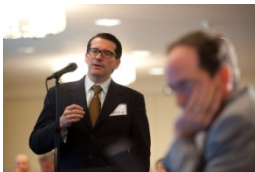


STATE OF THE SCIENCE REPORT

Highlights from
the 17th Annual PCF
Scientific Retreat

September 2010



Provided with the compliments of
the Prostate Cancer Foundation



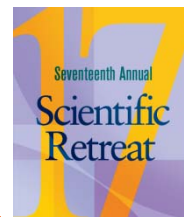


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Introduction

For the seventeenth consecutive year, the Prostate Cancer Foundation brought together the world's top prostate cancer physicians and scientists in a collaborative forum to share new and emerging data. The overall purpose of the meeting was to accelerate the end of death and suffering for men facing prostate cancer.

The program forum provided attendees opportunities to network and meet with new colleagues, long-time friends and patrons. Scientific presentations and collaboration were the focal point of the retreat. The Retreat also included:

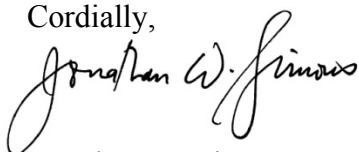
- 358 biomedical research attendees from 9 countries, 72 academic institutions, 18 biopharmaceutical companies, and 6 medical research foundations
- A critical mass of talent assembled in the form of 144 MDs, 73 MD-PhDs, 4 PharmDs, 102 PhDs, 3 ScDs
- 44 presentations and panels made by 52 speakers and panelists with data from 18 research subfields, 13 of which have never before been highlighted at a Scientific Retreat
- 34 speakers presented first-in-field data at a PCF Scientific Retreat for the first time
- Leadership from the National Cancer Institute, Department of Defense, and the U.S. Senate and House of Representatives
- 31 Patrons and 14 PCF Board members
- A Young Investigator Leadership Forum where 46 new PCF-funded early-career scientists wrote RFAs for mid-level and senior investigators and mentors

This year's presentations offered some transformational insights into genomics, epigenetics, disease signaling pathways, updated clinical results, treatment sciences, and emerging new targeted therapies for men with metastatic prostate cancer. The Retreat program also included a special dinner presentation highlighting 27 new Young Investigators from the Class of 2010, a \$6.1 million funding commitment from PCF donors, and new PCF Creativity Award recipients.

Michael Milken, PCF founder and chairman, delivered the keynote lecture emphasizing that “encouraging and identifying the best and brightest Young Investigators can change the world.” He also stressed that, “PCF has spent a great deal of time focused on the next generation of 50 Young Investigators, and persuading their mentors to recognize that the impossible is possible.”

In the report you will find a summary of every presentation given at the retreat. The highlights are intended to inform you of what's new in the field and where research barriers remain. Our aim is to translate these new findings, as rapidly as possible, into clinical investigation. Toward that end, we hope this report will stimulate further dialogue, data exchange, and questioning. If you have specific questions, please contact Dr. Katrin Ericson at kericson@pcf.org.

Cordially,



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



Howard R. Soule, PhD
Chief Science Officer

Session 1

Molecular Targeting of Apoptosis in Prostate Cancer

Major Points from Session 1:

- Gamitrinibs, agents that target mitochondrial heat shock protein 90, showed significant anti-cancer activity in preclinical studies.
- OGX-427 is currently in Phase II clinical trials and inhibits heat shock protein 27 resulting in cancer cell death. Phase I studies reported significant decline in PSA and stable disease in patients with advanced prostate cancer.
- New combination therapies that include agents which target cell autophagy (“self-eating”) may overcome drug resistance mechanisms.
- Par-4 is a powerful protein that stimulates normal cell death. Loss of Par-4 expression is common in prostate cancer cells. Therapies that re-activate Par-4 could improve clinical outcomes for patients with advanced disease.

Introduction:

Advanced prostate cancer is considered a highly heterogeneous disease because it hijacks control over many different signaling pathways that regulate cell proliferation, survival and invasion. Currently, most targeted therapies are designed to destroy these processes. Conversely, the apoptosis, the cell death pathway, which is frequently turned “off” in cancers, has not been adequately tested as a target for therapy in prostate cancer. The opening session of the 17th Annual PCF Scientific Retreat reported results of very new findings of experimental therapeutics that turn the cell death switch from “off” to “on” in cancer cells specifically.

Dario Altieri, MD

Wistar Cancer Center

Targeting Mitochondrial Hsp90 Chaperones for Prostate Cancer Therapy

What this means for patients: Gamitrinibs may be an important new therapy for advanced prostate cancer.

The first presentation described the role of a family of proteins called heat shock proteins in apoptosis. Dr. Dario Altieri, the session moderator, introduced Heat Shock Protein 90 (HSP90) as a promising therapeutic target in new ways that have not yet been considered. HSP90 inhibitors have been generally disappointing with significant side effects and minimal clinical activity in a number of clinical trials for advanced prostate cancer. Dr. Altieri described the anti-cancer activity of inhibitors that target HSP90 protein only in the subcellular organelle called mitochondria. The mitochondrion is the energy “factory” of human cells, which is very important in the process of apoptosis. To date, HSP90 inhibitors were not selective and affected the protein in all cellular compartments. A drug candidate called Gamitrinib was shown to block activity of HSP90 in only mitochondria. Results from laboratory experiments demonstrated that the specific inhibition of mitochondrial HSP90 in cancer cells induces the collapse of the mitochondria which stimulates apoptosis in vitro. Additional studies in animal models of prostate cancer revealed that Gamitrinibs have significant anti-tumor effects in several different animal

models of advanced prostate cancer. These agents were well-tolerated; the animals showed little weight loss even after long term treatment and tissue histology of the liver, lung and lymph nodes revealed no off-target effects. Together these findings demonstrate that mitochondrial HSP90 is a critical regulator of apoptosis and that Gamitrinibs may be an important new therapy to advance into clinical trials.

Model for Gamitrinib mechanism of action

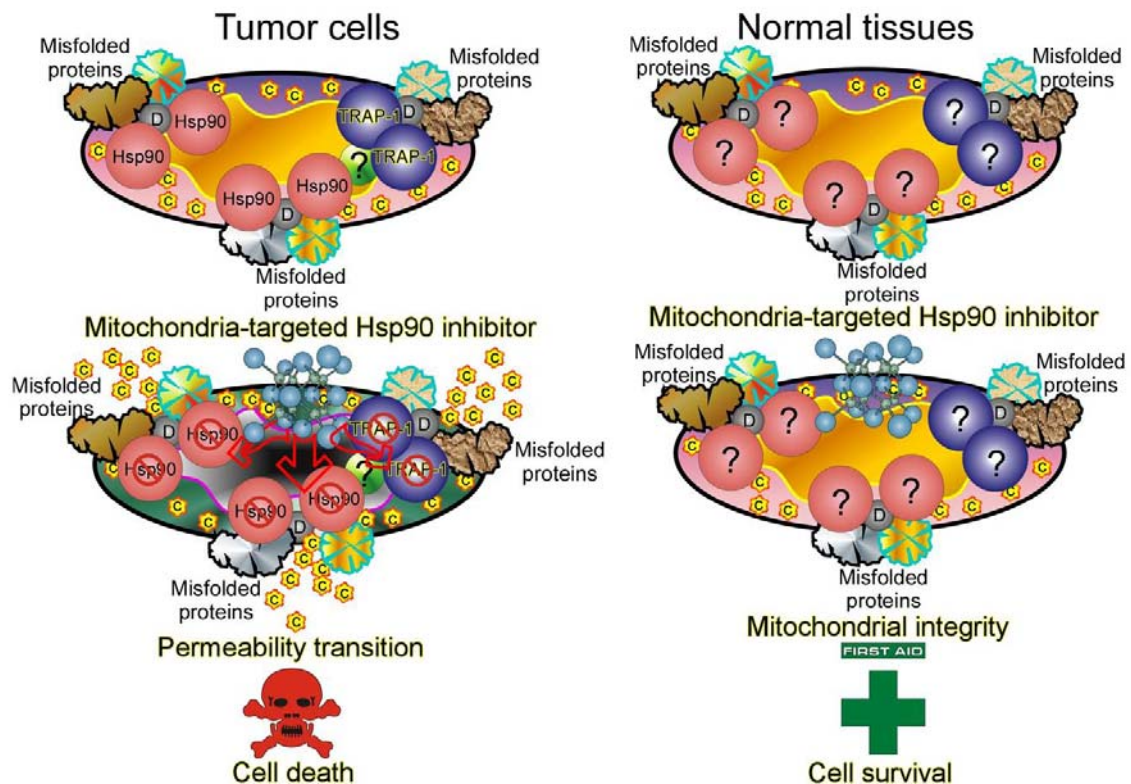


Figure 1: This model depicts how Gamitrinib specifically target tumor cells for cell death. At the top are illustrations of a tumor cell mitochondria (left) and a normal cell mitochondria (right) without any treatment. Notice the presence of HSP90 (pink circles) in the tumor mitochondria but not in the normal mitochondria (pink question marks). On the bottom both the tumor cells and the normal tissue were treated with Gamitrinib (blue molecule). Since Gamitrinibs target mitochondrial HSP90 only the tumor cell undergoes cell death sparing normal tissue.

Amina Zoubeidi, PhD
University of British Columbia
Therapeutic Targeting of Hsp27 in Prostate Cancer

What this means for patients: OGX-427 is a promising new agent in clinical trials for prostate cancer.

Preclinical results for heat shock protein, HSP27, were presented by Dr. Amina Zoubeidi. She stated that HSP27 is involved in regulating several pathways that control cell survival and cancer progression. Her findings demonstrate that HSP27 increases with increasing prostate cancer stage and is associated with poor clinical outcome. Dr. Zoubeidi and colleagues developed a compound called OGX-427 which abolishes the production of HSP27 protein in cancer cells. The data presented showed that depleted levels of HSP27 in treated cancer cells resulted in significant cell death. This agent is currently in Phase II clinical trials for the treatment of advanced stage solid tumors. In the Phase I trial, 3 of the patients with advanced prostate cancer had significant PSA declines, while 5 patients had stable disease for over three months. While the data is still preliminary, it suggests that OGX-427 may be a valuable therapy for the treatment of advanced prostate cancer.

Hsp27 knockdown delays tumor progression post-castration

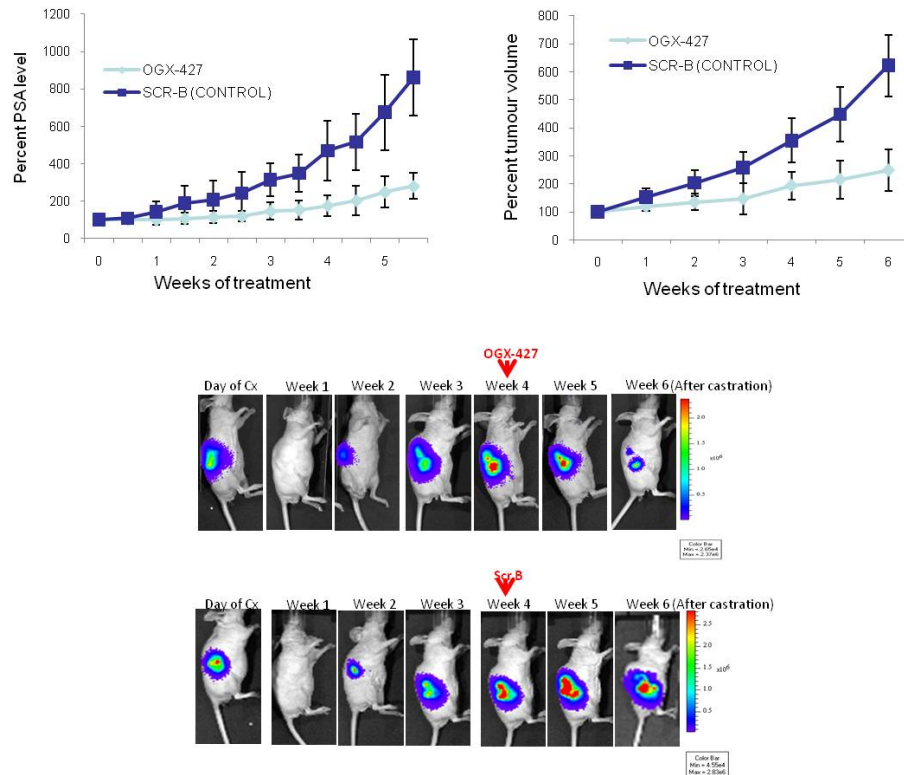


Figure 2: This figure demonstrates the anti-tumor effects of OGX-427. In top left graph, observe the light blue lines which represent PSA levels and tumor volume (top right graph) of a prostate cancer mouse models treated with OGX-427 compared to the untreated controls represented by the dark blue lines. At the bottom are images of mice with abundant prostate cancer growth, marked by the heat circles, that were either treated with OGX-427 (top panel) or not (bottom panel) at 4 weeks. The mice treated with OGX-427 experienced a reduction in tumor volume by week 6 (top panel, far right) compared to control mice (bottom panel far right).

Robert DiPaola, MD
The Cancer Institute of New Jersey
Targeting Apoptosis and Autophagy

What this means for patients: Agents in the pipeline that target autophagy may prevent development of resistance to other anti-cancer drugs.

The third speaker, Dr. DiPaola discussed several promising agents that target apoptosis in pre-clinical studies. However, he cautioned that many cancers will develop resistance to these single agents because of a cellular process known as autophagy. Autophagy induces a state of dormancy in response to stress, in which cancer cells stop growing but don't die. Once stress conditions are relieved, usually when therapy is stopped, the cells are released from dormancy and begin to grow again. Dr. DiPaola's research is focused on developing new drugs that target autophagy as a mechanism of resistance. He hypothesizes that future treatments that combine targeted therapies with medicines that block autophagy will improve clinical outcomes in prostate cancer treatment.

Vivek Rangnekar, PhD
University of Kentucky
A Paradigm for Cancer Selective Apoptosis

What this means for patients: Par-4 is a new therapeutic target for prostate cancer.

Dr. Rangnekar presented his research results on studies of a protein called Par-4, a tumor suppressor in prostate cancer. Par-4 can activate apoptosis via a signaling pathway called Death Receptor. Dr. Rangnekar and colleagues identified the region of the Par-4 protein responsible for promoting cell death, called the SAC domain. The investigators generated a mouse model that has elevated levels of SAC and showed that these mice have increased longevity and are resistant to spontaneous tumors. These mice could not grow prostate cancer tumors, indicating that Par-4 is a powerful inhibitor of cancer cell growth and survival. Future development of novel therapies capable of elevating the levels of active Par-4 in humans may provide prostate cancer patients with a new treatment to specifically target the cell death pathway.

Special Lecture

Immuno-Oncology: Creating the Operating Framework for a New Era of Cancer Therapy

Axel Hoos, MD, PhD
Bristol-Myers Squibb

Major Points from the Special Lecture:

- Immuno-Oncology is a new discipline of medicine that focuses on development and delivery of immunotherapy treatments for cancer patients.
- Cancer Immunotherapy Consortium (CIC) is a global working group organized to provide guidelines to regulatory groups and science-based recommendations for the development of immunotherapy for cancer.
- CIC has already defined solutions for some of the major challenges facing immunotherapy drug development. (*See table below*)

What this means for patients: CIC will accelerate the development of new effective immunotherapy treatments for prostate cancer.

Discussion:

Dr. Axel Hoos, the Group Director and Medical Lead of Global Clinical Research – Oncology at Bristol-Myers Squibb, discussed the need for a new discipline in medicine that focuses on cancer immunotherapy, Immuno-Oncology. Cancer immunotherapies are designed to activate and arm a patient's immune system to seek and destroy cancer cells. 2010 marks the first year the FDA approved a therapeutic vaccine for the treatment of cancer. This vaccine is Provenge, manufactured by Dendreon Corporation, and was approved on April 29th for use in the treatment of prostate cancer.

The initial success of Provenge has motivated others to produce treatments in the Immuno-Oncology field. For example, Prostavac, another vaccine developed for the treatment of prostate cancer like Provenge, also showed a survival benefit in randomized Phase II clinical studies. Similarly, Ipilimumab, an inhibitor of CTLA-4 (an immune checkpoint inhibitor: “immune system brakes”) showed survival benefit in advanced stage melanoma.

The challenge however, is while oncology is an established field; immuno-oncology is different and uncharted. The best practice for regulatory development of immune-oncology products is not defined. This is best evidenced by the observation that both Provenge and Prostavac showed no effect on disease progression while an improved overall survival was observed. These findings prompted Dr. Hoos and others in the oncology field to recognize these differences and to create a global working group to produce guidelines and recommendations to regulatory bodies.

As a result, Dr. Hoos's organization BMS and approximately 70 other institutions, including academia, industry and non-profits, formed a non-profit Cancer Immunotherapy Consortium (CIC). CIC is spearheading the efforts of creating a new operating framework for immuno-

oncology. The goal is to improve patient care by making cancer immunotherapy part of the standard-of-care in oncology. Dr. Hoos outlined CIC's current framework, listing the challenges and the solutions formulated for each. (See below)

Challenge		Solution
1	Use of chemotherapy principles for clinical development of immunotherapy.	New clinical development paradigm for immunotherapy.
2	Clinical trial endpoints are not immunotherapy-focused.	Adjustment of endpoints to immunotherapy biology.
3	No system to measure all patterns of immunotherapy clinical activity.	Immune-related response criteria.
4	High data variability for immune monitoring in multi-center trials.	Harmonizing guidelines and quality assurance for immune monitoring assays.
5	Inconsistent reporting of immune monitoring results in publications.	Minimal Information About T-cell Assays (MIATA) reporting framework.
6	Absence of regulatory guidance for cancer immunotherapy development.	Facilitation of broad scientific exchange including regulators to support guidance document development.

Session 2

Genomics of Prostate Cancer

Major Points from Session 2:

- Advancements made in conserving tumor specimen DNA for whole genome sequencing enables production of well-controlled, high quality data necessary to identify “driver” genetic alterations.
- Chromosomal rearrangements are common in “high risk” prostate cancers (median of ~90 per tumor). Determining their function in prostate cancer initiation and progression is paramount.
- Different mutations occur in exons across metastatic lesions even within a patient. However, there are several mutations that may be recurrent across patients. These mutations may be new therapeutic targets for prostate cancer.
- Discoveries of treatment strategies that target the molecular subtypes (based on gene fusion status) of prostate cancer.

Discussion:

The study of cancer genomics is founded on the premise that cancer is initiated and progresses as a result of evolving and compounding genomic alterations. The goal of prostate cancer genomics is to identify the “driver” genetic events and develop new targeted therapies that abolish the lethal functional output of these mutations. All four speakers of this session discussed different areas of research within the genomics domain.

Elaine Mardis, PhD

The Genome Center at Washington University School of Medicine

Prostate Cancer: Meeting the Challenges of Whole Genome Sequencing and Analysis

What this means to patients: Advancing whole genome sequencing methods enable analysis of more prostate cancers which may lead to the discovery of new therapeutic targets.

Dr. Elaine Mardis focused her lecture on the complex process of whole genome sequencing of cancer samples from the perspective of a director of a very large and prolific genomics center at Washington University. She identified three primary challenges of whole prostate cancer genome sequencing. First since prostate cancer presents multi-focally (tumor grows in clusters throughout the prostate) with variable heterogeneity among the foci; it is difficult to isolate pure populations of cancer cells. This requires laser capture microdissection (LCM), which is a tool that enables researchers to cut out small sections of cancer from a biopsy, leaving behind normal, healthy tissue. However, LCM-isolated tumor cells yield very low amounts of DNA, not optimal for whole genome sequencing. Second, the standard tissue fixation techniques do not preserve DNA. This leads to low amounts of DNA due to DNA degradation in the tissue specimen. Third, new biotechnologies are required to amplify sufficient quantities of DNA for sequencing and validation experiments. To address these challenges, Dr. Mardis shared some of the new biotechnologies developed in her laboratory to conserve DNA integrity and quantity. She also demonstrated the successful application of these methodologies in sequencing experiments.

