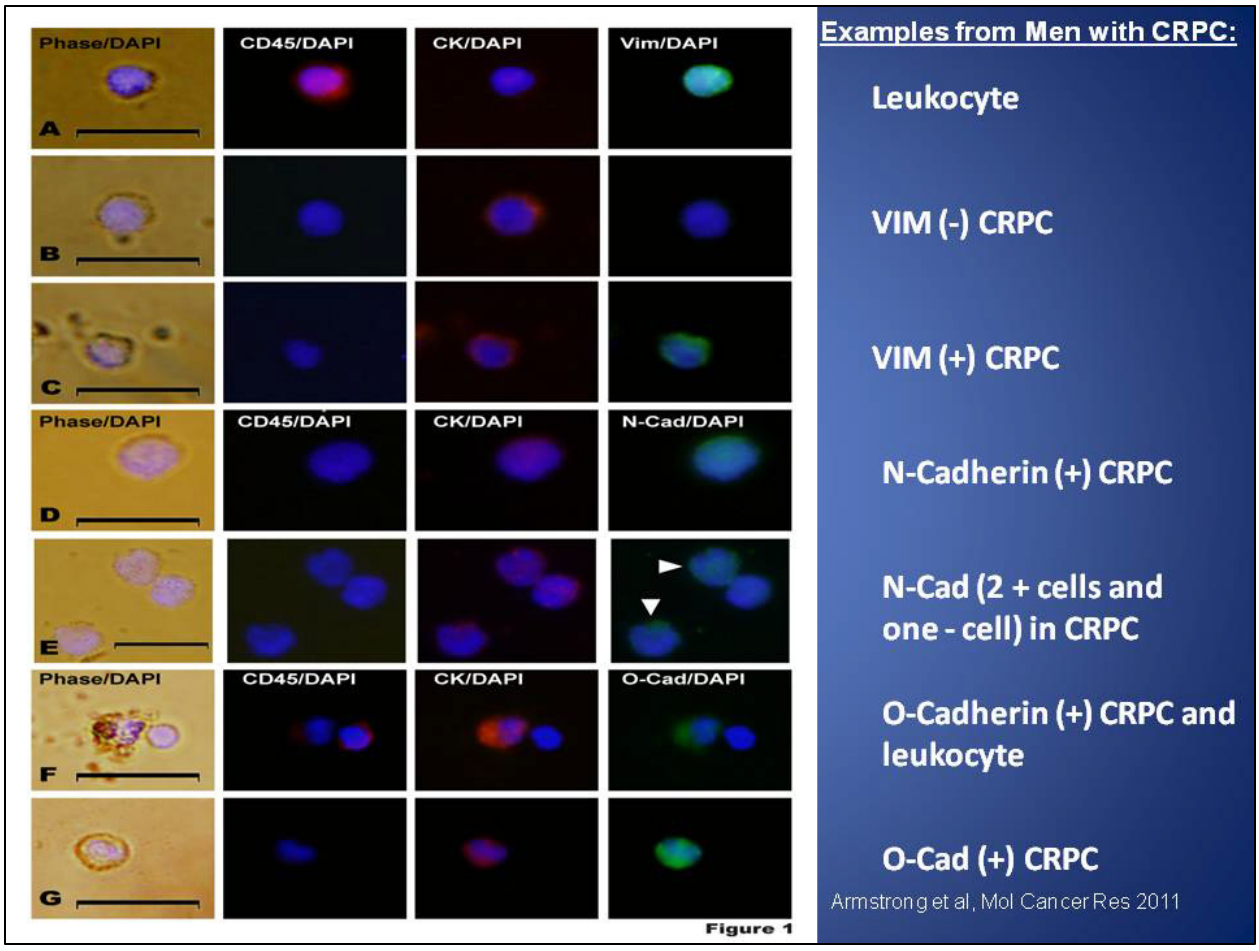


Figure 10: Co-expression of epithelial and mesenchymal proteins in CTCs from men with metastatic castration-resistant prostate cancer (mCRPC).

Dr. Armstrong is currently working on developing and testing a novel EMT-based CTC capture ferrofluid in collaboration with the diagnostic company, Veridex (a subsidiary of J&J). This methodology is currently being tested in patients and healthy volunteers.

Session 3: Young Investigators # 1

Daniel Hamstra, MD, PhD

University of Michigan

Prostate Cancer Radiation Enhancement via PI3K Pathway Inhibition – More than PTEN - The Role of the Tumor Stromal Interaction

Funded by a Rahr-PCF Young Investigator Award

What this means for patients: Combining radiotherapy with targeted therapy may increase survival and eliminate relapse of high-risk locally advanced prostate cancer. A Phase I trial studying the combination of the medication everolimus, an inhibitor of cell signaling, with hormonal ablation and external beam radiation is currently underway.

Radiation therapy (RT) is an effective method for the treatment of primary prostate cancer. Combining radiation with targeted therapy of cancer-specific cellular growth pathways may maximize clinical benefit. PCF-funded young investigator Dr. Daniel Hamstra hypothesized that targeting the PI3K pathway will improve patient response to RT. The PI3K pathway (that involves three crucial steps: PI3K→AKT→mTORC1) is a cell signaling pathway that is involved in multiple crucial cellular functions such as growth, proliferation, differentiation, motility, survival and intracellular trafficking. This pathway is frequently activated in prostate cancer with ~42% of primary prostate tumors and almost 100% of metastatic cases presenting alterations in PI3K signaling. In a healthy cell, the PI3K pathway is kept in check by the tumor-suppressing activity of the protein PTEN. Approximately 50% of prostate cancers have a loss of the *PTEN* gene at the time of diagnosis resulting in the activation of the PI3K signaling pathway.

Dr. Hamstra hypothesized that since PTEN loss and the concomitant activation of the PI3K pathway will lead to increased prostate cancer survival, the inhibition of this signaling cascade should improve patient response to radiation therapy. In his experiments, Dr. Hamstra observed that in cells that lacked the tumor suppressor PTEN, inhibiting the downstream step of the PI3K signaling pathway, i.e. mTORC1 did sensitize cells to radiation therapy. These results show that targeting the PI3K pathway in the large subset of prostate cancer patients that lack PTEN, will sensitize their tumors to radiation therapy, thereby improving chances of long-term survival. When this team tested their results in mice, they observed that mTORC1 inhibition in combination with radiation therapy not only sensitizes tumors lacking PTEN, but also shows significant effects on tumors containing PTEN. The latter effect appears to be due to an inhibition of abnormal blood-vessel growth in the prostate cancers. To validate these results in prostate cancer patients, Dr. Hamstra and his colleagues have initiated a multi-institutional Phase I study of everolimus added to hormonal and radiation therapy for high risk, locally advanced PCa patients (Figure 11). Everolimus is an FDA-approved mTORC1 inhibitor that is currently being used for the treatment of advanced kidney and metastatic pancreatic tumors. In their trial, Dr. Hamstra and his team will define the

safety of everolimus when delivered orally in combination with hormonal ablation and external beam radiation in 40 high-risk, locally advanced prostate cancer patients.

Event	Study Day
Enrollment	
Begin everolimus	0
Marker Placement & Biopsy	10-14
Begin Anti-androgen (bicalutamide 50 mg/daily)	10-14
Begin LHRH Agonist (Lupron 22.5 mg Q3 months)	15-25
RT Simulation	50-60
Start RT	60-70
End RT / End bicalutamide / End everolimus	120-130
End Lupron	24 months
Last Study Follow-up	36 months from end of RT

Figure 11: The trial design for the multi-institutional Phase I trial of combination therapy with everolimus+ hormonal therapy+ radiation therapy using TITE-CRM (Time to Event Continual Reassessment Model), in high risk locally advanced prostate cancer patients.

Steve Y. Cho, MD

Johns Hopkins Medicine

Low Molecular Weight PSMA-Based PET Imaging of Prostate Cancer

Funded by Grauer-PCF Young Investigator and PCF Creativity Awards

What this means to patients: Dr. Cho's research has demonstrated that PSMA-targeted PET scans can potentially detect locally advanced or progressive prostate cancer before existing, routine imaging technology. Early detection will result in earlier or more appropriate treatment with the potential to prevent widely metastatic prostate cancer.

Molecular imaging to detect early recurrent metastatic prostate cancer is a significant unmet medical need. Dr. Steve Cho and colleagues at Johns Hopkins University presented results on the early clinical testing of a molecular imaging technology that appears very promising.

Prostate-specific Membrane Antigen (PSMA) is a prostate cancer-specific cell surface marker. The expression of PSMA is highly increased during prostate cancer progression and metastasis and increased expression is linked with more aggressive disease and recurrence. PSMA is being targeted as an imaging biomarker for the detection of early metastatic prostate cancer by Dr. Cho and his team. Small molecule inhibitors or binders to PSMA have been coupled to PET imaging tracers. When injected into patients, the PSMA-directed PET tracer will permeate and bind to prostate tumors and

can be detected by PET scanning the patient with equipment readily available in most hospital settings.

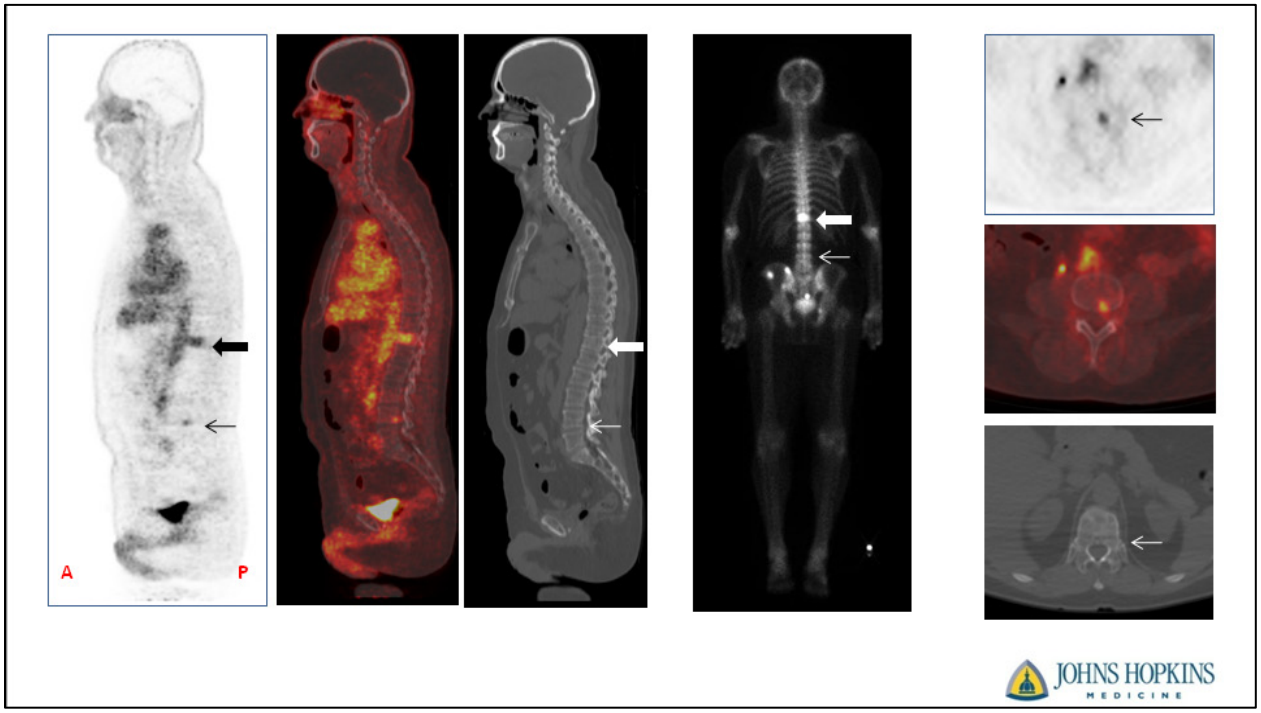


Figure 12: Example of PET/CT scanning using the PSMA-targeted imaging radiotracer, [^{18}F] DCFBC, compared to a standard conventional bone scan (CT) in the same patient.

Dr. Cho presented his results from a Phase I, first-in-human study of one such PSMA PET tracer. In this study, Dr. Cho studied the safety, biodistribution (where the tracer binds and is excreted) and radiation dosimetry (the quantity of radiation dose from radiotracer present in all organs and blood) in five metastatic prostate cancer patients (Figure12). These subjects had PSA>1 and radiologic evidence of new or progressive metastatic disease. None of the patients experienced any significant adverse side effects attributable to the radiopharmaceutical, which could conclusively detect metastatic prostate cancer lesions. The early PET scans demonstrated the localization of prostate cancer not detectable by routine bone and CT scans.

Nima Sharifi, MD

University of Texas Southwestern Medical Center

The Origins of Dihydrotestosterone in Castration-Resistant Prostate Cancer

Funded by a PCF Young Investigator Award

What this means for patients: Dr. Sharifi's results show that DHT (Dihydrotestosterone), the potent male hormone metabolite of testosterone can be synthesized through a metabolic pathway not requiring testosterone (T), which is contrary to the currently-held paradigm. Therefore, targeting the synthesis of T alone (e.g. by ADT) is not sufficient to cripple prostate cancer cells. If these results are validated in larger populations of prostate cancer patients, 3βHSD, the enzyme that is required for synthesis of T as well as this alternative mechanism for DHT will represent a new target for therapy of advanced prostate cancer.

The male hormones, testosterone and **D**i**H**ydro**T**estosterone (DHT), are believed to be the main fuels that drive prostate cancer proliferation, invasion and survival. DHT which is chemically=Testosterone + 2 hydrogen atoms, is five times more potent than testosterone in driving cancer. It has long been assumed in the scientific community that DHT is derived from testosterone by the addition of two hydrogens and therefore targeting the synthesis of testosterone alone would stop cancer spread.

Androgen Deprivation Therapy (ADT) is the first line of treatment for metastatic prostate cancer patients and involves medications like Lupron. This treatment depletes testosterone which initially shrinks prostate tumors. Testosterone is synthesized in a complex metabolic cascade. Abiraterone inhibits an enzyme, CYP17A1, central to the synthesis of testosterone. Unfortunately many patients are resistant to abiraterone and those that respond will eventually become resistant as well.

In his presentation Dr. Nima Sharifi described his discovery of a whole new pathway for the synthesis of DHT that completely bypasses testosterone. His findings demonstrate that DHT is actually synthesized in copious amounts not from T, but from its precursor. Dr. Sharifi's data point out that DHT synthesis occurs in *two* steps and not through the single step conversion from T, as has been assumed all along in the resistant form of prostate cancer (Figure 13). It has been counter-intuitive to assume that DHT is synthesized in two steps instead of the single-step synthesis directly from testosterone. These results have been tested in laboratory models of prostate cancer and from fresh samples from 2 patients with advanced disease.

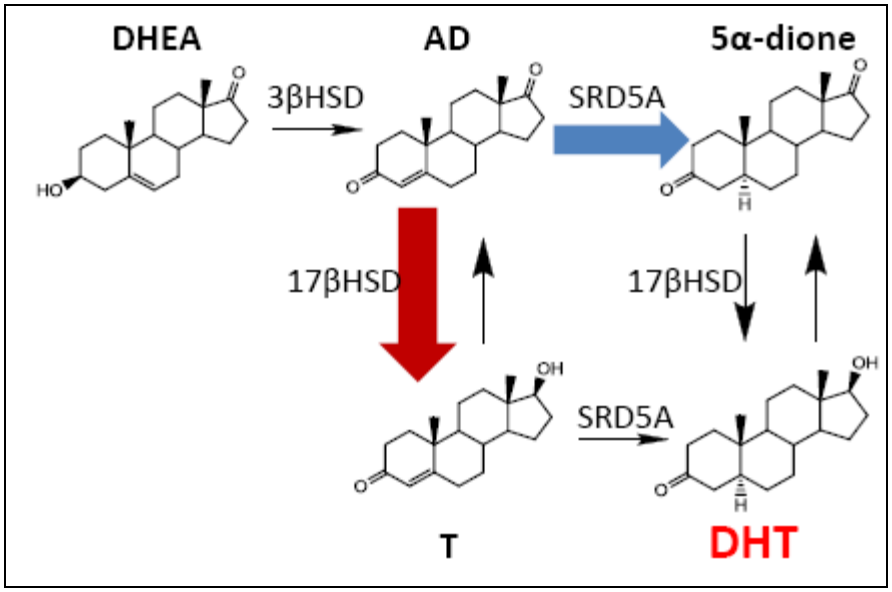


Figure 13: The synthesis of testosterone (T) and dihydrotestosterone (DHT). The red arrow denotes the synthesis of T from AD. It was believed earlier that T gave rise to DHT by a single-step process. Dr. Sharifi's results show that DHT is synthesized, not from T but from AD, in two steps (AD →5-α-dione→DHT).

These studies open the field for discovery of medications against the driver of DHT synthesis, 3βHSD (the enzyme 3 beta-hydroxysteroid dehydrogenase), the discovery and validation of which provides a potentially druggable target for a new therapy. An inhibitor of 3βHSD in combination with abiraterone has high potential as a new treatment strategy for ADT resistance in prostate cancer patients.

Special Lecture: The History of Development of Radium-223

Oliver Sartor, MD
Tulane University

What this means for patients: Alpharadin (Radium-223) improves overall survival of patients with bone-metastatic castration-resistant prostate cancer patients. This medication is on the fast-track to approval by the FDA.

Approximately 90% of men with castration-resistant prostate cancer show bone metastases which are the main cause of debilitating pain, weakened bones and a reduced survival. Currently, very few medications are available for advanced mCRPC that has progressed to the bone. Phase II and III clinical investigations of alpharadin (Radium-223), a bone-targeted radiopharmaceutical have demonstrated few side effects and prolonged survival in patients with mCRPC in bone. Dr. Oliver Sartor helped

to design the Phase III trial and was North American PI for the initial preclinical studies as well as the clinical trials for this radiopharmaceutical. Dr. Sartor presented an overview of the development of this medication.

The therapeutic benefits of alpharadin derive from targeting of bone with a very powerful isotope, Radium-223. This radiopharmaceutical emits alpha radiation which kills cells but has a very short distance of activity, thereby sparing normal adjacent tissue. Alpharadin shows potent and localized tumor cell-killing activity in a 10-cell radius, with minimal damage to surrounding bone marrow. A half-life of 11.4 days makes alpharadin ideal for cancer therapy. This therapeutic has been shown to be well-tolerated in patients.

In a randomized Phase II trial in bone-metastatic CRPC patients, Radium-223 caused a decline in PSA as well as bone biomarkers, demonstrating that this medication acts on both the tumor as well as its stromal environment. A Phase III clinical trial of alpharadin was carried out in 922 patients in a study named ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer). The results of this investigation showed that alpharadin improved overall survival of mCRPC patients by 2.8 months (14 vs 11.2 months) (Figure 14). Based on the survival advantage of this therapy, the IDMC (Independent Data Monitoring Committee) stopped the trial prematurely and offered alpharadin to patients receiving placebo.

