

# STATE OF THE SCIENCE REPORT

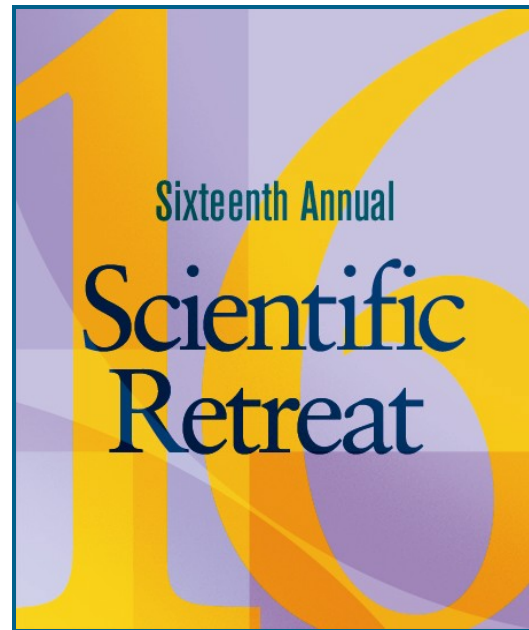
Highlights From  
the 16<sup>th</sup> Annual PCF  
Scientific Retreat

September 2009



Provided with the compliments of  
the Prostate Cancer Foundation





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**PCF Young Investigator, Lorelei Mucci, ScD, MPH, speaks during one of several panel discussions at the PCF 16<sup>th</sup> Annual Scientific Retreat.**

## **Introduction**

“We shall not cease from exploration, and the end of all our exploring will be to arrive where we started and know the place for the first time.”

*Little Gidding No.4 of Four Quartets (1942)*  
T. S. Eliot

## **Feedback and Metrics for “Best Retreat Ever”**

In the year of the “great recession,” the 16<sup>th</sup> Annual Scientific Retreat was the greatest in the Foundation’s history. How is that assertion justified? Using the following measures, the 16<sup>th</sup> Annual Scientific Retreat was assessed the best that PCF has ever had: 1) the absolute number of truly new, “first in field” concepts presented with new data; 2) the diversity of scientific disciplines attending; 3) the number of new, young investigators who (with their new data) were introduced; and 4) post-meeting written feedback. In fact, at least five scientists who had attended 8 or more PCF Scientific Retreats wrote PCF to tell us that this was the “best Retreat ever” – verbatim.

Dr. Howard R. Soule, our Executive Vice President of Discovery and Translation, and Chief Science Officer, did a magnificent job as the Chair of the Scientific Program Committee. Howard and our team cut meeting costs without diminishing the overall PCF experience, the meeting's outcome, or total attendance. Our appreciation also goes to members of the PCF research family who served on this year's program development committee: Donald S. Coffey, PhD, John Hopkins University School of Medicine; Marco Gottardis, PhD, Bristol-Meyers Squibb; Barbara Graves, PhD, The University of Utah; David Heber, MD, PhD, UCLA; Massimo Loda, MD, Dana-Farber Cancer Center; Christopher Logothetis, MD, M.D. Anderson Cancer Center; Pete Nelson, MD, Fred Hutchinson Cancer Center; Kenneth Pienta, MD, University of Michigan; Michael Pollak, MD, McGill University; Donald J. Tindall, PhD, The Mayo Clinic; Jedd Wolchock, MD, PhD Memorial Sloan-Kettering Cancer Center; and Owen Witte, MD, UCLA.

In his 16<sup>th</sup> annual Keynote Address, PCF Founder and Chairman, Michael Milken concluded that despite retractions in the global economy, we are demonstrably experiencing the greatest increase in knowledge expanding our understanding of human disease. Mike's speech can be found at PCF.org. In addition to Mike, PCF was also blessed this year to have a number of Board members in attendance including R. Christian B. Evensen, Arthur Kern, Stuart Holden, MD, Larry Stupski, Steve Burd, E.J. Milken and other major donors. They came to Tahoe to actively question, converse, and motivate the research community that attended.

If there were an arithmetic-shorthand way of describing the meeting it might look like this:

### **Metrics:**

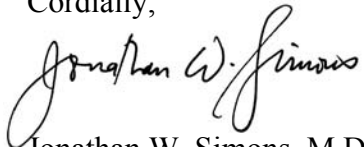
- 81 scientific papers were presented in two and a half days
  - 47 original scientific papers were presented in the main “podium” sessions
  - 22 of these 47 papers (47%) were presented by researchers with leading data who were also giving their first paper at a PCF meeting
  - 34 New Investigators (young MDs, MD PhDs, MD MPHs, and PhDs) gave scientific papers in a special session on Wednesday
- 93 Research Posters were presented
- 174 Total Scientific Presentations
- 21 disciplines involved in prostate cancer research were represented by attendees (Biochemistry, Biomedical Engineering, Chemistry, Computer Science, Endocrinology, Epidemiology, Exercise physiology, Genetics, Healthcare economics, Immunology, Medical Oncology, Microbiology, Molecular Biology, Nuclear Medicine, Pathology, Pharmacology, Physics, Radiation Oncology, Statistics, Urology)
- 98 cancer research centers were represented by attendees
- 8 countries US, UK, Canada, Belgium, Australia, Norway, Netherlands, Italy were represented— the attendees were as global as PCF;
- 5 kinds of research-training backgrounds were represented:

- 127 MDS
- 87 PhDs
- 60 MD PhDs
- 23 Masters degrees e.g. MPH, MBA

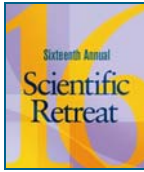
On a personal note, as an oncologist and physician-scientist, this was the most provocative meeting I have ever attended in my 21 years in the field of prostate cancer research. Why? As a habit, I put an exclamation mark in my notes next to every new hypothesis around a new scientific finding that strikes me as entirely new and unexpected. I then go “to the literature” on every exclamation point. This year, I had 24 exclamation marks in my notes at the end of the meeting. Each of these exclamation-mark hypotheses could be a “game changer” for how we prevent, treat, detect, monitor and eradicate prostate cancer. All 24 are on the new PCF “portfolio list.” As we head into 2010, PCF will advocate for funding support for each of these 24 critical ideas.

The summary that follows is a distillation of the meeting. If you have any specific questions, please contact us at [dzenka@pcf.org](mailto:dzenka@pcf.org). The entire PCF staff works diligently to put on this Scientific Retreat, but I want to personally acknowledge and highlight the particular contributions and leadership of Howard Soule our EVP and Chief Science Officer, Jan Wolterstorff, our VP of Development Operations, and Dan Zenka our VP of Communications for this year’s successful retreat and retreat communications.

Cordially,



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



# Key Areas of Discovery and Development

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## 1. Survivorship

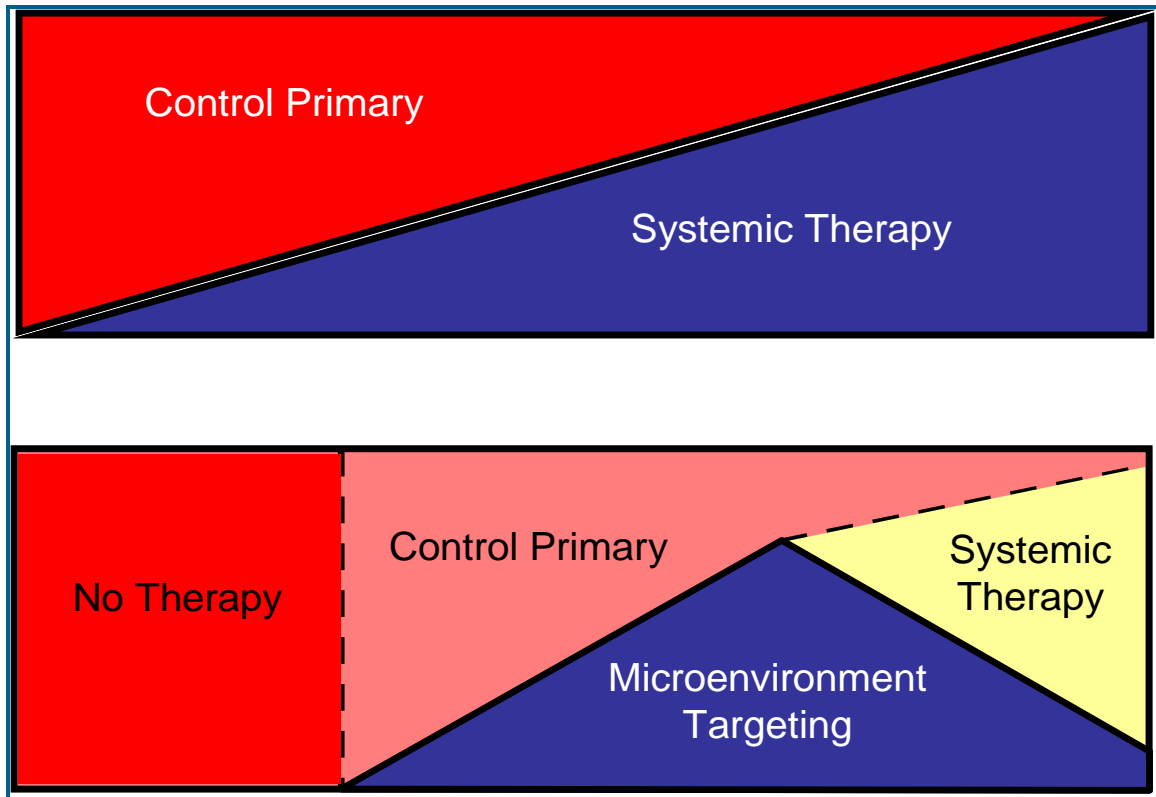
**Presentation:** *New Clinical Trial Designs that Extend Patient Survival*  
**Investigator:** Christopher Logothetis, MD  
**Institution:** University of Texas MD Anderson Cancer Center  
**PCF Funding:** Therapeutic Clinical Investigation Consortium