Sequencing of 3 whole prostate cancer genomes acquired from LCM tumor sections of both primary tumors and metastatic lymph nodes were reported. These data demonstrate that whole prostate cancer genome sequencing methods are becoming more advanced and capable of overcoming the many challenges of the soon-to-be past.

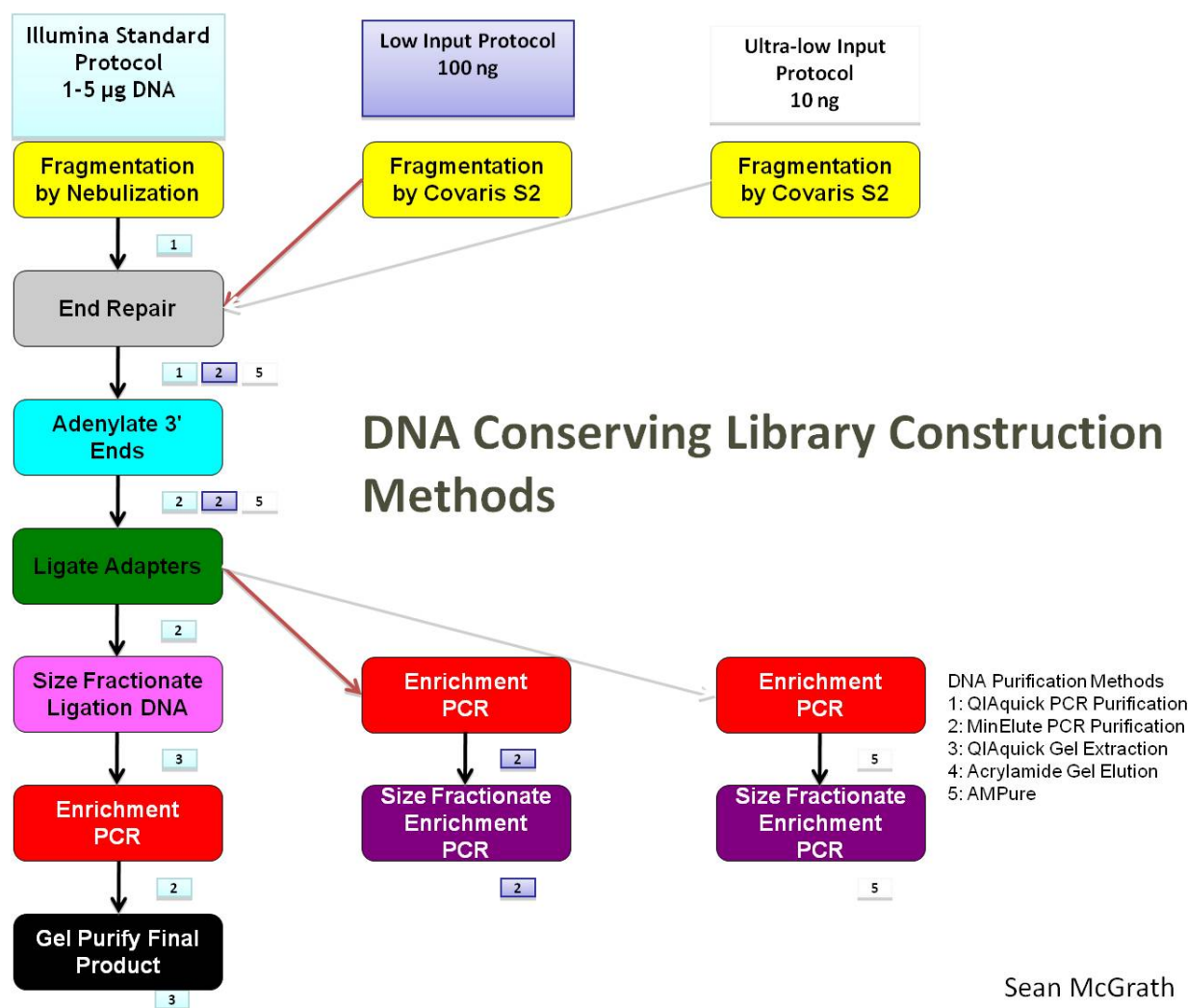


Figure 3: This schematic shows the new methods Dr. Mardis' laboratory has designed to conserve DNA when challenged by low DNA yield from tumor specimens. On the left is the standard protocol for DNA extraction and enrichment to the right are the new protocols developed demonstrating fewer steps overall.

Levi Garraway, MD, PhD

Dana-Farber Cancer Institute, Harvard School of Medicine, The Broad Institute of Harvard and MIT

Genome Sequencing Studies of Prostate Cancer

What this means to patients: Identifying the genetic alterations and their function in prostate cancer will help in understanding the biology of lethal disease and should reveal new directions for therapeutic interventions.

Dr. Garraway's presentation showed some of the early findings from the expansive data set he and his team produced from whole genome sequencing of prostate cancers. To date, the team has successfully sequenced seven high grade prostate cancers isolated from radical prostatectomy specimens. They found that chromosome rearrangements (the shuffling of DNA segments) are prevalent across all seven cancer genomes (range: 43-213), indicating an important disease biology that must be better understood. Several genomes contained inter- and intra-chromosomal rearrangements involving an exchange of "breakpoint arms." This pattern of breakage and rejoining is termed "closed chain" rearrangements and occurred specifically in cancers with TMPRSS2:ERG gene fusions. The significance of this pattern is unknown and must be further investigated.

Additionally, two novel candidate tumor suppressor genes were described, which may uncover new mechanisms of prostate cancer initiation and progression. Dr. Garraway's research highlights the power of genome-wide sequencing.

Jay Shendure, MD, PhD
University of Washington

Exome Sequencing in Metastatic Prostate Cancer

What this means to patients: Exomic sequencing may uncover new genetic alterations in prostate cancer that can be therapeutically targeted.

The exome is the total gene coding region of the genome and is comprised of separate exons (gene coding sequences) that comprise 1% of the entire human genome. The advantage of exomic sequencing is that only a small number of sequences need to be studied which reduces the time and cost. While mutations, amplifications and deletions of coding regions can be studied, the downside is that the vast non-coding and regulatory portions of the genome, “dark DNA,” are not analyzed. Dr. Shendure explained that this method allows his team to identify genetic alterations that directly affect the function of proteins that may impart cancer cell growth and survival signal. Dr. Shendure presented results from comparing the exome sequencing data of 6 metastatic lesions from 3 patients (2 lesions per patient). He found that there were 58 mutations across all 6 metastatic lesions. Fifty of the 58 were previously described mutations. The metastatic lesions within a patient shared ~90% of the same mutations. One patient had a lymph node metastasis compared to a bladder metastasis and these lesions shared only ~11% of mutations. These data provoke the following hypotheses: 1) metastatic lesions in the same organ are clonal, 2) mutations by be affected by the organ site, or 3) the genetic alterations within a cancer clone may cause it to home to a specific metastatic organ site. Only 6 mutations were shared across all six metastatic sites. Dr. Shendure concluded by saying he and his team are sequencing many more patient samples to identify the genetic alterations that drive prostate cancer initiation and progression.

Shared mutations between metastases

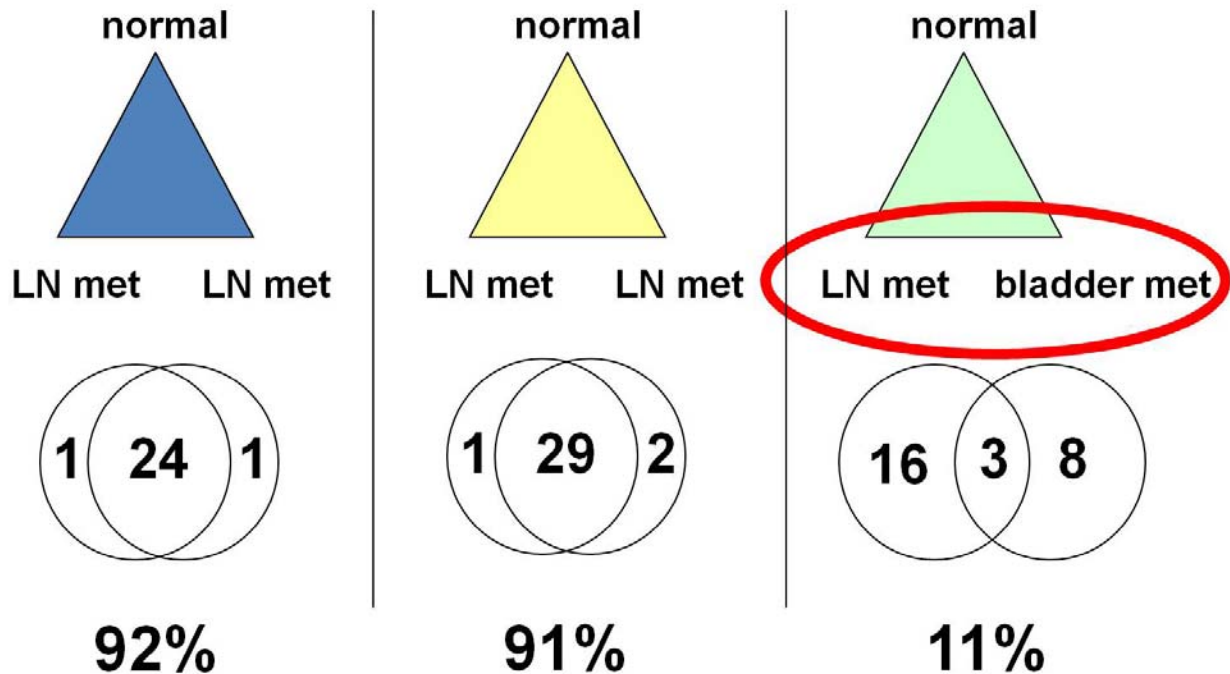


Figure 4: This figure shows the number of mutations identified from tissue extracted from three different prostate cancer patients (blue, yellow and green triangles). In each experiment metastases from an individual were compared to each other. The patient's normal tissue was used as a control (baseline). The results illustrate that metastases from the same tissue type share ~90% of the same exon mutations while metastases from different tissues share only 11%. These data indicate that the tissue microenvironment may influence the type of mutations that occur in the cancer cells.

Arul Chinnaiyan, MD, PhD
University of Michigan

Recurrent Gene Fusions in Common Solid Tumors: Implications for Personalized Medicine

What this means to patients: Dr. Chinnaiyan is matching prostate cancer gene fusion status to treatment strategy to patients with advanced prostate cancer.

Analysis of transcriptomics, the study of RNA sequences generated from DNA gene coding sequences subsequently translated into protein, was the method Dr. Chinnaiyan and colleagues used to discover gene fusions (the erroneous juxtaposition of two genes from disparate regions of the genome) in prostate cancer. The most common gene fusion in prostate cancer is TMPRSS2:ERG, discovered by Chinnaiyan's laboratory in 2005. In the past year, Dr. Chinnaiyan and colleagues discovered many more gene fusions present in prostate cancer; the total number of gene fusions defined in prostate cancer to date is 23. Most gene fusions, ~60% harbor an ETS gene family. A common cancer-causing gene called RAF was found as part of unique gene fusions in ~2% of prostate cancers. Since RAF codes for a druggable protein, prostate cancers that harbor RAF gene fusions are therapeutically actionable. Dr. Chinnaiyan presented new work on identifying therapies that specifically target some of the gene fusions considered most aggressive. The investigators used prostate cancer cell-lines with different gene fusions to test drug candidates that can potentially abolish the cancer-causing activity of the gene fusion. In summary, Dr. Chinnaiyan stated that prostate cancer can now be stratified into molecular subtypes, which has significant implications for personalized treatment strategies.

Session 3

New Developments in Clinical Practice, “A Whitmorean Panel Discussion”

Panelists: Skip Holden, MD (Cedars-Sinai Medical Center)
Peter Scardino, MD (Memorial Sloan-Kettering Cancer Center)
Howard Sandler, MD (Cedars-Sinai Medical Center)
Phil Kantoff, MD (Dana-Farber Cancer Institute)
Jonathan Simons, MD (Prostate Cancer Foundation)

Major Points from Session 3:

- Active surveillance, a new paradigm, is becoming a more accepted “treatment” approach to surgeons.
- Radiation oncology has made significant improvements in eliminating radiation exposure to healthy tissue while increasing radiation dose to the tumor.
- There are several promising prostate cancer medicines currently under clinical investigation, including Abiraterone which demonstrated a 4 month survival advantage in patients with lethal prostate cancer.

What this means for patients: The treatment of prostate cancer patients is evolving due to new treatment strategies. The introduction of new treatments demands change in practice pattern. This change is underway but for the time being will only be available at centers of radiologic, medical oncology and urologic expertise.

Discussion:

Dr. Skip Holden moderated this panel and opened the panel by providing background on Dr. Willet F. Whitmore and his legacy in urologic oncology. Dr. Whitmore practiced for over 30 years at what is now Memorial Sloan-Kettering Cancer Center and is known globally as the dean of “urologic oncology.” He was famous for asking the following questions: is a cure possible for those in whom it is necessary? And, conversely, is a cure necessary for those in whom it is possible?

Each panelist took turns highlighting the most recent advancements in their respective disciplines. Dr. Peter Scardino, a urologic oncologist, began by stating that the most prominent paradigm shift in surgery is that physicians are beginning to accept active surveillance as an appropriate treatment strategy for men with very low risk prostate cancer. This shift will hopefully re-balance many years of over treatment. Dr. Scardino noted however that there needs to be large, multi-institutional prospective studies on active surveillance to determine biomarkers that indicate a cause for intervention to protect men from developing a lethal cancer while under active surveillance.

Representing radiation oncologists, Dr. Sandler discussed the significant improvements made in dose escalation of External Beam Radiation Therapy (EBRT; radiation is directed at the tumor

from outside the body) while reducing side effects. Likewise, Intensity Modulated Radiation Therapy (IMRT; a highly focused beam of radiation that allows for a higher dose of radiation) has also improved. IMRT is now image-guided to enable tracking of the prostate, a mobile organ. This advancement ensures that only the cancer is irradiated and not the surrounding healthy tissue.

Dr. Kantoff, a medical oncologist, discussed the growing list of systemic therapies currently under clinical investigation. He highlighted some of the therapies he considers the leading agents in the pipeline to follow that may have a significant impact on prostate cancer treatment. Some of these include:

- **Abiraterone:** an inhibitor of the enzyme CYP17, which results in blockade of tumor androgen synthesis in metastatic castration resistant prostate cancers. Phase III results released after the meeting showed that Abiraterone therapy resulted in a significant survival advantage (~4 months). It's likely that this drug will be approved by the year 2011.
- **MDV3100:** an androgen receptor inhibitor. Phase III trials for advanced prostate cancer are underway globally.
- **Denosumab:** an antibody that blocks the protein RANKL, which prevents osteoporosis, has been shown in randomized Phase III trials to prevent skeletal fractures in men undergoing androgen deprivation therapy.
- **PROSTVAC:** an immunotherapy that reinvigorates a patients' immune system to attack prostate cancer cells. PROSTVAC is currently in Phase III clinical trials.
- **XL184:** a compound that has dual inhibitor activity against VEGFR2 and MET, two genes which promote prostate cancer progression. Early results in advanced prostate cancer have encouraged fast-tracking the development of this agent.
- **Dasatinib:** a dual inhibitor which blocks both BCR/ABL and SRC proteins, developed initially for the treatment of drug resistant CML. Clinical trials for Dasatinib in prostate cancer are focusing on patients with a heavy burden of bone metastases.

Dr. Simons, President and CEO of PCF, concluded that the future of medical oncology depends on investigations that identify the functional role of gene fusions in prostate cancer. These studies will define new systemic approaches to battling prostate cancer.

Session 4

Targeting the Tumor Microenvironment

Major Points from Session 4:

- Prostate Botox injections may be a novel therapy for the treatment of localized prostate cancer.
- Immune cells infiltrate the prostate tumors and release a cancer-promoting factor, lymphotoxin. New medicines that block the activity of lymphotoxin are under development.
- Development of medicines that target reactive stroma may prevent progression to lethal prostate cancer.
- Mathematical modeling of prostate cancer can help build new hypotheses concerning mechanisms of disease progression.

Introduction:

Solid tumors, like prostate cancer, have an intimate relationship with the surrounding normal tissue known as the microenvironment. Cancer cells interact with the microenvironment in a coordinated mechanism based on signals and soluble factors to affect the natural history of the tumor. At advanced stages of cancer much of the surrounding tumor microenvironment is commandeered to function solely for the purpose of supporting and nourishing the tumor. Many cancer researchers are developing therapies to target the tumor microenvironment. This therapeutic approach can alter the tumor's "habitat" causing cancer cell "extinction."

Gustavo Ayala, MD

Dan L. Duncan Cancer Center, Baylor College of Medicine

Targeting the Neural Microenvironment in Prostate Cancer

What this means for patients: Botox injections may prevent local prostate cancer progression.

Dr. Ayala, the session moderator, showed that neural tissue, strands of nerves, surround and emerge from the prostate gland. He showed images of prostate cancer specimens demonstrating that prostate cancer is neurotropic, meaning that prostate cancer cells grow towards neurons. Results from a series of in vitro and in vivo mouse model experiments demonstrated that both neurons and prostate cancer cells grow towards each other, indicating that both cells might release soluble factors that attract the other cell type. Dr. Ayala and others showed that perineural diameter, a measure of prostate associated nerve tissue, is a strong predictor of prostate cancer specific death. To strengthen the argument that nerves promote prostate cancer progression, Dr. Ayala and his team showed that Botox (botulinum toxin; a neurotoxin) injections, which cause significant nerve cell death, reduced the size of prostate tumors in a mouse model. These findings were positive. Dr. Ayala received a 2010 PCF Creativity Award for his proposed clinical trial study using Botox in prostate cancer patients. In the study Botox will be injected into one side of patient's prostates 4 weeks prior to a planned radical prostatectomy. Dr. Ayala will analyze the subsequent prostatectomy specimens to determine whether the Botox injections changed the behavior of prostate cancer cells by destroying the nerves.

Michael Karin, PhD

University of California, San Diego

IkK- α - a Critical Regulator of Prostate Cancer Metastasis and Castration Resistance

What this means for patients: Agents that inhibit lymphotoxin may prevent prostate cancer progression to a lethal castration resistant state.

Immune cell also represent a component of the tumor microenvironment. In prostate cancer, lymphocytes can comprise as much as 60% of the total tumor volume. Dr. Michael Karin from UCSD reported on the effect of the inflammatory infiltrate (immune cells) on prostate cancer progression. Dr. Karin used a castration resistant prostate cancer (CRPC: most advanced stage of prostate cancer) mouse model to answer this question. He first presented data showing that androgen ablation (mimics androgen deprivation therapy; standard first-line therapy for advanced prostate cancer) caused a significant influx of immune cells into the prostate. Dr. Karin demonstrated that B cells, a type of immune cell, alone are able to accelerate the formation of CRPC. He showed that the mechanism underlying this cancer-promoting effect was a factor called lymphotoxin, which is released by B cells. Blocking lymphotoxin with an antibody in a prostate cancer mouse model caused a 2-fold increase in overall survival. Dr. Karin and colleagues proved that lymphotoxin is responsible for activating the NF κ B pathway, a well described cancer promoting signaling pathway, in cancer cells. His work highlights the critical cross-talk between tumor cells and their surrounding microenvironment. Dr. Karin is testing an experimental therapy that neutralizes the cancer-promoting activity of lymphotoxin.