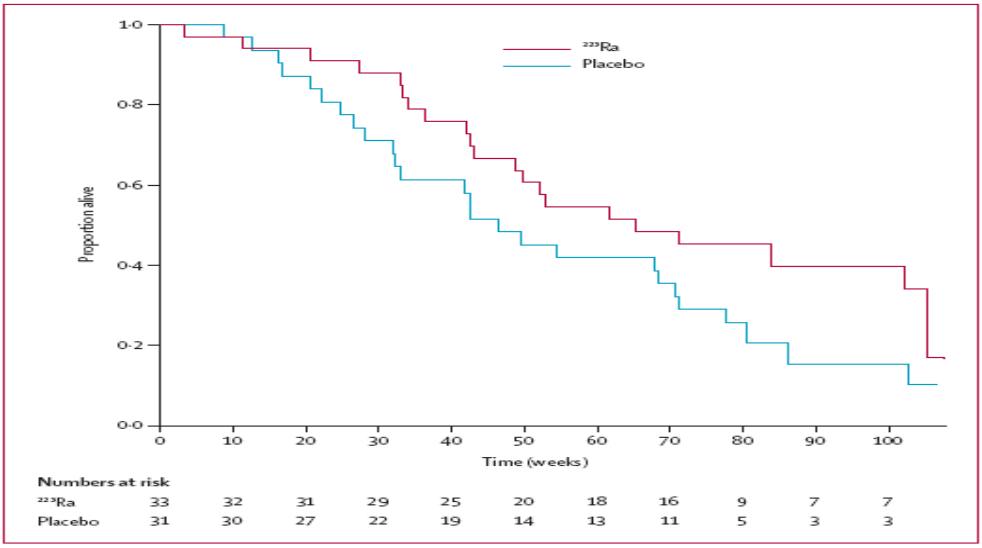


Figure 14: Kaplan-Meier curves depicting the effects of Radium-223 (Alpharadin) on patient overall survival in a Phase II trial. Median overall survival was 65·3 weeks (48·7—∞) for223Ra and 46·4 weeks (32·1—77·4) for placebo (p=0·066, log rank). The hazard ratio for overall survival, adjusted for baseline covariates was 2·12 (1·13—3·98, p=0·020, Cox regression). Median time to PSA progression was 26 weeks (16—39) versus 8 weeks (4—12; p=0·048) for 223Ra versus placebo, respectively.

This first-in-class, highly-targeted alpha-emitting radiopharmaceutical is being developed by the Norwegian pharma company, Algeta, in partnership with Bayer Pharmaceuticals. It should be noted that Alpharadin is still an investigational agent and has not been approved by the FDA.

Session 4

Genomics and Genetics of Prostate Cancer: What We Have Learned in the Last Year

Introduction

In order to completely understand the processes of cancer initiation, progression and metastases, it is vital to study alterations in the prostate cancer genome. This research will reveal alterations in cellular genetics including gene expression, gene mutations, gene deletions or gene amplification in a cancer cell in comparison to its healthy counterparts. These studies will also provide information on the differential expression of genes during the various stages of cancer. In addition, sound knowledge of the prostate cancer genome will enable personalized medicine by identifying genetic variations that are treatable with therapies that are most effective.

Major Points from Session 2:

- To date, whole genome sequencing has not shown a consistent pattern of a high frequency of a few targetable mutations in prostate cancer.
- Prostate cancer has a lower frequency of mutations than melanoma. However, the mutations that do occur are usually limited to a few genes.
- Chromosomal rearrangements, such as the TMPRSS2-ERG fusions are a hallmark of the prostate cancer genome.
- The TMPRSS2-ERG fusion status of a cancer cell determines the mechanism of tumorigenesis.
- *SPOP*, *CADM2* and *CHD1* are examples of mutated genes that have been discovered in this genomic research.
- In a new personalized medicine initiative, the MI-ONCOSEQ protocol adopted by the University of Michigan will conduct high-throughput sequencing of patient tumors to inform appropriate treatment. The entire process of sequencing tumors→deciding upon actionable targets→initiating treatment will take 30 days per patient.
- Epigenetics is the study of chemical modifications of DNA that alters gene expression. Malfunctioning genes in prostate cancer are modified both at the genetic level (mutations) and the epigenetic level (addition of chemical 'marks'). Therefore, combinatorial targeting of both the genetic and epigenetic defects is important for effective therapy.
- A new method of tumor-targeting currently being tested under a PCF Challenge Award project is ISLET (Induction of Synthetic LEThality). This methodology

turns 'on' the 'good' genes cancer switches off. ISLET also turns on 'bad' genes so that new therapies can be tested in this model.

Levi Garraway, MD, PhD

The Broad Institute and Dana-Farber Cancer Institute

New Insights from the Prostate Cancer Genome

What this means to patients: Dr. Levi Garraway's team at the Broad and Cornell carried out the first total genome-wide assessment of genomic changes that underlie prostate cancer. His findings provide a discovery tool for new diagnostics and therapeutics. Taking us closer to the goal of personalized medicine, his results will help predict lethal prostate cancer and holds a potential to inform individualized therapy.

Dr. Levi Garraway and his team have completely sequenced the genomes of 22 high-grade primary prostate tumors obtained from radical prostatectomy. These included six Gleason 9 grade tumors and eight tumors each of Gleason grades 8 and 7. These extensive sequencing efforts revealed that prostate cancer has a very low frequency of somatic nucleotide substitutions, the average point mutation rate being approximately 1 per Mb (megabase pairs) which translates to about 13-28 mutations per genome. To date, no recurrent mutations have been discovered.

Dr. Arul Chinnaiyan and his PCF-funded team led discovered recurrent gene fusions in human prostate cancer involving the androgen-regulated gene *TMPRSS2* and ETS family genes (*ERG*, *ETV1* or *ETV4*) in approximately 50% of prostate cancers. These gene fusions are the result of chromosomal rearrangements resulting from the juxtaposition of two genes that are not usually present side-by-side in a healthy cell. Dr. Garraway's whole-genome sequencing results find no clear correlation between Gleason grade or cancer stage to the presence/absence of these gene fusions (Figure 15). Instead, Dr. Garraway and his team observed that genomic rearrangements in prostatic tumors can be common, non-random, complex, and co-incident with specific tumor-promoting alterations, e.g. the TMPRSS2-ERG rearrangement. This team also investigated the dynamic interactions that lead to genomic derangements. They found that genomic break points tend to associated with regions where the DNA was not very tightly coiled, including the DNA-binding sites for AR and ERG. In tumors lacking the TMPRSS2-ERG fusion, however, rearrangement breakpoints were inversely correlated with those regions, and in fact, more rearrangement breakpoints were observed in tightly packed DNA. This pattern therefore suggests different mechanisms for tumorigenesis, depending on whether the tumor initiating cell has a TMPRSS2-ERG gene fusion or not.

These sequencing efforts at the Dana Farber and the Broad Institute have revealed some new genes that may have critical roles in determining the fate of a prostate cancer cell, such as the genes *SPOP*, *CADM2* and *CHD1*. Dr. Garraway summarized his presentation by stating that genomics approaches hold promise to address several of

the most important unanswered questions in prostate cancer biology, such as the specific genetic features that distinguish lethal from indolent prostate cancer; the therapeutically tractable dependencies of lethal PCa tumors; the mechanisms of resistance of these tumors to anti-androgen therapy; the effects of ancestry on prostate tumor biology etc. Thus, such large-scale genome sequencing studies may hold the key to better prostate cancer management.

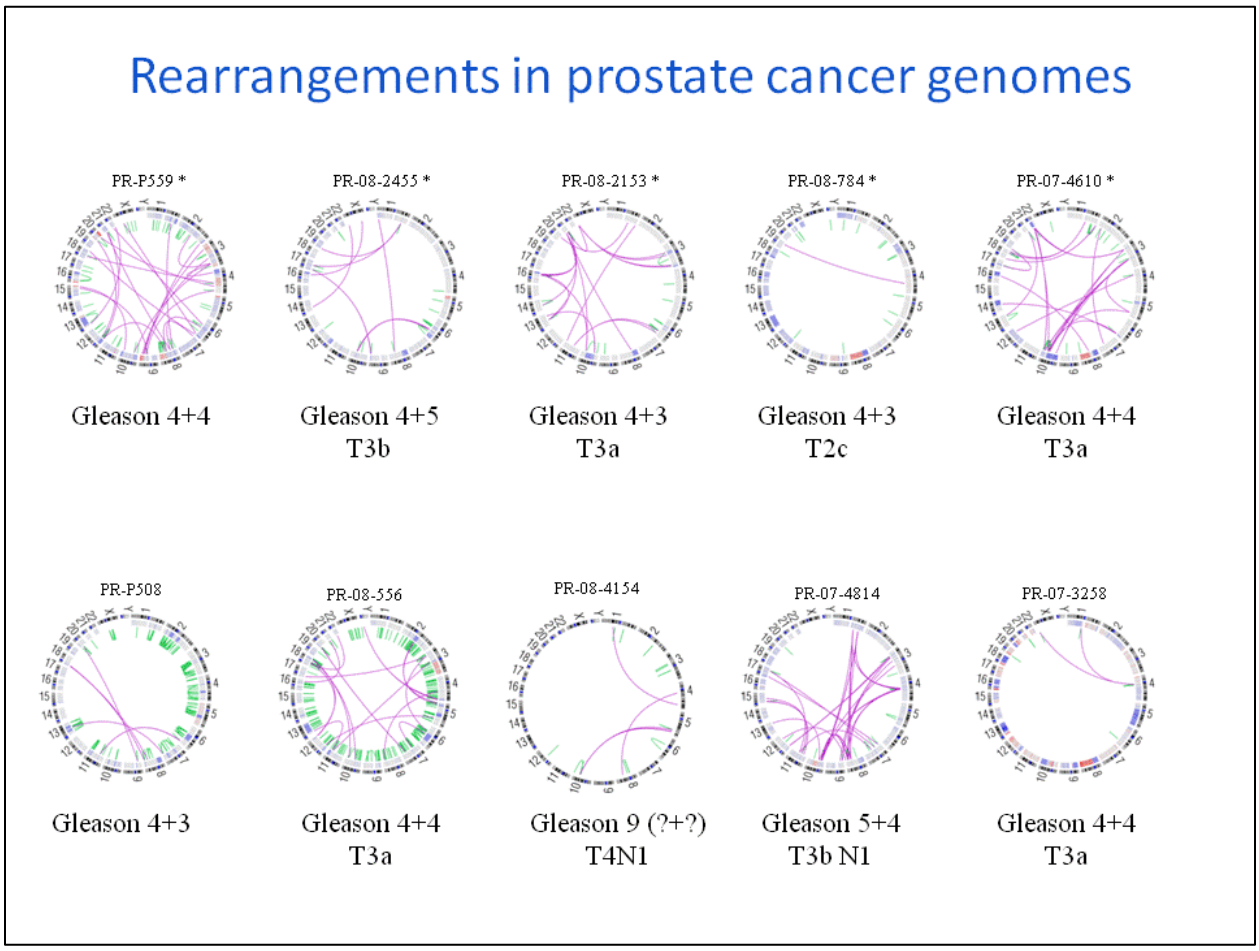


Figure 15: Circos plots to depict chromosomal rearrangements in prostate cancer genomes. Each Circos plot depicts the genomic location in the outer ring and chromosomal copy number in the inner ring (red, copy gain; blue, copy loss). Interchromosomal translocations (DNA fusions) and intrachromosomal rearrangements (deletions of the DNA code) are shown in purple and green, respectively. These plots show that chromosomal rearrangements do not correlate with Gleason grade or the aggressiveness of the tumor, e.g. Gleason 8 tumors show more rearrangements than Gleason 9.

Arul Chinnaiyan, MD, PhD
University of Michigan
The Application of Integrative Sequencing for the Personalization of Prostate Cancer Therapy
Funded by a PCF Special Challenge Award

What this means to patients: In a major move towards personalized medicine, the University of Michigan is performing comprehensive genetic analysis of all cancer patients' tumors presenting at their Comprehensive Cancer Centre. The goal of these analyses is to match genetic alterations with the most effective, currently available, FDA-approved or experimental medications.

Prostate cancer is a heterogeneous disease, with each patient presenting a different combination of underlying genetic alterations. Dr. Arul Chinnaiyan pointed out that targeting the underlying mutations in certain solid tumors that cause disease progression is an effective means of personalized therapy. He cited the example of the V600E mutation in metastatic melanoma which is directly targeted with a small molecule inhibitor against the mutated kinase. An effective means to thoroughly understand each individual patient's cancer is high-throughput sequencing of their tumors; the results of which can then be translated for personalized oncology. Dr. Chinnaiyan emphasized that this comprehensive sequencing analysis of the mutational landscape is important because many contributing cancer mutations are rare (e.g. the RAF gene fusions in prostate cancer are seen only in ~5% patients in PCa) and can potentially be missed out during targeted sequencing analyses.

Dr. Chinnaiyan described the integrative sequencing protocol that has recently been approved by the IRB and adopted at the **MI**chigan **ONCO**logy **SEQ**unecing center, called the MI-ONCOSEQ effort, directed towards sequencing bio-specimens from patients of advanced disease. Under this protocol, tumors from patients will be subjected to: one, genome sequencing (to identify DNA structural rearrangements, copy number alterations etc); two, exomal DNA sequencing (i.e. sequencing the portions of DNA that actually produce products, to detect point mutations, insertions, deletions etc.) and three, transcriptome sequencing (to study gene expression and structural rearrangements). The results of these integrative sequencing approaches will then be submitted to computational pipelines to identify genomic alterations that are linked to the development/progression of cancer. The read-out from these three individual sequencing efforts will overlap in many cases, thereby validating the underlying mutation in the patient's tumor by three orthogonal approaches. The findings will then be submitted to a Multi-Disciplinary Sequencing Tumor Board that will analyze the key findings for treatment (Figure 16).

This integrative sequencing approach will comprehensively identify the genomic alterations of an individual tumor and will provide information on the disrupted pathways and networks in the patient's cancer. This insight can then be used to enrich

Phase I/II trials aimed at identifying drugs that target the identified mutations. The MI-ONCOSEQ group proposes to carry out these high-throughput sequencing studies in a clinically relevant timeframe, with a 30-day turn-around time per patient. They also propose a MIONCOSEQ-Lite version for targetable genes. The team at Michigan has carried out this integrative sequencing analysis on 18 patients with a variety of hematologic malignancies and solid tumors, six of who were metastatic prostate cancer patients. In his presentation at the Retreat, Dr. Chinnaiyan described the sequencing results from one mCRPC patient that clearly showed AR amplification (both by genome as well as exome assessment), TMPRSS2-ERG fusion and an inactivating mutation in the tumor suppressor p53. A novel finding was a new fusion of the mitotic kinase, NEK11 which is a candidate target for further research. Dr. Chinnaiyan also detailed a new University of Michigan initiative by Dr. Kenneth Pienta to systematically procure bio-specimens and establish a cohort of living hormone naïve metastatic PCa patients.

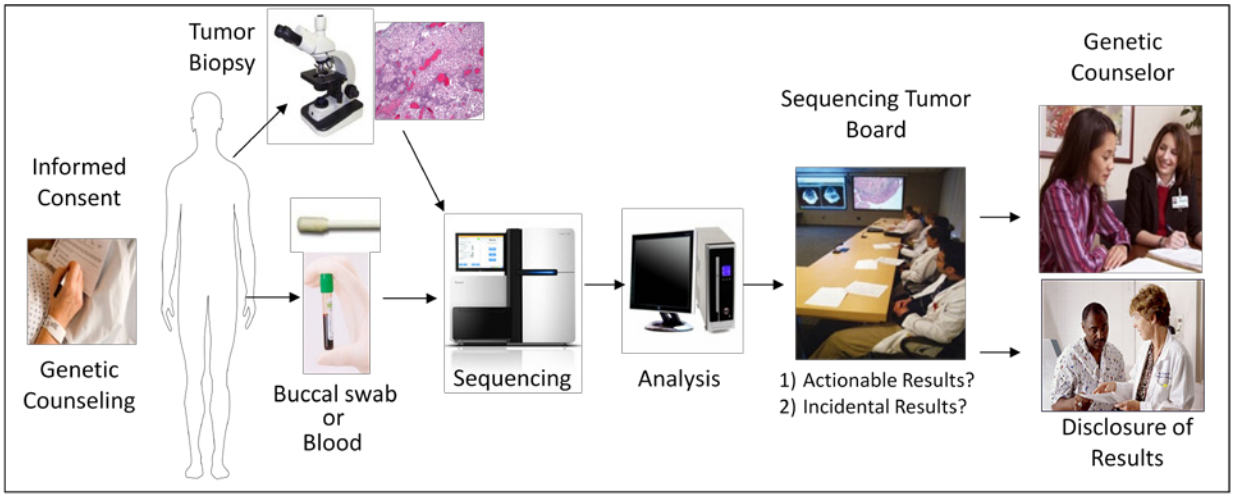


Figure 16: The IRB-approved protocol for high-throughput sequencing of patient tumors that will guide personalized treatment, under the MI-ONCOSEQ project at the University of Michigan.

This program is a major step forward for personalizing cancer treatment by gaining a thorough understanding of the genetic alterations in a patient's tumor.

Mark Rubin, MD
Weill Cornell Medical College
Next Steps for Next Generation Discoveries
Funded by a PCF Challenge Award

What this means to patients: 1. Fast and efficient whole genome sequencing methods will enable analysis of more prostate cancers which will allow subtyping of prostate cancer and the discovery of new therapeutic targets. This classification, in time, will support personalized treatment for patients. **2.** Approximately 10-14% of patients with prostate cancer have mutations in the *SPOP* gene and up to 30% over-express the protein, Aurora Kinase A. These discoveries may enable the assessment of therapeutic targets within the SPOP complex that may represent new treatments for metastatic prostate cancer.

Dr. Mark Rubin pointed out that computational pipelines (that conduct extensive high-throughput prostate cancer genome studies) produce enormous amounts of information on mutations in prostate cancer. He emphasized that it is important to classify these into 'driver', 'passenger' as well 'co-driver' mutations, i.e. identify the main mutations that play a driving role in cancer and therefore, need therapeutic targeting. Dr. Rubin pointed out that molecular pathology is progressively shifting its focus from the cellular basis of disease to a molecular classification of cancer. What this means is that in the future prostate cancer and other human malignancies will be treated on the basis of the key molecular alterations, through information obtained from comprehensive genetic analyses. Commenting on the MI-ONCOSEQ initiative presented by Dr. Chinnaiyan at the Retreat, Dr. Rubin emphasized that the computational pipelines that evaluate the integrative sequencing data, should be able to query for the important and rare mutations seen most commonly in prostate cancer to expedite the treatment process The value of this important data will increase over time as mutations found today can be linked to emerging therapies. Dr. Rubin also focused on the need to identify the functional downstream effects of these mutations.

Dr. Rubin and colleagues have identified a unique class of prostate cancer patients, those that have mutations in the *SPOP* gene. This subset of patients is distinct from those with *TMPRSS2-ERG* gene fusions. The SPOP mutations result in increased invasiveness of the tumor cells which leads to the metastatic spread of prostate cancer. Mutations in the *SPOP* gene were identified by Dr. Rubin in collaboration with Dr. Levi Garraway in approximately 10-14% of clinically localized, uniformly ETS gene rearrangement negative prostate cancers. Their results show that mutations in this gene are most commonly associated with alterations in chromosomes 5 and 6 in this subset of patients. With funding by a PCF Challenge Award, Dr. Rubin and his team are currently studying the mechanisms by which the *SPOP* gene gets inactivated and the downstream effects of this genetic dysregulation. They are also investigating the function of SPOP in basic embryonic development. These findings will help in the design

of effective therapeutics for this class of prostate cancer patients. The team will inform the discovery of effective therapeutics for this subtype of prostate cancer patients.