### Major Points:

- Early chemotherapy for advanced prostate cancer has not improved outcome, calling into question the traditional paradigm for development of cytotoxic agents.
- A proposed prostate cancer treatment paradigm stresses the importance of targeting the microenvironment along with the primary tumor.
- This proposed paradigm defines clinical trials that are no longer linear for a single agent and focuses on extension of life as the primary endpoint.
- Data management program, Prometheus, is under development to collect and organize clinical and experimental data from these investigations. Access to these data will result in better informed and accelerated drug development.

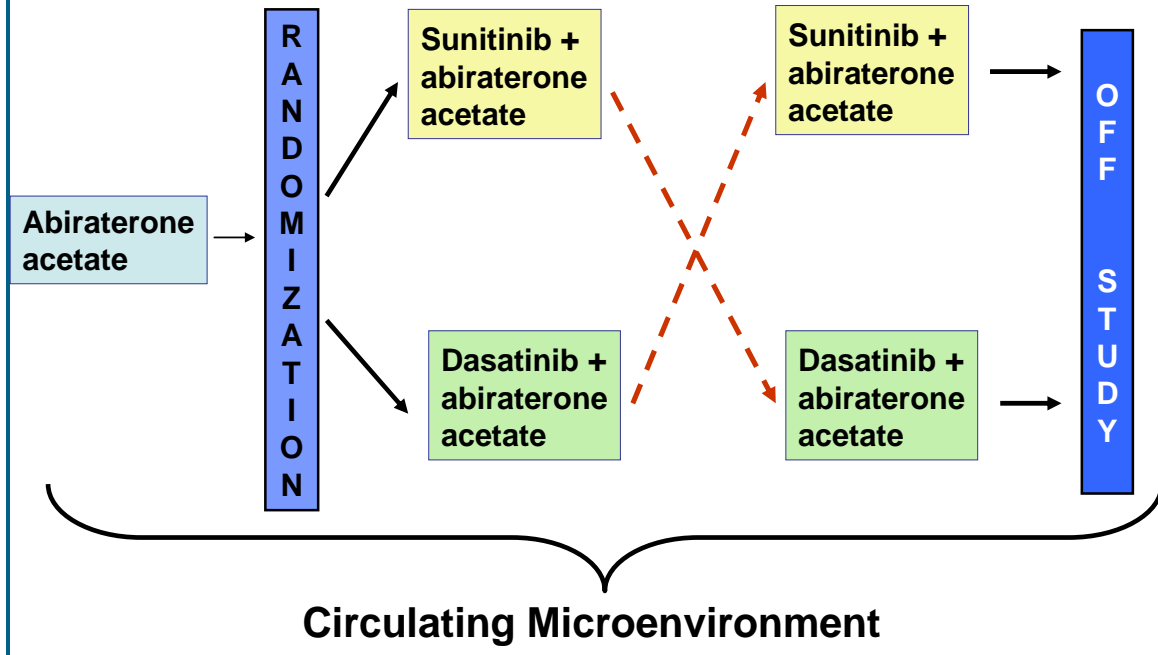
### Discussion:

Dr. Logothetis' opening lecture stimulated much discussion when he outlined evidence to support his proposed "treatment science" approach for treating advanced prostate cancer. He demonstrated with data that clinical investigations should not continue to follow the solid tumor chemotherapy treatment paradigm used for other solid tumors. Most prostate cancer patients will not gain a survival benefit from early intervention with chemotherapy. Paradoxically, he suggests that chemotherapy resistance for common prostate cancer may be greater early in disease. A major component of his new treatment paradigm is to use combination therapies that target the primary prostate cancer cells and simultaneously the surrounding tumor microenvironment. He suggests that systemic chemotherapies should be used at castrate resistant progression or in aggressive prostate cancer variants ("anaplastic"). Dr. Logothetis provided an example clinical trial schema depicting the use of targeted therapies in a non-linear fashion to extend patient survival and speed the drug approval process.



The model at the top of the image represents the current solid tumor treatment paradigm. On the bottom is Dr. Logothetis' proposed treatment science approach. In his model he suggests that in early disease most patients should be carefully observed by active surveillance. However, at the time of disease progression, both the primary tumor and the surrounding cells supporting the tumor must be co-targeted. In late stage prostate cancer, when targeted treatment combinations have failed, systemic therapies should be considered.

# Study Schema



A proposed trial, following a non-linear schema, includes randomizing patients treated with Abiraterone to [Dasatinib + Abiraterone] or [Sunitinab + Abiraterone] and then crossing over treatment to the opposite arm at time of disease progression. Dr. Logothetis argues that such clinical trials may provide extended overall survival for patients and will accelerate the development of new medications for advanced prostate cancer.



## 2. Prostate Cancer Somatic Genomics

### Keynote Lecture

**Presentation:** *ETS Transcription Factors: The Promise of Cancer Genetics for Prostate Cancer*  
**Investigator:** Barbara Graves, PhD  
**Institution:** University of Utah  
**PCF Funding:** Creativity Award

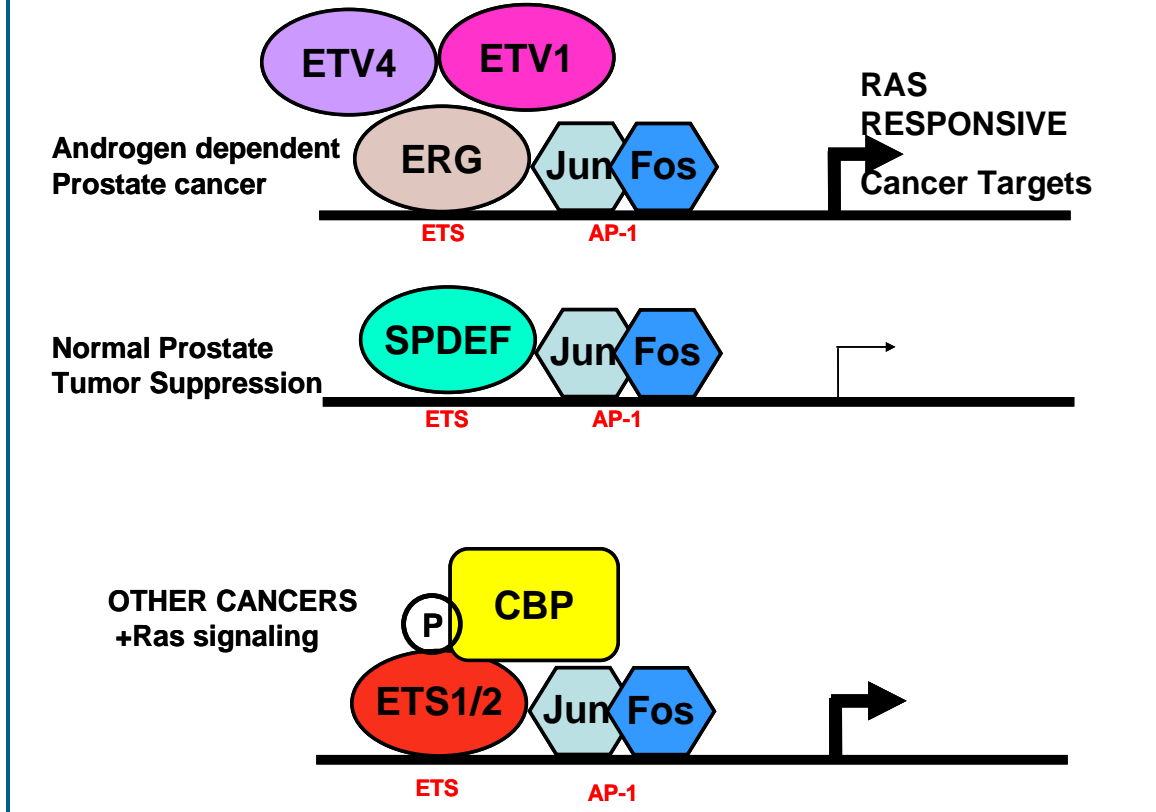
### Major findings:

- Discovered that DNA binding domains for ETS (a family of transcription factors-proteins that can turn genes on or off) are highly conserved.
  - ETS binding sites can be found throughout the genome.
  - This implies diverse biological roles and divergent functions in the different family members of ETS proteins.
- ETS protein ETV1 has 9,000 genomic binding sites in prostate cell lines.
  - These binding sites link with nearby genes enriched for pathways that regulate development, angiogenesis, hypoxic response and motility: a cancer signature.
  - There is an enrichment of ETS and AP1 binding motifs in bound regions suggesting targets may be RAS responsive genes.
- Model: In normal prostate tissue the ETS genes, such as tumor suppressor SPDEF, are expressed and prevent oncogenic signaling; however, when other ETS factors such as ERG, ETV1 and ETV4 are expressed oncogenic signaling is propagated. The oncogenic ETS may bypass the need for RAS signaling.

### Discussion:

Dr. Graves' presentation demonstrated the importance of how each of the 27 human ETS family members plays different functional roles in the context of different tissue types. Only recently were ETS genes considered important in prostate cancer, following the discovery of gene fusions harboring ETS genes such as ERG in over 40% of prostate cancer patients. Based on her genomic studies she suggests that ETS factors ERG, ETV1 and ETV4 are likely positive regulators of tumor cell growth and survival through changing expression of downstream target genes. Understanding the complex interaction of ETS transcription factors in prostate cancer may provide new druggable targets.

## ETS NETWORK IN PROSTATE CANCER



This model demonstrates that in normal prostate tissue the ETS family member, SPDEF binds to DNA (black line) at ETS specific sites. However, in prostate cancer cells SPDEF is replaced by other ETS family members (ETV1, ETV4 and ERG), that are not normally expressed in the prostate, which results in the expression of cancer causing genes in the RAS pathway.

**Presentation:** *Steroid Hormone Receptors in Prostate Cancer: A Hard Habit to Break?*  
**Investigator:** Gerhardt Attard, MD, PhD  
**Institution:** The Institute of Cancer Research and the Royal Marsden NHS Foundation Trust  
**PCF Funding:** Young Investigator Award

**Major findings:**

- Patients who progress on Abiraterone or MDV-3100 (medicines that target androgen synthesis and the androgen receptor, respectively) harbor prostate cancer that is still dependent on AR signaling.
  - When Abiraterone (or MDV-3100) treatment is stopped, the disease progresses even more rapidly.
  - Some of these patients respond to other approaches of steroid hormone blockade (provided data showing patients responding to [Dexamethasone + Abiraterone] after disease progression on Abiraterone alone).
- CTCs analyzed from patients undergoing Abiraterone treatment were assayed for: ERG fusion, PTEN loss and AR status
  - ERG fusions occur before PTEN loss and AR copy gain.
  - A change in CTC gene alteration status may correlate with treatment response.
  - Analysis of whole-mount human prostate tissue reveals that different parts of the tumor contain cells with different genetic alterations highlighting the heterogeneity of prostate cancer.

**Discussion:**

Dr. Gerhardt Attard reviewed data from Abiraterone Phase II clinical trials which demonstrated that some patients experience a durable response while others progress rapidly. He provided preliminary evidence suggesting that some patients, even after progressing on Abiraterone treatment, could be “re-sensitized” to Abiraterone by a combination treatment including the synthetic steroid Dexamethasone. However, the challenge remains how to identify patients who will benefit from Abiraterone or MDV3100 treatment and who will not. Dr. Attard suggests that by molecularly characterizing CTCs (determine which genetic alterations have occurred in a patients circulating tumor cells, such as identifying ETS fusion status) and correlating this genetic information with response to treatment, physicians may be able to tailor treatment to each individual.

**Presentation:** *In Vivo Deconstruction of the microRNA Oncogenic Network in Prostate Cancer*  
**Investigator:** Pier Paolo Pandolfi, MD, PhD  
**Institution:** Harvard-Beth Israel Deaconess Medical Center  
**PCF Funding:** Creativity Award and Challenge Award

**Major findings:**

- Demonstrated that PTEN (a tumor suppressor gene) is downregulated by specific microRNAs (miRNAs).
  - 70% of advanced prostate cancers have low levels of PTEN expression.
  - Discovered 5 new families of miRNAs that are able to downregulate PTEN and that are scattered across the genome in miRNA clusters.
- One miRNA cluster is found within the locus of a common oncogene.
  - This oncogene is overexpressed in prostate cancer and is under the control of another oncogene, MYC.
  - 10-50% of clinical prostate cancer specimens overexpress associated miRNAs as well.
- Demonstrated that overexpression of one of the discovered miRNA clusters in a mouse model causes prostate cancer.

**Discussion:**

Micro-RNAs (miRNAs) are small single stranded RNA molecules that arise from non-coding regions of the DNA (regions that do not code for proteins) and regulate gene expression. Only in the last few years miRNAs have been studied in cancer. These small molecules harness the power to decrease the production of proteins, which makes those miRNAs that modulate tumor suppressors especially dangerous. Dr. Pier Paolo Pandolfi has identified specific miRNAs that are found to decrease the levels of the tumor suppressor gene PTEN and are overexpressed in human prostate cancer specimens. He also showed that mice with high levels of these miRNAs developed prostate cancer. His work provides the field with new therapeutic targets that may lead to the development of new medicines that block prostate cancer causing miRNAs.

**Presentation:** [An Integrated Network of AR and TMPRSS2:ERG Gene Fusion in Prostate Cancer](#)  
**Investigator:** Arul M. Chinnaiyan, MD, PhD  
**Institution:** University of Michigan  
**PCF Funding:** Challenge Award

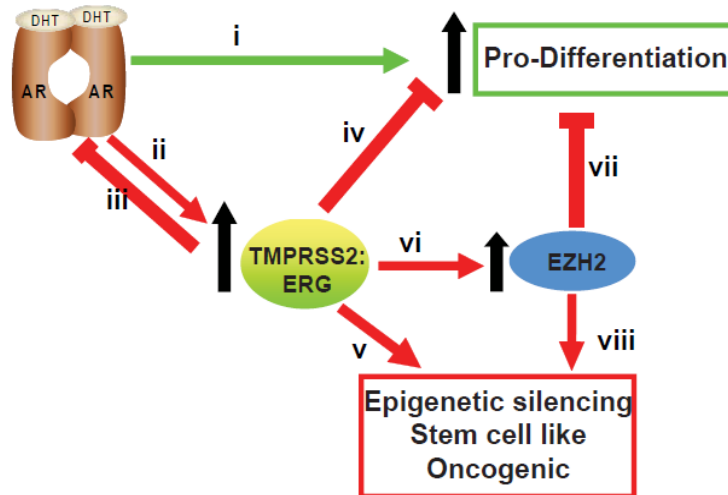
**Major findings:**

- Studied the interaction of AR (androgen receptor) and ERG (an ETS gene, commonly found in prostate cancer gene fusions) and found that ERG unexpectedly blocks AR signaling.
- Showed that AR and ERG proteins physically interact.
- Discovered that ERG also activates EZH2, a protein that can modulate epigenetic changes and has been associated with prostate cancer.
- Proposed that the common TMPRSS2:ERG fusion in prostate cancer therefore can inhibit AR, and suggests high dose testosterone treatment may promote normal prostate tissue growth and hinder cancer progression in patients without TMPRSS2:ERG fusions.

**Discussion:**

Dr. Chinnaiyan's work remains at the forefront of understanding the molecular mechanisms that underlie the initiation and progression of prostate cancer. His discovery that AR and ERG physically interact reveals a new therapeutic target for drug discovery. Additionally, Dr. Chinnaiyan hypothesizes that because ERG is repressing AR signaling and activating EZH2, the cancer cells are acquiring stem cell characteristics which include maintaining an undifferentiated state and self-renewal (both lethal properties of cancer). This is possible given that EZH2 is a gene capable of re-setting the epigenetic landscape from a lineage committed prostate epithelial cell to an undifferentiated stem cell. Therefore, blocking AR signaling is imperative in patients with TMPRSS2:ERG fusions in order to deter the induction of a stem cell fate via EZH2. In contrast, he proposes that patients without TMPRSS2:ERG fusions are strong candidates for high dose testosterone therapy, paradoxical to current androgen deprivation therapies. Such therapy would promote normal prostate epithelial differentiation. Previous preclinical studies demonstrate that administering high levels of testosterone inhibited prostate cancer cell growth in contrast to very low levels which promoted cancer cell growth. The data presented by Dr. Chinnaiyan provides new mechanisms for regulating prostate cancer progression and might be the basis of new treatment strategies.