LT produced by B cells is required for re- emergence of androgen –independent CaP

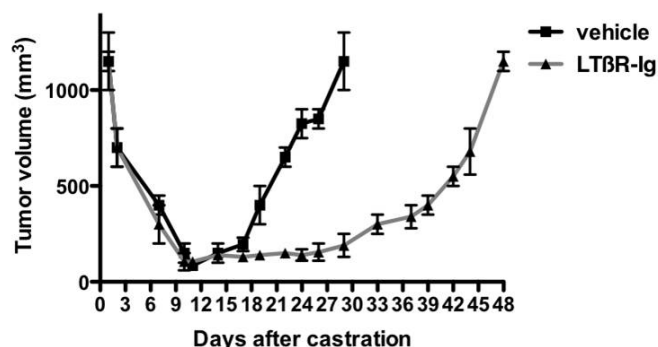


Figure 5: This graph shows how blockade of lymphotoxin activity (gray line) postpones progression to lethal, castration resistant prostate cancer in a mouse model.

David Rowley, PhD
Baylor College of Medicine

Co-Evolution of Reactive Stroma in Prostate Cancer Progression

What this means for patients: A new tool that will quantify the amount of reactive stroma surrounding a man's prostate cancer may differentiate indolent from lethal disease.

Stromal cells (connective tissue) surround prostatic glands and are a major component of the tumor microenvironment. Dr. Rowley, an expert on stromal cell biology, began his talk by showing that the stromal cell compartment of normal prostate is very different from prostate cancer. Prostate cancer stromal cells are differentiated from normal stromal cells based on the level of certain proteins. This was the first indication that the stromal cells in prostate cancer, termed reactive stroma, are different and may play an important role in tumor biology. Dr. Rowley and colleagues have published several reports showing that the quantity of reactive stroma is a predictor of poor prognosis in prostate cancer. He and his team currently focus on identifying the cell-of-origin of reactive stroma to discover agents that will destroy reactive stroma at diagnosis and potentially prevent prostate cancer progression. Dr. Rowley is also developing a new imaging technology that automatically measures the amount of reactive stroma in a tumor specimen. The goal is to provide physicians with a predictive tool that will inform early for the presence of lethal prostate cancer so that these patients can be treated aggressively immediately.

The Reactive Stroma Response:

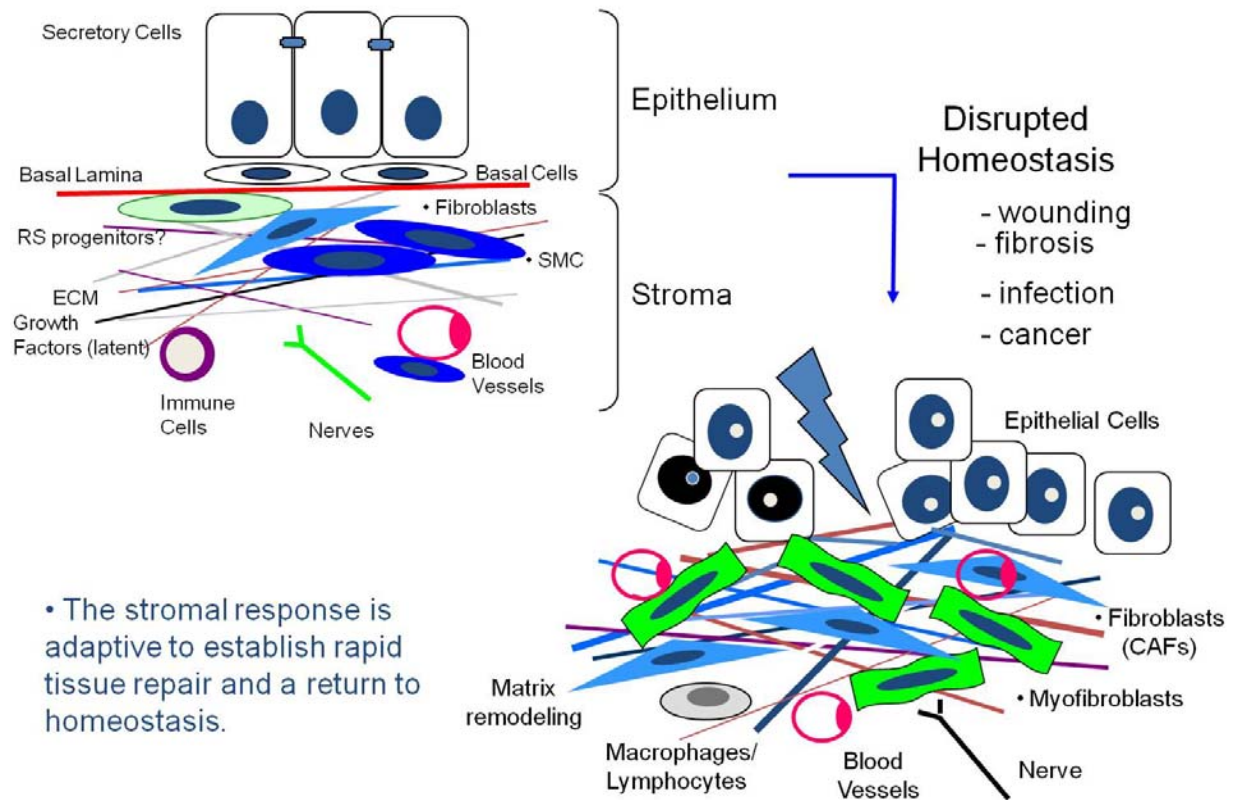


Figure 6: This is a model of how cancer causes normal stroma (all cells beneath the red line (basal lamina)) to transform into “reactive stroma.” The top left shows the steady state in normal, healthy tissue. The bottom depicts the disruption in homeostasis caused by cancer (black cells) and the generation of a tumor microenvironment. Notice an increase in blood vessels (pink), the appearance of immune cells (gray macrophage/lymphocyte), the appearance of myofibroblasts (green, type of reactive stromal cell) and cancer associated fibroblasts (blue; CAFs another type of reactive stromal cell). These changes in the microenvironment of prostate cancer promote the progression of the disease.

Alexander “Sandy” Anderson, PhD

H. Lee Moffitt Cancer Center and Research Institute

A Systems Approach to Prostate Cancer Progression: From Pathways to Pathology

What this means for patients: Application of mathematical modeling in cancer research can help distinguish research hypotheses with the greatest promise for success.

Dr. Anderson, the fourth speaker in this session, is a mathematician who models cancer cell growth and survival in the context of a dynamic environment in which the microenvironment and cancer interact in both a spatial and temporal manner. He formulated a complex equation that models prostate cancer from an ecosystem perspective, much like the models used to predict hurricane systems. As an example, Dr. Anderson showed a computer simulated experiment that altered the concentration of a growth factor, TGF β , in each sample. The model predicted that increased concentrations of TGF β would induce an overproduction of extracellular matrix proteins (ECM: the scaffolding material cells adhere to in space) which would cause cancer cell death. To validate this finding, Dr. Anderson and colleagues examined a mouse model with elevated levels of TGF β and observed increased ECM and abundant tumor cell death, as predicted by the math model. Dr. Anderson concluded by stating that this mathematical modeling system can be used to test hypotheses and provoke new hypotheses in prostate cancer research.

Special Lecture

Functional Characterization of Signaling Pathways in Cancer Cells: Application to Rare Cell Populations Such as CTCs

David Parkinson, MD
Nodality, Inc.

Major Point from Session:

- A test using a patient's cancer cells can predict therapy sensitivity and/or resistance before and during a treatment course, guiding treatment decision-making in real time.

What this means for patients: Patients will be prescribed medicines early-on that are predicted to achieve significant cell death in their unique cancer.

Discussion:

Dr. David Parkinson is the CEO of Nodality, a company producing predictive tests to optimize the treatment of patients with cancer. The Nodality test involves isolating patient cancer cells to discover in vitro the changes that occur at the molecular level in response to different therapies. Molecular profiling of fresh cancer cells treated with a variety of anti-neoplastic medications can identify drug sensitivity or resistance to a prescribed course of therapy. Resistant cells can be further analyzed to identify mutations that may be targetable by other agents enabling customized treatment care for each patient. This test was successfully applied to leukemia patients allowing physicians to provide up-front successful therapy. The goal is to optimize this assay for use on circulating tumor cells (CTCs; rare cancer cells that have broken away from the tumor and entered circulation) to track the natural history of solid tumors, such as prostate cancer, over time and after different therapies in each patient. This process would enable personalized oncology in real time. Nodality is already developing a next generation assay which can analyze 50-100 proteins simultaneously in a single cell. Analysis of 50-100 proteins will provide even higher resolution of the dynamic signaling pathways altered in tumor cells. Dr. Parkinson is leading this effort to design treatment strategies that would more effectively treat cancer.

Single Cell Dynamic Network Profiling

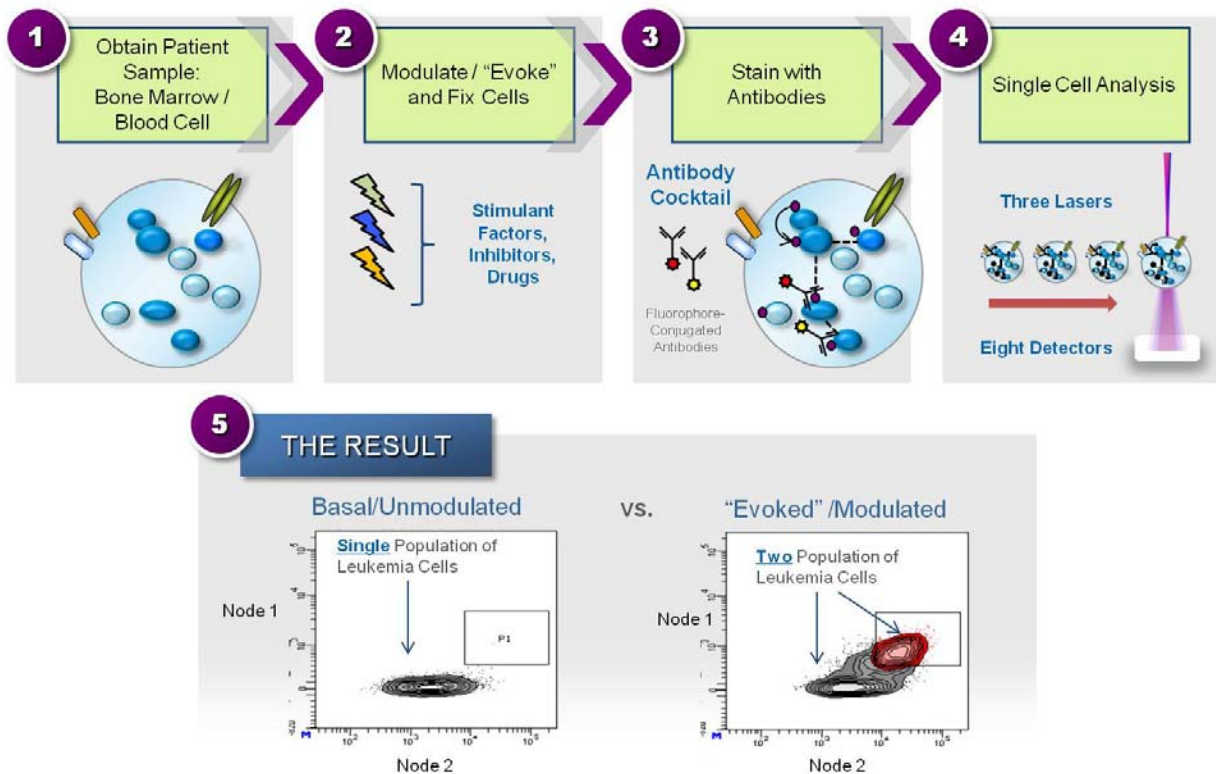


Figure 7: A schematic of the assay developed by Nodality to predict therapy sensitivity and/or resistance in patients before a course of cancer treatment. This assay has been shown to be useful for certain leukemia patients. Step 1: leukemic cells are isolated from patient bone marrow and treated in vitro with a therapy (Step 2). Steps 3 and 4: Cells are marked with labels (antibody cocktail) to determine differences between treated and untreated cells and are then analyzed by an instrument. Step 5: Cells (tiny black dots in the graph to the left) that were untreated are almost all identical except for a small population in the box marked P1. The graph on the right shows that the cell populations changed after therapy. Observe the increase in frequency of cells (tiny red dots) in the box. The red cells may represent a therapy-resistant population of leukemic cells. These findings demonstrate that certain therapies can change the molecular profile of cancer cells and may provide important insights on therapy resistance.

Session 5

The Pathologists' Sign-Out for Prostate Cancer in 2030 Panel Discussion

Panelists: David Parkinson, MD (Nodality, Inc.)
Mark Rubin, MD (Weill Cornell Medical School)
Angelo De Marzo, MD, PhD (Johns Hopkins University)
Scott Tomlins, MD, PhD (University of Michigan)
Massimo Loda, MD (Dana-Farber Cancer Institute)

Major Points from Session 5:

- In the future the pathology department may be termed the “Department of Integrated Diagnostics” because diagnosing a patient’s disease will require the interpretation of many different test results that will provide the pathologist with a spectrum of molecular and cellular characteristics.
- Such analyses will cause a shift from prognosis to prediction. A pathologist will likely play a more constant role, predicting therapy sensitivity or resistance before and during a treatment course.
- The next generation of pathologists will need a new curriculum that includes bio-informatics and epidemiology.

Discussion:

This panel discussion led by Dr. Parkinson focused on the future role of prostate cancer pathologist in the next twenty years. Historically, pathology was a medical specialty concerned with the diagnosis of disease based laboratory analysis of bodily fluids, such as blood, urine, and tissues using the tools of chemistry, microbiology, hematology and molecular pathology. Today, with the advent of “-omics” technologies, pathologists are faced with a critical decision, do they expand their expertise to include molecular profiling at the genomic, transcriptomic, proteomic and metabolomic level?

To adapt to this changing landscape of technology, pathology residents will have to become familiar with bio-informatics and epidemiology. Dr. Loda suggested that the department of pathology may become the “Department of Integrated Diagnostics” because of the numerous assays available to analyze a person’s disease. Pathologist would be responsible for interpreting all of the combined data to make clinical decisions.

The panel speculated that much of pathology would shift from prognosis to prediction. Pathologist could become central to predicting therapeutic response by analyzing changes in patient tissue or circulating tumor cells (CTCs). Dr. Tomlins noted that sub-typing prostate cancers based on genetic alterations such as TMPRSS2:ERG gene fusions and matching each subtype to a targeted therapy will be a critical advancement that pathologists could spearhead.

Dr. Rubin stated that in the future integrating molecular imaging results with tissue biopsies will also become essential. Such analyses will enable pathologists to decipher drivers of disease progression and predict the “best-fit” therapeutic agent.

The panel agreed that the development of biomarkers, even for molecular imaging, will likely be another role many pathologists undertake.

In summary, pathology will clearly remain an important medical discipline; however the assays used and clinical responsibility may be changing. Therefore, training the next generation of pathologists will require a remodeling of the curriculum to address and adapt to these changes.

Special Lecture

Targeting Transcription Factor-DNA Interfaces by Small Molecules

Peter Dervan, PhD
California Institute of Technology

Major Points from the Special Lecture:

- Polyamides are small compounds that interfere with protein-DNA binding.
- New polyamides that block AR binding to DNA results in prostate cancer cell death in lethal castration resistant cell lines.

What this means for patients: Polyamides are a new class of experimental anti-androgen signaling agents.

Discussion:

Androgens (male hormones, including testosterone) and the androgen receptor (AR: a protein that binds androgens and turns “on” genes) work together to fuel prostate cancer growth and survival. Androgens enter the cell and bind to AR which instructs AR to enter the cell nucleus and attach to DNA. When AR attaches to DNA it turns “on” cell growth and survival genes. Therapeutic agents that block androgen synthesis or activity of AR directly have significant clinical efficacy in advanced prostate cancer. However, in most patients this activity is transient and results in resistance, termed castration resistant prostate cancer (CRPC), a lethal form of the disease. However, even in CRPC AR signaling remains active despite androgen deprivation therapy, suggesting the need for new therapies that target AR differently than current therapies.

Dr. Dervan presented a new class of molecules, designed in his laboratory, that interfere with AR’s DNA binding ability. In the absence of DNA binding, these small molecules, called polyamides, induced significant cancer cell death in CRPC cell lines. Dr. Dervan and his team showed that a large percentage of AR driven genes are indeed turned “off” in the presence of specific polyamides. However, some genes remained “on.” This is because AR can also turn genes “on” by connecting with other proteins that can directly bind DNA. Dr. Dervan and colleagues are currently working on identifying the other AR protein binding partners to develop polyamides that interfere with their direct interaction. Dr. Dervan plans to produce a cocktail of polyamides that would completely abolish the androgen signaling system in prostate cancer cells and cause tumor cell death.

Special Lecture

Using mTOR Inhibitors as a Platform for Developing Rational Combination Therapies

Karen Cichowski, PhD
Harvard Medical School

Major Points from the Special Lecture:

- DAB2IP is a tumor suppressor gene that blocks two potent cancer-promoting signaling pathways.
- Loss of DAB2IP in prostate cancer mouse models results in lethal prostate cancer with widespread metastases. These models represent important new tools for prostate cancer research.
- DAB2IP protein levels in prostate biopsies are inversely correlated with human prostate cancer stage.

What this means for patients: Mimicking DAB2IP activity by suppressing both the RAS and NF κ B pathway is a druggable therapeutic strategy worth of testing

Discussion:

Dr. Karen Cichowski studies the molecular mechanisms that drive progression of advanced and/or metastatic prostate cancer. She noted that the RAS signaling pathway (a potent tumor promoting pathway) is over activated in advanced prostate cancer. However, the mechanism by which RAS becomes activated is largely unknown. This motivated Dr. Cichowski and colleagues to investigate a class of proteins called RAS-GAP proteins that coordinate with the RAS pathway. There are a total of 14 RAS-GAP factors in humans. One of the RAS-GAPs, NF-1, has already been described as a tumor suppressor (a gene that has anti-cancer activity) in 4 different types of cancer. Could other RAS-GAPs function as tumor suppressors in prostate cancer?

Dr. Cichowski developed a RAS-GAP tumor suppressor screening assay (a high throughput method of testing the function of multiple proteins in different cell populations) which identified DAB2IP as a potent tumor suppressor RAS-GAP. She showed that human prostate cells with deficient DAB2IP levels formed high grade prostate cancers when injected into mice. The data revealed that these tumors promoted cancer cell invasion and wide-spread metastasis. Analysis of human prostate cancer specimens revealed that DAB2IP levels are progressively lost in advanced prostate cancer. Dr. Cichowski found that DAB2IP loss causes aggressive prostate cancer because it controls both the RAS pathway and NF κ B pathway (another tumor-promoting signaling pathway). Reports from Dr. Jer-Tsong Hsieh's laboratory previously showed that another protein, EZH2, is progressively elevated in prostate cancer and directly lowers the level of DAB2IP. Dr. Cichowski's research findings are the first to show the consequences of DAB2IP loss in prostate cancer. She is currently developing novel combination therapy strategies that will target both the RAS pathway and cell stress pathways in prostate cancer to produce potent cancer cell death. Dr. Cichowski is building a foundation for rational targeted therapy design.