Srinivasan Yegnasubramanian, MD, PhD

Johns Hopkins Medicine

Lessons from the Prostate Cancer Epigenome

Funded by a PCF Creativity Award

What this means for patients: Cancer cells find ways to switch off genes that function to keep the growth and architecture of normal cells in check. Dr. Yegnasubramanian is working on deciphering the mechanisms that cancer cells use to switch off 'good' genes and ways to therapeutically turn these genes 'on' again. The new medications being discovered by this team will attack tumors in new ways and combined with currently available treatments will provide new therapies for metastatic prostate cancer.

Epigenetics (Greek: epi-above/over), is the study mechanisms above-and-beyond the genetic sequence that can control gene expression. As an analogy, the genetic code in a cell can be thought of as a very large, multi-volume, instruction manual. The genetic sequence in a cell is analogous to the printed words/sentences on the instruction manual. The epigenetic code is used by the cell to interpret the genetic code in a context-specific manner, and is analogous to bookmarks or "sticky notes" strewn throughout the manual to help the cell interpret the manual in a context-specific manner. It turns out that cancer cells figure out ways to evade the rules that govern the growth and architecture of normal cells by both altering the words on the instruction manual and also the location and instructions on these "sticky notes" – i.e. altering both the genetic and epigenetic code. One such epigenetic process is called DNA methylation, literally a mark placed on the DNA similar to a sticky note placed on a page. Changes to these DNA methylation "sticky notes" can allow cancer cells to turn on "bad" genes, for example by removing the DNA methylation "sticky note", or turn off "good" genes, by adding new DNA methylation "sticky notes".

Dr. Srinivasan Yegnasubramanian is studying how the epigenetic code interacts with the genetic code (DNA) to cause multiple alterations that result in the initiation and progression of prostate cancer. His high-throughput sequencing approaches capture these epigenetic DNA modifications and identify their locations on prostate tumor genomes. He described that these DNA markings are seen not just in genes but also in regions of the genome that are gene deserts (i.e. regions that are currently not known to produce any functional product) that likely have as-yet-unidentified functional roles. In a unique method of pictorially representing these results, Dr. Yegnasubramanian and his team have constructed 'cityscape' models from their data with each chromosome represented as a neighborhood in the city and each gene a building in the neighborhood. The height of these buildings corresponds to the frequency of the

epigenetic modifications seen in that gene across tumors from different patients, as illustrated in Figure 17 below.

These results show that on an average >1,000 genes are epigenetically modified in a given prostate tumor, literally re-programming the cancer cell to behave totally differently than a normal prostate cell. These modification patterns are consistent in all tumors from one patient; however, heterogeneity is seen across patients, with the epigenetic patterns varying from patient to patient. Thus each individual prostate cancer patient has his own unique fingerprint of epigenetic alterations. Therefore, each patient's unique set of alterations can be targeted in a personalized manner.

Dr. Yegnasubramanian's analysis revealed certain genes with consistent modification across all tumor genomes, such as the gene *GSTP1* which is modified in almost 100% of all prostate tumors. *GSTP1* is known to play a key role in susceptibility to cancer. Thus this technology of studying epigenetic changes in cancer will help identify alterations that play a driving role in cancer initiation and progression. Additionally, by combining both genetic copy number and DNA methylation analysis, Dr. Yegnasubramanian's group has identified a novel gene that can control the ability of prostate cancer cells to invade and metastasize. These results suggest new targets for treatment of advanced prostate cancer, and highlight the importance of studying both the genetic and epigenetic defects in a cancer cell in an integrated fashion.

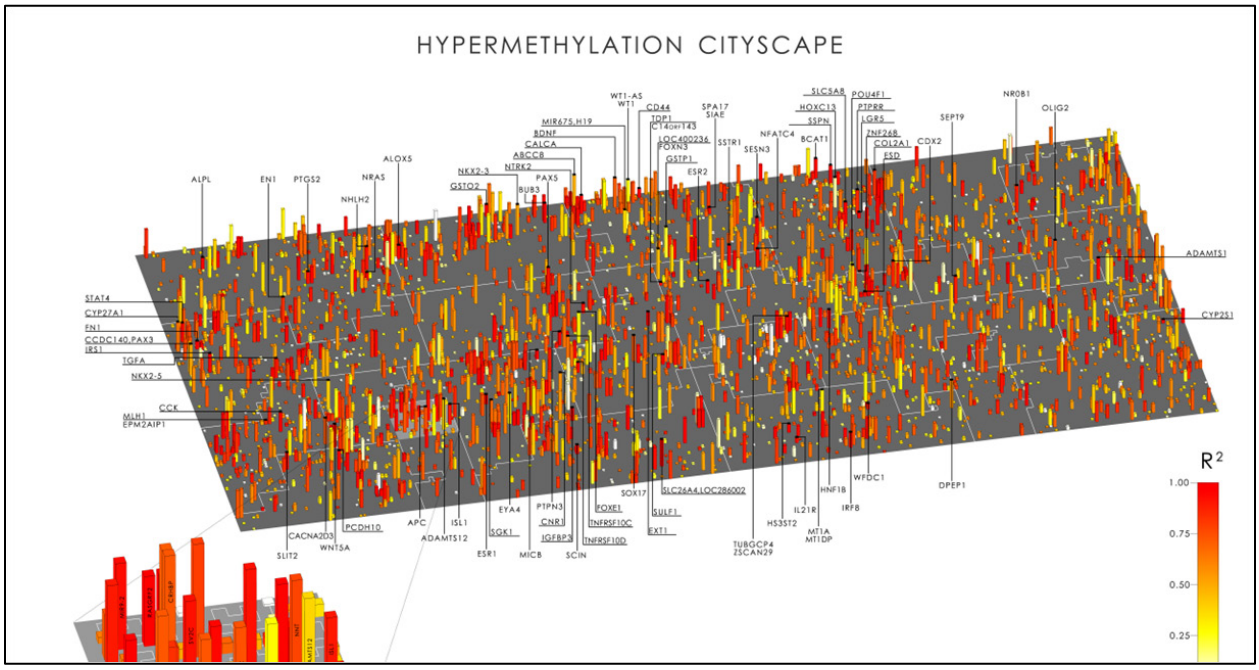


Figure 17: The 'Cityscape Model' built by Dr. Srinivasan Yegnasubramanian to depict the epigenetic changes in DNA. Each chromosome represents a neighborhood in the city and each gene on the chromosome represents a building in the neighborhood. The height of these buildings and therefore the genes is representative of the frequency of

the epigenetic alterations in that gene. This can be compared between cancer cells and normal cells to determine the driving alterations in cancer.

Dr. Yegnasubramanian is currently testing the ISLET (Induction of Synthetic Lethality with Epigenetic Therapy) approach for treating prostate cancer. Under this collaborative, PCF-Challenge Award funded project with Dr. William Nelson, Dr. Yegnasubramanian and his team are working towards the discovery of innovative new medicines that will turn these switched-off genes back on so that currently available medications can be used to effect tumor regression. The reversal of gene-silencing by these new medications will have a two-pronged effect; one, switching on the 'good' genes that cancer cells switch 'off' and two, reprogramming the cancer cells so that they can be effectively targeted and destroyed by the currently available medications.

Special Lecture: Prostate Cancer Targets the Hematopoietic Stem Cell Niche during Metastasis to Bone

Russell Taichman, DMD
University of Michigan Dental School

What this means for patients: Dr. Taichman's results provide insight into the mechanisms used by prostate cancer cells to settle into bone metastases and occupy a niche usually held by blood cells-forming stem cells, during cancer progression. He has studied agents that can force out PCa cells from the bone niche which will re-sensitize the tumor cells to elimination with existing therapies.

Despite significant strides in therapeutics, the prognosis for prostate cancer that has metastasized to bone metastasis is generally poor. A fundamental understanding of why prostate cancer homes to bone in the most serious for of the disease and how to release and destroy these tumor cells is absent. Biological research in Dr. Taichman's laboratory has revealed that the process of bone homing by prostate cancer cells is the same as that used by hematopoietic stem cells (HSCs, i.e. stem cells that reside in the bone marrow and give rise to blood cells). Dr. Taichman observed that within 24 hours of injecting red-stained HSCs and green-stained PCa cells into the heart of mice, both cell types co-localize to the bone surface, and compete for the same niche (binding area). Eventually cancer cells push out HSCs from their niche in the bone and settle there, forming metastatic lesions (Figure 18). The displaced HSCs move back into the blood circulation as demonstrated in the model below. These results were validated in patients with disseminated disease as they carried larger loads of HSCs in their blood compared to patients with early disease. During his presentation, Dr. Taichman compared this niche competition between HSCs and cancer cells to brood parasitism where a parasitic bird manipulates the host to raise its own young. His experiments also revealed that altering the niche size was directly proportional to metastasis, an increase

in niche size reflected in a hike in metastatic lesions. These results identify the bone marrow HSC niche as a potential therapeutic target for metastatic disease.

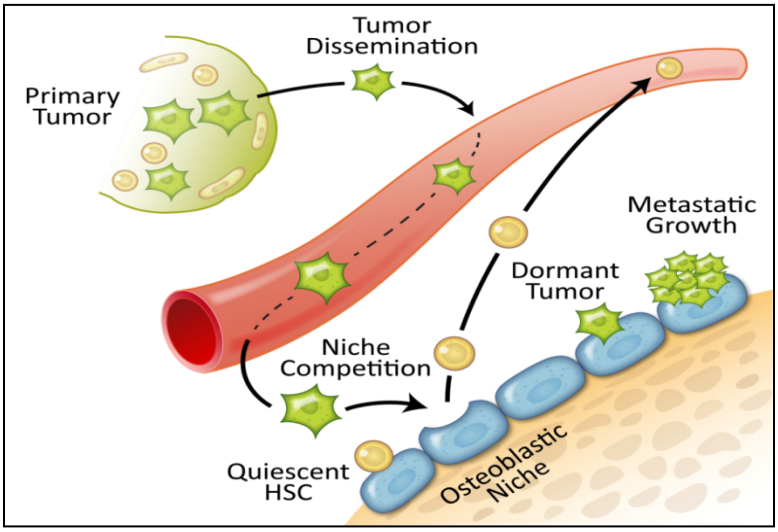


Figure 18: Metastatic prostate cancer cells compete for the Hematopoietic Stem Cell niche in the bone, pushing out the HSCs and establishing cancerous lesions in the bone.

An important finding from this work is that prostate cancer cells can displaced from the bone niche using the same agents that coax HSCs to move from the marrow to blood, such as the granulocyte-colony stimulating factor (GCSF) or the medication AMD3100. It is believed that the tumor cells, once displaced from bone, will be exquisitely sensitive to killing by chemotherapy or other anti-prostate cancer treatments.

Special Lecture: Improving Outcome from Advanced Prostate Cancer

Johann De Bono, MD, PhD
Royal Marsden Hospital and Institute of Cancer Research

What this means for patients: Dr. de Bono is a leader in the development of new medications for the treatment of advanced metastatic prostate cancer. His current clinical research targets all important disease states of advanced prostate cancer with focus on metastatic castration resistant disease. He has several encouraging new anti-neoplastic medications under development. Dr. de Bono presented his results on several medications targeted towards the treatment of both, advanced disease as well as abiraterone-resistant prostate cancer.

Dr. de Bono has been instrumental in developing new molecular targeted therapies to improve treatment of prostate cancer. He is currently evaluating more than 20 drugs in early phase clinical trials and recently led the European Phase III trials for abiraterone

and cabazitaxel, which led to global regulatory approval. Both of these agents improved overall survival for patients with advanced metastatic, castration-resistant PCa. At the PCF Scientific Retreat Dr. de Bono emphasized that "Biomarker-driven, well-designed and expertly-conducted, reiterative and adaptive clinical trials will change cancer medicine through the questioning and answering of robust scientific hypotheses, utilizing rationally designed and molecularly targeted drugs".

Dr. de Bono is currently developing a large number of anti-prostate cancer drugs. He stated that the reason for the highly efficient drug discovery and development program at the Royal Marsden is the methodology they have adopted. This drug development paradigm which they named Pharmacological Audit Trail (PhAT) is based on testing drugs in patients whose tumor molecular profile matches the specificity of the medication. PhAT is therefore an upgrade of the previous methodology for directly testing drugs in all patients to see who respond best. It is a rationally designed approach of first determining the molecular profile of a patient's tumor and then administering the most appropriate medication. With a focus of molecular-targeted therapies, Dr. de Bono is a proponent of testing all hypotheses using biomarkers in clinical trials. This biomarker-driven trial design allows molecular stratification of patients based on their response and this patient enrichment may accelerate the development of newer drugs.

Dr. de Bono was the European PI for the abiraterone and cabazitaxel Phase III trials, both of which have recently been approved by the FDA and other global regulatory agencies for advanced CRPC patients. For the cabazitaxel trial, he and his team studied overall survival in men with advanced CRPC (all previously treated with docetaxel), randomized to cabazitaxel or to mitoxantrone. The Phase III abiraterone trials randomized patients to abiraterone or placebo. Significant overall survival was increased in both of these clinical investigations. Dr. de Bono is currently testing a new AR-degrading medication in abiraterone-resistant patients. Preliminary results show that this experimental medication causes a remarkable loss of AR expression upon treatment.

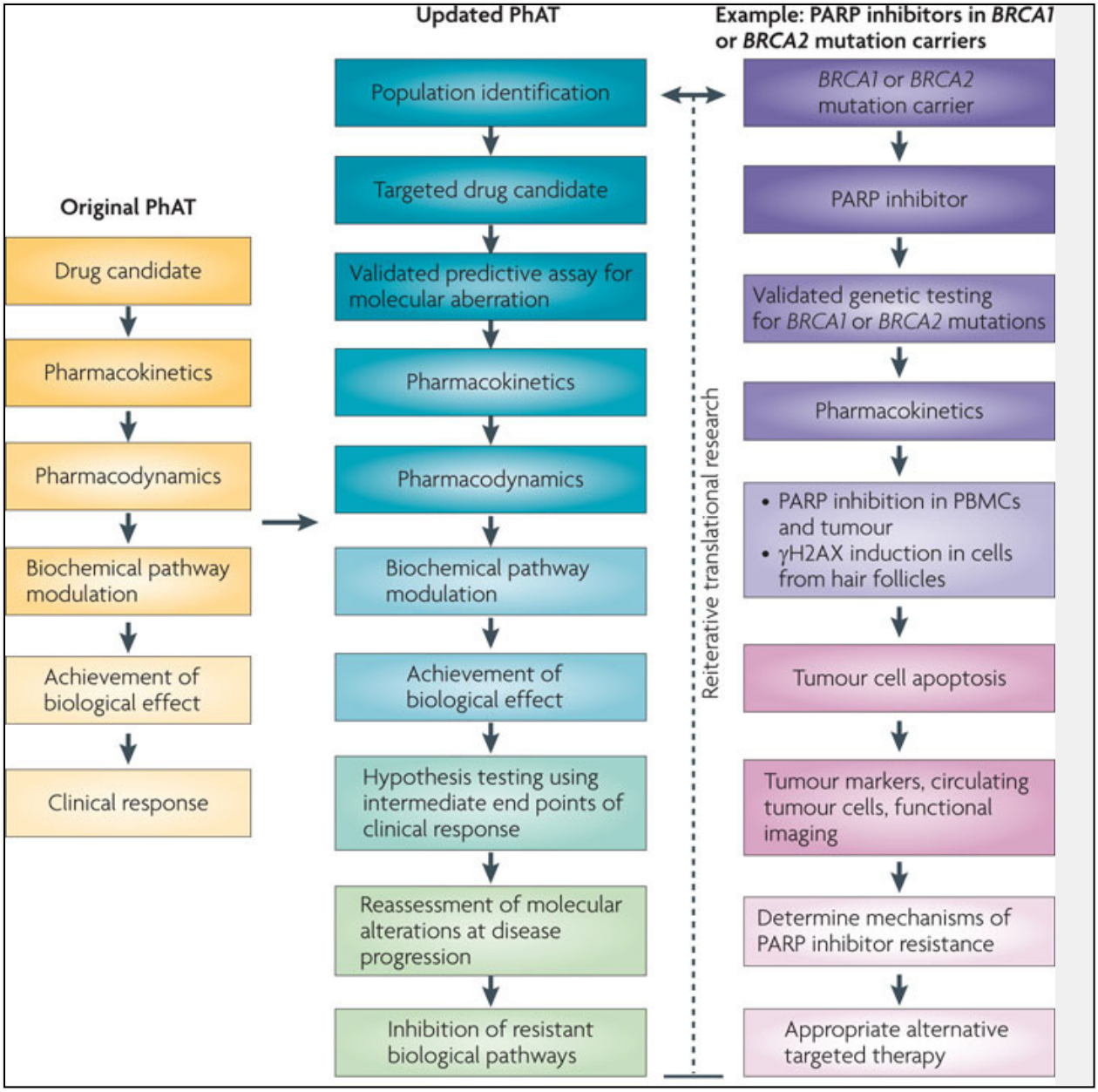


Figure 19: A comparison of the original PHarmacological Audit Trail (PHAT) to the one adopted by Dr. Johann de Bono's team for drug discovery.

All the strategies outlined by Dr. de Bono and the medications being tested by his team are changing our understanding and treatment of advanced prostate cancer.

Special Lecture: Modeling Metastatic Prostate Cancer from Mouse to Man – Molecular Determinants of Therapeutic Response

Cory Abate-Shen, PhD
Columbia University

What this means for patients: Dr. Abate-Shen has generated several genetically engineered mouse models that partly mimic human prostate cancer. These models are new tools for discovery and testing that can identify new therapeutic targets. These models are useful for testing new experimental medications prior to clinical investigations in patients. Dr. Abate-Shen's studies in these mouse models have identified 13 master regulators of prostate cancer progression, which can serve as biomarkers of advanced disease.

Dr. Cory Abate-Shen updated her research progress in three distinct parts. The first part of her presentation concerned the development of novel genetically engineered mouse models for prostate cancer which recapitulate many stages of the human disease. She is studying early-stage prostate cancer models to understand how the disease is initiated and her work has uncovered novel mechanisms for cancer prevention. More importantly, she has developed mouse models of advanced, metastatic prostate cancer that are being investigated to study the mechanisms of cancer progression and metastases. These genetically engineered mouse models not only help in the identification of therapeutic targets, they also help in the preclinical validation of targeted therapies against these targets. Dr. Abate-Shen emphasized that it is important to start all experiments in these state-of-the-art mouse models with a clinically relevant question, the answers of which should then be validated in human clinical specimens.

In the second part of her discussion, Dr. Abate-Shen presented a series of new mouse models in her lab that mimic the subtypes of human prostate cancer. These models have identified unique subtypes of prostate cancer that will be validated in human tissue samples. The hope is that these subtypes will be useful for personalizing therapy for advanced prostate cancer patients.

In the final section of her presentation, Dr. Abate-Shen presented recent findings from her mouse model of metastatic prostate cancer. Two pathways that are known to be deregulated in over 90% prostate cancer metastases are the PTEN (mTOR/AKT) and KRAS pathways. While generating the advanced prostate cancer model, Dr. Abate-Shen and colleagues removed the PTEN and KRAS genes and observed that the resulting prostate tumors were highly aggressive, metastasizing with a 100% frequency to soft tissues and distant organs (Figure 20). Their experiments on human and mouse metastatic cancer cells helped them build a 'malignancy signature' of genes that are

expressed in metastatic prostate cancer. These results have revealed 13 master regulators of prostate cancer progression, which can serve as biomarkers of advanced disease.