## A Working Model for Androgen Signaling and ETS Gene Fusions in Prostate Cancer



AR Signaling

= GOOD (normal differentiation)

AR Signaling + TMPRSS2-ERG

= BAD (lineage specific differentiation blocked)

Above is Dr. Chinnaiyan's working model. He shows how increasing testosterone could promote normal prostate differentiation in the absence of TMPRSS2:ERG fusion however inducing AR signaling in the presence of TMPRSS2:ERG fusion activity would have deleterious effects and may initiate a self-renewing cancer stem cell-like fate.

**Presentation:** *Characterizing the Prostate Cancer Genome*  
**Investigator:** Levi Garraway, MD, PhD  
**Institution:** Dana-Farber Cancer Institute at Harvard  
**PCF Funding:** Challenge Award

**Major findings:**

- Dr. Garraway presented results for deep sequencing the first complete prostate cancer genome.
  - Showed that deep, whole-genome sequencing is becoming economically feasible at a significant scale.
  - The goal is to create a tissue bank of over 200 qualified clinical specimens for whole-genome or whole-exome sequencing.
- Discovered high incidence of chromosomal rearrangements, which generate gene fusions such as TMPRSS2:ERG.
  - Preliminary analysis revealed greater than 100 rearrangements with a possible enrichment of known cancer genes within or near the rearrangements.

**Discussion:**

By sequencing the whole prostate cancer genome, Dr. Garraway and colleagues may discover genetic alterations responsible for the initiation and progression of prostate cancer. Using a genome-wide deep sequencing approach enables unbiased discovery. Massively parallel whole-genome sequencing is becoming economically feasible on a wider scale due to major technological advances. Preliminary findings reveal a large number of interchromosomal and intrachromosomal rearrangements. The ultimate hope for this work is the discovery of the network of genetic changes that drive the proliferation, invasion and metastasis of prostate cancer. Many such alterations could identify new therapeutic targets for patients with lethal disease.

**Presentation:** *Epigenetic Strategies in Androgen Receptor-Dependent Interchromosomal Networking and Translocation Events in Prostate Cancer*  
**Investigator:** Michael G. Rosenfeld, MD  
**Institution:** University of California, San Diego  
**PCF Funding:** Challenge Award

**Major findings:**

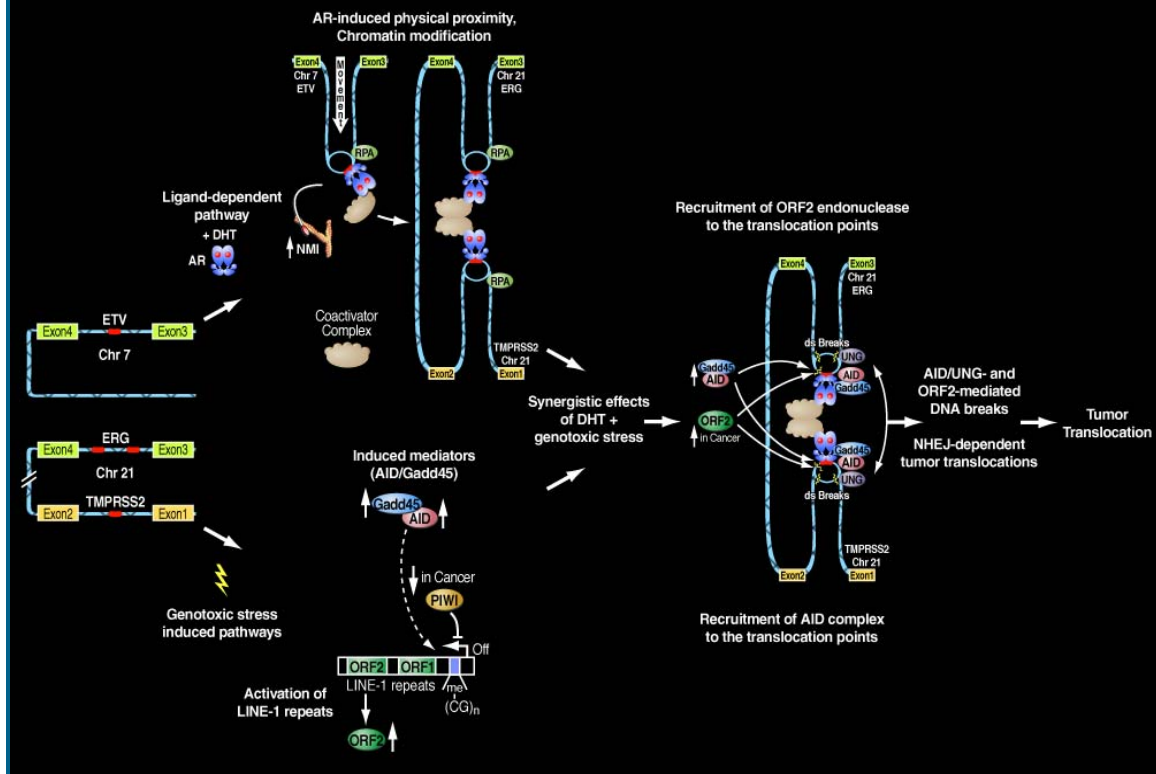
- Dr. Rosenfeld proposed a model where nuclear molecular motors control interchromosomal genomic interactions and translocations (gene rearrangements) under the control of steroid hormone receptors, such as AR (androgen receptor) and, potentially, ER $\alpha$  (estrogen receptor).
- He suggests that AR-dependent translocations are enhanced in cancer by genotoxic stress (when the integrity of a cell's genetic material is made vulnerable by carcinogenic agents).
- They are generating a high-throughput method to identify compounds that might block the activity of molecular motors or other factors involved in genomic translocations, which can be used to select anti-neoplastic compounds from high-throughput screening activities.

**Discussion:**

Dr. Rosenfeld presented his pioneering work in the field of cancer epigenetics. He has already made significant progress in elucidating the mechanisms that control the formation of gene fusions. His work suggests that the steroid receptors, such as AR, bind to DNA on different chromosomes. Through the recruitment of other proteins (including nuclear motors) these chromosomes come into close proximity to each other. This process, under cancer causing conditions (genotoxic stress), facilitates the formation of gene fusions, such as TMPRSS2:ERG. A high-throughput screening program has been established to discover compounds that block the process of gene fusion. These compounds represent leads to new treatment options for advanced prostate cancer and should advance our understanding of the biology of chromosomal rearrangements.



## Model of Induced Tumor Translocation Events



This diagram shows the cellular machinery Dr. Rosenfeld and his group believe is involved in creating gene fusions, also termed chromosomal rearrangements. Also, note that the androgen receptor (AR) is hypothesized to play a critical role in the generation of gene fusions.

### 3. Androgen Receptor in Lethal Prostate Cancer (Just When You Thought You Knew Something About AR...)

**Presentation:** *Molecular Portrait of Ligand-Independent Androgen Receptors in Castration Resistant Prostate Cancer*  
**Investigator:** Jun Luo, PhD  
**Institution:** Johns Hopkins University

#### Major findings:

- Described androgen receptor variant AR-V7 as an important truncated form of the androgen receptor which is detectable in clinical samples and promotes androgen independent growth in cell lines.
- M-phase genes (genes involved in cell growth) such as CDC20, UBE2C and CDK1 are all overexpressed in AR-V7 expressing cells.

#### Discussion:

The majority of advanced prostate cancer patients treated with androgen deprivation therapy (ADT; designed to block AR signaling) who progress still exhibit active AR signaling in their tumors. The discovery of new variants, such as AR-V7 provides insight on how prostate cancer cells evade ADT and highlights the need for medicines that impair signaling caused by these variant forms of the receptor. Dr. Luo presented data showing that prostate cancer cell lines expressing AR-V7 have an enhanced growth rate. Currently, the goal is to assess how each AR variant functions, when they are expressed during the natural history of the disease and to identify patients that express variants. Ultimately, there is a need to correlate expression of variant androgen receptors to clinical outcome.