The Ras pathway is commonly deregulated in human cancer

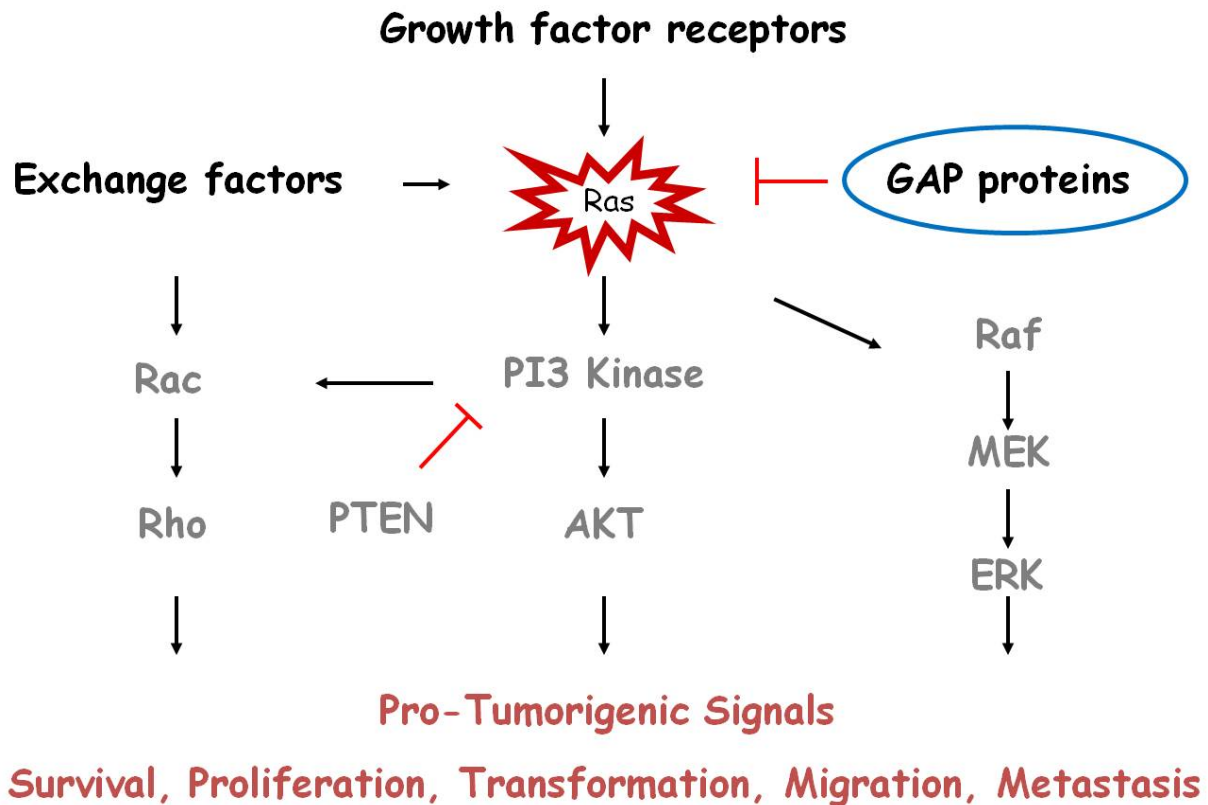


Figure 8: This figure shows the network of proteins that comprise the RAS signaling pathway. DAB2IP is a member of the GAP proteins which inhibit the activity of RAS (red inhibitory symbol). The arrows denote protein activation.

Special Lecture

Oncogenic Feedback – Basic and Clinical Implications

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

Major Points from Session:

- Cancer cells acquire mutations in parallel signaling pathways that converge to turn “on” the same cell growth and survival genes.
- Inducing widespread cancer cell death requires combination therapies that target all cancer-promoting pathways.

What this means for patients: Understanding redundancy in signaling pathways will help to predict appropriate therapies and pathways that will allow escape (resistance).

Discussion:

Dr. Rosen discussed the conundrum of therapeutic resistance to agents that target critical cancer-causing cellular networks. He hypothesizes that using a single targeted agent is not enough because cancers have a strong selection bias for mutational activation of parallel pathways that converge and activate the same downstream genes. These tumors also have “feed-forward” systems in some cases. Dr. Rosen showed results from experiments performed on cancer cells with mutational activation of the oncogene K-RAS, a common event in human tumors. The data showed that agents that inhibit MEK, a protein downstream of K-RAS, had a significant anti-cancer effect on some cell lines but not all. They discovered that the cancer cells that were resistant also had a mutation in a parallel signaling pathway called PI3K/AKT, another commonly activated pathway in human cancers. The resistant cancer cells could be killed by using combined therapy with both a MEK inhibitor and an AKT inhibitor (a protein downstream of PI3K activity). Prostate cancer cells treated with combined therapies that together blocked multiple oncogenic signaling pathways enhanced the frequency of cell death. Dr. Rosen concluded by stating that the future of oncology is combination therapies that target all major oncogenic pathways in a patient’s tumor.

Session 6

Pro-Active Surveillance

Major Points from Session 6:

- Active surveillance is not watchful waiting or “wishful waiting.”
- Selecting patients for active surveillance is a prediction problem that should consider stage and grade of tumor biopsies but not PSA levels.
- Nine copy number variants (CNVs) were identified as prostate cancer risk markers. Early results already show that one of the CNVs causes increased prostate cancer cell growth.

Introduction:

Although PSA screening has saved many men’s lives it has also increased the number of men diagnosed with very low grade cancer who undergo potentially unnecessary treatments which often compromise their quality of life. Active surveillance refers to observation and regular monitoring of prostate cancer without invasive treatment. Active surveillance can be used when an early stage, slow-growing prostate cancer is suspected. Pro-active surveillance is defined as the field of study that carefully observes men on active surveillance in a large, well-defined population over a long period of time (decades). The goal of Pro-Active Surveillance is to establish a multi-institutional collaboration to discover biomarkers that determine a need for treatment intervention and/or maintenance of indolent disease. The speakers in this session each discussed some of the challenges of Pro-Active Surveillance and how their research aims to provide solutions.

H. Ballentine Carter, MD
Johns Hopkins University

Pro-Active Surveillance: An Underutilized Management for Localized Prostate Cancer

What this means for patients: Patient selection for active surveillance is under careful investigation to ensure that only patients with an indolent form of the disease are given this option.

Dr. Ballentine Carter, the moderator and first speaker of the session, clearly stated that active surveillance is not watchful waiting or “wishful waiting.” He defined active surveillance as follows: 1) Careful **selection** of men at low risk of harm from prostate cancer without treatment, 2) careful **monitoring** of those who select surveillance, and 3) curative intervention for men who no longer meet criteria for surveillance. Dr. Carter summarized the outcomes of current Active Surveillance programs stating that the most common triggers for intervention are rising PSA and grade change on surveillance biopsy. Approximately 25-50% of men will receive active treatment after 5-10 years of active surveillance. Cancer specific survival across cohorts is >95% with short follow-up ~5-10 years. However, Dr. Carter noted that a critical challenge to overcome is to definitively define “lethal” prostate cancer. Markers of an aggressive cancer are needed that will be used to identify those who need treatment and for which active surveillance is not a safe option.

Watchful Waiting versus Surveillance

	Watchful Waiting	Active Surveillance
Primary aim	Avoid treatment	Individualize management
Patient /Tumor Characteristics	Limited life expectancy/ advanced disease	Fit for radical treatment/ localized disease
Treatment Timing	Delayed	Early
Treatment intent	Palliative	Curative

Adapted from Parker C, Lancet Oncology 2004

Figure 9: This table illustrates the important differences between watchful waiting and active surveillance.

Andrew Vickers, PhD
Memorial Sloan-Kettering Cancer Center
Statistical Basis of Patient Selection for Active Surveillance

What this means for patients: Careful statistical modeling can improve patient selection for active surveillance.

Dr. Andrew Vickers, a bio-statistician, presented compelling evidence suggesting that selecting patients for Active Surveillance is a prediction problem and should not be based on clinical judgment. To explain, he showed that when a clinician examines patient data he/she not only considers the prostate cancer specific clinical characteristics but also patient preference, anxiety, social support, etc., while a statistician only models the prediction based on quantitative measurements specific to prostate cancer. Dr. Vickers proposed a selection algorithm for patients involving baseline characteristics (i.e. pre-surgery stage, grade and PSA: Epstein criteria) and following patients until a clinical event occurs such as biochemical relapse. These data are then used to determine relationships between baseline characteristics and the event. Using this model Dr. Vickers showed that in a study coordinated at MSKCC use of PSA at baseline as a predictor of Epstein criteria failure increases the risk of treatment intervention by 67%. Of the 34 men who failed by PSA, only 5 (15%) had an upgraded biopsy (increase in Gleason grade compared to first biopsy). He suggests that stage and grade of tumor biopsies drive risk and that PSA and PSA velocity may be important indicators for biopsy but not treatment.

Francesca Demichelis, PhD
Weill Cornell Medical College

Germline Copy Number Variants (CNVs) as Risk Markers for Prostate Cancer

What this means for patients: Discovery of copy number variants (CNVs) that predict prostate cancer risk will identify those patients who need close monitoring to ensure an early diagnosis when the cancer may be curable.

Dr. Francesca Demichelis studies heritable genetic factors that predict prostate cancer risk. Identification of heritable risk factors could help select patients for either Active Surveillance or treatment. Since the complete sequencing of the human genome, many groups reported findings on single nucleotide polymorphisms (SNPs: a single letter change in the DNA code of over 3 billion letters) that predicted prostate cancer risk. However, none of these reports indicated the functional significance of these small mutations and how they confer an increased risk for prostate cancer. Dr. Demichelis is investigating a different type of genetic alteration called copy number variants (CNVs) which are defined as amplifications (duplicated, triplicated, etc.) or deletions of a region of DNA. Approximately 6% of the human genome contains CNVs. CNVs can directly impact the quantity or function of proteins. To discover CNVs that predict prostate cancer risk, Dr. Demichelis is collaborating with an Austrian group from the Innsbruck Medical University (Innsbruck, Austria) who has a highly annotated cohort of over 5,000 men with follow-up data (Tyrol Prostate Cancer Early Detection Program) and with the Brigham and Women's Hospital, Harvard Medical School (Boston, MA). Dr. Demichelis shared early results showing that approximately 200 CNVs were associated with prostate cancer risk and 67 were nominated as best candidates based on statistical modeling. After confirming the validity of the results in a smaller independent cohort, they are now testing the associations in a U.S. cohort. Dr. Demichelis and colleagues have begun experiments to determine the functional significance of the identified prostate cancer risk CNVs. Using prostate cancer cell lines she has already shown that one of the CNVs dramatically increases the proliferation rate and the invasive ability of both normal prostate and prostate cancer cells. Dr. Demichelis stated that the discovery of genetic markers of aggressive prostate cancer risk would enable clinicians to identify patients that may need routine screening, or aggressive treatment at the time of diagnosis, early on.

CNVs associated with PCA Risk

Biological Impact

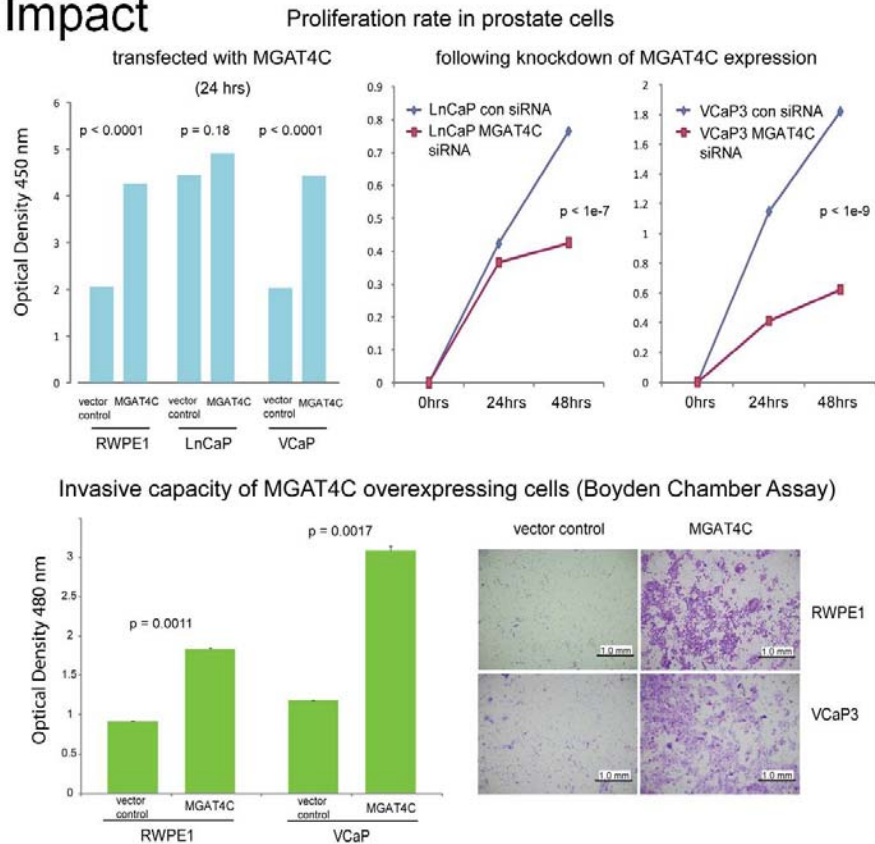


Figure 10: Copy Number Variants (CNVs) are genetic alterations that result in the amplification or deletion of large regions of DNA. One of the identified CNVs associated with prostate cancer risk amplified a region of DNA that harbored the gene MGAT4C. These graphs show that when normal prostate and prostate cancer cells express high levels of this gene they proliferate at a faster rate (top panel) and are more invasive (bottom panel). These data demonstrate how this particular CNV imparts increased risk.

Session 7

Adiposity, Metabolism and Prostate Cancer Progression

Major Points from Session 7:

- Caloric restriction improves overall cardiovascular health and reduces chronic inflammation, a critical cancer risk factor.
- Balancing the proportion of protein intake in an overall healthy diet may be important to protect against cancer progression.
- PEDF is a regulator of both tumor blood vessel formation and fat metabolism making it an attractive therapeutic target for prostate cancer.
- Metformin reduces activated AKT, a cancer promoting signaling molecule elevated in prostate cancer. Prospective clinical trials are underway to examine the anti-cancer activity of Metformin.

Introduction:

Cellular metabolism (all biochemical reactions that occur in a cell used to synthesize molecules, such as proteins) is directly impacted by diet. The balance of fat, protein and carbohydrates as well as total calorie consumption influence the type of biochemical reactions occurring in our cells, which is especially important in the context of cancer. The speakers' presentations in this session were very diverse in topic area. However, the message was similar; imbalance of any metabolic process can be exploited for cell growth and survival by cancer cells.

Luigi Fontana, MD, PhD

Washington University in St. Louis

Italian National Institute of Health

Long-Term Effects of Caloric Restriction on Cancer Risk Factors

What this means for patients: Both calorie and protein intake may be important to monitor in cancer patients.

Dr. Luigi Fontana, the moderator of the session, studies the long-term effects caloric restriction (CR) on cancer and other chronic diseases. He reviewed the literature for animal studies of CR and showed that in mice, CR without malnutrition protects against a wide range of spontaneous, radiation- and chemical- induced tumors. These mice also experienced significant increased longevity. In monkeys, 20 years of CR resulted in 50% less mortality from cardiovascular disease and cancer.

Dr. Fontana designed a study in humans that compared 3 groups: Group 1: sedentary individuals on a western diet, Group 2: active lifestyle (master athletes eating a western diet), and Group 3: caloric restriction diet (CR: 25-30% fewer calories than western diet) with adequate nutrition (at least 100% of RDA for each nutrient). The results of this study revealed that CR humans have an optimal cardiometabolic profile, including low LDL-cholesterol, high HDL-cholesterol, low

triglycerides, low fasting insulin and glucose, low C-reactive protein, low blood pressure, no plaques in their carotid arteries, and a much more elastic and young heart. These individuals are also protected against obesity, insulin resistance, inflammation and oxidative stress, which are important factors implicated in the pathogenesis of many epithelial cancers, including prostate cancer. Plasma testosterone levels, the critical fuel for prostate cancer, were also reduced in CR individuals. In addition, Dr. Fontana found that protein intake is more important than energy intake in regulating plasma concentrations of IGF-1, a growth factor that plays an important role in prostate cancer growth. Unlike in rodents, long-term severe CR does not reduce total and free IGF-1 levels in humans if protein intake is high. Lowering protein intake in these individuals significantly reduced plasma IGF-1 concentration, which may reduce the risk of developing prostate cancer. These results indicate that prostate cancer patients should consider regulating protein intake as part of a healthy and balanced diet.

Finally, Dr. Fontana analyzed the gene expression profile of skeletal muscle in the CR and western diet groups, and found that caloric restriction results in some of the same gene expression adaptations related to longevity in CR rodents. Fontana concluded by saying that more studies are needed to elucidate the molecular mechanisms underlying the beneficial effects of CR and other dietary interventions (e.g. fasting, protein restriction, intake of combinations of phytochemicals). Such studies have the potential to lead to drugs and therapies for prevention and treatment of a broad-spectrum of cancers.

CR practitioner before starting CR and after 7 years of CR

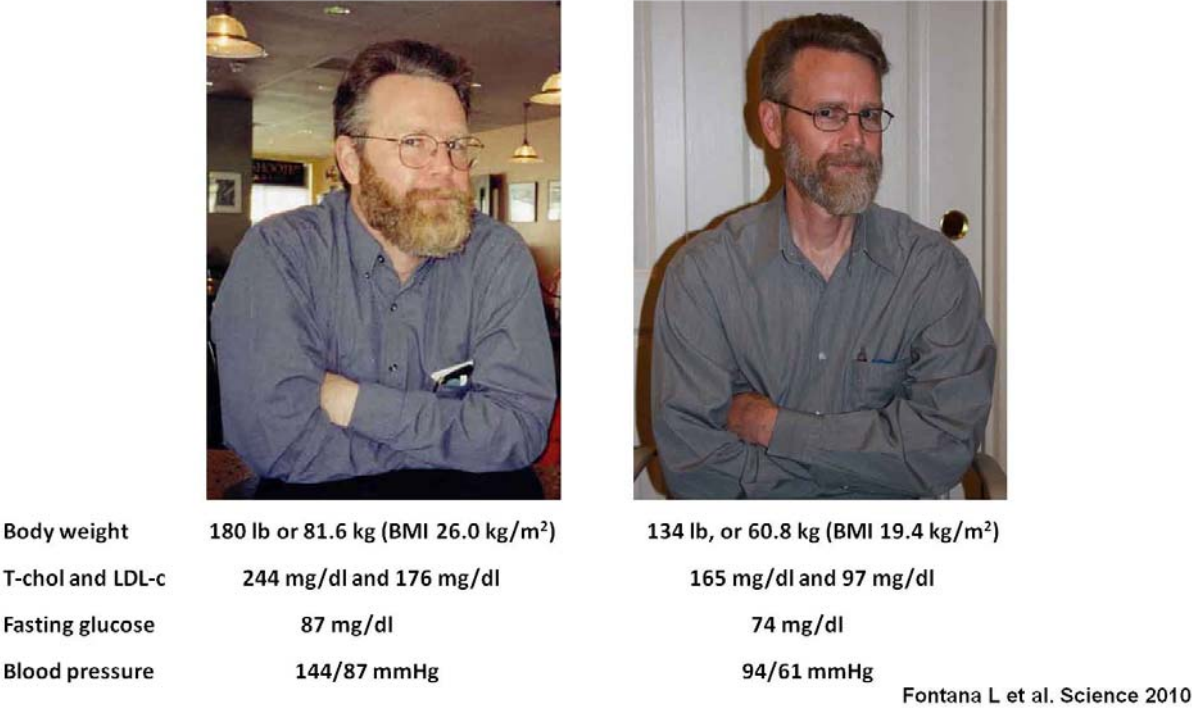


Figure 11: This figure shows the before and after physical and clinical characteristics of a caloric restriction practitioner.