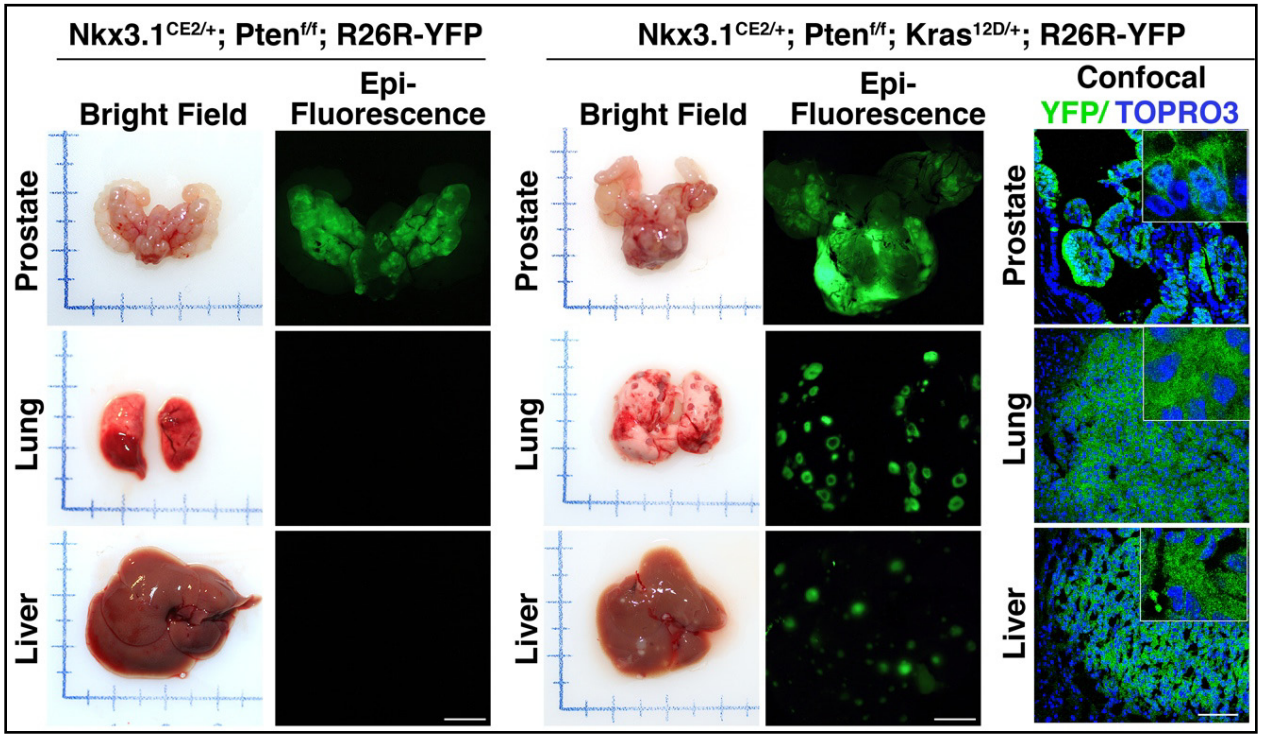


Figure 20: Distant metastases of mice tumors that develop when the gene *PTEN* alone is deleted (left panel) and when both *PTEN* and *KRAS* genes are deleted. Tumors lacking both *PTEN* and *KRAS* are aggressive with a 100% tendency to metastasize.

This team at Columbia University interrogated this mouse model of advanced PCa with a combination of therapeutics against the deregulated genes, MEK and mTOR, using targeted inhibitors PD0325901 and Rapamycin, respectively. They observed that this combination therapy reduces tumor burden in metastatic sites; improves survival, and changes tumor phenotype to that of a normal, healthy cell.

Session 5

Panel Discussion: The New Era of Molecular Pathology

Panelists: **Skip Holden, MD (Cedars-Sinai Medical Center)**
Angelo Dr Marzo, MD, PhD (Johns Hopkins Medicine)
Steve Shak, MD (Genomic Health)
Joel Nelson, MD (University of Pittsburgh)

Dr. Skip Holden moderated this panel and opened by stating that there is rapid change on the horizon with a shift in pathology from traditional anatomic pathology (study and diagnosis of the disease based on the gross examination of tissues, organs etc.) to the incorporation of molecular pathology (i.e. the study and diagnosis based on the examination of molecules within the tissues, organs, body fluids etc.). In this new era of molecular pathology, as we move towards our common goal of personalized medicine, patients, prostate cancer scientists, oncologists and clinicians face the challenges of:
1. Identifying and validating new markers;
2. Integrating these biomarkers into clinical practice
3. Identifying mechanisms to pay for challenges 1 and 2 in an ACO (Accountable Care Organization)-world. Setting the stage with the new paradigm of molecular pathology and the challenges we face in reaching our goals, Dr. Holden invited the three speakers to present their take from the viewpoint of 1. a medical oncologist developing diagnostic tests in industry, Steve Shak, MD 2. a urologic oncologist, Joel Nelson, MD and 3. a research-based molecular pathologist, Angelo De Marzo, MD PhD.

Dr. Steve Shak, the Chief Medical Officer of the predictive diagnostics company GenomicHealth outlined the principles for the successful identification of good biomarkers for prostate cancer diagnosis, prognosis and treatment:

1. Delivering what patients, physicians, regulators, and payers need
    a) Most importantly, tests must be "*Fit for Purpose*" with evidence relevant to that specific purpose - ACTIONABLE
    b) Consistent results across multiple well-designed studies
    c) Test must be shown to have value beyond traditional measures
2. Technical innovation brought to *standardized implementation*
3. Requires *collaboration*, and the skills, processes, and resources to do it right.

He suggests that the roadmap to clinical utility should involve the following steps:

1. Define the purpose
2. Technical feasibility
3. Development studies
4. Analytical methods finalization
5. Analytical methods validation
6. Clinical validation studies, including comparative effectiveness

7. Treatment decision studies
8. Health economic analysis

Dr. Joel Nelson, from the University of Pittsburgh School of Medicine presented a urologist's view of molecular pathology as it affects the diagnosis and prognosis of his patients. Citing Dr. Willet Whitmore's famous quote 'Is cure possible? Is cure necessary? Is cure possible only when it is not necessary?' Dr. Nelson said that a clinically relevant biomarker should influence a clinical decision and if it is difficult to make a decision, there should be no test. It is also important to understand that additional biomarker information usually does not make clinical decision-making easier because the next step in the clinic is often based on available therapies rather than on disease characteristics.

Dr. Angelo De Marzo from the Johns Hopkins University School of Medicine next presented a pathologist's opinion on the major challenges in the field today as 1. the availability of proper datasets, study designs and specimens to validate the analytical performance, reproducibility and clinical performance of novel molecular markers as applicable to patients. 2. The ability to determine the extent of improvement in clinical utility of these new tests for them to become a part of routine care. Dr. De Marzo remarked that we are soon approaching an age where patients will have 'apps' on their mobile phones that will make quick diagnoses and put patients in touch with their doctors.

Dr. Holden summarized the discussion by stating that it important for all prostate cancer scientists, pathologists, clinicians and oncologists to work collaboratively towards the identification and validation of new actionable biomarkers to make the process of prostate cancer diagnosis, prognosis and treatment easier and patient-centric.

Session 7

Modulation of Therapeutic Response by Tumor Adaptation to Target Inhibition

Introduction:

Cells sense and respond to their environment. When cancer cells are faced with an onslaught of drugs, they survive by adapting to the environment and switching on a different set of pro-survival genes that bypass the pathways inhibited by the drug. This emphasizes the need to understand tumor biology from the standpoint of secondary changes that may evolve in a cancer cell, when treated with medications. Recent studies have shown that these mechanisms of adaptation in a cancer cell operate by means of crosstalk between various signaling pathways such that inhibiting one node of a pathway sends out a signal to other pro-cancer pathways to ramp up production of other 'bad' genes. Therefore, it is critical to attenuate tumor adjustment to treatment by attacking all adaptive mechanisms at the same time, strongly stating the case for combination therapy.

Major Points from Session 7

- Signaling pathways in a cancer cell are interconnected such that inhibition of one activates the other.
- This reciprocal feedback regulation is seen between the two cell signaling pathways that are most often de-regulated in prostate cancer, PI3K/AKT and AR signaling, such that inhibiting AKT signaling, enhances AR activity and therefore prevents cancer cell death.
- These results explain the inability of PI3K/AKT inhibitors alone to achieve complete tumor regression.
- Combination therapy against both PI3K/AKT and AR signaling will be superior to single-agent therapeutics and is currently being tested in clinical trials.
- On the same logic, combined inhibition of both the PI3K-AKT-mTOR pathway and proteins called Receptor Tyrosine Kinases (RTKs) will have marked clinical efficacy.

Brett Carver, MD

Memorial Sloan-Kettering Cancer Center

Targeting Oncogenic Feedback Pathways in Prostate Cancer: Rationale Design of Combination Therapy

Funded by the Koch-PCF Young Investigator Award

What this means to patients: Drs. Neal Rosen and Brett Carver have identified cross-regulation in the two most commonly de-regulated oncogenic pathways (AR and PI3K signaling), such that inhibiting one activates the other pathway allowing tumor survival even in the presence of inhibitors. Their results strongly propose the case for combined therapy against both the pathways for effective treatment of prostate cancer.

Dr. Brett Carver first summarized the work of Dr. Neal Rosen. The main theme of Dr. Rosen's research is the fact that feedback regulation is a fundamental aspect of cellular signaling. These feedback mechanisms can be hijacked in a cancer cell to subvert cellular regulators resulting in cancer initiation and progression. Dr. Rosen's research has highlighted that in cancer, individual nodes of one signaling pathway can regulate the flow of information through another pathway. Therefore most effective therapy will require combinations of therapeutics that simultaneously inhibit multiple signaling pathways. Dr. Rosen's research shows that the commonly de-regulated cancer signaling pathway, PI3K-AKT-mTOR, feedback regulates the expression of proteins called RTKs (Receptor Tyrosine Kinases). Inhibiting AKT alone, increases RTK expression which has deleterious effects clinically. Dr. Rosen proposes that combined inhibition of both the PI3K-AKT-mTOR pathway and the RTKs will have marked clinical efficacy.

Dr. Carver then presented his work on the AR and PI3K signaling pathways whose activation and hyper-activity is very common in prostate cancer. Currently, several PI3K pathway inhibitors are in clinical development. Inhibitors of AR and PI3K signaling as single agents have not caused long-term and complete tumor regression in prostate cancer models. Dr. Carver's experiments in preclinical models and patient specimens revealed that inhibition of the PI3K pathway activated the AR signaling pathway. Thus cancer cells adapt to drug treatment by switching on alternate mechanisms of survival. Dr. Carver's findings provide a case for simultaneous, combined inhibition of both the PI3K and AR signaling pathways in prostate cancer. These two oncogenic pathways cross-regulate each other by reciprocal feedback, thereby coordinately supporting tumor survival and proliferation.

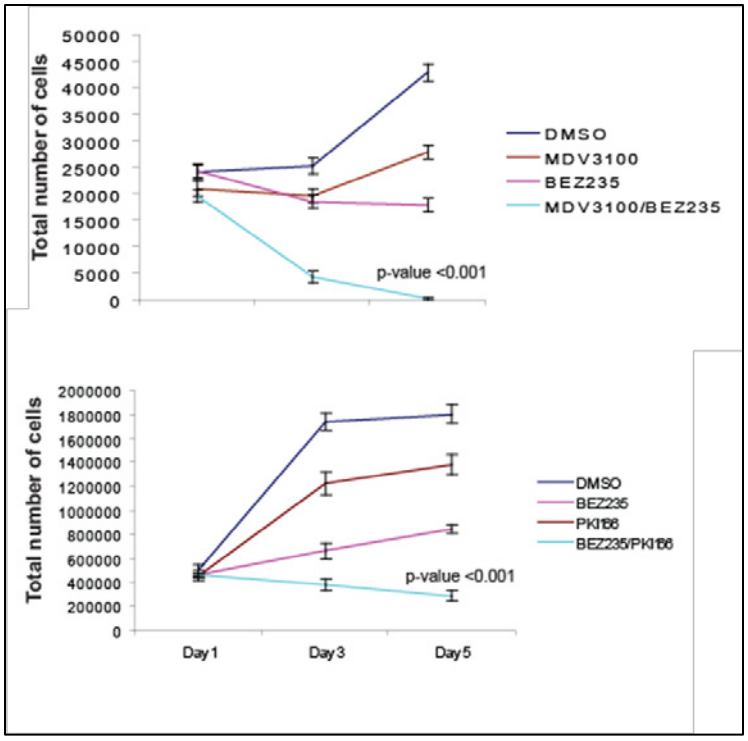


Figure 21: Results of the study evaluating combined inhibition of both the PI3K (BEZ235) and AR (MDV3100) signaling. Combination therapy (BEZ235+ MDV3100) produces profound tumor responses.

Dr. Carver validated his results by demonstrating that combinatorial inhibition of both PI3K and AR signaling produces profound tumor regression in mouse models (Figure 21). He is currently developing clinical trials to evaluate combined inhibition of both PI3K and AR signaling in prostate cancer patients. He is currently profiling 40 Genetically Engineered Mouse (GEM) models of advanced prostate cancer to evaluate both the primary events dysregulated in cancer as well as to identify secondary changes in a cancer cell that evolve over time as the cancer spreads. His preliminary results show that pathways altered in these GEM models are the same as the ones that eventually get de-regulated in advanced prostate cancer patients such as AR amplification.

David Mulholland, PhD

University of California, Los Angeles

Autonomous Role of PTEN in Regulating Castration Resistant Prostate Cancer Growth

What this means to patients: From their independent research, both Drs. Carver and Mulholland independently reached the same conclusions that combined inhibition of the AR and PI3K-AKT signaling pathways in castration-resistant prostate cancer patients

is essential to achieve tumor regression. Thus these results are thoroughly cross-validated.

After initial treatment with androgen-depletion therapy (ADT), most prostate cancer patients progress to a treatment-resistant stage with the cancer spreading, especially to bone in a process called metastasis. Metastatic prostate cancer is difficult to treat and is the chief cause of mortality due to the disease. Therefore for the design of new medications targeting metastases, it is essential to understand the underlying mechanisms by which the tumor cells develop resistance to medication. Dr. David Mulholland has shown that cancer cells adapt very rapidly to targeted drug therapy by switching on alternate pathways for survival. His results demonstrate that inhibition of the Androgen Receptor (AR) pathway activates the PI3K/AKT pathway, two complex cell signaling engines, which allow prostate cancer cells to maintain proliferation (Figure 22). These data suggest that an optimal treatment strategy for metastatic prostate cancer will require a combination that simultaneously targets both the AR and PI3K/AKT pathways. These results provide useful insight for the design of new treatment approaches by preventing the crosstalk between two malfunctioning pathways in the cancer cell.

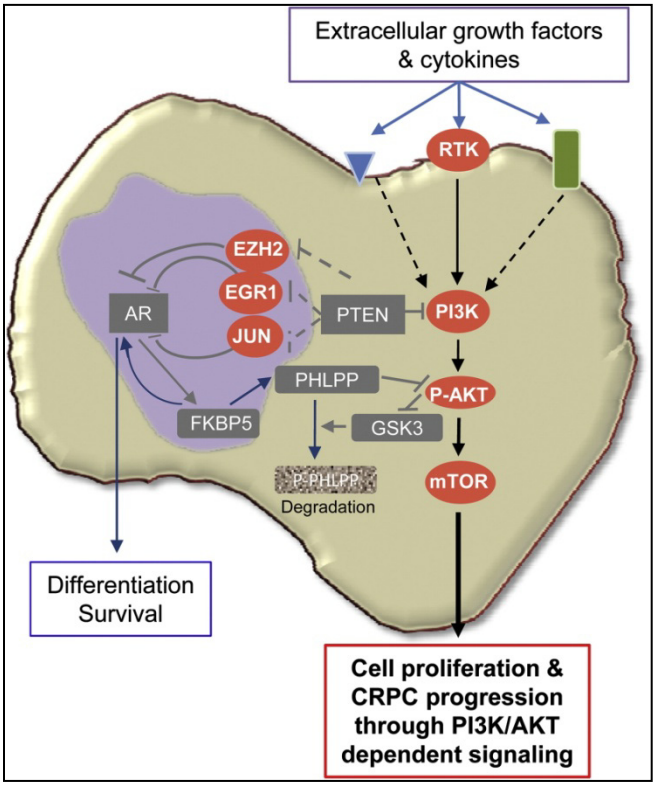


Figure 22: The two important cell signaling pathways PI3K-AKT-mTOR and AR that cross-regulate each other allowing cancer cell survival and proliferation. Therefore, inhibiting one pathway alone is insufficient for effective therapy.

Special Lecture: Prostate Cancer Medical Oncology Clinic in 2025

Howard Scher, MD
Memorial Sloan-Kettering Cancer Center

Funded by the PCF-DoD Therapy Consortium

Dr. Scher described eight significant milestones in prostate cancer research and treatment since 1971 when President Nixon first declared the war on cancer as follows:

1. **December 23, 1971**: Senate Bill 1928: Nixon Declares War on Cancer: The Congress **finds and declares** that . . . to provide the **most effective attack on cancer** . . . use **all** of the biomedical resources of the National Institutes of Health.
2. **October, 1991:** NCI SPORE (Specialized Program of Research Excellence): Translational medicine from concept to practice is important.
3. **November 5, 1993:** CaPCURE launch in The U.S. Senate: Clarification of purpose using business paradigms.
4. **February, 2004:** Docetaxel prolongs life: the first cytotoxic drug to demonstrate a survival benefit was FDA-approved.
5. **March 3, 2005:** FDA Oncology Drug Advisory Committee (ODAC) on Prostate Cancer Clinical Trial Endpoints.
6. **November 2005:** Launch of the Department of Defense and Prostate Cancer Foundation Prostate Cancer Clinical Trials Consortium: Enabling infrastructure to support collaboration: Opened 100 protocols, 2900+ men on Phase I/II trials and helped advance 8 products to Phase III.
7. **March 2008:** Prostate Cancer Working Group 2 Guidelines for Clinical Trial Conduct in CRPC published in the Journal of Clinical Oncology: aligned clinical research with clinical practice.
8. **May, 2010:** In a face-to-face meeting, with an objective to accelerate drug approvals, the Veridex Circulating Tumor Cell Assay enters a formal qualification effort with the United States Food and Drug Administration as a surrogate biomarker for survival.

Dr. Scher stated that despite having the best generation of investigators in history working in PCa research, producing excellent results that are translatable to the clinic, the field still faces significant challenges due to the following:

- Technology development and drug development takes time. Will the “market” accept these timelines and invest for the “long haul”?
- We are drowning in information, but often don’t have the “right” information at the right time to make the best decisions.
- Bureaucracy is increasing to the point where much of the time spent by Laboratory and Clinical Researchers and Clinicians is not “value added” either for our patients or for our programs.

- Our interactions with payers are often not “collaborative”.
- Pharmaceutical Companies have downsized their research programs, in preference for in licensing, limiting collaboration.
- Preclinical “packages” on which development decisions are made are often “thin”.
- Venture capital has been sitting on the sidelines: this will impact drug availability downstream.

How well we succeed will depend on both the level of investment in research and the level of scientific/medical progress. Importantly, long term investment in basic research has already led to the identification of new aspects of the malignant process that if successfully targeted, can provide significant benefit to patients.