**Presentation:** *Novel Alternative Pathways of AR Activation by Integrin Cell Surface Receptors*  
**Investigator:** Lucia R. Languino, PhD  
**Institution:** University of Massachusetts Medical School

**Major findings:**

- Integrins are cell adhesion molecules, which are factors expressed on the cell surface and are specifically upregulated in cancer.
- Integrins upregulated in prostate cancer include  $\alpha_v\beta_6$ ,  $\beta_3$ ,  $\beta_1$  and  $\alpha_6$ .
- Dr. Languino's team has shown that integrin  $\alpha_v\beta_6$  can upregulate AR activity in the absence of androgen.
- Her team has discovered that Survivin, a major cell survival signaling protein, is the main downstream target of AR.

**Discussion:**

Dr. Languino's findings highlight the importance of investigating the relationship between cell adhesion factors and AR signaling. She showed that  $\alpha_v\beta_6$  integrin is expressed in early pre-neoplastic and neoplastic prostate cancer tissue but not in normal prostate tissue. Dr. Languino's studies show that the communication between  $\alpha_v\beta_6$  integrin and AR results in the upregulation of Survivin, a protein that enables cells to evade death. These results show that it is critical to block such communication in a cancer cell. Dr. Languino, in collaboration with Dr. Violette at Stromedix (Cambridge, MA), is testing *in vivo* monoclonal antibodies to  $\alpha_v\beta_6$  integrin, to block the communication line to AR and therefore abrogate a cell survival pathway via Survivin. This strategy may provide prostate cancer patients with high  $\alpha_v\beta_6$  integrin expression in their tumors a new treatment option.

**Presentation:** *Interaction of Ligand Dependent and Independent Androgen Receptors on Progression to Castrate Resistant Prostate Cancer*

**Investigator:** Steve R. Plymate, MD

**Institution:** University of Washington School of Medicine

**Major findings:**

- Discovered a new variant of AR, which is missing coding regions (5, 6 and 7), termed exons.
- Increased levels of the variant AR-V5,6,7 results in a decrease in IGF-1R (insulin growth factor-1 receptor) expression, which has been linked to poor prognosis in prostate cancer.
- AR-V5,6,7 is always active even without androgen.
- Many different variants were discovered in samples from men receiving ADT as well as in metastatic prostate cancer specimens obtained by autopsy.
- In mouse models, androgen withdrawal causes an increase in expression of variant AR.

**Discussion:**

Dr. Plymate's work suggests that ADT may cause a switch to an androgen independent state by promoting the expression of variants such as AR-V5,6,7 which can cause tumor proliferation, invasion and survival without androgen. These findings argue that long term ADT is detrimental and may select cancer cells that can survive without androgen via the expression of AR variants, thus resulting in prostate cancer progression. These data also stress the value of understanding how cancer cells adapt to their environment. This knowledge will fuel the development of treatments that anticipate and block cancer cell adaptation.

## 4. Nutrition, Exercise and Supplements in the Prevention and Treatment of Prostate Cancer

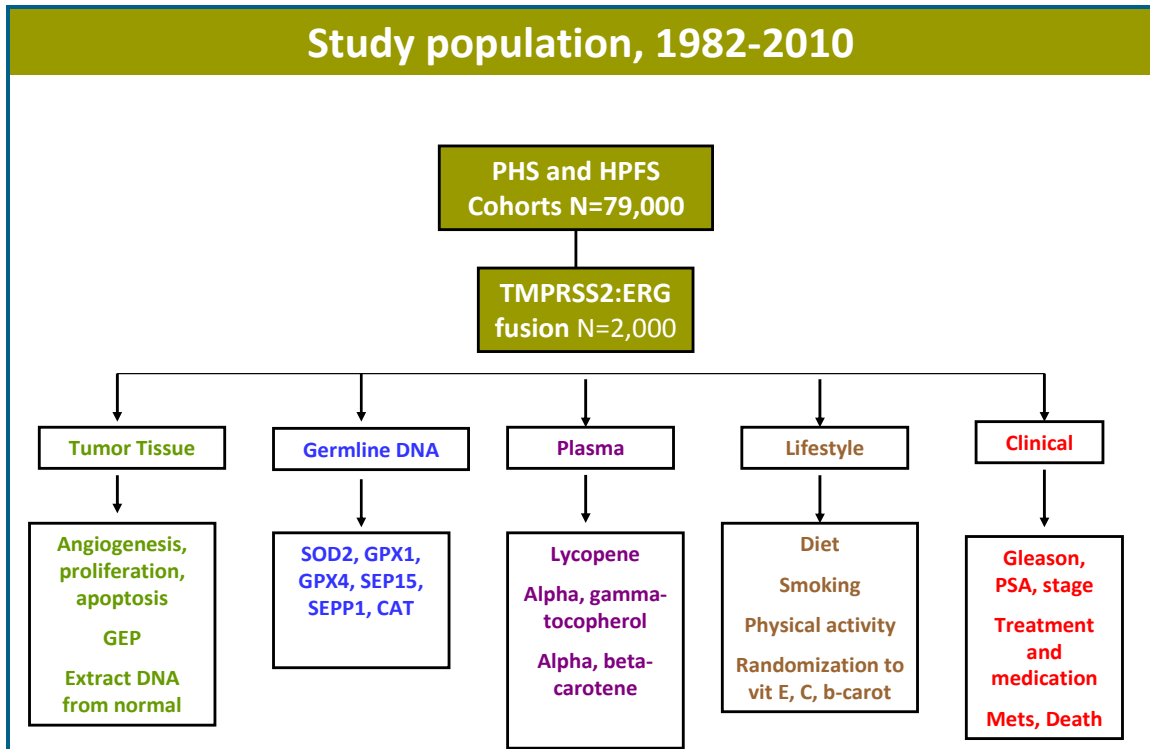
**Presentation:** *Do Antioxidants Prevent Risk of TMPRSS2:ERG Fusion Prostate Cancer?*  
**Investigator:** Lorelei Mucci, ScD, MPH  
**Institution:** Harvard School of Public Health  
**PCF Funding:** Young Investigator Award

### Major Findings:

- Dr. Mucci is an epidemiologist who studies lifestyle and genetic findings and correlates them with prostate cancer risk.
- The Physicians' Health Study and the Health Professional Follow-up Study track the health history of 80,000 people (and ~8,000 men have been diagnosed with prostate cancer in these cohorts)
  - To date, 393 prostate cancer cases have been analyzed for TMPRSS2:ERG gene fusion status in tumors. Forty-two percent of men were positive.
  - $\beta$ -carotene intake did not correlate with occurrence of gene fusions.
  - Blood plasma levels of  $\alpha$ - and  $\gamma$ -tocopherol were inversely associated with gene fusion occurrence.
- 2 single nucleotide polymorphisms (SNPs) in SOD2, an enzyme that scavenges cancer-causing oxygen radicals, were significantly associated with the gene fusion status. These common variants in SOD2 were also associated with a more aggressive form of prostate cancer.
- Patients with genomic alterations in another gene called SEPP1 have an increase in TMPRSS2:ERG fusion occurrence.

### Discussion:

These studies identified common variants in genes (SOD2 and SEPP1) that were correlated with the occurrence of gene fusions, thereby providing a potential predisposition marker for a subset of prostate cancer. Future studies aimed at elucidating the function of these genes may provide important insights on the molecular mechanisms of gene fusion generation and how they may be therapeutically inhibited. Additionally, Dr. Mucci showed that  $\alpha$ - and  $\gamma$ -tocopherol (antioxidants) in the blood of patients was inversely associated with gene fusion status. This provides further support for the health-benefits of antioxidants in prevention and treatment of prostate cancer. Such discoveries should prompt younger men at high risk for prostate cancer (i.e. family history, African American ethnicity) to make healthy life-style choices that would include an increased intake of antioxidants.



**This figure illustrates the numerous areas of study Dr Mucci and her team is pursuing to better understand prostate cancer risk and progression.**

**Presentation:** *Translational Research in Nutrition and Prostate Cancer*  
**Investigator:** William Aronson, MD  
**Institution:** University of California, Los Angeles

### **Major Findings:**

- Developed a bioassay using serum from obese men before and after a strict dietary intervention.
  - Serum from obese men prior to dietary intervention accelerated the growth of prostate cancer cells in culture.
  - Following dietary intervention in these men there was a reduction of insulin growth factor 1(IGF-1) and an increase in an IGF inhibitory protein 1 (IGFBP-1).
- Current clinical investigations focus on modulating the dietary ratio of omega-6 and omega-3 fatty acids (omega-6: omega-3 in American men is ~15:1 vs. ~4:1 in Asian men, where prostate cancer incidence is low).
  - Hypothesis: Changing dietary fat (omega-6: omega-3) ratio levels will result in decreased PGE-1 levels, decreased COX-2 expression, and dietary fat reduction will lower IGF-1 and increase IGFBP1, thereby improving prostate cancer outcomes.
- Dietary Intervention Trial (Western; 15:1 and Experimental; 2:1)
  - Chefs prepare meals and ship to patients.
  - Men lost weight in both arms of the study.
  - Cell membrane fatty acid profile changed in red blood cells and benign and malignant prostate tissue of experimental group.