Jennifer Doll, PhD
NorthShore University HealthSystem Research Institute
Dysregulated Lipid Metabolism in Prostate Cancer

What this means for patients: PEDF, a master regulator of fat and tumor blood vessel formation, is a novel candidate therapeutic target for prostate cancer.

Dr. Jennifer Doll presented her research results concerning a molecule called Pigment Epithelium-Derived Factor (PEDF), which is an inhibitor of angiogenesis (blood vessel growth). Angiogenesis is an important process in cancer progression and is the target of many anti-neoplastic treatments. Previously, Dr. Doll and colleagues reported that PEDF levels are reduced in prostate cancer as compared to normal prostate tissue. Dr. Doll showed that mice deficient in PEDF have increased fat mass due to increased adipogenesis (generation of fat cells). These mice also exhibited prostate hyperplasia (increased cell proliferation of prostate cells). Obesity is a strong predictor for prostate cancer risk and at diagnosis a strong predictor of prostate cancer specific death. Together these findings motivated Dr. Doll to propose a study to investigate the relationship between fat metabolism, PEDF, and prostate cancer for which she received a 2010 PCF Creativity Award. In this study she will determine the metabolic profile of different fat depots (visceral and subcutaneous fat) in obese men with prostate cancer to identify factors that may lead to prostate cancer progression. Visceral fat is most abundant in obese patients. To date, she discovered a difference in the balance of fatty acids between visceral and subcutaneous fat but she has yet to uncover the functional significance of this difference. Her future work will elucidate how the fatty acid profiles from visceral fat correlate with tumor characteristics, obesity measures and PEDF levels.

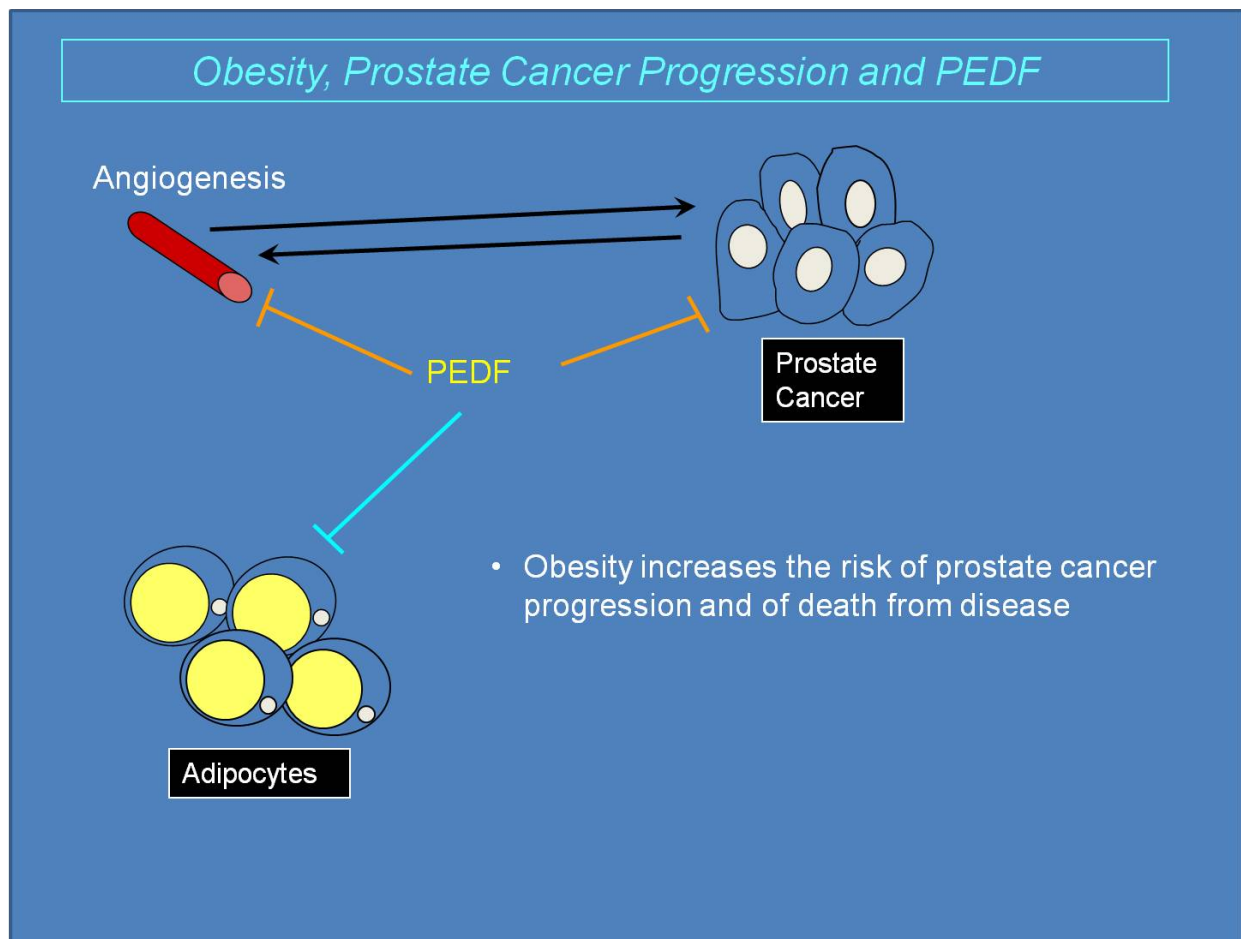


Figure 12: This model shows how the protein PEDF is a critical negative regulator of fat generation, blood vessel formation and prostate cancer. PEDF protein levels are progressively lost with increasing stage of prostate cancer.

Akash Patnaik MD, PhD

Harvard: Beth Israel Deaconess

Targeting the Metabolic Milieu and PI3K/mTOR Signaling Pathways in Advanced Prostate Cancer

What this means for patients: Metformin, a diabetes medicine, is under clinical investigation for the treatment of prostate cancer.

Dr. Akash Patnaik, a 2010 PCF Young Investigator, shared preclinical data to target key signaling and metabolic molecules known to drive prostate cancer cell growth which include PI3K/AKT, mTOR and MEK. He is also studying the anticancer mechanism of a medication, metformin, typically used to treat Type 2 diabetes. Several reports showed that patients prescribed metformin experience a lower risk of prostate cancer, and those already diagnosed with prostate cancer have better clinical outcomes. Dr. Patnaik's research is focused on understanding the mechanism by which biguanides, such as metformin, produce an anti-neoplastic effect. Pre-clinical data revealed that prostate cancer cells in culture treated with related biguanide phenformin inhibit metabolic pathways that are hyperactivated in prostate cancer. Dr. Patnaik designed a clinical study, a central component of his 2010 PCF Young Investigator Award proposal, which will randomize patients undergoing radical prostatectomy to metformin or placebo. After treatment the patients' prostates will be removed and examined for evidence of change in cancer cells. Dr. Patnaik's research findings will reveal new combinatorial therapeutic strategies, which would include the use of metformin, to improve mortality from prostate cancer.



Glucose-Lowering Therapies in Type II Diabetes & Cancer Risk

- Pts on insulin or insulin secretagogues were more likely to develop solid pancreatic and colon cancers.
- Metformin use was associated with lower risk of pancreatic and colon cancers. (*Diabetologia*. 2009 Sep;52(9):1766-77)
- Diabetic patients receiving metformin and neoadjuvant chemotherapy for early-stage breast cancer have a 3-fold higher pCR rate than diabetics not receiving metformin. (*J. Clin Oncol* 2009 27:3297-3302)

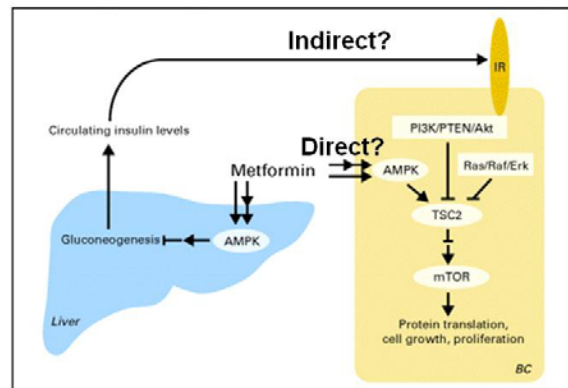


Figure 13: This figure lists some of the reports that first observed the lower risk of cancer in patients treated with glucose-lowering therapies such as Metformin. The illustration shows that Metformin activates the protein AMPK in both a liver (blue) and a cancer (yellow) cell. Activation of AMPK in a cancer cell inhibits the cell growth and proliferation signal.

Special Lecture

Co-opting Moore's Law: Design of Vaccines and Therapeutics on a Wafer

Joseph DeSimone, PhD
University of North Carolina

Major Points:

- The PRINT platform is a scalable system that can design highly customized nanoparticles for vaccine and medicine delivery.
- Nanoparticle delivery of chemotherapies directly to tumors may overcome some of the harsh side effects caused by standard intravenous chemotherapy.
- Nanoparticles packaged with siRNA (molecules that can block expression of specific genes) that target key cancer-promoting proteins previously deemed “undruggable” will open up new avenues for drug discovery and development.

Discussion:

Major challenges in drug development are the numerous biological barriers, such as the cell membrane, that prevent medicines from entering and destroying them. Applying nanotechnology to drug development has the potential of overcoming biological barriers. Nanotechnology is a field that develops materials and devices on a nanoscale (atomic and molecular scale). Dr. DeSimone, a bioengineer, is at the leading edge of nanotechnology and medicine. He has adapted the emerging techniques from the microelectronics industry to design and fabricate new vaccines and medicines. In the 1970s the minimum size of a semiconductor was 10 microns (size of a large cell), today its 45 nanometers (the size of a virus); ideal for drug delivery. As a result, Dr. DeSimone and colleagues created the Particle Replication in Non-wetting Templates (PRINT) platform. PRINT affords tight control over key design parameters for nanoparticles, such as: size, shape, chemical composition, deformability and surface chemistry. Medications can be incorporated into these particles. The ability to manipulate any one of these features enables tailored synthesis of nanoparticles that are optimal for a particular drug and its target cell. For example, Dr. DeSimone showed that nanoparticles targeted to the liver should be less than 150nm in size while particles targeted to tumor tissue must be less than 100nm in size. He also showed that an increase in deformability (lower in stiffness) results in better biodistribution (particles disseminate to all tissues) and a longer elimination half-life (longer lasting drug activity).

For prostate cancer treatment, Dr. DeSimone showed that PRINT particles carrying docetaxel (standard chemotherapy for advanced prostate cancer patients) can deliver the same cytotoxic effect as docetaxel alone but with lower drug concentrations. The data showed that there was twice the amount of docetaxel in the tumor in the mice treated with the nanoparticles. The hope is that this technology could significantly reduce the many side effects of all chemotherapies in humans.

Dr. DeSimone also showed that PRINT particles could efficiently deliver siRNA (molecules that can directly block expression of important cancer-causing genes) in mouse models of prostate cancer, resulting in a significant reduction in tumor growth.

Dr. DeSimone is a pioneer in the field of medicinal nanotechnology. His research will improve delivery and lower toxicity of currently available medicines and enable the delivery of novel targeted therapies to previously deemed “undruggable” targets.

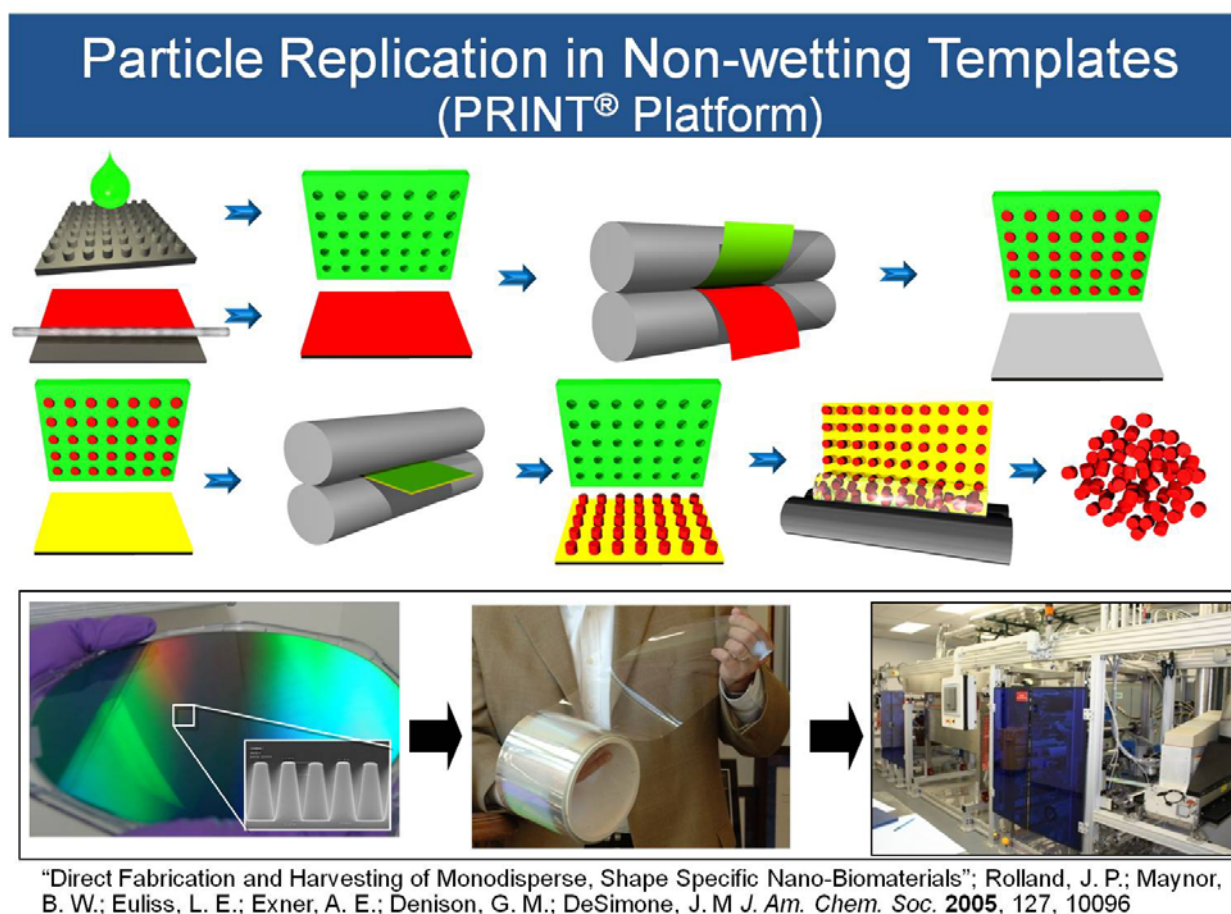


Figure 14: This schematic shows each step of the nanoparticle PRINT production process. The first step involves layering two different types of biomaterials onto two separate plates. One plate (the top with green color) is covered with an adhesive material formed according to the desired nanoparticle shape. The other plate contains the bio-material (the bottom with red color) destined to become the nanoparticle. The two plates are opposed to each other and pressed through a rolling machine. This produces one plate with both materials adherent to each other in the defined shape. The next step involves transferring the red bio-material onto a less adhesive plastic material (yellow in schematic, shown in middle bottom panel) which enables the final release and collection of the nanoparticles.

Session 8

microRNA and Prostate Cancer Progression

Major Points from Session 8:

- Pseudogenes once considered “junk DNA” and commonly amplified or deleted in cancer, may be important new therapeutic targets in cancer.
- miR-21 is a potent cancer-promoting molecule and is a promising target for therapy.
- miRNAs isolated from patient blood may be diagnostic, prognostic and potentially predictive of therapy response.
- Delivery of miR-26 induced significant cell death in prostate cancer mouse models opening up a new treatment approach for prostate cancer.

Introduction:

microRNAs (miRNAs) are small molecules that bind to and silence messenger RNAs, molecules which code for the production of proteins. One miRNA can recognize a dozen mRNAs. In human cancers, miRNA levels are commonly altered to regulate expression of oncogenes (cancer-causing genes) and repress the production of tumor suppressor genes (anti-cancer genes). The speakers in this session discussed discoveries related to miRNA regulation of prostate cancer progression.

Pier Paolo Pandolfi, MD, PhD

Harvard Medical School and Beth Israel Deaconess Medical Center

A Novel Biological Dimension for Coding and Non-Coding mRNAs and Its Role in Tumorigenesis

What this means for patients: Targeting pseudogenes, non-coding genes, may be a promising new treatment strategy for cancer.

Dr. Pier Paolo Pandolfi introduced a new theory on how RNA transcripts can communicate. His theory is the first to describe a cellular role for the ~17,000 pseudogenes (genes that are almost identical to genes that code for a protein but are non-coding) in the human genome. Since their DNA sequences are so similar, pseudogenes and their counterpart genes have almost identical RNA (code produced as a result of translating DNA) sequences. Dr. Pandolfi has named these similar RNAs: competitive endogenous RNAs (ceRNAs). He reasoned that because of the similarity, microRNAs that target a pseudogene will also target the counterpart gene.

How does this translate to prostate cancer progression? In prostate cancer the levels of the PTEN tumor suppressor gene are frequently reduced, which increases cell proliferation and survival of cancer cells. Dr. Pandolfi showed that when the PTEN pseudogene, PTENP1, is overexpressed in prostate cancer cells the level of PTEN increases. This is because PTENP1-ceRNA competes for the same pool of microRNAs as PTEN-ceRNA; this depletes the miRNA pool targeting PTEN-ceRNA thus increasing the amount of PTEN protein produced. In human cancers, the PTENP1 pseudogene has been found to be deleted which reduces competition for the

microRNAs that silence PTEN causing an increase in PTEN targeting microRNAs, thus leading to a loss in PTEN protein levels, and increasing the chances of developing cancer.

Discovering the role of pseudogenes advances our understanding of cell biology. In particular, it will help us understand how the genetic alterations in non-coding regions of the DNA, such as pseudogenes, can impact the function of coding DNA. This will lead to new therapeutic targets and more rational, targeted treatment strategies for the individual patient.