Dr. Scher pointed out that the prostate cancer medical oncology clinic in 2025 will be dramatically different and more patient-centric: diagnoses will be more precise and treatment more patient tumor specific. He suggested that this will require continued investment in discovery, technology and human capital. It is important that we continue to make major breakthroughs in the diagnosis and treatment of cancer.

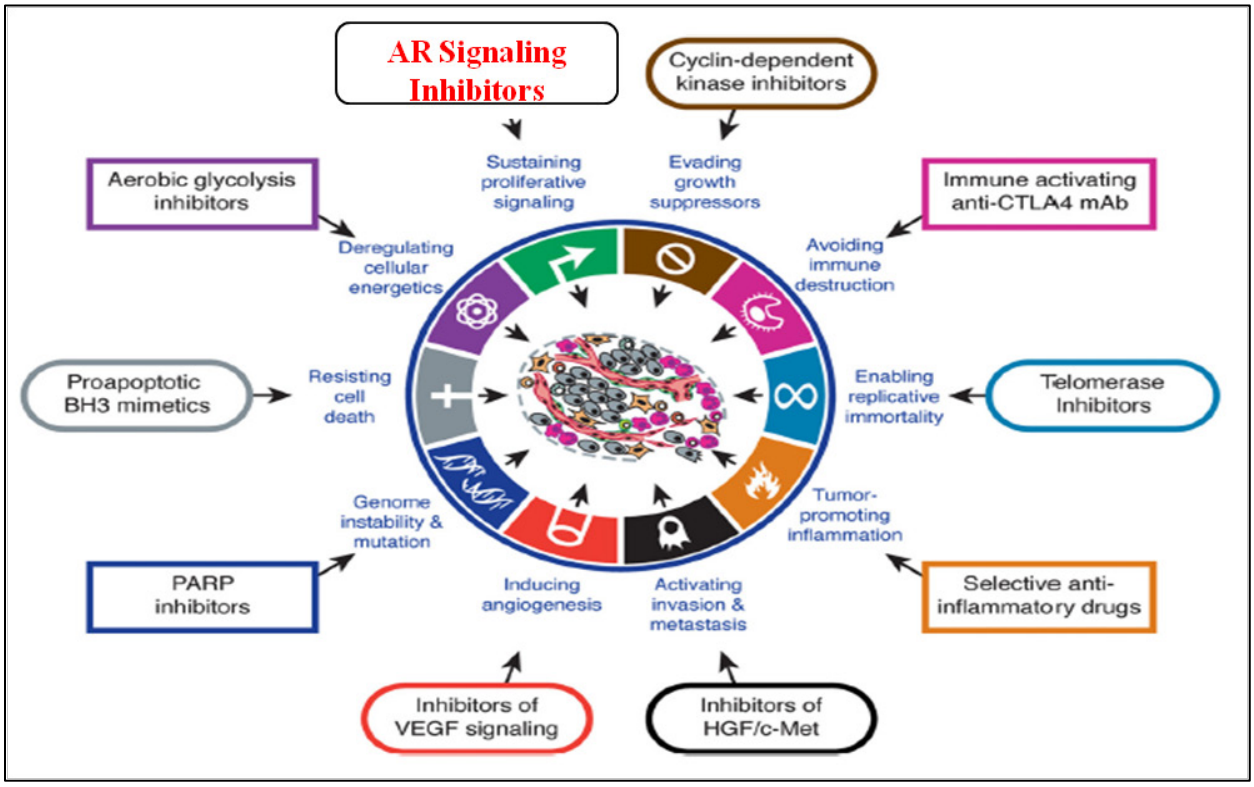


Figure 23: The currently available classes of medications against the various networks and cellular signaling pathways that get de-regulated in prostate cancer (Modified from Hanahan and Weinberg, Cell 144:646, 2011).

Session 8

PARP in Prostate Cancer

Introduction:
A normal cell has several mechanisms to repair DNA damage as it prefers error-free DNA to be passed on its daughter cells. Mutations accumulate in a cell when the DNA repair machinery starts malfunctioning, leading to the onset of cancer.

Cancerous cells divide and replicate much faster than neighboring healthy cells. For their fast proliferation, these cells require efficient DNA repair. Therefore, cancer cells face a paradox in which the very mechanism that leads to their genesis (inefficient DNA repair) is also critical for their proliferation. Cancer cells respond to this situation by becoming crucially dependent on DNA repair pathways that are different from the one that originally led to the initiation of cancer. One of the examples of this cancer cell addiction is seen in breast and ovarian cancer cells which result, in a majority cases, due to mutations in two very crucial DNA break-repair proteins, BRCA1 and BRCA2. Cancer cells with mutated BRCA1 and BRCA2 become dependent upon the other DNA repair enzyme PARP (Poly-(ADP-Ribose) Polymerase) for repairing any DNA damage that occurs when the tumor cells rapidly divide and replicate. Therefore, breast and ovarian cancer cells are 'addicted' to PARP and therapeutic PARP-inhibition causes the accumulation of several breaks in DNA, eventually leading to cancer cell death.

PARP-inhibition is based on the concept of synthetic lethality, which involves blocking a compensatory mechanism a cell starts relying upon, when the chief pathway is paralyzed. Synthetic lethality is one of the most exciting and new concepts in recent drug development strategies.

Major Points from Session 8:

- PARP inhibitors show promise in the treatment of triple negative breast cancer patients.
- *TMPRSS2-ERG* gene fusions are found in almost 50% prostate cancer patients. ERG recruits PARP1 to cancer cell DNA.
- The presence of PARP1 on tumor DNA makes these cancer cells resistant to radiation therapy (RT).
- PARP1 inhibitors re-sensitize cells to RT. Adding PARP inhibitors to the standard treatment regimen of ADT and RT has shown dramatic reduction of tumor growth and is currently being tested in a Phase I/II trial.
- A Phase I trial is currently testing PARP inhibitors in combination with abiraterone in mCRPC patients.
- PARP not only plays a major role in DNA repair, it also promotes the activity of AR. Therefore inhibiting PARP has a dual effect of impairing DNA damage repair

along with blocking AR signaling. Thus PARP inhibitors should be added to treatment modalities that employ AR-targeted therapies.

- Therefore, PARP plays several critical roles in prostate cancer: one, it rapidly repairs DNA damage to allow cancer cell replication and proliferation; two, by enhancing the activity of two major pro-cancer proteins ERG and AR, PARP spurs tumor invasiveness and progression, and three, PARP makes cancer cells resistant to radiation therapy. Thus inhibiting PARP will have a multi-pronged effect on cancer cells and its addition to therapeutic regimens will promote tumor regression.

Mark Robson, MD

Memorial Sloan-Kettering Cancer Center

Clinical Development of PARP Inhibitors in Breast Cancer: Opportunities and Challenges

What this means for patients: PARP inhibitors are rational therapeutics for aggressive prostate and breast cancers.

PARPs (Poly- (ADP-ribose) Polymerases) are a family of proteins that perform several important functions in the cell. PARPs 1-3 are involved in DNA damage repair. As described above, employing the concept of synthetic lethality, PARP inhibition is a rational therapeutic for breast and ovarian cancer patients that carry mutations in the genes for the other DNA repair proteins, BRCA1 and BRCA2. This is because *BRCA1-BRCA2* mutated cancers completely lose their ability to repair DNA damage upon inhibiting PARP1, which eventually leads to cancer cell death. PARP inhibition is not toxic to healthy cells because these cells have active DNA repair machinery that can take over in the absence of PARP repair mechanisms. Therefore PARP inhibition enables targeted killing of cancerous cells alone. Dr. Robson presented an overview of the use of PARP inhibitors currently under development for the treatment of breast cancer. The following is a list of agents that are currently being evaluated by various pharmaceutical companies for breast cancer treatment:

Agent	(Pharma)	Phase
Iniparib	(Sanofi-Aventis)	III
Olaparib	(Astra-Zeneca)	II/III
Veliparib	(Abbott)	II
PF-01367338	(Clovis)	I/II
MK-4827	(Merck)	I
CEP-9722	(Cephalon)	I
BMN-6703	(BioMarin)	I

Triple negative breast cancer (TNBC) is a very aggressive subtype of breast cancer that responds poorly to standard therapy and is usually associated with poor prognosis. Dr.

Robson showed that approximately 80% patients carrying a mutation in their *BRCA1* gene have the triple-negative variety of breast cancer. TNNBC is hypothesized to be associated with inherent defects in DNA repair, making these cancers a rational target for PARP inhibitor therapy. Dr. Robson presented the results of a Phase II clinical trial that tested adding the small-molecule PARP inhibitor, iniparib to chemotherapy for the treatment of 123 metastatic TNBC patients. Iniparib improved overall response from 32% (with chemotherapy alone) to 52% (with iniparib+chemo) and an increased overall survival to 11.8 months as against 11.1 months. Unfortunately, during ASCO 2011, Sanofi-Aventis announced that the Phase III trial of iniparib in mTNBC patients had failed to meet its primary end points of overall survival and progression-free survival. Dr. Robson suggested that the reasons for the failure of PARP inhibitor therapy may be the reversion of BRCA mutation; the loss of proteins such as 53BP1 (p53-Binding Protein 1); or the overexpression of P-GlycoProtein (PGP) which plays important roles in DNA repair.

Felix Feng, MD

University of Michigan

PARP1 Inhibitors as a Strategy for Targeting Radiosensitization of ETS-Positive Prostate Cancers

Funded by the Rahr-PCF Young Investigator Award

What this means to patients: Approximately half of all prostate cancers harbor ETS gene rearrangements, which are typically fusions between an androgen-driven gene, such as *TMPRSS2*, and a gene encoding the protein ERG. These ETS fusions cause androgen-driven overexpression of ERG, resulting in elevations of ERG levels. ERG is a protein that turns on many other pro-cancer genes. Recently, Dr. Feng and his team have discovered that overexpression of ERG causes treatment resistance in preclinical models of prostate cancer.

Currently, very little is known about the proteins ERG interacts with, to effect its pro-cancer activity. In collaboration with Dr. Arul Chinnaiyan, Dr. Feng and his team have discovered that ERG binds to the DNA-repair protein PARP1 and increases its activity. Radiation therapy damages DNA, however, ERG-induced PARP1 over-activity repairs DNA damage, resulting in radiation resistance. This radio-resistance can be reversed with inhibition of PARP1 (Figure 24). Therefore, therapeutically targeting ETS gene fusions in prostate cancer may benefit a large subset of prostate cancer patients. PCF Young Investigator Dr. Felix Feng is testing the efficacy of targeting these gene fusions with PARP1 inhibitors, both in localized prostate cancer and in metastatic disease.

Dr. Feng is currently investigating whether PARP1 inhibition can increase the efficacy of radiation therapy in patients with high-risk localized prostate cancer. In a planned phase I/II trial, Dr. Feng and colleagues will investigate the effects of adding a PARP1 inhibitor to the standard therapy of radiation therapy and androgen deprivation therapy (bicalutamide and lupron) for this patient population.

Working with Dr. Maha Hussain and others, Dr. Feng will also evaluate the benefit of PARP1 inhibitors in patients with metastatic castration-resistant prostate cancer, in a Phase II trial. This trial will evaluate the benefits of administering abiraterone with or without PARP inhibitors to two sets of patients; one, positive for ETS gene fusions and two, those who do not have ETS gene fusions. The primary objective of this study is to evaluate whether the addition of PARP1-targeted therapy is superior to abiraterone alone, based on the fusion status of these patients.

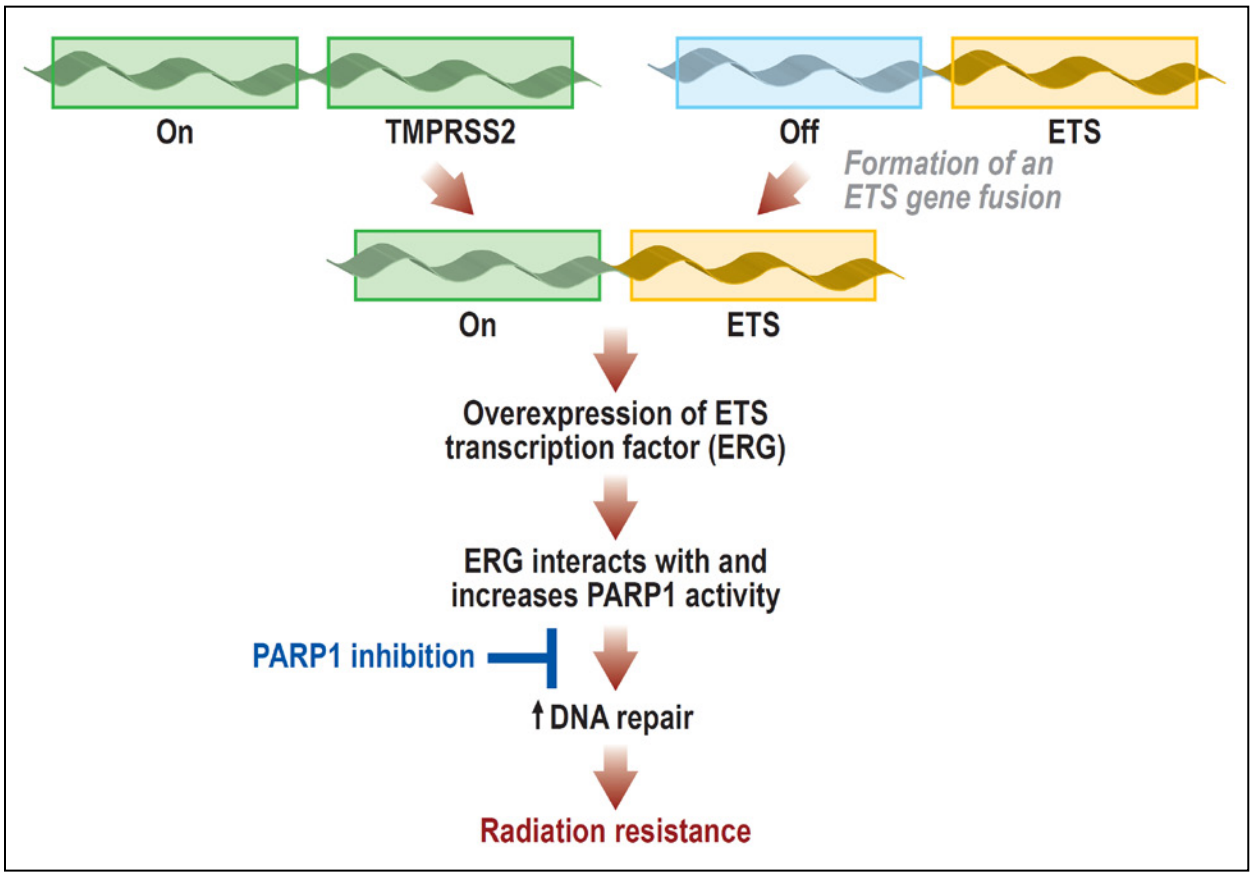


Figure 24: The protein ERG is overexpressed in cancers containing the TMPRSS2-ERG fusions. ERG binds to and increases the activity of PARP1. Efficient repair by PARP1 allows these cancers to gain resistance to radiation and potentially chemotherapy. PARP inhibitors stop this process and may be efficient therapeutics for both localized and metastatic prostate cancer.

Karen Knudsen, PhD

Thomas Jefferson University

Leveraging the Dual Functions of PARP1 in Controlling AR and DNA Repair to Improve Prostate Cancer Management

What this means to patients: Combination therapy with PARP inhibitors and AR-directed therapeutics holds potential for treating both primary and advanced prostate cancer.

A chief driving factor of prostate cancer progression is the overexpression of AR and its elevated signaling activity that drives the expression of pro-cancer genes. Dr. Karen Knudsen is working on the interaction of the DNA repair protein, PARP1 with AR. Her findings show that the activity of PARP1 is enhanced in advanced prostate cancer and it is recruited to sites of AR function. PARP1 is required for AR activity, both in hormone-dependent as well as castration-resistant disease. Inhibiting PARP results in a sharp decline in the expression of genes that are activated by AR such as PSA, TMPRSS2, FKBP5 etc.

When used as single agent therapeutics, PARP inhibitors sensitize cancer cells to other forms of stress. Administering PARP inhibitors in combination with other AR-directed therapies inhibits prostate tumor proliferation in both early and late stage (castrate-resistant) PCa. Thus PARP inhibition has dual effects on cancer cells; one, its inhibition impairs DNA repair in the tumor and two, it suppresses AR signaling, halting cancer progression. Therefore, combining PARP inhibitors with existing therapeutics will improve the response to therapeutic intervention and may serve as a means to prevent disease progression (Figure 25).

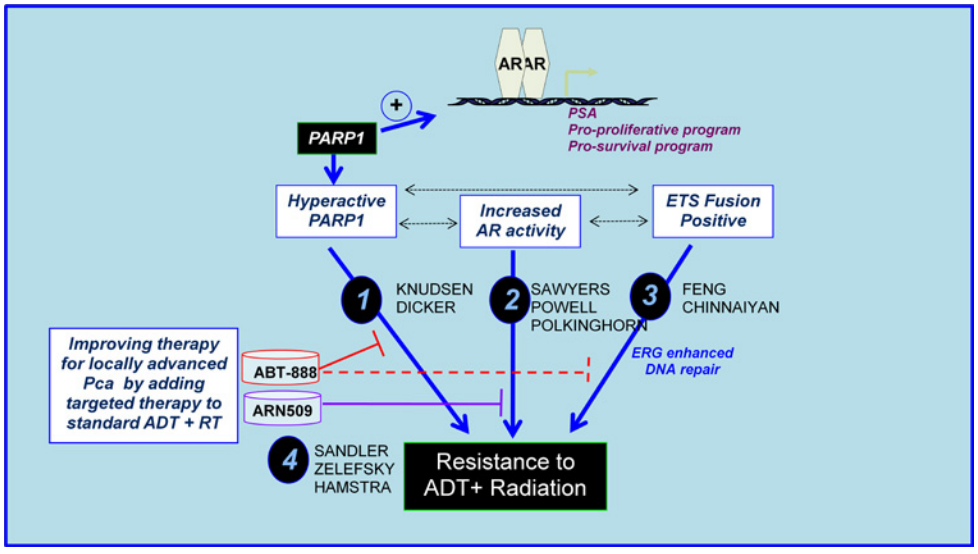


Figure 25: This schema shows the various research groups involved in studying the role of PARP1 in prostate cancer. Dr. Karen Knudsen has shown that PARP1 is recruited

to the sites of AR activity and activates the pro-survival and pro-proliferative programs in PCa. Drs. Feng and Chinnaiyan are studying the role of PARP1 in DNA repair in prostate cancer cells. Thus, adding PARP1 inhibitors to ADT+RT combination therapeutic regimens will improve prostate cancer treatment.

Session 9

Clinical and Biological Update: Status and Plans for Cabozantinib

Introduction:
The medication cabozantinib is known to inhibit a family of proteins called Receptor Tyrosine Kinases (RTKs). The most potent effects of cabozantinib action are seen on the activity of the RTKs, MET and VEGF. Cabozantinib causes tumor regression in bone and soft tissue in patients with advanced PCa. PCF is funding several grants around further research that will take this experimental medication to the clinic.