### **Discussion:**

Dietary changes that result in a reduction in the ratio of omega-6: omega-3 fatty acids may aid in the prevention of primary prostate cancer and slow the progression of established disease. Preliminary evidence from the Dietary Intervention trial, led by Dr. Aronson, suggests that the changes in omega fatty acid ratios are in fact changing the fatty acid composition in cells. It remains to be seen whether this change in fatty acid profile will actually modulate PGE-2 and COX-2 levels and IGF-1 and IGFBP-1 levels in human prostate tissue and effect prostate cancer outcomes.

**Presentation:** *An Update on Pomegranate Juice/Extracts in Prostate Cancer*  
**Investigator:** Michael Carducci, MD  
**Institution:** The Sidney Kimmel Comprehensive Cancer Center Johns Hopkins University  
**PCF Funding:** Therapeutic Clinical Investigation Consortium

**Major findings:**

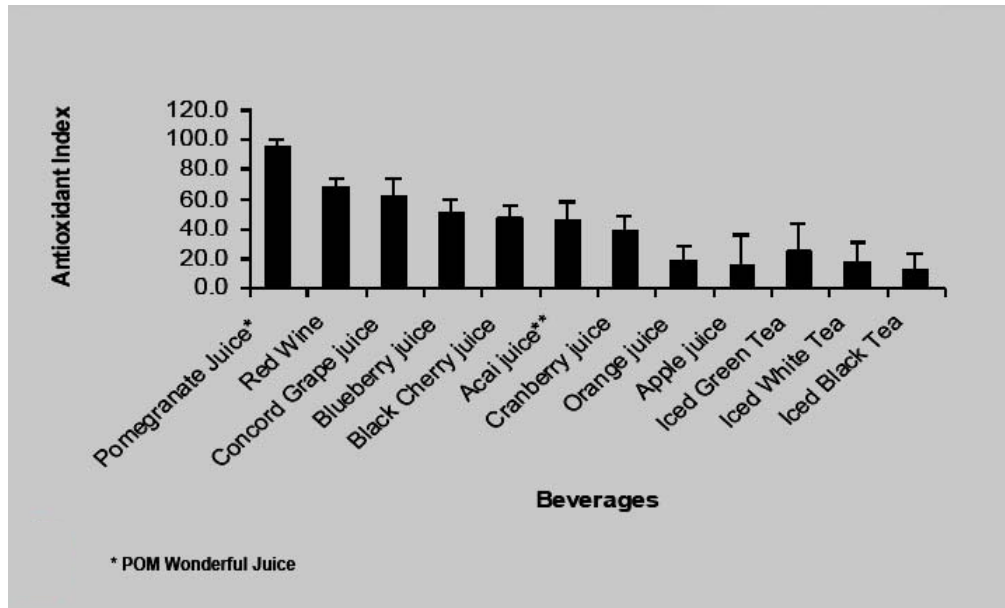
- Pomegranate contains the most potent antioxidant activity of all natural products.
  - Pomegranate supplements prepared using the entire fruit, including the skin, has the most antioxidant activity.
  - Not all commercially available pomegranate juices have the same measure of nutritional values.
- In models of prostate cancer, pomegranate supplementation treatment delays cancer progression, reduces cell growth, increases cell death, and reduces PSA in both prostate cancer cell lines and animal models of prostate cancer (xenografts).
- Current maturing Phase II clinical trials (100 pts. total) studied patients with rising PSA without metastatic disease.
  - 1 vs. 3 capsules per day of POM-X (Pomegranate concentrate) capsules was tested.
  - Preliminary data at 1 year, mean PSA doubling time increased from 11.2 months to 17.3 months across the study, no information as to dose effect at this time.
  - Some negative PSA slopes were observed.
  - These encouraging preliminary results are the basis of more advanced clinical investigations.
- Phase III investigation of POM-X capsules are underway but there is no data available at this time.
- Neoadjuvant trial with POM-X capsules are ongoing to define the potential anti-neoplastic mechanism of action of this material.

**Discussion:**

Dr. Carducci is one of the leading researchers investigating the potential anti-cancer effects of pomegranate-based antioxidant therapy for prostate cancer. Preliminary results from the Phase II clinical trials are encouraging. He updated data from a previously published UCLA study showing that ~82.5% of men with a rising PSA after local therapy had a reduced PSA doubling time after 5 years. Phase III clinical testing is underway and will be critical in assessing whether tumor growth is effected and how POM-X acts mechanistically in human prostate cancer.



# Pomegranate Juice Anti-oxidant Potency



Dr. Carducci presented these data showing the variable levels of antioxidants found in different beverages. POM Wonderful juice and red wine contain the highest level of antioxidants, the basis for potential anti-cancer activity.

## 5. Prostate Stem Cell Biology and Clinical Translation

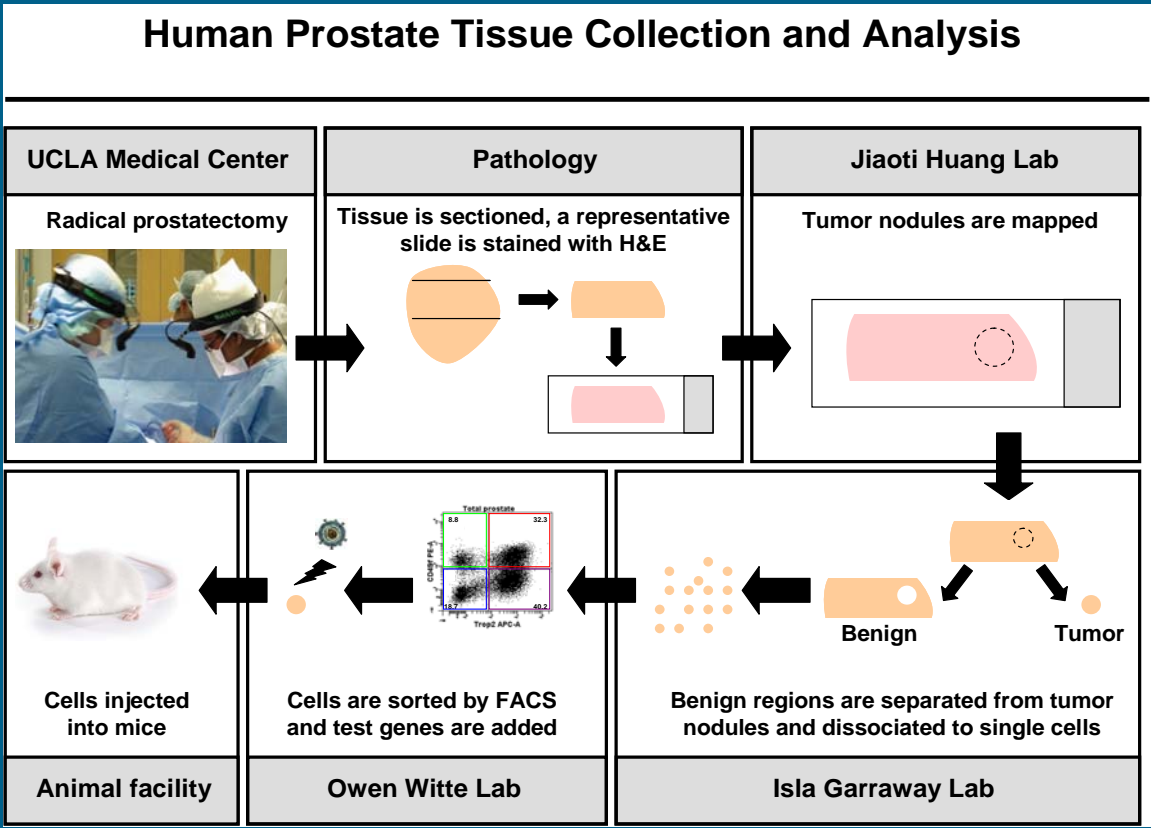
**Presentation:** [Prostate Stem Cells and Cancer Progression](#)  
**Investigator:** Owen N. Witte, MD  
**Institution:** University of California, Los Angeles  
**PCF Funding:** Challenge Award

### Major findings:

- Mouse prostate basal epithelial cells transformed with human ERG gene can induce tumors in mice.
- Demonstrated for the first time the generation of prostate glands in an experimental model using fresh human prostate epithelial cells.
- Also showed for the first time that fresh human cells genetically modified by the overexpression of several oncogenes caused pre-malignant hPIN
  - The human hPIN lesions expressed PSA and AMACR (another prostate cancer related protein) *in vivo*.