PTENP1-3'UTR regulates cellular PTEN levels

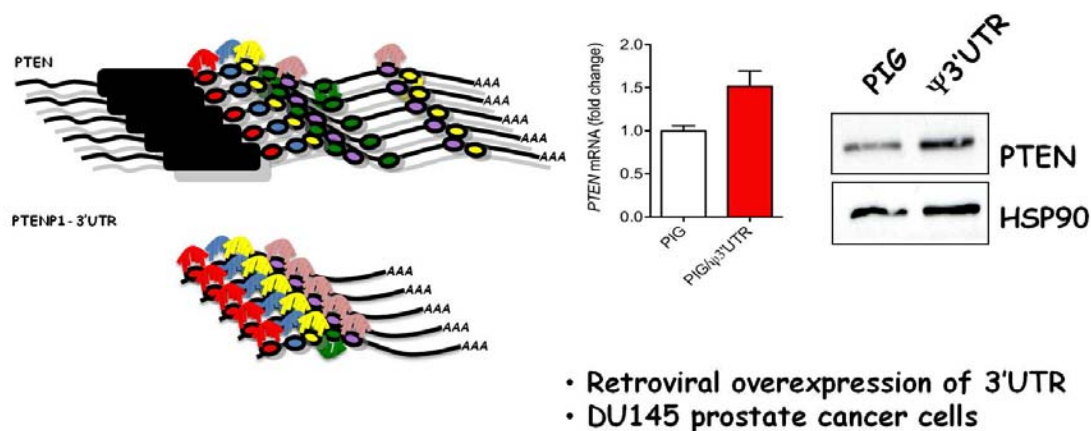


Figure 15: This figure illustrates how the psuedogene of PTEN, PTENP1, can regulate the level of PTEN protein levels. The black strands on the left represent PTEN mRNA (top) and PTENP1 mRNA (bottom). The miRNAs (different colored shapes) bind to the mRNA strand and block protein production. Notice that the presence of PTENP1 mRNA sequesters miRNA away from PTEN mRNA which results in protein production. The graph shows that when PTENP1 is abundant (red bar) then the PTEN protein levels increase (darker band in second column).

Shawn Lupold, PhD
Johns Hopkins University

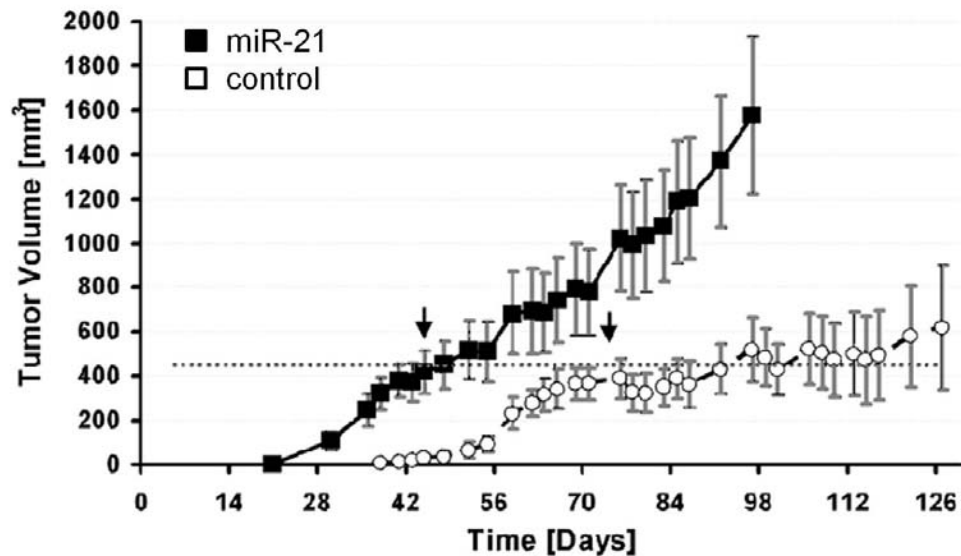
Androgen Receptor Regulated microRNAs in Prostate Cancer

What this means for patients: Development of medicines that inhibit miR-21 activity may prevent progression to lethal prostate cancer.

The androgen axis is considered the most critical signaling pathway in prostate cancer. At the top of this pathway is the androgen receptor (AR) which is activated by binding to androgens, male hormones such as testosterone (prostate cancer fuel). When activated AR binds to DNA a program of gene expression is initiated resulting in prostate cancer proliferation and survival. Dr. Shawn Lupold reported results concerning the relationship of AR control of miRNAs and their contribution to prostate cancer progression. Fifteen miRNAs were elevated in response to androgen treatment in two different prostate cancer cell lines. miR-21, described as highly expressed in 36 different human tumor types, was one of most elevated miRNAs. Dr. Lupold and colleagues showed that miR21 levels increased in response to androgen treatment and that treatment with Casodex, a drug commonly used for the treatment of advanced prostate cancer, depleted miR-21. Increasing the level of miR-21 by five-fold in prostate cancer cells was enough to impart castration resistant prostate cancer (prostate cancer that can grow without androgens). These cells also grew faster in xenograft models even at the time of castration.

Analysis of primary human prostate tumors revealed that 6/10 patients had 5-fold increase in miR-21. Further analysis of these human specimens demonstrated that miR-21 correlates with Gleason grade. Dr. Lupold's findings suggest that miR-21 is a critical regulator of prostate cancer progression and may be important in controlling the transition from androgen-dependent to the lethal androgen-independent form of the disease. Development of new therapies that target miR-21 or its downstream targets is warranted.

Elevated miR-21 is sufficient for Castration Resistant Prostate Cancer growth *in vivo*



Ribas et al, Can Res 69, 2009

Figure 16: This graph shows how elevating the level of miR-21 in mouse prostate cancer tumors (black boxes) results in growth of castration resistant prostate cancer.

Muneesh Tewari, MD, PhD
Fred Hutchinson Cancer Research Center
Circulating microRNAs in Cancer

What this means for patients: Development of a new “liquid biopsy” that measures miRNAs in blood could not only help clinicians with diagnosis and prognosis but also aid clinicians in determining the best treatment strategy for a patient.

Dr. Muneesh Tewari and colleagues reported in 2008 the existence of miRNAs in the blood of cancer patients. They showed that there were different species of miRNAs in cancer patients and that mir-141 was diagnostic for prostate cancer. This was an important finding because it has implications for the use of miRNAs as blood-based biomarkers of cancer, which could have a major impact on cancer diagnosis, prognosis, and treatment planning. Since 2008, greater than 40 papers were published describing the presence of miRNAs in the blood of patients with cancer, cardiovascular disease, liver injury, sepsis and stroke. Dr. Tewari showed data revealing that the circulating miRNAs come in two distinct packages: 1) in exosomes (small vesicles) and 2) in a protein complex. Dr. Tewari and his team are currently studying the biology of the different types of circulating miRNAs to determine whether one compartment provides more diagnostic information over another. They are also investigating whether cancer specific circulating miRNAs correlate to clinical outcomes. Dr. Tewari’s work may provide the field with a new “liquid biopsy” that could inform physician’s of a patients’ cancer characteristics and response to therapy in real-time. This could dramatically advance the field towards better, more personalized treatment strategies.

Josh Mendell, MD, PhD
Johns Hopkins University

microRNA Reprogramming in Cancer: Mechanisms Therapeutic Opportunities

What this means for patients: Therapeutic delivery of certain miRNAs, such as miR-26, may have a significant anti-cancer effect in prostate cancer patients.

Dr. Joshua Mendell studies the miRNAs that are highly expressed in normal tissues but commonly lost in human cancers. These miRNAs represent promising candidate therapeutic targets. He showed that in a cancer mouse model driven by elevated levels of the oncogene MYC (a cancer-causing gene commonly upregulated in prostate and other cancers) a number of miRNA species were reduced, including miR-26. Dr. Mendell and colleagues treated cancer cells with miR-26 and found that the cancer cells stopped growing. In the MYC-driven mouse cancer model, systemic therapeutic delivery of miR-26 resulted in significant tumor growth inhibition as compared to controls. Molecular analysis of these tumors showed that markers of proliferation were absent in the miR-26 treated tumors, while markers of cell death were abundant. Dr. Mendell's findings support the hypothesis that re-introducing miRNAs that were lost in cancer cells results in significant anti-cancer effects. This approach may open up a new avenue of cancer therapeutics that target miRNA regulation of cancer cell survival and proliferation.

Therapeutic miR-26a delivery suppresses tumorigenesis

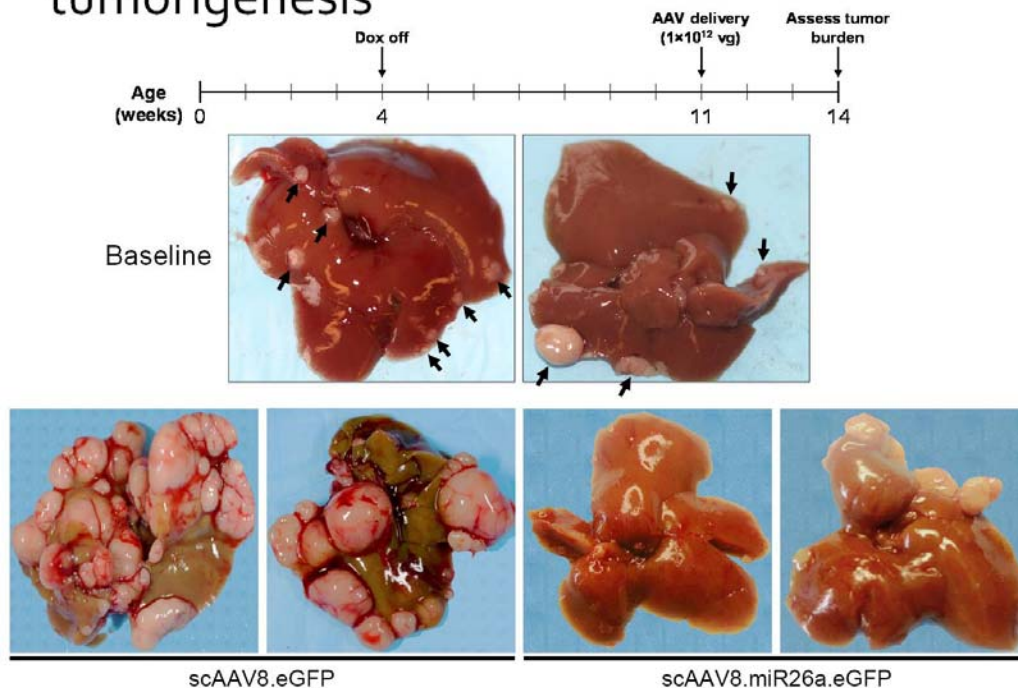


Figure 17: These are images of mouse livers with cancer. The top images show the amount of tumor burden at baseline. The two images on the bottom left are examples of livers that were untreated while the two images on the bottom right show the livers that were treated with miR-26. Observe the significant reduction in tumor volume in the miR-26 treated livers.

Special Lecture

Triaging the Pipeline of New Treatments for Advanced Prostate Cancer

Christopher Sweeney, MBBS
Harvard Medical School

Major Points from Session:

- A major challenge in drug development is identifying and prioritizing medicines that have the greatest potential for success to accelerate the process of FDA-approval for patients.
- Dr. Sweeney has generated a systematic approach to defining which agents in the pipeline should be prioritized for clinical trial investigations in prostate cancer.
- Matching the molecular profile of each patient's cancer with therapies that target molecular change in that tumor is critical for the future of predictive oncology and drug development.

What this means for patients: Delivering more, effective agents quickly to patients with advanced prostate cancer is possible if the research community and the FDA implement a system to prioritize medicines with the greatest chance of success.

Discussion:

Dr. Christopher Sweeney began by highlighting a critical challenge in drug discovery. Greater than 800 anti-cancer drugs are currently under development yet only 2-5 are FDA-approved per year. The question is how to prioritize the right drugs for accelerated delivery to patients. Dr. Sweeney presented an outline of his proposed process for triaging the drug pipeline for prostate cancer. First, prioritize medicines that target factors in patients predicted to provide a response. As an example, patients with BRAF gene fusions should be selected for trials that test therapies which target BRAF activity. Second, develop agents that have a similar mechanism of action as previously approved drugs to build on previous successes. This would include drugs that target the androgen receptor (AR; the most critical prostate cancer cell survival and growth pathway) axis and cytotoxic agents such as docetaxel (Taxotere; first-line standard chemotherapy for advanced prostate cancer). Abiraterone is a good example. This medicine blocks androgen synthesis in tumor cells at the sites of metastatic cancer, moved swiftly through clinical development and is predicted to be approved by early next year. Another example is Cabazitaxel. This agent has a similar chemical composition and mechanism of action as docetaxel, but is active in some patients who become resistant to docetaxel. Cabazitaxel was approved in 2010. Last, Dr. Sweeney said, "evaluate and study the literature." Prioritize agents that target non-AR pathways also shown to drive disease progression. Examples include drugging the metabolic or inflammatory systems, both widely described as critical drivers of prostate cancer progression.

Dr. Sweeney's presentation exhibited lists of pipeline drugs as examples for each category outlined in his triage proposal. In summary, he stated that drugs must be judiciously evaluated and matched to an activated pathway before proceeding into clinical trials. Once in trials, studies must provide a proof-of-concept by identifying the activated signature in patients and correlating it with therapy response. Clinical studies also need to consider combination therapies and optimal scheduling of specific treatments.

Session 9

Innovative Molecular Imaging

Major Points from Session:

- Measuring all tumor lesions in a patient over time during a treatment course is not only critical to understanding the disease but also essential for drug development.
- Standardizing the data collection and interpretation of molecular imaging scans will result in the identification and qualification of biomarkers that are reliable and reproducible across institutions globally.
- PSMA-based radiopharmaceuticals are very sensitive and specific prostate cancer imaging probes that produce high resolution images of prostate cancer lesions throughout the body.
- PSCA-mini-bodies are engineered antibodies that bind to prostate cancer cells and “light up” a tumor on a PET scan.
- NaF PET/CT imaging is under clinical investigation for its use in measuring response to bone-targeting agents.

Introduction:

Molecular imaging is a technology that enables non-invasive visualization of the cellular processes occurring within an organism. This type of imaging is different from common imaging modalities such as tomography or ultrasound because it uses probes (also termed tracers) that are specific to a molecular process or cell surface molecule of interest. Dr. Glenn Liu, the session moderator, opened the session with a discussion on developing molecular imaging as a biomarker for prostate cancer drug development. Similarly, Dr. Morris drew attention to the careful process required to define molecular imaging biomarkers. The remaining session speakers honed in on specific imaging tracers and their potential impact on prostate cancer research and drug development.

Glenn Liu, MD

University of Wisconsin

Translational Imaging Research in Prostate Cancer: Seeing Is Believing

What this means for patients: Identifying molecular imaging biomarkers has the potential to provide clinicians with a tool for prostate cancer detection, prognosis, therapy selection, therapeutic response, and treatment efficacy and resistance.

Dr. Liu highlighted the following challenges in prostate cancer: 1) advanced disease has metastases almost exclusive to bone, 2) models of prostate cancer metastases in animal models are lacking, 3) bone biopsy needles miss tumor deposits often, and 4) tumors are heterogeneous. Conventional imaging for bone lesions, bone scintigraphy or the common Technetium bone scan, does not measure tumor activity but measures bone remodeling (changes in bone growth). It has low resolution and overall offers little prognostic value. Additionally, the material needed for bone scintigraphy, Technetium-99-MDP, is in short supply. Thus, the critical unmet need is to define an imaging biomarker that can rapidly and reliably measure change in tumor lesions, specifically bone metastases, non-invasively and in a spatial and temporal context. Dr. Liu

proposes that molecular imaging can meet these challenges and provide the field with a biomarker capable of measuring prostate cancer tumor burden in real-time. Dr. Liu showed several examples of case studies that revealed how use of different molecular imaging tracers can inform clinicians of tumor heterogeneity and the distinct underlying biology. He also showed that molecular imaging can assess ALL lesions by introducing a new method called quantitative bone imaging (QTBI), which assesses functional changes in total bone. This may be an essential tool to determine predictive markers of therapy response. Dr. Liu concluded that the ability to assess pharmacodynamic effect (study of the physiologic effects of a drug inside the body) of treatment will improve efficiency of prostate cancer drug development.

Quantitative Total Bone Imaging (QTBI)

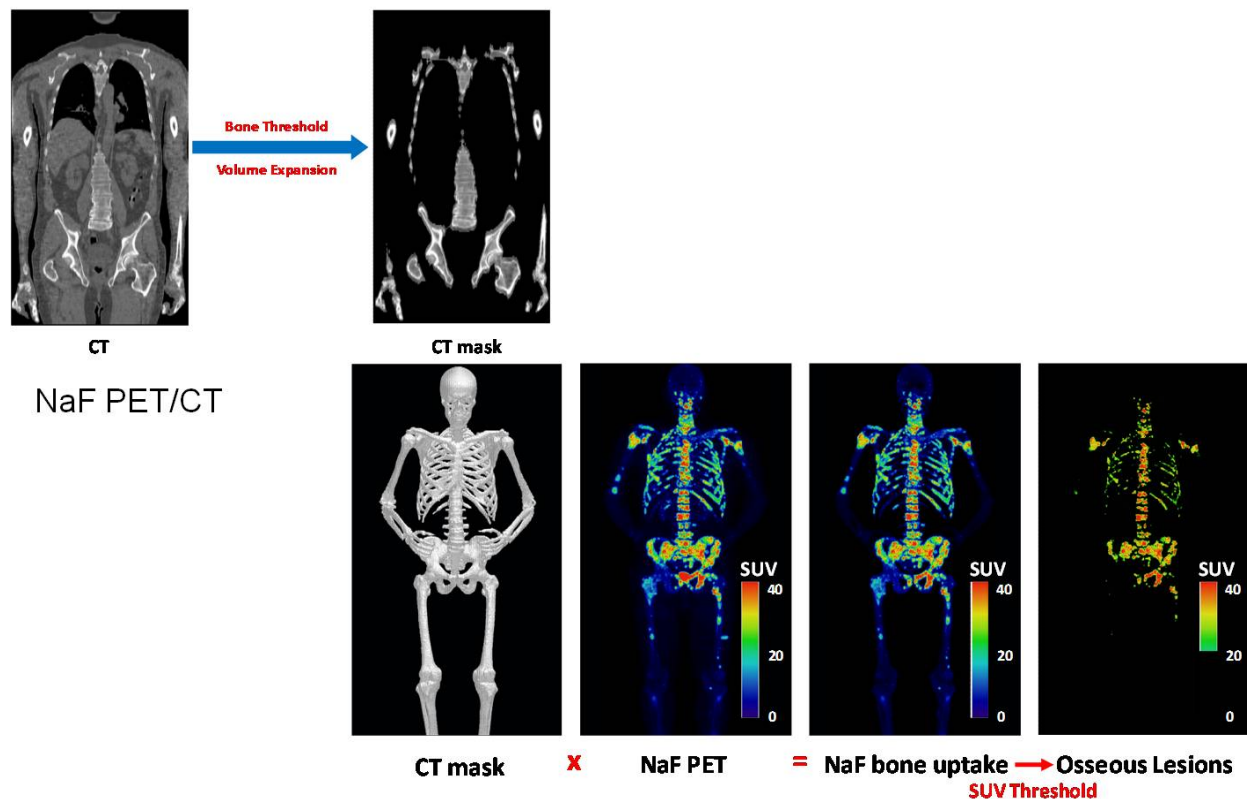


Figure 18: Quantitative Total Bone Imaging: The above images are examples showing how a software program can eliminate all soft tissue leaving behind the skeleton (top panel). The skeleton is then used to give spatial context to a PET image (colored scans) from the same patient (bottom panels). This overlay is then used to quantify the amount of cancer specifically in bone. The final image (lower right) isolates bony prostate cancer lesions.

Michael Morris, MD

Memorial Sloan-Kettering Cancer Center

AR and Other Novel Molecular Imaging in Prostate Cancer: Moving Beyond a Pretty Picture

What this means for patients: Dr. Morris and others are leading the way to clinically qualify molecular imaging biomarkers for use in prostate cancer treatment and drug development.