Major points from Session 9:

- Phase II trials of cabozantinib (in patients with melanoma, non-small cell lung cancer, breast, gastric, ovarian, pancreatic or prostate cancer) show significant reduction in tumors present in bone and soft tissue.
- These results are unique in that monotherapy with cabozantinib shows almost complete tumor regression, unlike any other medication in the past (apart from AR-targeted therapies).
- Continued treatment with cabozantinib is important for sustained cancer remission.
- Phase III trials evaluating cabozantinib dose, patient pain response and patient survival are currently ongoing to evaluate the effectiveness of this medication.
- Preliminary results show that cabozantinib is active at lower doses (20 and 40mg) than were used in the previous trial (100mg).
- Cabozantinib inhibits several RTKs such as MET, VEGF, c-KIT etc.
- No other RTK inhibitor has shown as dramatic an anti-cancer activity as cabozantinib.
- This medication has activity against both, cancer cells as well as their microenvironment.

Matthew Smith, MD, PhD
Massachusetts General Hospital Cancer Center
Clinical Evaluation of Cabozantinib in Metastatic CRPC

What this means for patients: Cabozantinib (XL184) has shown dramatic shrinkage of cancerous lesions in the bone and soft tissues in a Phase II trial in metastatic CRPC

patients. Cabozantinib shows potential as an important new addition to advanced prostate cancer chemotherapeutic regimens.

Dr. Smith presented Phase II trial results of the medication cabozantinib in patients with several types of solid tumors, such ovarian, liver and prostate cancer. These results showed that cabozantinib shrank tumors and halted bone metastases. This clinical trial conducted in 483 patients, employed a unique design called randomized discontinuation: all patients were administered cabozantinib (100 mg) for 12 weeks, after which patients not responding to therapy were removed from the trial (Figure 26). Patients who responded to cabozantinib therapy were then randomly assigned to two groups, one receiving the medication and the other receiving placebo. This trial methodology was adopted to assess the actual effects of cabozantinib in stabilizing disease.

Of these 483 total patients, 171 were men with mCRPC, all of who had measurable disease. Cabozantinib treatment resulted in a significant reduction in both, bone pain (70% patients) and narcotic pain medication use (56% patients), with a concomitant reduction in soft tissue lesions with 74% patients demonstrating evidence of tumor regression. 85% of men had improvement in bone metastases as assessed by bone scans and this improvement bone scans correlated directly with clinical effects of the medication. In the patients assigned to the placebo after week 12, bone scans promptly worsened demonstrating that continued treatment with cabozantinib is important for disease control. Re-treatment with cabozantinib to these patients resulted in prompt reduction in bone lesions (Figure 27).

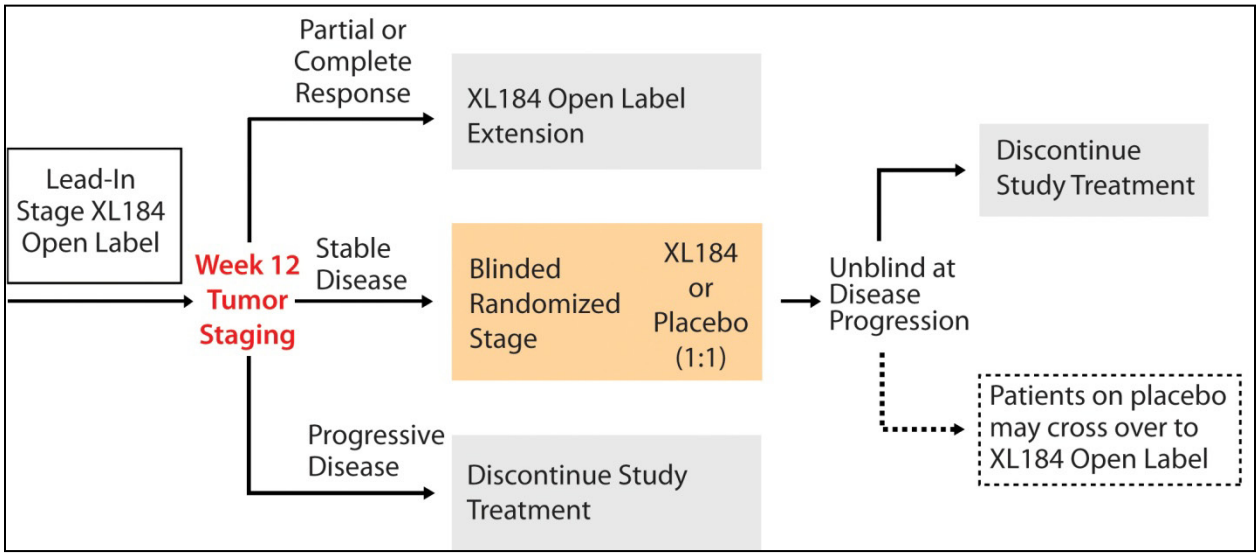


Figure 26: The randomized discontinuation protocol adopted in the Phase II trial that evaluated the efficacy of cabozantinib in patients with melanoma, non-small cell lung cancer, breast, gastric, ovarian, pancreatic or prostate cancer.

Dr. Smith emphasized that the strategy of randomized discontinuation at week 12 for cabozantinib complicates the interpretation of RECIST response and other efficacy assessments. He is currently conducting a non-randomized extension study of the previous trial in mCRPC patients in which all patients will be administered cabozantinib continuously, with the primary end-point of this trial being bone scan response. Dr. Smith also presented his preliminary results from Cabozantinib-Dose Finding Study he is currently involved in, which is evaluating the effects of 3 lower doses of cabozantinib (20 mg, 40 mg, 60 mg) in mCRPC patients, with 11 patients in each cohort. In preliminary results of the first cohort (40 mg daily), 10/11 patients had a bone scan response (>30% decrease in bone lesion area by bone scan) and two patients had resolution of bone disease. These preliminary results suggest that cabozantinib is active at lower doses (40 mg daily) than the ones used in the original trial (100 mg).

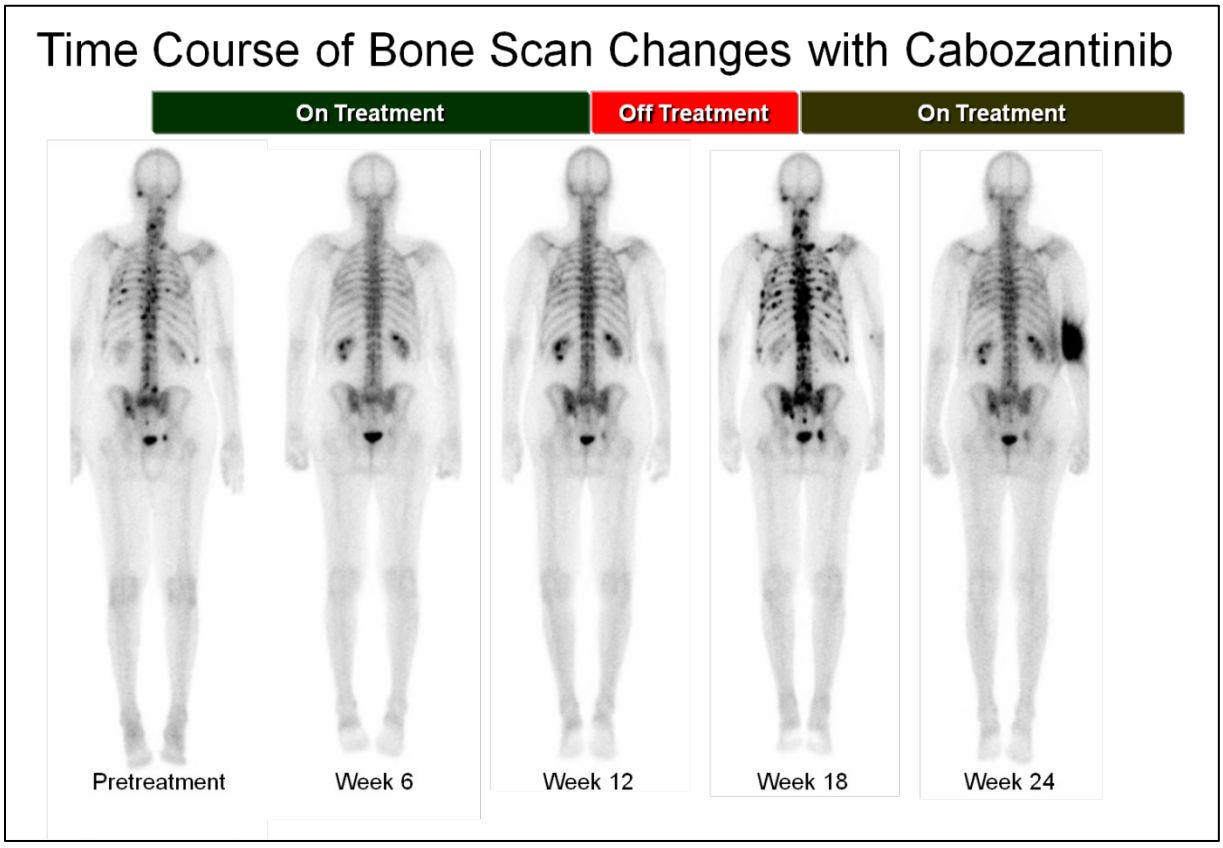


Figure 27: The effects of the oral experimental medication, cabozantinib (XL184) in prostate cancer patients (at a dose of 100mg) evaluated by bone scans in a Phase II trial. Cabozantinib causes dramatic reduction of tumors in the bone. Patients assigned to placebo in the randomized discontinuation protocol of the trial (discussed in Figure 26), after 12 weeks on cabozantinib show an increase in tumors, which is again abrogated when patients are re-treated.

Dr. Smith also detailed plans for two Phase III trials planned for 2012 and beyond, to evaluate effects of cabozantinib on pain and survival in men with mCRPC.

Phillip Febbo, MD

University of California, San Francisco

Taking a Treatment Science Approach to Understanding Cabozatinib's Mechanism of Action in Men with CRPC

Dr. Phillip Febbo from UCSF presented an overview of our current understanding of cabozantinib mechanism of action. In his presentation at the Retreat, Dr. Febbo described how, apart from AR-targeting therapies, no medication has shown significant inhibition of signaling pathways when administered alone. A remarkable exception to these observations is the activity of cabozantinib (XL184) whose Phase II monotherapy trial results have shown dramatic tumor regression. While XL184 is known to target a family of proteins called the Receptor Tyrosine Kinases, (RTKs) including MET and VEGFR2, the exact mechanism of action of this drug is still not completely understood.

Dr. Febbo suggested that applying a treatment science approach to such novel therapies like XL184 will help us understand their underlying mechanism of action. It is important to understand how a drug works for several reasons, such as for deciding appropriate dosage of the medication, designing suitable combination therapies to further extend disease response, etc. Dr. Febbo presented a brief overview of all the proposed targets of XL184 and their roles in prostate cancer progression. Two chief RTKs targeted by XL184 are MET and VEGFR2. MET expression increases as cancer progresses and this protein promotes proliferation, invasion and metastasis. The expression of VEGF and its receptor including, VEGFR2 are elevated in mCRPC compared to localized PCa and these elevated levels correlate with poor prognosis of the disease and bone metastasis. VEGF has been proposed to play a crucial role in cancer 'homing' to the bone and VEGFR2 is one of the chief targets of XL184. However, VEGFR2 inhibition alone does not result in as dramatic improvement in overall survival as that seen with XL184 (Figure 28). Another one of the several targets of cabozantinib is c-KIT that is known to be activated in several types of cancer. While activating mutations of c-KIT have not been found in prostate cancer, c-KIT expression is correlated with disease recurrence in high-risk localized PCa cases as well as tumor bone metastases.

Dr. Febbo detailed the pharmacodynamic and biomarker changes associated with XL184 treatment. Pharmacodynamic evidence suggests inhibition of MET and downstream signaling through the PI3K and MAPK pathways. While there is some evidence that XL184 may be selectively active in mCRPC due to interactions with the Androgen Receptor (AR) and the AR-driven expression of TMPRSS2, there is no consistent association between XL184 treatment, clinical response and PSA response suggesting that the mechanism of XL184 action is not directly through inhibition of the AR.

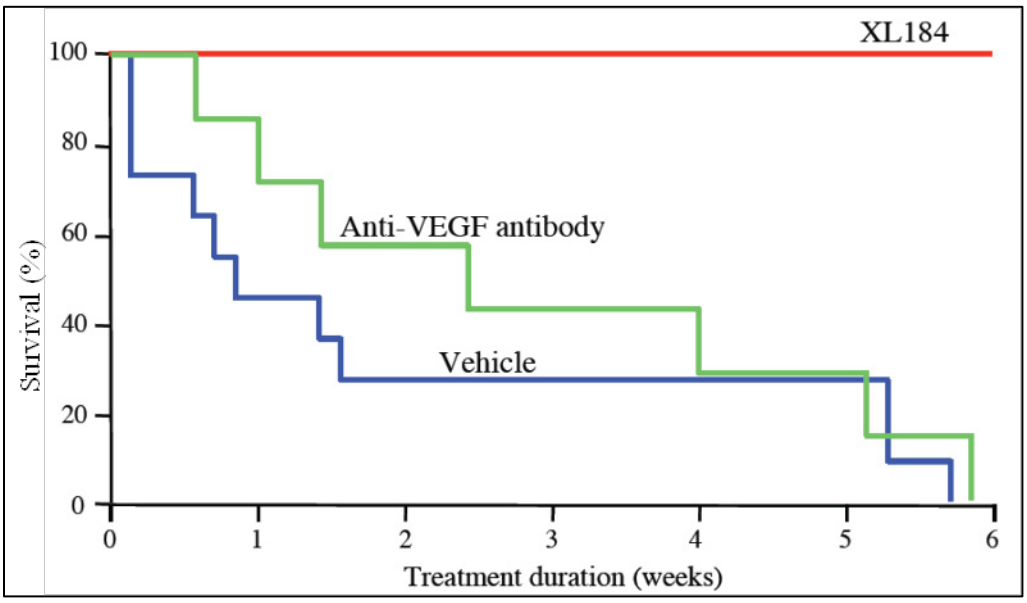


Figure 28: Kaplan-Meier curves demonstrating the improvement in overall survival upon the administration of a VEGF inhibitor alone (anti-VEGF antibody) or XL184 in a mouse neuroendocrine tumor model system. The differences in the effects on overall survival of both medications imply XL184 targets other receptor tyrosine kinases as well.

Dr. Febbo also summarized recent findings from several groups that show that XL184 may impact the tumor microenvironment in addition to its activity against the mCRPC cells. A frequent decline in CTC count associated with XL184 administration is potentially because of an anti-tumor impact of the therapy, as well as a likely direct impact on the bone microenvironment. Dr. Febbo presented an overview of past clinical trials of agents that inhibit some of the same targets as XL184, e.g. sunitinib which inhibits VEGF/RET/KIT. Sunitinib showed a bone scan improvement in only 7 patients among 27 on the trial while cabozantinib shows a 53/62 response.

Taken together, Dr. Febbo suggests that XL184 is the first example of an effective medication that targets multiple pathways in mCRPC. The fact that one drug inhibits more than one pathway, and that combinatorial inhibition is effective is a fortuitous event that we need to leverage to improve our understanding of prostate cancer and the treatment of men with this disease.

Session 10

Bioinformatics for Discovery

Randall Millikan, MD, PhD
The University of Texas MD Anderson Cancer Center

Prometheus: A Novel Discovery Platform

What this means to patients: Prometheus is a computational oncology diagnostic platform, designed to predict appropriate therapy for patients depending on their tumor profile, effective treatment combinations and potential patient response to therapy. This will not only aid research by predicting previously unknown connections but will have translational significance in the clinic.

Prometheus is a browse-and-query interface for doing research as well as a mechanism of informing therapeutics by integrating clinical, translational and basic science observations in one place. Dr. Millikan and his team at MD Anderson have designed this oncology diagnostic platform that allows comprehensive analysis of a patient's tumor, patient stratification, and the efficacy predictability of not only individual targeted cancer therapeutics, but also of most effective treatment combinations (Figure 29). This platform has the ability to measure the expression and activation of specific cancer pathways with high levels of sensitivity and specificity via tissue or blood samples. This technology has the potential to be used not only in the development process to select drugs and evaluate their efficacy, but also, in the clinical setting, to enable real-time patient tumor profiling, monitor drug effectiveness, and direct the use of a growing number of targeted therapies.

This new technology applies the principles of personalized medicine to the diagnosis and treatment of cancer. By integrating therapeutics and diagnostics, this platform may provide comprehensive solutions to treat cancer.

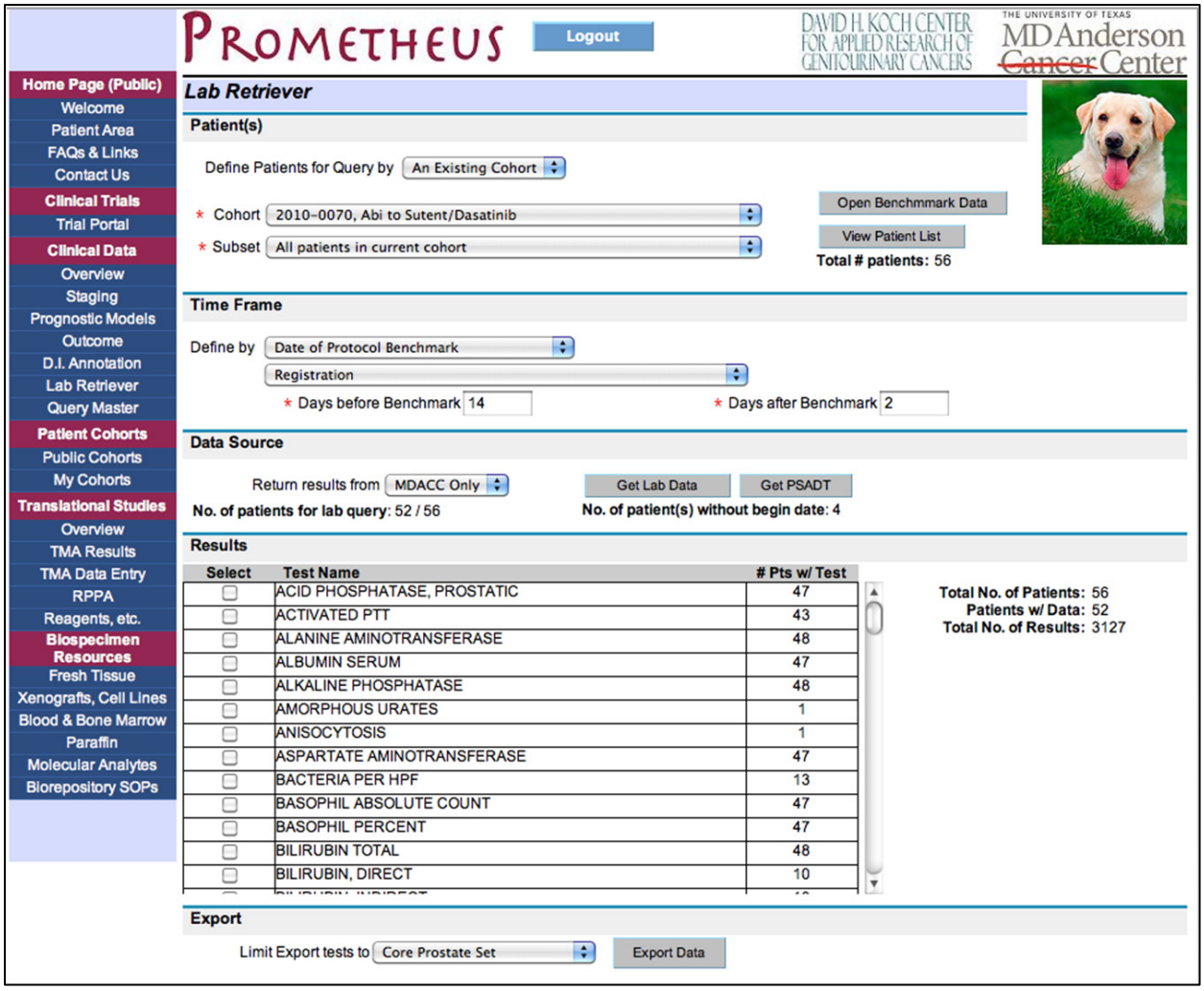


Figure 29: A snapshot of the Prometheus interface.