### Discussion:

These studies reveal that modulation of oncogenes in human prostate stem cells generates hPIN, the precursor to prostate adenocarcinomas. Dr. Witte stressed that his group was able to generate cancers from only one subpopulation of cells isolated from benign human prostate tissue, suggesting that only this stem cell population is capable of initiating cancer. These findings warrant further investigation on the human stem cell population and its role in prostate cancer initiation and progression. Importantly, the Witte group has also developed a new tool to test prostate cancer therapies on primary human cells *in vivo*, which is in contrast to the standard use of transformed human cell lines that lack thorough molecular characterization. This tool uses fresh human prostate epithelial cells that have been genetically altered using the expression of known prostate cancer oncogenes and places the cells inside the kidney capsule of an immune deficient mouse. Once inside the kidney capsule the cells will generate human prostate cancer and thus provides a model system that will more closely mimic human prostate cancer and will likely facilitate the discovery of the mechanisms that drive cancer initiation and progression.



This schema demonstrates the interdisciplinary team at UCLA involved in collecting and processing prostatic tissue from surgeries for research use in the laboratory.

**Presentation:** *A Luminal Epithelial Stem Cell that is a Cell of Origin for Prostate Cancer*  
**Investigator:** Michael M. Shen, PhD  
**Institution:** Columbia University Medical Center

**Major findings:**

- Discovered a mouse luminal stem cell population in the prostate which:
  - is castration resistant
  - expresses AR
  - expresses Nkx3.1
- Identified a self-renewing population following androgen deprivation that is luminal and capable of generating whole prostatic glands from a single cell.
- Generated tumors from luminal stem cells using genetic combinations of Nkx3.1 and Pten knockout expressing cells

**Discussion:**

Dr. Shen's studies are the first to describe a luminal stem cell population in the mouse prostate. This discovery is intriguing as most human prostate cancers are primarily comprised of luminal epithelial cells and suggests that perhaps a similar population of stem cells exists in the human and might be the population of origin of prostate cancer stem cells. Strictly defined, a cancer stem cell is a single cell that has the capacity to regenerate a tumor. Therefore, future studies will identify whether a comparable stem cell population exists in the human prostate and whether these cells individually are cancer propagating after oncogenic alterations.

## 6. Prostate Cancer Cell Metabolism

**Presentation:** [Metabolic Alterations in Prostate Cancer: Therapeutic Opportunities](#)  
**Investigator:** Massimo Loda, MD  
**Institution:** Dana-Farber Cancer Institute

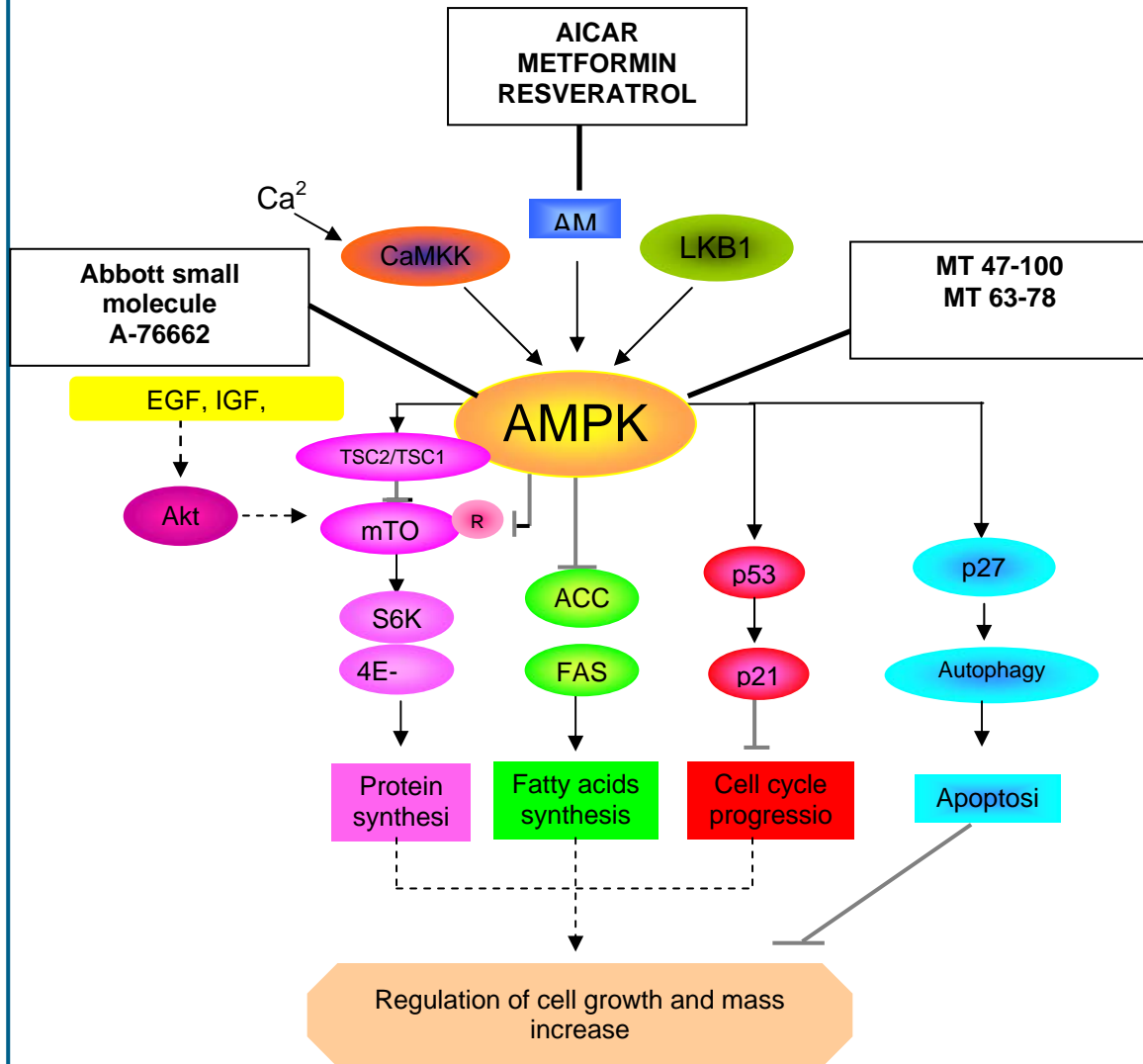
### Major findings:

- Discovered that fatty acid synthase (FASN) is upregulated in cancer and provides cancer cells with phospholipids necessary for cellular proliferation in a low nutrient environment.
- Described 4 single nucleotide polymorphisms (SNPs) which confer increased expression of FASN and promote aggressive prostate cancer in obese individuals.
- Generated a transgenic mouse with human FASN overexpression which resulted in hPIN (also showed that time to PIN is age dependent).
- Using direct activators of AMPK: MT 47-100, MT 63-78, and AICAR, in *in vitro* culture of LNCaP prostate cancer cells showed that these compounds directly impair cell growth, downregulate FASN and PI3K and, induce cell death.
- Metformin is an indirect activator of AMPK and is being considered for clinical investigation in advanced prostate cancer.

### Discussion:

Modulation of metabolic syndrome with an existing medication, such as Metformin, is currently being evaluated for the treatment of advanced prostate cancer. Evidence supports the use of Metformin in prostate cancer treatment. Men who have been prescribed Metformin display a reduced risk of being diagnosed with prostate cancer. Work in Dr. Loda's lab and others have shown that Metformin indirectly activates an enzyme termed AMPK. AMPK activation results in suppression of the PI3K/Akt pathway and fatty acid synthesis, both commonly dysregulated in prostate cancer. In addition, Dr. Loda is testing new experimental medications from Mercury Therapeutics that can directly modulate AMPK. Preclinical studies of these compounds have demonstrated anti-neoplastic activity in models of prostate cancer. These experimental medicines will be tested for the treatment of advanced prostate cancer.

## AMPK activators in cancer therapy



AMPK, which when activated, impairs fatty acid synthesis (green pathway) and protein synthesis (purple pathway). This slows cell growth and decreases tumor burden.

## 7. Insulin-Like Growth Factor Axis

**Presentation:** *Inhibition of Prostate Cancer with BMS-754807: A Selective IGF1R/IR Small Molecule Inhibitor*

**Investigator:** Marco Gottardis, PhD

**Institution:** Bristol-Myers Squibb

### Major findings:

- Phase I clinical trials of BMS-754807; an oral inhibitor of IGF-1 and insulin receptor tyrosine kinases:
  - Single agent was well tolerated and achieved preclinical efficacy blood levels in Phase I clinical studies.
- BMS-754807 was synergistic in preclinical models with anti-androgen therapy.
- Compound caused paradoxical PSA increases.