Dr. Michael Morris presented a thorough description of the analytical validation and qualification process necessary for the successful identification of molecular imaging biomarkers. He defined them as follows: 1) Analytic validation: the process of evaluating an assay and its measurement performance characteristics, and 2) Qualification: the evidentiary process of linking a biomarker with a biological process and clinical endpoints. As a proof-of-principal, Dr. Morris and colleagues began to test this process in bone scintigraphy and developed the bone scintigraphy index (BSI). An automated software system was designed that can quantify the total number of lesions identified in the scan. A standardized form for interpreting the scan was prepared and can be stored electronically to permit data sharing and assessment of scan reader reproducibility. Once BSI is analytically validated, Dr. Morris and colleagues concluded that time to disease progression on bone scans should be defined by the appearance of two new lesions. They are currently testing this in two large clinical studies (Abiraterone and MDV3100). At Memorial Sloan-Kettering Cancer Center, Dr. Morris and colleagues are already implementing the same process to define PET imaging as a biomarker. So far, methods of PET imaging measurements were standardized and are now under rigorous clinical qualification.

Dr. Morris showed compelling results of a novel PET tracer ^{18}F -DHT, which competes with androgens and binds to the androgen receptor, a critical cancer promoting signaling pathway in prostate cancer. The hope is that this tracer and other PET tracers will provide prognostic information, predict therapy response and determine drug pharmacodynamics.

Martin Pomper, MD, PhD
Johns Hopkins University

Imaging Prostate Cancer with Low Molecular Weight Agents: Focus on PSMA

What this means for patients: PSMA-based tracers are promising new agents for high resolution imaging of prostate cancer lesions in clinical settings where current imaging technology is ineffective.

Dr. Martin Pomper presented his findings on the synthesis of prostate-specific membrane antigen- (PSMA) based radiopharmaceuticals (small molecules, ideal for imaging). PSMA is a surface molecule found only at very high levels in prostate cancer cells and new tumor blood vessels. PSMA levels are also correlated with poor prognosis in prostate cancer. Dr. Pomper's PSMA tracers were first developed using a urea-based inhibitor of PSMA conjugated to a radioisotope ($[^{11}\text{C}]\text{DCMC}$ and $[^{18}\text{F}]\text{DCFBC}$) for imaging with positron emission tomography (PET). $[^{18}\text{F}]\text{DCFBC}$ has recently entered clinical trials, led by 2008 PCF Young Investigator Dr. Steve Cho. Dr. Pomper has generated other, new PSMA-based imaging agents for PET as well as for single photon emission computed tomography (SPECT) (see figure below), optical imaging and also for therapy. Dual modality and therapeutic agents are also under development. In collaboration with Michael Zalutsky at Duke University he is developing tracers that use a radiotoxic halogen, ^{211}At , which he showed selectively kills prostate cancer cells. Other collaborative work includes generating nanoparticles decorated with PSMA inhibitors for delivery of therapeutic or theranostic agents, i.e., those which can be used for imaging and therapy, concurrently. In summary, Dr. Pomper and colleagues have synthesized a number of new chemical entities that will likely play an important role in the future of prostate cancer imaging.

$[^{125}\text{I}]\text{YC-VI-11}$

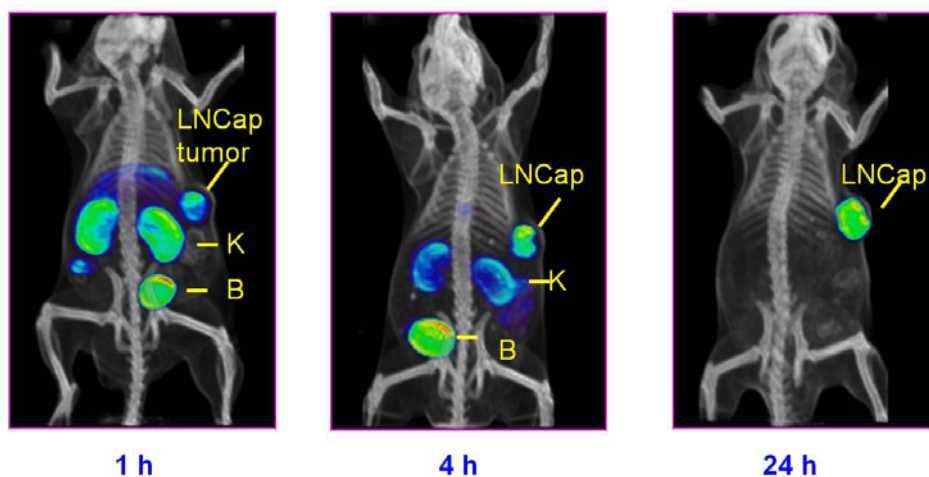


Figure 15: This figure shows images of a mouse with a prostate cancer xenograft (LNCaP tumor) that was injected intravenously with a radioiodinated PSMA-binding agent and imaged using a small animal SPECT scanner. One to four hours after the injection the imaging agent is still visible in the bladder and kidney, organs that filter and clear the body of extra probe. By 24 hours only the tumor is visible on the scan, demonstrating the high resolution and specificity afforded by this probe.

Robert Reiter, MD
University of California, Los Angeles
Engineered Antibodies and Prostate Cancer Imaging

What this means for patients: Mini-bodies that home to prostate cancer by binding to PSCA are next generation imaging probes that will enhance visualization of prostate cancer.

In contrast to Dr. Pomper's agents, Dr. Reiter and colleagues are developing modified antibodies (molecules that bind to cell surface molecules) as imaging probes. These probes are generally much larger than the radiopharmaceuticals described by Dr. Pomper. The advantages of targeting cell surface molecules are that the probes have a large binding surface area with diverse properties. Additionally, there are robust methods available for antibody generation and many antibodies have proven clinical utility; there are approximately 20 FDA-approved antibody drugs already on the market. Dr. Reiter and his colleague, Dr. Anna Wu, engineered truncated antibodies, called minibodies that achieve similar imaging results as radiopharmaceuticals. They have generated a humanized Prostate Stem Cell Antigen (PSCA) minibody, which is highly specific for prostate cancer cells. PSCA is present in normal prostate tissue but becomes highly elevated in prostate cancer. The anti-PSCA minibody is currently under investigation in a trial of 20 men with metastatic prostate cancer to assess its safety and imaging properties.

Evan Yu, MD

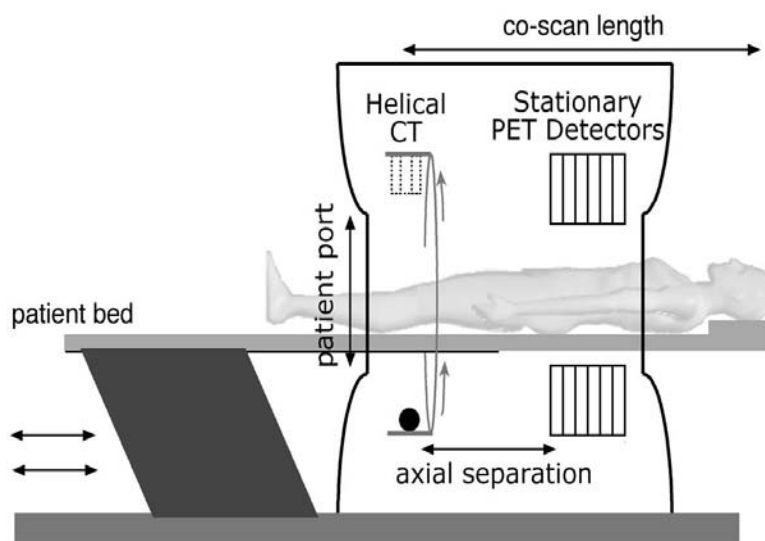
University of Washington School of Medicine

Imaging Prostate Cancer Bone Metastases with Sodium Fluoride (NaF) PET

What this means for patients: NaF PET/CT imaging can identify cancer lesions months before conventional imaging modalities.

Dr. Evan Yu ended the session with a presentation on the comparative advantages of using sodium fluoride (NaF) PET/CT (Positron Emission Tomography combined with Computer Tomography imaging) over conventional bone scans. NaF is already FDA-approved for PET imaging. Dr. Yu showed that NaF is more sensitive with PET/CT than either bone scans or ^{18}F -FDG (Fluorodeoxyglucose; a common radiopharmaceutical that is taken up by fast growing cells such as cancer cells) PET for metastatic bone lesions. The anatomical information from CT increases specificity and spatial context. Dr. Yu also showed that quantitative assessment of both normal bone and metastatic bone lesions is possible, unlike bone scans. An example of one patient who underwent both bone scan and PET imaging revealed that PET imaging identified new lesions nine months earlier. Dr. Yu and colleagues are currently testing NaF PET/CT imaging as a biomarker of response for bone-targeting agents, such as Dasatinib.

PET/CT Combines Molecular and Anatomical Imaging



(Alessio, Rad Clin N Amer, 2005)

Figure 20: This schematic shows the instrument used to build both a CT and PET scan image simultaneously. The results provide clinicians with both anatomical and molecular information, as well as spatial context.

Special Lecture

mTOR – a Shared Therapeutic Target in Epileptology and Cancer Biology

John Swann, PhD
Baylor College of Medicine

Major Points from Session:

- The mTOR signaling pathway is activated in prostate cancer and within the brain from patients with epilepsy.
- Pre-clinical data with rapamycin, a drug approved for mTOR inhibition in cancer, is effective in reducing seizure frequency.
- Decoding the molecular mechanisms that drive progression of different diseases uncover parallels and identify new uses for “old” drugs.

What this means for patients: Patients with epilepsy are benefitting from years of cancer research on the mTOR pathway and the portfolio of agents originally developed to target the mTOR pathway in cancer.

Discussion:

Common cell signaling pathways that drive the progression of cancer have also been found to be activated in the brain of patients with epilepsy. The mTOR signaling pathway is one such example. There are over 3 million people in the US alone who have epilepsy. The mTOR pathway has long been recognized as an oncogenic (cancer-causing) pathway in prostate cancer as well as in many other cancers. Dr. John Swann showed mTOR activation in two mouse models of epilepsy. The first was a genetic type of epilepsy caused by a gene called Tuberous Sclerosis Complex (TSC). In this model, treatment with rapamycin (inhibitor of mTOR), an FDA-approved drug, resulted in complete inhibition of all seizure events. A clinical trial in the US is currently recruiting patients with TSC induced epilepsy to test the efficacy of Everolimus (Rad001; an mTOR inhibitor). In a second model, rapamycin treatment of trauma-induced seizures significantly reduced seizure frequency.

Special Lecture

New Insights into the Prostate Cancer Genome and Therapeutic Implications

Charles Sawyers, MD
Memorial Sloan-Kettering Cancer Center

Major Points from Session:

- ARN-509, a next generation anti-androgen, showed powerful anti-cancer activity and induced durable remissions long after therapy completion in castrate resistant prostate cancer mouse models.
- Loss of PTEN, common in prostate cancer, may confer resistance to MDV-3100 therapy.
- A combination treatment strategy with MDV3100 is under development to overcome MDV3100 resistance.

What this means for patients: ARN-509 is a more potent anti-androgen than MDV-3100 and is in the pipeline for the treatment of castration resistant prostate cancer.

Discussion:

When new therapies are in the pipeline it is not only essential to understand the mechanism of action (how it works) but also mechanisms of resistance (why it doesn't work). Dr. Sawyers raised the issue of MDV3100 resistance, which occurs in ~15% of patients. MDV3100 is an anti-androgen in clinical development for the treatment of castration resistant prostate cancer that blocks the activity of the androgen receptor (AR), the most critical signaling pathway hijacked by prostate cancer cells to induce cell proliferation and survival. Dr. Sawyers offered two approaches to solving MDV3100 resistance. The first is to discover even better anti-androgens. He introduced a new medicine, called ARN-509, developed by Aragon Pharmaceuticals that showed stronger anti-tumor activity than MDV3100 in prostate cancer mouse models. Unlike MDV3100, ARN-509 treatment also induced durable remissions long after therapy was completed in the most advanced castration resistant prostate cancer mouse models. ARN-509 is currently in Phase I/II clinical trials.

A second approach to conquer MDV3100 resistance is to decipher resistance mechanisms and target them therapeutically. Dr. Sawyers and colleagues first tested whether AR splice variants circumvented MDV3100 activity. AR splice variants are a mutated species of AR that don't require androgens to become activated. However, the data revealed that prostate tumors with AR variants remained sensitive to MDV3100 treatment, indicating that MDV3100 resistance is not due to the presence of AR variants. Conversely, analysis of prostate tumors that have lost the presence of the tumor suppressor gene PTEN (a common event in prostate cancer) are resistant to MDV3100 treatment. Dr. Sawyers' team identified a combination therapy strategy that re-sensitized these tumors to MDV3100 treatment. These findings define PTEN loss as a candidate biomarker for MDV3100 resistance. The goal is to translate this combination therapy into the clinic for patients that are resistant to MDV3100 therapy and that have lost PTEN.

Session 10

Late Breaking Advancements

Major Points from Session:

- Advancements made in the design of CTC capture technology that enable automated CTC enumeration as well as cell visualization using different protein markers.
- A putative prostate cancer stem cell was identified and isolated from fresh human prostate cancer specimens.
- Studies concluded that basic science research can be subject to conflict of interest.
- Aptocine in combination with Ipilimumab immunotherapy showed enhanced activity in a prostate cancer model.
- Five new genes were identified as candidate prostate cancer biomarkers that could differentiate benign from lethal disease.
- Targeting AR protein binding partners opens a new avenue of prostate cancer therapeutics.

Introduction:

The final session of the retreat was a diverse mix of topics. Each speaker described their latest discoveries. For many it was their first opportunity to share their new findings in a public forum.

Richard Lee, MD, PhD

Massachusetts General Hospital

The Premise and Promise of Prostate Circulating Tumor Cells: Advances in CTC Chip Technology

What this means for patients: Advances in “liquid biopsy” technology moves the field closer to delivering personalized medicine.

Dr. Richard Lee presented the latest advancements made in circulating tumor cell (CTC) isolation technology. This work is part of a PCF Challenge Award headed by Dr. Daniel Haber of the Massachusetts General Hospital. CTCs are cancer cells that have broken off the primary or metastatic tumor and entered into circulation. Isolation of these cells requires a simple blood draw; a process often termed the “liquid biopsy.” Dr. Lee showed a study that revealed that of 116 metastatic cancer patients 115 had CTCs present in their blood. The microfluidic CTC chip that Dr. Lee and colleagues developed is coupled to an automated CTC enumeration system. The chip is designed in a herringbone configuration, as blood flows through the grooves micro-vortices increase the probability of a CTC will come into contact with the chip surface and adhere. The chip is made of plastic and is readily scaled-up. Once the CTCs are adherent to the chip walls the cells can be stained by immunohistochemistry/immunofluorescence methods (experiments that enable researchers to characterize cells based on the presence of specific proteins) which provide insight into the patient’s cancer biology. Dr. Lee showed that 60-70% of CTCs from metastatic prostate cancer patients had elevated levels of a cell proliferation marker, Ki67, indicating that the cells are actively dividing. The hope is that this new chip will enable researchers to gain new, critical knowledge about CTC biology and their relationship to the primary tumor, which would be invaluable for prostate cancer treatment and care.

Second Generation Capture Device: The Herringbone Chip

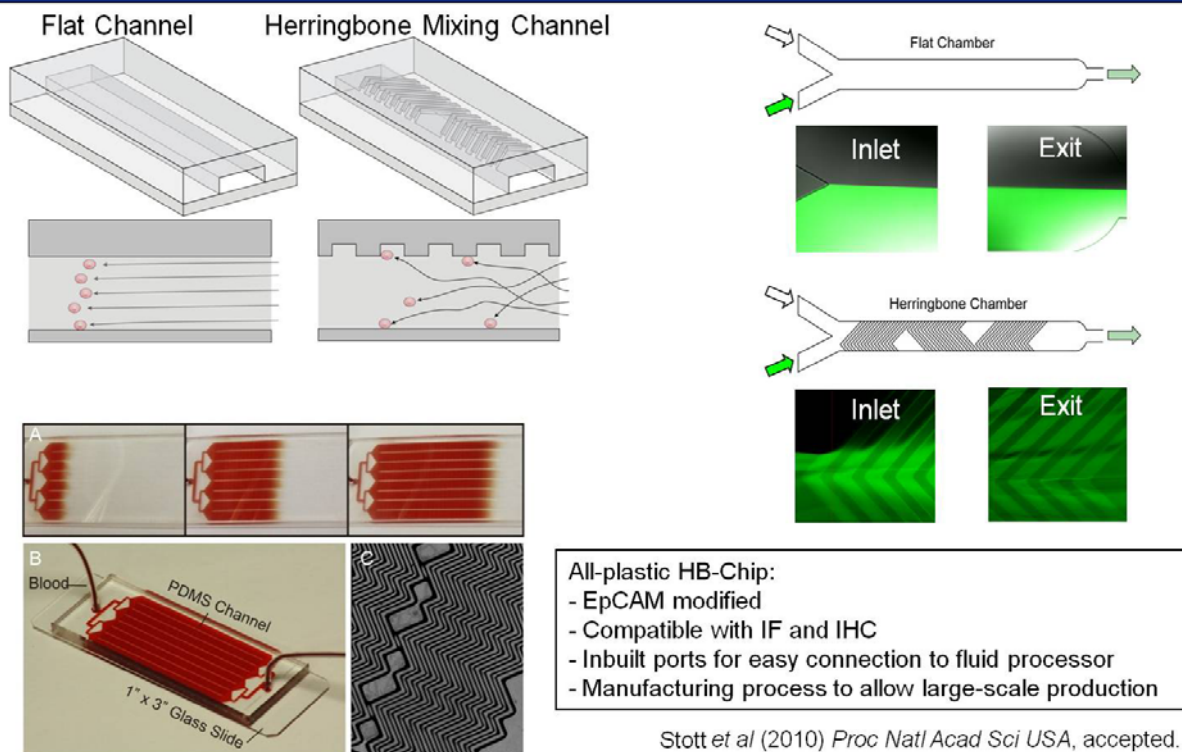


Figure 21: This slide shows the new Herringbone CTC capture chip. At the top is an illustration showing how the herringbone configuration increases the probability a CTC has of making contact with the chip surface while traveling through the chamber as compared to the old flat channel configuration. On the bottom left are images of patient blood moving through the chip.

Carlos Cordon-Cardo, MD, PhD
Columbia University

Identification and Characterization of Human Prostate Cancer Stem Cells: Clinical Implications

What this means for patients: Defining the elusive prostate cancer stem cell would enable researchers to identify therapies that could eradicate this cell population which would overcome resistance mechanisms as well as cancer recurrence.

Dr. Carlos Cordon-Cardo described the identification of a cancer stem cell from human prostate cancer samples. He states that these cells are negative for prostate epithelial markers such as cytokeratin and AR. To show that these cells are stem cells, the cells were isolated using flow cytometry (a machine that separates each single cell from a test tube based on the cell surface molecules of interest) and transplanted into immuno-compromised mice and formed tumors. He also showed that these cells could divide asymmetrically producing a stem cell and a daughter cell, a hallmark of a stem cell. Dr. Cordon-Cardo showed images of cells in human prostate cancer samples that were candidate prostate cancer stem cells because they lacked expression of the classic prostate cancer cell surface proteins. Future studies will determine the molecular profile of these cells and will enable rigorous testing on the function of these cells in prostate cancer initiation and progression. Identification of true prostate cancer stem cells would significantly advance the development of therapies to cure prostate cancer, as these cells are capable of regenerating a tumor and are likely very resistant to therapy.

Charles Bennett, MD, PhD

South Carolina College of Pharmacy, University of South Carolina Campus

Conflict of Interest in Pharmaceutical Sponsored Basic Science Research Studies: Is There Any Empirical Evidence for This?