Session 11: Young Investigators #2

Himisha Beltran, MD

Weill Cornell Medical College

Molecular Characterization of Neuroendocrine Prostate Cancer

Funded by the LeFrak-PCF Young Investigator Award

What this means to patients: Aurora Kinase A is a novel target for a very aggressive subtype of prostate cancers called the neuroendocrine prostate cancers. Dr. Beltran is planning to an inhibitor against this protein in current Phase I/II trials for the treatment of mCRPC and NEPC patients.

A normal prostate gland has a subset of cells called the neuroendocrine cells that regulate growth, differentiation and hormone secretory function of the prostate gland. When cancer develops in the gland, tumors may have a few neuroendocrine cells. Cancers that have high numbers of these neuroendocrine cells are very aggressive with a very poor survival rate of less than a year from diagnosis. These **N**euro**E**ndocrine **P**rostate **C**ancers (NEPC) do not produce AR and are therefore not targetable by standard therapies. These cancers also do not produce PSA and therefore, detection and monitoring disease progression is difficult.

Dr. Beltran is studying the development of this aggressive NEPC subset of prostate cancer. In a search for targetable agents expressed in these cancers, Dr. Beltran identified 27 proteins that are overexpressed in NEPC and not in other types of PCa. Of these, she presented her results on Aurora Kinase A at the PCF Retreat. Aurora Kinase A is implicated in cell division processes, its function being integral to cell proliferation. It has previously been shown to be overexpressed in several cancer types. Another protein that Dr. Beltran identified in NEPC is N-MYC which has previously never been linked to prostate cancer. Inserting N-MYC into prostate cancer cells transforms these normal cells to neuroendocrine prostate cancer tumors. This induction of very aggressive prostate cancer is mediated by the interaction between N-MYC and Aurora Kinase A (Figure 30).

Dr. Beltran's experiments have motivated her team to advance an Aurora Kinase A inhibitor into the clinic as a novel drug target for NEPC. She is currently conducting Phase I/II trials of the Aurora Kinase A inhibitor, MLN8237 in combination with Carboplatin in mCRPC and NEPC patients.

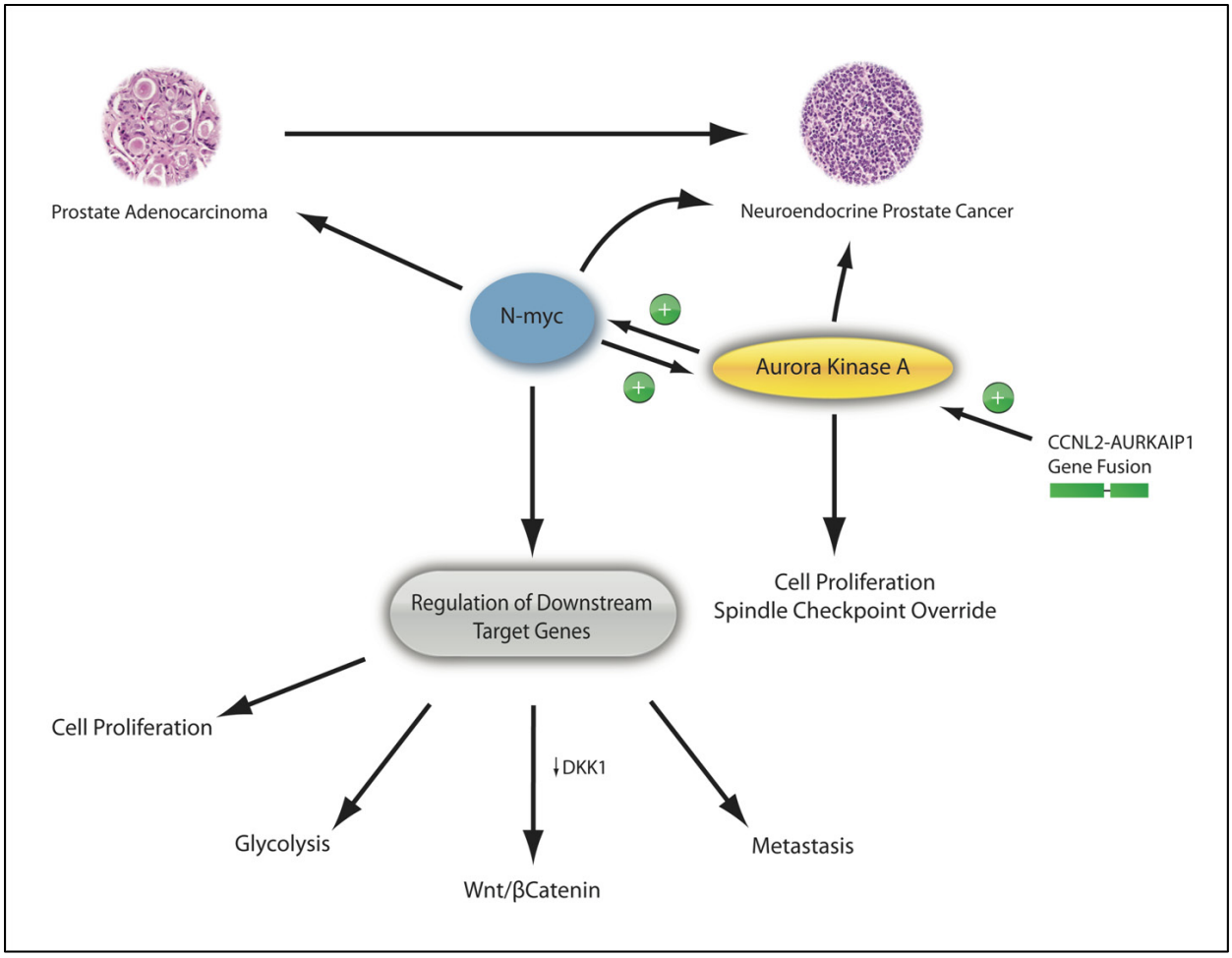


Figure 30: The proteins N-MYC and Aurora Kinase A cooperate and lead to the development of the very aggressive subset of PCa, NeuroEndocrine Prostate Cancer (NEPC).

Eleni Efstathiou, MD, PhD

The University of Texas MD Anderson Cancer Center

Mapping the Complexities of Androgen Signaling in Prostate Cancer Progression

Funded by the GenProbe-PCF Young Investigator Award

What this means to patients: Dr. Efstathiou's research improves our understanding of the modulation in androgen signaling over time and under the influence of therapy in prostate cancer. These findings will identify potential mechanisms of resistance that will be prioritized for further study. The findings will also lay the foundation for the optimal sequencing or combination of agents to inhibit androgen signaling, thereby pushing prostate cancer therapy development.

The male hormones, androgens fuel prostate cancer. Androgens bind to their receptor, AR and this Androgen-AR complex activates pro-cancer genes. Therefore, the first line of treatment for prostate cancer is Androgen Ablation Therapy (ADT) which stops the synthesis of the androgens. Patients unfortunately develop resistance to therapy limiting its effectiveness. Cancer cells bypass androgen ablation by either synthesizing their own supply of androgens or by producing AR in large amounts. Dr. Efstathiou's findings suggest that the ADT resistance emerges because AR changes or is amplified to compensate for reduced androgen production. Her results also show that, in response to therapy, androgen synthesis is increased or altered when the AR is blocked. Thus, a reciprocal feedback loop is set in place whereby ADT depletes androgen reserves in the cancer cell, but the cells respond/compensate by either increasing the amounts of AR and/or increasing androgen levels. Dr. Efstathiou and her team found this reciprocal feedback loop to operate in patient samples. Therefore, these findings are immediately applicable.

Dr. Eleni Efstathiou is studying these mechanisms by which prostate cancer cells develop resistance to medication. She is studying the effects of the FDA-approved medication, Abiraterone and MDV 3100 on tumors in the bone. Abiraterone inhibits androgen synthesis by blocking the enzyme, CYP17 that converts cholesterol to testosterone. Dr. Efstathiou's research has shown that both abiraterone and MDV3100 modulate androgen signaling in bone metastatic prostate cancer tumors. In an initial clinical trial to test if the earlier administration of abiraterone will benefit patients, Dr. Efstathiou is testing the efficacy of Abiraterone+ADT or ADT alone in a randomized trial in 60 patients. Her results suggest early treatment with abiraterone+ MDV3100 may thwart the development of resistance in selected patients.

Hans Hammers, MD, PhD

Johns Hopkins Medicine

Towards Effective Angiogenesis Inhibition in Prostate Cancer

Funded by the Bikoff-PCF Young Investigator Award

What this means to patients: Targeting the growth factor VEGF is not an effective strategy for anti-prostate cancer therapy because prostatic tumors soon develop resistance. Dr. Hammers has identified that this resistance is due to cells called pericytes which his research has validated as new targets against PCa.

Blocking the supply of nutrients and oxygen to cancer cells is an effective strategy for tumor shrinkage. This has traditionally been carried out by inhibiting the growth factor VEGF that helps in laying down new blood vessels around tumors. Dr. Hammers' research shows that inhibiting VEGF is not effective against prostatic tumors. He has found certain cells called pericytes that when inhibited can kill cancer cells.

Of all treatment modalities for metastatic prostate cancer, the strategy that has consistently remained unsuccessful is the inhibition of angiogenesis by targeting the

growth factor, VEGF. Angiogenesis is the process of generation of new blood vessels. As a tumor grows in size, cells in the inner layers get progressively cut off of blood supply and therefore, nutrient and oxygen delivery. Therefore, tumors stimulate the laying down of new blood vessels that can provide these cells at the centre, a regular supply of nutrients. Angiogenesis is a key step during the transition of tumors to malignancy. Targeting this genesis of new vessels with inhibitors is a unique strategy to cut off nutrient and oxygen supply to cancer cells that can lead to tumor shrinkage. Most of the inhibitors of angiogenesis target the growth factors that support the synthesis of blood vessels at these sites of cancer lesions. One such growth factor is VEGF, Vascular Endothelial Growth Factor, whose expression increases in invasive cancers. VEGF expression in cancers correlates with a poor disease prognosis and low survival rates. Several inhibitors of VEGF action are currently under development, such as monoclonal antibodies (bevacizumab (Avastin)), and orally-available small molecules that inhibit the tyrosine kinases stimulated by VEGF: lapatinib (Tykerb), sunitinib (Sutent), sorafenib (Nexavar), axitinib, and pazopanib. However, none of these have shown lasting effects on the treatment of different cancers, the effects of these inhibitors being transitory and the tumors progressively developing resistance, allowing resumption of growth and cancer progression.

Dr. Hammers studied various prostate cancer models to study their differing sensitivities and resistance to VEGF inhibitors. His results show that VEGF inhibition is not an effective anti-angiogenic strategy for prostate cancer because the tumors demonstrate resistance in a variety of ways. Cancer resistance to anti-VEGF therapies has been extensively studied in the past and studies have shown that tumors evade these therapeutics by mechanisms such as **evasive resistance**, i.e. employing other growth factors compensating for the absence of VEGF, such as FGF etc; or **intrinsic or pre-existing indifference**. Dr. Hammers' research has shown that prostatic tumors possess cellular mediators of resistance, i.e. cells called pericytes which play a critical role in blood vessel maturation. His results show that targeting pericyte recruitment and function is an effective way to target/break resistance of prostatic tumors to anti-VEGF therapies. Dr. Hammers is currently developing a high-content screening assay that can effectively report pericyte inhibition.

Establishing the most advantageous combinations will require a better understanding of the mechanisms of action of each anti-VEGF agent and the sensitivity of each tumor type, as well as development of robust biomarkers and imaging techniques to guide patient selection and protocol design. A deeper understanding of the mechanisms of antitumor activity of specific and multitargeted anti-VEGF agents in patients, how they can best be combined with other treatment approaches such as chemotherapy and radiation therapy, and how optimization of these effects can be monitored clinically, should contribute to significantly improved cancer treatment and extend survival of cancer patients in the near future.

Christopher Maher, PhD

Washington University

Transcriptome Sequencing Reveals Unannotated lincRNAs in Prostate Cancer

Funded by the Rahr-PCF Young Investigator Award

What this means to patients: Dr. Maher and his team have identified a new family of 121 molecules called PCATs that are associated with prostate cancer progression. These molecules can be detected in the urine and may serve as clinical biomarkers of disease, for diagnosis, prognosis and/or treatment.

Non-coding RNAs (ncRNAs) are emerging as key molecules in human cancer that perform several critical functions in a cell such as the regulation of gene expression. The expression of these ncRNAs increases in cancers and this is associated with cancer progression. ncRNAs are beginning to be exploited for cancer diagnosis (as disease biomarkers), prognosis (as agents that reveal tumor biology) and treatment (as targets of therapeutics). Dr. Christopher Maher is comprehensively studying the expression patterns of ncRNAs in prostate cancer to identify novel ncRNAs that characterize specific subtypes. He has analyzed 102 samples, of which 21 were prostate cancer cell lines, 20 benign adjacent prostate tissue samples; 47 were samples from localized prostate cancers and 14 were metastatic tumors.

Results from these extensive bioinformatics analyses conducted in collaboration with Dr. Arul Chinnaiyan's team at Michigan, suggest that, on average, the genes that code for these ncRNAs typically lie approximately halfway between protein-coding genes. Using these parameters, the team identified 121 novel ncRNAs associated with prostate cancer progression, which they named as PCATs i.e. Prostate Cancer Associated Transcripts. Some of these PCATs rank among the highest overall outliers seen in prostate cancer, their expression being even higher than ERG and ETV1.

Dr. Maher presented his results from the analysis of one such novel transcript, PCAT1. He showed that the gene for this ncRNA is found in a region of the genome that has multiple amplifications during prostate cancer. The team found that removing PCAT1 from the genome affects 370 different genes, up-regulating 255 genes' expression and down-regulating 115 genes (Figure 31). From the patterns of the genes impacted by this ncRNA, Dr. Maher proposes a role of PCAT1 in DNA-replication and as a repressor in a subset of prostate cancer patients.

Further characterization of all the PCATs identified in this study has the potential to stratify subsets of prostate cancer. The expression of these ncRNAs can be detected in urine. Therefore, these molecules may serve as novel agents for the non-invasive detection of clinical prostate cancer.

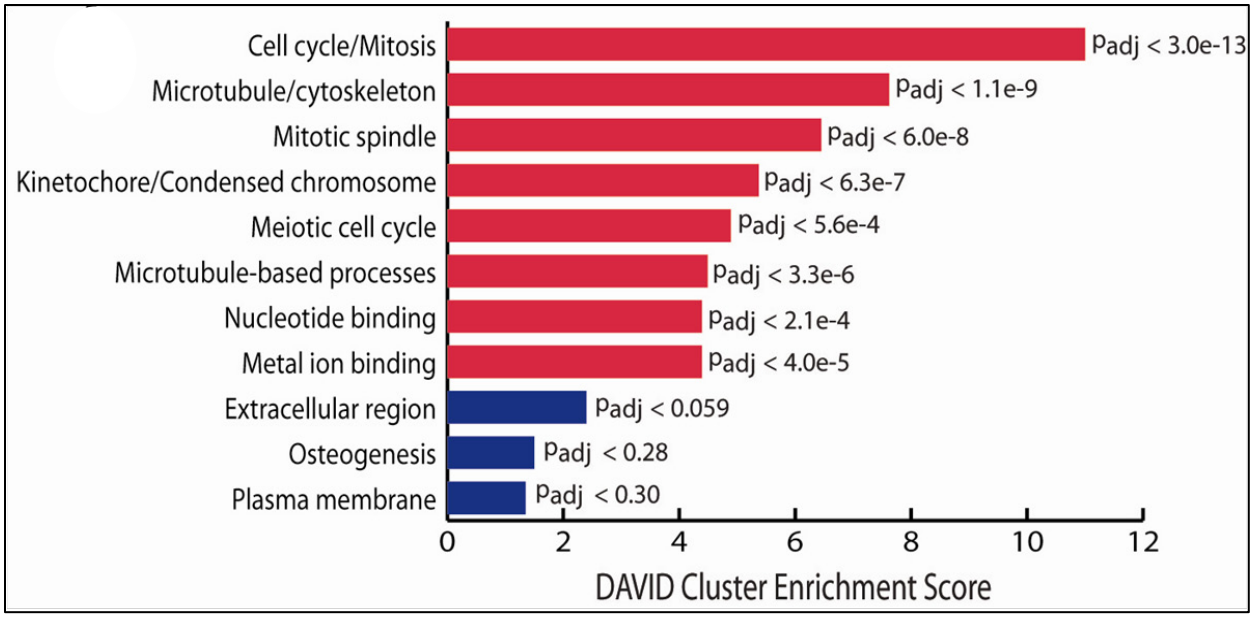


Figure 31: The chief cellular pathways and targets impacted upon *PCAT1* loss from the genome. The red bars represent the pathways that get upregulated upon PCAT1 removal and the blue bars are representative of pathways downregulated upon PCAT1 loss.

Amina Zoubeidi, PhD

The Vancouver Prostate Centre

Hsp27 Regulates EMT in Prostate Cancer

Funded by the Durden Foundation-PCF Young Investigator Award

What this means to patients: The heat shock protein, Hsp27 promotes castration resistance and prostate cancer metastasis. Therefore, targeting Hsp27 may prove to be a new treatment modality for aggressive prostate cancer.

A cancerous cell faces multiple stresses in its journey towards proliferation and metastasis. It responds to these stresses by continuously adapting and evolving. This process switches on several genes in the cancer cell that are usually inactive in a healthy cell. One such unique class of proteins that help cancers cope with stresses are the heat shock proteins (HSPs). HSPs act as cellular defenses against damage. Hsp27 is a small heat shock protein that in a healthy cell is associated in preventing cell death (apoptosis) and regulating cellular development. These roles are hijacked in a cancer cell and Hsp27 has been shown to be associated with many cancers such as ovarian, endometrial, breast, bladder, skin, lung and prostate cancer.

Hsp27 plays a key role in prostate cancer progression. Research carried out in 2009 in the University of Liverpool has previously identified Hsp27 as a very powerful biomarker for aggressive prostate cancer, demonstrating that men testing positive for Hsp27 at

diagnosis were twice as likely to die from the disease than men who did not have this protein. Dr. Zoubeidi's research has shown that Hsp27 mediates castration resistance in prostate cancer by activating several pro-survival pathways in the tumors. Her data show that chemotherapeutics such as taxotere induce the over-expression of Hsp27 (Figure 32) which in turn induces cellular plasticity, i.e. a cellular state where the cancer cell can choose to exist either as an epithelial cell or as a mesenchymal cell. These cells that have properties of both epithelial and mesenchymal cell types are usually the ones that leave a primary tumor and enter the blood circulation to establish tumors at distant sites.

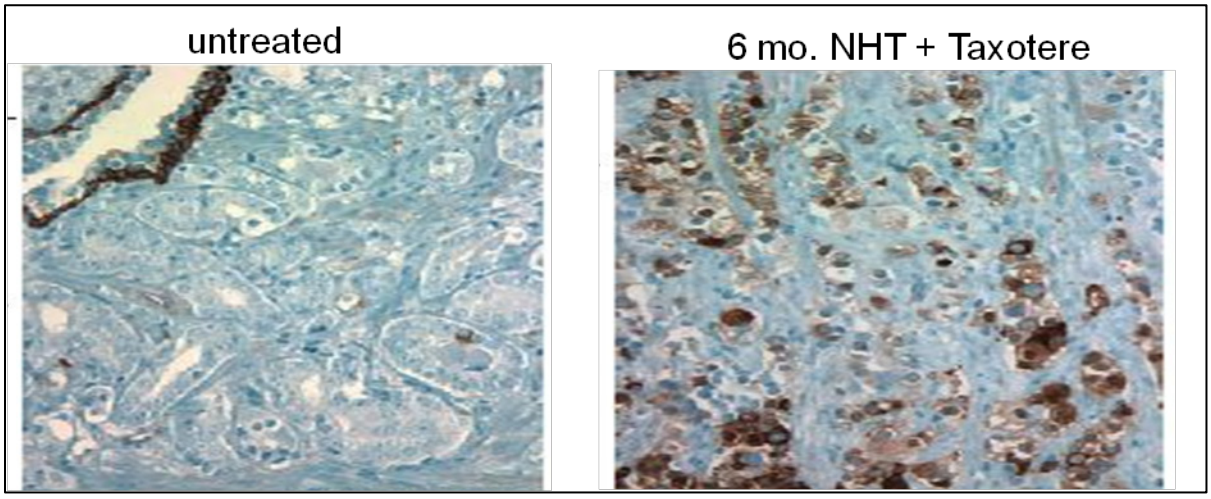


Figure 32: Dr. Zoubeidi's research shows that a 6-month combined treatment with Neoadjuvant Hormone Therapy (NHT) and Taxotere induces the up-regulation of the heat shock protein, Hsp27. This protein may be a new target for preventing prostate cancer metastases.

Dr. Zoubeidi's research points to a critical role played by Hsp27 in initiating prostate metastasis. Targeting this protein therapeutically holds great potential in preventing metastatic spread of prostate cancer.

Steven Frank, MD

The University of Texas MD Anderson Cancer Center

Stability and Characterization of the Cobalt Chloride Complex Contrast Agent (C4) for MRI-Based Prostate Cancer Treatment

Funded by the Earle Mack-PCF Young Investigator Award

What this means to patients: C4 (Cobalt Chloride Complex Contrast) is an effective, safe and non-toxic MR imaging marker for accurately placing radiation-emitting seeds in the prostate for radiotherapy.

Brachytherapy is a form of radiation therapy in which particles as small as rice, called 'seeds' are placed inside the prostate. These seeds emit radiation consistently and kill tumors in the prostate. The precise implantation of these seeds in the prostate is critical for targeted tumor killing. Improper seed placement has shown to cause severe side-effects in the past, such as incontinence, bowel injury etc. MR (Magnetic Resonance) scanning guides physicians in the proper implantation of these seeds in the prostate. During this process, it is important to localize the exact target for seed placement and radiation oncologists need appropriate markers that can guide seed delivery. Current imaging modalities are inefficient and inaccurate in identifying the placement of brachytherapy seeds.

Dr. Steven Frank and his team at MD Anderson have developed a novel MR marker for prostate brachytherapy called C4 (Cobalt Chloride Complex Contrast). This biomarker employs the chemical called Cobalt:N-Acetylcysteine (Co-NAC). Dr. Frank showed that C4 provides accurate MR localization of radiation delivery; is eliminated from the body rapidly and shows no toxicity. This marker is still visible in the prostate after exposure to high doses of radiation and is therefore effective in detection. Dr. Frank has completely characterized this MR marker in terms of its retention time in the body, its signal strength for detection and its stability in human plasma.

2011 Program Agenda

Thursday, September 22, 2011

Welcome and Introduction
2:00PM -2:05PM
Lakeside Ballroom

Taxanes: Targeted Therapy in the 21st Century

2:05PM – 3:35PM	**Moderators:** Evi Giannakakou, PhD Weill Cornell Medical College Natasha Kyprianou, PhD University of Kentucky
2:05PM – 2:15PM	**History of Taxane Development in Metastatic Prostate Cancer** Michael Morris, MD Memorial Sloan-Kettering Cancer Center
2:15PM – 2:30PM	**Taxanes Export the Androgen Receptor: A Tale Beyond Microtubule Targeting** Natasha Kyprianou, PhD University of Kentucky
2:30PM – 2:35PM	Discussion
2:35PM – 2:50PM	**Using Circulating Tumor Cells to Dissect Mechanisms of Clinical Taxane Resistance** Evi Giannakakou, PhD Weill Cornell Medical College
2:50PM – 2:55PM	Discussion
2:55PM – 3:10PM	**Role of Clusterin in Stress Response, Autophagy and Taxane Resistance** Martin Gleave, MD The Vancouver Prostate Centre
3:10PM – 3:15PM	Discussion
3:15PM – 3:30PM	**Targeting Signaling Pathways to Circumvent Taxane Resistance** Ahmed Ashour Ahmed, MD, PhD University of Oxford, England
3:30PM – 3:35PM	Discussion

New Concepts in Stem Cell Biology

3:35PM – 4:40PM **Moderator:** Owen Witte, MD
University of California, Los Angeles

3:35PM – 4:05PM **Defining Prostate Cancer Therapeutic Targets in Non-Mutated Cellular Pathways**
Owen Witte, MD
University of California, Los Angeles

4:05PM – 4:10PM Discussion

4:10PM – 4:20PM **Late-Breaking Research on Prostate Stem Cells**
Andrew Goldstein, PhD
University of California, Los Angeles

4:20PM – 4:25PM Discussion

4:25PM – 4:35PM **Epithelial Plasticity and Stemness in Circulating Tumor Cells from Men with Metastatic Prostate Cancer**
Andrew Armstrong, MD, MSc
Duke University

4:35PM – 4:40PM Discussion

Young Investigator Session # 1

4:40PM – 5:25PM **Moderator:** Howard Soule, PhD
Prostate Cancer Foundation

4:40PM – 4:50PM **Prostate Cancer Radiation Enhancement via PI3K Pathway Inhibition - More than PTEN - The Role of the Tumor Stromal Interaction**
Daniel Hamstra, MD, PhD
University of Michigan

4:50PM – 4:55PM Discussion

4:55PM – 5:05PM **Low Molecular Weight PSMA-Based PET Imaging of Prostate Cancer**
Steve Cho, MD
Johns Hopkins Medicine

5:05PM – 5:10PM Discussion

5:10PM – 5:20PM **The Origins of Dihydrotestosterone in Castration-Resistant Prostate Cancer**
Nima Sharifi, MD
University of Texas Southwestern Medical Center

5:20PM – 5:25PM Discussion

5:25PM – 5:40PM *Next Generation Platform Therapeutics and Research Tools*

Jeffrey Karp, PhD
Brigham & Women's Hospital
Harvard Medical School, Division of Health Sciences and Technology

Introduction by Howard Soule, PhD
Prostate Cancer Foundation
5:40PM – 5:45PM Discussion

5:45PM – 6:00PM *Annual State of the Foundation Speech*

Jonathan W. Simons, MD
Prostate Cancer Foundation

Dinner
7:00PM – 10:00PM
Regency Ballroom

2011 PCF Research Awards
7:30PM – 7:45PM
Presented by Howard Soule, PhD

Poster Session and Dessert
8:00PM – 10:00PM

Friday, September 23, 2011

Breakfast

6:30AM – 8:00AM

Lone Eagle Grill

8:00AM – 8:15AM *SPECIAL LECTURE*

The History of Development of Radium-223

Oliver Sartor, MD
Tulane University

Introduction by Jonathan W. Simons, MD
Prostate Cancer Foundation
8:15AM – 8:20AM Discussion

Genomics and Genetics of Prostate Cancer: What We Have Learned in the Last Year

8:20AM – 9:40AM

Moderator: Levi Garraway, MD, PhD
The Broad Institute and Dana-Farber Cancer Institute

8:20AM – 8:35AM **New Insights from the Prostate Cancer Genome**
Levi Garraway, MD, PhD
The Broad Institute and Dana-Farber Cancer Institute

8:35AM – 8:40AM Discussion

8:40AM – 8:55AM **The Application of Integrative Sequencing for the Personalization of Prostate Cancer Therapy**

Arul Chinnaiyan, MD, PhD
University of Michigan

8:55AM – 9:00AM Discussion

9:00AM – 9:15AM **Next Steps for Next Generation Discoveries**
Mark Rubin, MD
Weill Cornell Medical College

9:15AM – 9:20AM Discussion

9:20AM – 9:35AM **Lessons from the Prostate Cancer Epigenome**
Srinivasan Yegnasubramanian, MD, PhD
Johns Hopkins Medicine

9:35AM – 9:40AM Discussion

Friday, September 23, 2011

9:40AM – 10:00AM *SPECIAL LECTURE*

Prostate Cancer Targets the Hematopoietic Stem Cell Niche During Metastasis to Bone

Russell Taichman, DMD
University of Michigan Dental School

Introduction by Kenneth Pienta, MD
University of Michigan

10:00AM – 10:10AM Discussion

10:10AM – 10:30AM *SPECIAL LECTURE*

Improving Outcome from Advanced Prostate Cancer

Johann De Bono, MD, PhD
Royal Marsden Hospital and Institute of Cancer Research

Introduction by Eric Small, MD
University of California, San Francisco
10:30AM – 10:40AM Discussion

KEYNOTE LECTURE

10:40AM – 10:50AM **Brian Sandoval**
Governor, Nevada

10:50AM – 11:50AM **Mike Milken**
Prostate Cancer Foundation

Introduction by Stuart Holden, MD
Cedars-Sinai Medical Center

Lunch
11:50AM – 1:05PM
Cottage Green

1:05PM – 1:20PM **Modeling Metastatic Prostate Cancer from Mouse to Man – Molecular Determinants of Therapeutic Response**

Cory Abate-Shen, PhD
Columbia University

Introduction by Peter Nelson, MD
Fred Hutchinson Cancer Research Center
1:20PM – 1:25PM Discussion

1:25PM – 1:55PM *PANEL DISCUSSION*

The New Era of Molecular Pathology

Moderator: Stuart Holden, MD
Cedars-Sinai Medical Center

Panelists:

Angelo De Marzo, MD, PhD
Johns Hopkins Medicine

Steve Shak, MD
Genomic Health

Joel Nelson, MD
University of Pittsburgh
1:55PM – 2:10PM Discussion

Presentations from Companies Developing New Era Molecular Pathology Tests

2:10PM – 3:40PM

Moderator: Stuart Holden, MD
Cedars-Sinai Medical Center

2:10PM – 2:20PM **Enabling Global Molecular Pathology Testing for Prostate Cancer**

Ryan Dittamore
Ventana Medical Systems, Inc., a member of the Roche Group

2:20PM – 2:25PM Discussion

2:25PM – 2:35PM **Prostate Cancer Gene Expression Profiling and Clinical Outcomes: Recent Progress Using Quantitative RT-PCR Optimized for Core Biopsies Fixed in Paraffin**

Steve Shak, MD
Genomic Health

2:35PM – 2:40PM Discussion

2:40PM – 2:50PM **Use of Exosomal mRNA for Non-Invasive Transcriptional Analysis of the Prostate**
Leileata Russo, PhD
Exosome, Diagnostics Inc.

2:50PM – 2:55PM Discussion

2:55PM – 3:05PM **Cell Cycle Progression Genes Differentiate Indolent from Aggressive Prostate Cancer**
Steve Stone, PhD
Myriad Genetics, Inc.

3:05PM – 3:10PM Discussion

3:10PM – 3:20PM **An *in situ* Proteomics, Disease Biology-Based Approach for Development of a Prognostic Test for Prostate Cancer**
Peter Blume-Jensen, MD, PhD
Metamark Genetics, Inc.

3:20PM – 3:25PM Discussion

3:25PM – 3:35PM **A Non-Invasive Multi-Analyte Assay to Reduce Unnecessary Prostate Biopsies**
Anthony Shuber, PhD
Predictive Biosciences, Inc.

3:35PM – 3:40PM Discussion

Modulation of Therapeutic Response by Tumor Adaptation to Target Inhibition
3:40PM – 4:50PM

Moderator: Neal Rosen, MD, PhD
Memorial Sloan-Kettering Cancer Center

3:40PM – 4:00PM **Feedback and Redundancy in Oncoprotein Activated Pathways—**

Basic and Therapeutic Implications
Neal Rosen, MD, PhD
Memorial Sloan-Kettering Cancer Center

4:00PM – 4:10PM Discussion

4:10PM – 4:25PM **Targeting Oncogenic Feedback Pathways in Prostate Cancer: Rationale Design of Combination Therapy**
Brett Carver, MD
Memorial Sloan-Kettering Cancer Center

4:25PM – 4:30PM Discussion

4:30PM – 4:45PM **Autonomous Role of PTEN in Regulating Castration Resistant Prostate Cancer Growth**
David Mulholland, PhD

University of California, Los Angeles

4:45PM – 4:50PM Discussion

4:50PM – 5:10PM ***Prostate Cancer Medical Oncology Clinic in 2025***

Howard Scher, MD
Memorial Sloan-Kettering Cancer Center

Introduction by Neal Rosen, MD, PhD
Memorial Sloan-Kettering Cancer Center
5:10PM – 5:15PM Discussion

Reception and Cocktails
5:30PM – 7:00PM
Lakeshore Home of Mike Milken
Shuttles provided

Friday, September 23, 2011

7:30PM – 10:00PM *Special Dinner Program and Entertainment*

Regency Ballroom

8:00PM – 8:15PM **Movember Presentation**

Donny Killian
Movember U.S.

Introduction by Howard Soule, PhD
Prostate Cancer Foundation

8:45PM – 10:00PM **Apollo Robbins – The Gentleman Thief**

An expert in the field of con-artistry, sleight of hand and pickpocketing

"An artful manipulator of awareness" – Forbes

Saturday, September 24, 2011

Breakfast

6:00AM – 8:15AM

Lone Eagle Grill

PARP in Prostate Cancer

8:30AM – 9:30AM

Moderator: Karen Knudsen, PhD
Thomas Jefferson University

8:30AM – 8:45AM **Clinical Development of PARP Inhibitors in Breast Cancer: Opportunities and Challenges**
Mark Robson, MD
Memorial Sloan-Kettering Cancer Center

8:45AM – 8:50AM Discussion

8:50AM – 9:05AM **PARP1 Inhibitors as a Strategy for Targeting Radiosensitization of ETS-Positive Prostate Cancers**
Felix Feng, MD
University of Michigan

9:05AM – 9:10AM Discussion

9:10AM – 9:25AM **Leveraging the Dual Functions of PARP1 in Controlling AR and DNA Repair to Improve Prostate Cancer Management**
Karen Knudsen, PhD
Thomas Jefferson University

9:25AM – 9:30AM Discussion

Clinical and Biological Update: Status and Plans for Cabozantinib
9:30AM – 10:10AM

Moderator: Matthew Smith, MD, PhD
Massachusetts General Hospital Cancer Center

9:30AM – 9:45AM **Clinical Evaluation of Cabozantinib in Metastatic CRPC**
Matthew Smith, MD, PhD
Massachusetts General Hospital Cancer Center

9:45AM – 10:00AM **Taking a Treatment Science Approach to Understanding Cabozatinib's Mechanism of Action in Men with CRPC**
Phillip Febbo, MD
University of California, San Francisco

10:00AM – 10:10AM **Discussion**

10:10AM – 10:25AM *SPECIAL LECTURE*

First Annual Movember Lecture

Growing Mo's to Grow Collaborations - The Irish Experience

William G. Watson, PhD
University College Dublin

Introduction by Colleen Nelson, PhD
Australian Prostate Cancer Research Centre - Queensland
10:25AM – 10:30AM Discussion

Bioinformatics for Discovery
10:30AM – 10:45AM

10:30AM – 10:40AM **Prometheus: A Novel Discovery Platform**
Randall Millikan, MD, PhD
The University of Texas MD Anderson Cancer Center
10:40AM – 10:45AM Discussion

Saturday, September 24, 2011

Young Investigator Session # 2

10:45AM – 12:15PM

Moderator: Howard Soule, PhD
Prostate Cancer Foundation

10:45AM – 10:55AM **Mapping the Complexities of Androgen Signaling in Prostate Cancer Progression**
Eleni Efstathiou, MD, PhD
The University of Texas MD Anderson Cancer Center

10:55AM – 11:00AM Discussion

11:00AM – 11:10AM **Towards Effective Angiogenesis Inhibition in Prostate Cancer**
Hans Hammers, MD, PhD
Johns Hopkins Medicine

11:10AM – 11:15AM Discussion

11:15AM – 11:25AM **Gene Fusion Discovery in Prostate Cancer Transcriptomes**
Christopher Maher, PhD
Washington University

11:25AM – 11:30AM Discussion

11:30AM – 11:40AM **Hsp27 Regulates EMT in Prostate Cancer**
Amina Zoubeidi, PhD
The Vancouver Prostate Centre

11:40AM – 11:45AM Discussion

11:45AM – 11:55AM **Molecular Characterization of Neuroendocrine Prostate Cancer**
Himisha Beltran, MD
Weill Cornell Medical College

11:55AM – 12:00PM Discussion

12:00PM – 12:10PM **Stability and Characterization of the Cobalt Chloride Complex Contrast Agent (C4) for MRI-Based Prostate Cancer Treatment**
Steven Frank, MD
The University of Texas MD Anderson Cancer Center

12:10PM – 12:15PM Discussion

Meeting Adjourned

Speaker	PCF Funding
Martin Gleave, MD	2007, 2009
Owen Witte, MD	1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2008, 2011
Andrew Goldstein, PhD	2011
Andrew Armstrong, MD	2008
Daniel Hamstra, MD, PhD	2010
Steve Cho, MD	2008, 2011
Nima Sharifi, MD	2008
Levi Garraway, MD, PhD	2005, 2006
Arul Chinnaiyan, MD, PhD	2001, 2005, 2006, 2007, 2008, 2009
Mark Rubin, MD	2003, 2009, 2011
Russell Taichman, DMD	2005, 2006,
Johann De Bono, MD, PhD	2011
Cory Abate-Shen, PhD	2008
Angelo De Marzo, MD, PhD	
Joel Nelson, MD	1995, 1996, 1997, 1998, 1999
Neal Rosen, MD, PhD	1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006
Brett Carver, MD	2010
Howard Scher, MD	1993, 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011
Karen Knudsen, PhD	
Felix Feng, MD	2010
Matthew Smith, MD, PhD	1998, 2000, 2001, 2003, 2006, 2008, 2010, 2011
Phillip Febbo, MD	2010, 2011
Eleni Efstathiou, MD, PhD	2008, 2011
Hans Hammers, MD, PhD	2010
Christopher Maher, PhD	2010
Amina Zoubeidi, PhD	2010
Himisha Beltran, MD	2010
Steven Frank, MD	2008

The table above identifies the speakers who are or have been funded by the Prostate Cancer Foundation.

PROSTATE CANCER FOUNDATION

1250 Fourth Street, Santa Monica, CA 90401 | Tel 800.757.CURE (2873) Fax 310.570.4701 | www.pcf.org