What this means for patients: Regulating conflict of interest even at the basic science level is important because it protects patients from being subjected to potentially harmful medicines.

Dr. Charles Bennett discussed conflict of interest in medical research. He stated that in clinical when investigators have financial relationships with pharmaceutical manufacturers they are less likely to criticize the safety, efficacy, or cost-effectiveness of agents supplied by the manufacturers. However, the effects of financial relationships in the basic science setting have not been evaluated. Dr. Bennett and colleague sought to address this issue. They focused their study on the following: the relationship between manufacturer involvement and laboratory results in studies of erythropoietin receptors (EpoRs; molecules that elicit a cell growth signal in response to erythropoietin) in cancer cells. In the early 1990s erythropoietin stimulating agents (ESAs) were approved for chemotherapy-induced anemia. However, safety concerns were raised when ESAs were found to accelerate bad outcomes in lung cancer patients. Dr. Bennett and his team researched the Medline database (a resource for all peer-reviewed scientific articles) for publications on EpoR presence and ESA-induced cell signaling in cancer cells from 1988-2008. They categorized each article into one of three groups: 1) no ESA manufacturer funding, 2) academic receiving ESA manufacturer funding and 3) ESA manufacturer employee. They found that academics that received no funding from the manufacturer were more likely to report that ESAs are potentially promoting tumor cell growth and are therefore likely harmful to cancer patients. Academic investigators receiving funding as well as manufacturer employees often did not reach the same conclusions. Analyses of presentations given at international meetings on EpoRs and ESAs identified a similar pattern. These findings are counter to the belief that basic science studies are not subject to conflict of interest. Further studies will determine whether these findings are validated across a larger number of independent studies.

Llew Keltner, MD, PhD
Light Sciences Oncology

Synergistic Effects of Local Light-Activated Drug Therapy and Systemic Anti-CTLA4 antibody in a Prostate Tumor Model

What this means for patients: Aptocine might prime the anti-tumor immune response enhancing treatment of prostate cancer with Ipilimumab.

In 2009, Light Sciences Oncology reported that their lead agent Aptocine, a light activated drug therapy which has completed Phase 3 human trials in two cancer indications, reduced tumor volume and induced an immune response. Aptocine therapy is a light activated drug that has two components. The first is a very small, single-use disposable LED probe that is inserted into the primary tumor in a biopsy-like procedure. The second component is an agent that is injected intravenously. The injected agent is only activated to kill cells in the presence of light, which is emitted from the probe inside the tumor. Dr. Llew Keltner described results from recent studies in collaboration with Dr. Jim Allison of Memorial Sloan-Kettering Cancer Center to determine whether Aptocine could be paired with immunotherapy strategies to enhance its anti-tumor effects. They found that Aptocine and Ipilimumab (CTLA-4 inhibitor), which releases the immune system breaks, are synergistic in a prostate cancer mouse model. The mice experience significant reduction in total tumor volume and live longer. Dr. Keltner and colleagues are moving this treatment strategy from pre-clinical to clinical studies with the goal of improving clinical outcomes for patients with advanced prostate cancer.

Tarek Bismar, MD
University of Calgary

Molecular Pathways Associated with ERG Rearranged PTEN Deleted Castration Resistant Prostate Cancer

What this means for patients: Discovery of prostate cancer biomarkers that reliably distinguish indolent from lethal disease will have a profound impact on prostate cancer diagnosis, prognosis and treatment decision-making.

Recently Dr. Bismar and colleagues published results which showed that the presence of both TMPRSS2:ERG (a common genetic aberration in prostate cancer when the TMPRSS2 gene fuses with the ERG gene) and PTEN (an anti-tumor gene) deletion was significantly associated with high grade prostate cancer. Dr. Bismar's findings indicate that these genetic alterations may cause a more aggressive prostate cancer. He also showed that these genetic alterations are early events in prostate cancer development, which is in agreement with other published studies. To understand how TMPRSS2:ERG and PTEN deletion alter the behavior of prostate cancer cells, Dr. Bismar compared the molecular profile of tissue samples from patients who were either positive or negative for these genetic alterations. In his comparative analysis he identified a list of genes that are either elevated or depleted in prostate cancers with both TMPRSS2:ERG and PTEN deletion. So far, Dr. Bismar has discovered 5 novel, candidate prostate cancer biomarkers (a molecule that indicates a biological process or pathogenesis) that differentiate benign tissue, from localized and lethal prostate cancer in tissue samples. Some of these genes may also represent new therapeutic targets for patients with prostate cancer. Dr. Bismar and his team are currently working on validating their findings in larger studies.

Ganesh Raj, MD, PhD

University of Texas, Southwestern Medical Center

The Social Network of the Androgen Receptor: a Promising Target for Therapy

What this means for patients: Discovery and development of compounds that target AR protein binding partners may represent a new effective anti-cancer treatment approach.

Dr. Raj showed that the androgen receptor signaling pathway drives prostate cancer initiation and progression at all stages of the disease. The interaction of androgens with AR triggers a cascade of cellular events necessary for prostate cancer initiation and progression. AR signaling progresses through 2 distinct pathways: genomic and non-genomic. The genomic pathway involves AR movement into the nucleus where it binds to DNA and turns on cancer-promoting genes. The non-genomic action defines a situation when AR interacts with other steroid receptors (proteins that bind steroids, such as estrogen) to elicit a cell growth response. Dr. Raj presented his research which has identified other proteins in this pathway, termed co-factors that work as AR teammates in facilitating its deleterious effects. He has discovered that a protein called PELP1 physically binds to AR and is necessary for both the genomic and non-genomic actions of AR in prostate cancer. Analysis of the crystal structure of PELP1 (determination of the 3D structure of the protein) Dr. Raj has led the discovery of a surface region of the PELP1 protein that binds to AR (similar to a key and a lock). This information was used to design a chemical compound that mimics the chemical structure of the PELP1:AR interface (space between a key and a lock). Treatment of prostate cancer cells with this compound blocked the activity of AR and PELP1 and blocked AR induction of prostate cancer cell proliferation and survival. Preliminary data from prostate cancer mouse models revealed that this compound caused prostate tumor regression. Dr. Raj and colleagues are working on developing this compound for future testing in humans. The hope is that this agent could further blunt the activity of the AR signaling pathway in prostate cancer and provide advanced prostate cancer patients with a new, effective treatment strategy.

2010 Program Agenda

Wednesday, September 15, 2010

Welcome and Introduction

7:30AM – 7:45AM

Jefferson/Lincoln West

Opening Remarks

Howard Soule, PhD
Prostate Cancer Foundation

R&B Artist Charlie Wilson Opens with “God Bless America”

Molecular Targeting of Apoptosis in Prostate Cancer

7:45AM-9:05AM

Jefferson/Lincoln West

Moderator: Dario Altieri, MD
Wistar Cancer Center, Philadelphia

7:45AM-8:05AM

Targeting Mitochondrial Hsp90 Chaperones for Prostate Cancer Therapy

Moderator: Dario Altieri, MD
Wistar Cancer Center, Philadelphia

8:05AM-8:25AM

Therapeutic Targeting of Hsp27 in Prostate Cancer

Amina Zoubeydi, PhD
University of British Columbia

8:25AM-8:45AM

Targeting Apoptosis and Autophagy

Robert DiPaola, MD
The Cancer Institute of New Jersey

8:45AM-9:05AM

A Paradigm for Cancer Selective Apoptosis

Vivek Rangnekar, PhD
University of Kentucky

9:05AM-9:35AM

SPECIAL LECTURE

Axel Hoos, MD, PhD

Bristol-Myers Squibb

Immuno-Oncology: Creating the Operating Framework for a New Era of Cancer Therapy

*Introduction by: James Allison, PhD
Memorial Sloan-Kettering Cancer Center*

Genomics of Prostate Cancer

9:40AM-11:00AM

Moderator: Arul Chinnaiyan, MD, PhD
University of Michigan

9:40AM-10:00AM
Implications for

**Recurrent Gene Fusions in Common Solid Tumors:
Personalized Medicine**

Moderator: Arul Chinnaiyan, MD, PhD
University of Michigan

10:00AM-10:20AM

**Prostate Cancer: Meeting the Challenges of Whole Genome
Sequencing and Analysis**

Elaine Mardis, PhD
The Genome Center at Washington University School of Medicine

10:20AM-10:40AM

Exome Sequencing in Metastatic Prostate Cancer

Jay Shendure, MD, PhD
University of Washington

10:40AM-11:00AM

Genome Sequencing Studies of Prostate Cancer

Levi Garraway, MD, PhD
Dana-Farber Cancer Institute, Harvard Medical School,
The Broad Institute of Harvard and MIT

New Developments in Clinical Practice: "A Whitmorean Panel Discussion"

11:00AM-12:00PM

Moderator: Skip Holden, MD
Cedars-Sinai Medical Center

11:00AM-11:45AM

Panelists:

Peter Scardino, MD
Memorial Sloan-Kettering Cancer Center
Howard Sandler, MD
Cedars-Sinai Medical Center
Phil Kantoff, MD
Dana-Farber Cancer Institute
Jonathan Simons, MD
Prostate Cancer Foundation

11:45AM-12:00PM

Q & A

12:00PM-1:30PM

Columbia Hall 3-8

LUNCH

Targeting the Tumor Microenvironment

1:30PM-2:50PM

Moderator: Gustavo Ayala, MD
Dan L. Duncan Cancer Center, Baylor College of Medicine

1:30PM -1:50PM

Targeting the Neural Microenvironment in Prostate Cancer

Moderator: Gustavo Ayala, MD
Dan L. Duncan Cancer Center, Baylor College of Medicine

1:50PM-2:10PM

I κ B- α - a Critical Regulator of Prostate Cancer Metastasis and Castration Resistance

Michael Karin, PhD
University of California, San Diego

2:10PM-2:30PM

A Systems Approach to Prostate Cancer Progression: From Pathways to Pathology

Alexander "Sandy" Anderson, PhD
H. Lee Moffitt Cancer Center & Research Institute

2:30PM-2:50PM

Co-Evolution of Reactive Stroma in Prostate Cancer Progression

David Rowley, PhD
Baylor College of Medicine

Diagnostics and Theranostics for Prostate Cancer

2:50PM-4:00PM

2:50PM-3:10PM

SPECIAL LECTURE

David Parkinson, MD

Nodality, Inc.

Functional Characterization of Signaling Pathways in Cancer Cells: Application to Rare Cell Populations Such as CTCs

3:10PM-4:00PM

Panel Discussion: Moderated by David Parkinson, MD

The Pathologists' Sign-Out for Prostate Cancer in 2030

Panelists:

Mark Rubin, MD
Weill Cornell Medical School
Angelo De Marzo, MD, PhD
Johns Hopkins University
Scott Tomlins, MD, PhD
University of Michigan
Massimo Loda, MD
Dana-Farber Cancer Institute

4:10PM-4:40PM

SPECIAL LECTURE

Peter Dervan, PhD

California Institute of Technology

Targeting Transcription Factor-DNA Interfaces by Small Molecules

Introduction by: Howard Soule, PhD

Prostate Cancer Foundation

4:40PM-5:10PM

SPECIAL LECTURE

Karen Cichowski, PhD

Harvard Medical School

Using mTOR Inhibitors as a Platform for Developing Rational Combination Therapies

Introduction by: Neal Rosen, MD, PhD

Memorial Sloan-Kettering Cancer Center

5:10PM-5:40PM

SPECIAL LECTURE

Neal Rosen, MD, PhD

Memorial Sloan-Kettering Cancer Center

Oncogenic Feedback - Basic and Clinical Implications

Introduction by: Karen Cichowski, PhD

Harvard Medical School

Pro-Active Surveillance

5:40PM-6:40PM

Moderator: H. Ballentine Carter, MD
Johns Hopkins University

5:40PM-6:00PM

Pro-Active Surveillance: An Underutilized Management for Localized Prostate Cancer

Moderator: H. Ballentine Carter, MD
Johns Hopkins University

6:00PM-6:20PM

Statistical Basis of Patient Selection for Active Surveillance

Andrew Vickers, PhD
Memorial Sloan-Kettering Cancer Center

6:20PM-6:40PM

Germline Copy Number Variants as Risk Markers for Prostate Cancer

Francesca Demichelis, PhD
Weill Cornell Medical College

Dinner

International Ballroom West

7:30PM-8:30PM

8:30PM-9:20PM

Special Dinner Program

8:30PM-8:50PM

PCF and the Greatest Discovery Year Ever

Jonathan Simons, MD
Prostate Cancer Foundation

8:50PM-9:05PM

Awards Presentation

Howard Soule, PhD
Prostate Cancer Foundation

9:05PM-9:20PM

Movember Presentation

Adam Garone
Co-Founder and Chief Executive Officer
Movember
&
Paul Villanti
Chairman of the Board
Movember
&
Colleen Nelson, PhD
Movember Global Scientific Advisory Committee
Prostate Cancer Research,
Institute of Health and Biomedical Innovation,
Queensland University of Technology

Thursday, September 16, 2010

Breakfast

7:00AM – 8:00AM

International Ballroom West

Adiposity, Metabolism and Prostate Cancer Progression

8:00AM-9:00AM

Jefferson/Lincoln West

Moderator: Luigi Fontana, MD, PhD
Washington University

8:00AM-8:20AM

Long-Term Effects of Calorie Restriction on Cancer Risk Factors

Moderator: Luigi Fontana, MD, PhD
Washington University

8:20AM-8:40AM

Dysregulated Lipid Metabolism in Prostate Cancer
Jennifer Doll, PhD

NorthShore University HealthSystem Research Institute

8:40AM-9:00AM

Targeting the Metabolic Milieu and PI3K/mTOR Signaling Pathways in Advanced Prostate Cancer

Akash Patnaik, MD, PhD
Harvard: Beth Israel Deaconess

9:00AM-9:30AM

SPECIAL LECTURE

Joseph DeSimone, PhD

University of North Carolina

Co-opting Moore's Law: Design of Vaccines and Therapeutics on a Wafer

Introduction by: Robert Getzenberg, PhD

Johns Hopkins University

microRNA and Prostate Cancer Progression

9:30AM-10:50AM

Moderator: Pier Paolo Pandolfi, MD, PhD
Harvard: Beth Israel Deaconess

9:30AM-9:50AM

A Novel Biological Dimension for Coding and Non-Coding mRNAs and Its Role in Tumorigenesis

Moderator: Pier Paolo Pandolfi, MD, PhD
Harvard: Beth Israel Deaconess

9:50AM-10:10AM

Androgen Receptor Regulated microRNAs in Prostate Cancer

Shawn Lupold, PhD
Johns Hopkins University

10:10AM-10:30AM

Circulating microRNAs in Cancer

Muneesh Tewari, MD, PhD
Fred Hutchinson Cancer Research Center

10:30AM-10:50AM

microRNA Reprogramming in Cancer: Mechanisms and Therapeutic Opportunities

Josh Mendell, MD, PhD
Johns Hopkins University

11:00AM-12:00PM

KEYNOTE LECTURE

Mike Milken

Prostate Cancer Foundation
Introduction by: Skip Holden, MD
Cedars-Sinai Medical Center

12:00PM-1:30PM

LUNCH

International Ballroom West

1:30PM-2:00PM

Special Lecture

Chris Sweeney, MBBS

Harvard Medical School

Triaging the Pipeline of New Treatments for Advanced Prostate Cancer

Introduction by: Oliver Sartor, MD
Tulane University Medical School

Innovative Molecular Imaging

2:00PM-3:40PM

Moderator: Glenn Liu, MD
University of Wisconsin

2:00PM-2:20PM

Translational Imaging Research in Prostate Cancer: Seeing Is Believing

Moderator: Glenn Liu, MD
University of Wisconsin

2:20PM-2:40PM

Imaging Prostate Cancer with Low Molecular Weight Agents: Focus on PSMA

Martin Pomper, MD, PhD
Johns Hopkins University

2:40PM-3:00PM

AR and Other Novel Molecular Imaging in Prostate Cancer: Moving Beyond a Pretty Picture

Michael Morris, MD
Memorial Sloan-Kettering Cancer Center

3:00PM-3:20PM

Engineered Antibodies and Prostate Cancer Imaging

Robert Reiter, MD
University of California, Los Angeles

3:20PM-3:40PM

Imaging Prostate Cancer Bone Metastases with Sodium Fluoride (NaF) PET

Evan Yu, MD
University of Washington School of Medicine, Fred Hutchinson Cancer Research Center

3:45PM-4:15PM

Special Lecture

John Swann, PhD

Cain Foundation Laboratories; Duncan Neurological Research Institute; Neuroscience and Translational Biology and Molecular Medicine at Baylor College of Medicine

mTOR – a Shared Therapeutic Target in Epileptology and Cancer Biology

*Introduction by: Howard Soule, PhD
Prostate Cancer Foundation*

4:15PM-4:45PM

Special Lecture

Charles Sawyers, MD

Memorial Sloan-Kettering Cancer Center

New Insights into the Prostate Cancer Genome and Therapeutic Implications

*Introduction by: Jonathan Simons, MD
Prostate Cancer Foundation*

Late Breaking Advancements: Three-Slide Rapid Presentations

4:45PM-6:15PM

Moderator: Howard Soule, PhD
Prostate Cancer Foundation

4:45PM-5:00PM

The Premise and Promise of Prostate Circulating Tumor Cells: Advances in CTC-Chip Technology

Richard Lee, MD, PhD
Massachusetts General Hospital

5:00PM-5:15PM

Identification and Characterization of Human Prostate Cancer Stem Cells: Clinical Implications

Carlos Cordon-Cardo, MD, PhD
Columbia University

5:15PM-5:30PM

Conflict of Interest in Pharmaceutical Sponsored Basic Science Research Studies: Is There Any Empirical Evidence for This?

Charles Bennett, MD, PhD
South Carolina College of Pharmacy/University of South Carolina Campus

5:30PM-5:45PM

Synergistic Effects of Local Light-Activated Drug Therapy and Systemic Anti-CTLA4 antibody in a Prostate Tumor Model

Llew Keltner, MD, PhD
Light Sciences Oncology

5:45PM-6:00PM

Molecular Pathways Associated with ERG Rearranged PTEN Deleted Castration Resistant Prostate Cancer

Tarek Bismar, MD
University of Calgary

6:00PM-6:15PM

The Social Network of the Androgen Receptor: a Promising Target for Therapy

Ganesh Raj, MD, PhD
University of Texas, Southwestern Medical Center

Dinner

7:00PM-9:00PM

Columbia Hall

Speaker	PCF Funding
Tarek Bismar, MD	2008
Arul Chinnaiyan, MD, PhD	2001, 2005, 2006, 2008
Angelo DeMarzo, MD, PhD	2000, 2001
Joseph DeSimone, PhD	2008
Robert DiPaola, MD	1999
Jennifer Doll, PhD	2010
Levi Garraway, MD, PhD	2005, 2006
Phil Kantoff, MD	1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003
Michael Karin, PhD	2004
Massimo Loda, MD	1995, 1997, 2001, 2003, 2004
Pier Paolo Pandolfi, MD, PhD	2008
Akash Patnaik, MD, PhD	2010
Ganesh Raj, MD	2008
Vivek Rangnekar, PhD	1997
Robert Reiter, MD	1996, 1997, 1998, 1999, 2000
Neal Rosen, MD	1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006
David Rowley, PhD	1997, 1998
Mark Rubin, MD	2009
Peter Scardino, MD	1996, 1997, 1999, 2000
Jay Shendure, MD, PhD	2008
Muneesh Tewari, MD, PhD	2008
Scott Tomlins, MD, PhD	2007
Amina Zoubeidi, PhD	2010

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