### Discussion:

Phase I clinical trials of BMS-754807 show tolerability at dose levels where preclinical efficacy was observed. BMS-754807 is an orally active small molecule inhibitor of neoplastic signaling through the insulin receptor (IR) and insulin-like growth factor 1 receptor (IGF-1R) tyrosine kinase.

**Presentation:** *Clinical Development of the Anti-IGF-1R Monoclonal Antibody Figitumumab*  
**Investigator:** Antonio Gualberto, MD, PhD  
**Institution:** Pfizer Oncology

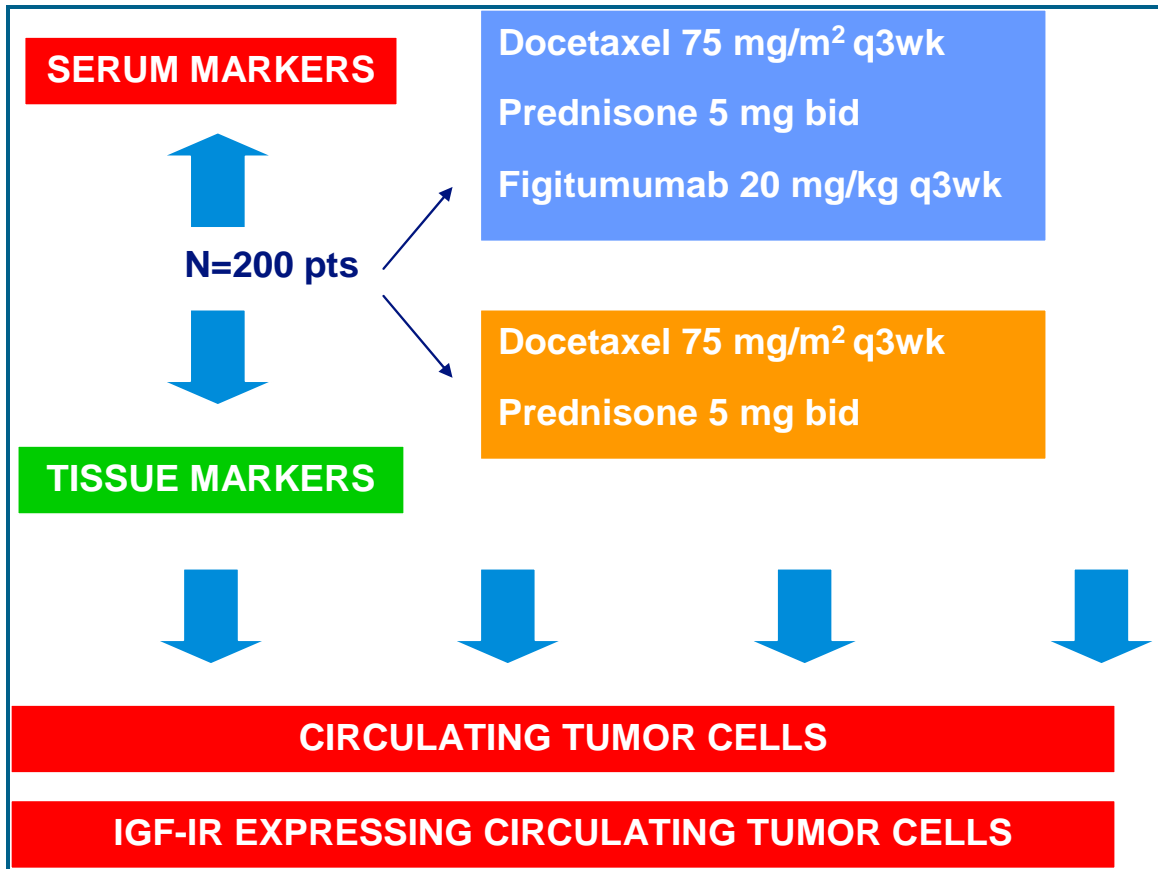
### **Major Findings:**

- Figitumumab is fully human IgG2 monoclonal antibody against IGF-1R.
- It has an effective half-life of ~20 days in man.
- Tolerated in Phase I-II setting in many human solid tumors.
- Phase II-III investigation in NSCLC is ongoing.
  - Synergistic with paclitaxel and carboplatin.
  - Circulating levels of free (bioactive) IGF-1 are highly predictive of disease progression.
  - Patients with elevated free IGF-1 levels appear particularly sensitive to Figitumumab.
- 200 patient randomized Phase II clinical trial in chemotherapy naïve castration resistant prostate cancer patients.
  - Primary endpoint is PSA response.
  - IGF-1R is being measured on CTCs. Serum markers (IGFs, IGFBPs) are also being determined.
  - Early Phase I investigations show that CTCs decline before PSA in a responding patients.

### **Discussion:**

Figitumumab is a monoclonal antibody that binds to the insulin-like growth factor type I receptor, which is activated in prostate cancer and signals cell proliferation, invasion and survival. Dr. Gualberto presented data showing efficacy in early clinical studies in lung cancer patients. The data also revealed that free IGF-1 levels (measured in blood) may be an important predictive biomarker for patients who would benefit from Figitumumab. Pfizer just completed enrollment (August, 2009) for a randomized Phase II clinical trial in CRPC patients. Expression of IGF-1R on circulating tumor cells (CTCs) and serum markers will be analyzed in relation to the efficacy of the antibody. Data are not yet available and await follow-up of patients.





Above is the schema for a Phase II clinical trials strategy for Figitumumab in CRPC. The clinical trial incorporates testing of tissue and serum markers to assess IGF-1R expression on CTCs and levels of free IGF-1 as treatment effect biomarkers.

## 8. Prostate Cancer Tumor–Stromal Interaction and Communication

**Presentation:** *Targeting the Tumor Ecosystem for Prostate Cancer Therapy*  
**Investigator:** Kenneth J. Pienta, MD  
**Institution:** University of Michigan  
**PCF Funding:** Challenge Award

### Major Points:

- Hypothesizes that genetic instability is a result of a change in the environment. Suggests that in order to eliminate cancer cells, treatments need to target the surrounding tumor microenvironment as well.
  - Focuses on tumor associated macrophages (TAMs), which produce a number of growth factors that promote tumor cell growth.
  - ~50-70% of the mass of metastatic prostate cancer lesions from prostate cancer from rapid autopsy specimens are macrophages.
- A Phase II Clinical Trial in advanced prostate cancer is underway with use of a monoclonal antibody against CCL2, which inhibits monocyte differentiation into macrophages.

### Discussion:

Dr. Pienta presented a comprehensive review of the logic behind targeting the tumor microenvironment in cancer therapy. He discussed the rationale by comparing the tumor microenvironment to ecosystems and suggested that in order for a species (i.e. cancer cells) to become extinct, the environment must become unsustainable. He provided data from his own lab indicating the essential role tumor-associated macrophages (TAMs) play in prostate cancer metastases in bone. Currently, a CCL2 antibody (CNT0888), which blocks the generation of TAMs, is in Phase II clinical trials. Data are not yet available.

**Presentation:** *An Absence of Stromal Caveolin-1 is Associated with Advanced Prostate Cancer, Metastatic Disease and Epithelial AKT Activation*  
**Investigator:** Michael Lisanti, MD, PhD  
**Institution:** Thomas Jefferson University

**Major Findings:**

- Loss of caveolin-1 (Cav-1) in ER positive human breast cancer patients is a biomarker for poor prognosis.
- Cav-1 is completely absent in metastatic prostate cancer lesions.
- Cancer-associated fibroblasts (CAFs) may be physical carriers for tumor cells, supporting invasion and metastasis.
- Loss of fibroblast Cav-1 is associated with increased p-AKT signaling in prostate epithelial cells.
- Loss of Cav-1 is associated with metastatic prostate cancer ( $p=10^{-17}$ )
- Patient stratification based on fibroblast Cav-1 status may predict a bad outcome prompting earlier and more aggressive treatment.

**Discussion:**

Caveolin-1 (Cav-1) is a protein expressed in most cells. Dr. Lisanti's work shows that loss of Cav-1 expression in cells surrounding prostate cancer cells correlates with metastatic disease and may be a new biomarker predictive of aggressive prostate cancer. Compounds that increase Cav-1 expression may represent a new treatment option for prostate cancer and warrant a drug discovery effort.

**Presentation:** Reactive Stroma in Prostate Cancer  
**Investigator:** Michael Ittmann, MD, PhD  
**Institution:** Baylor College of Medicine and Michael E. DeBakey VAMC

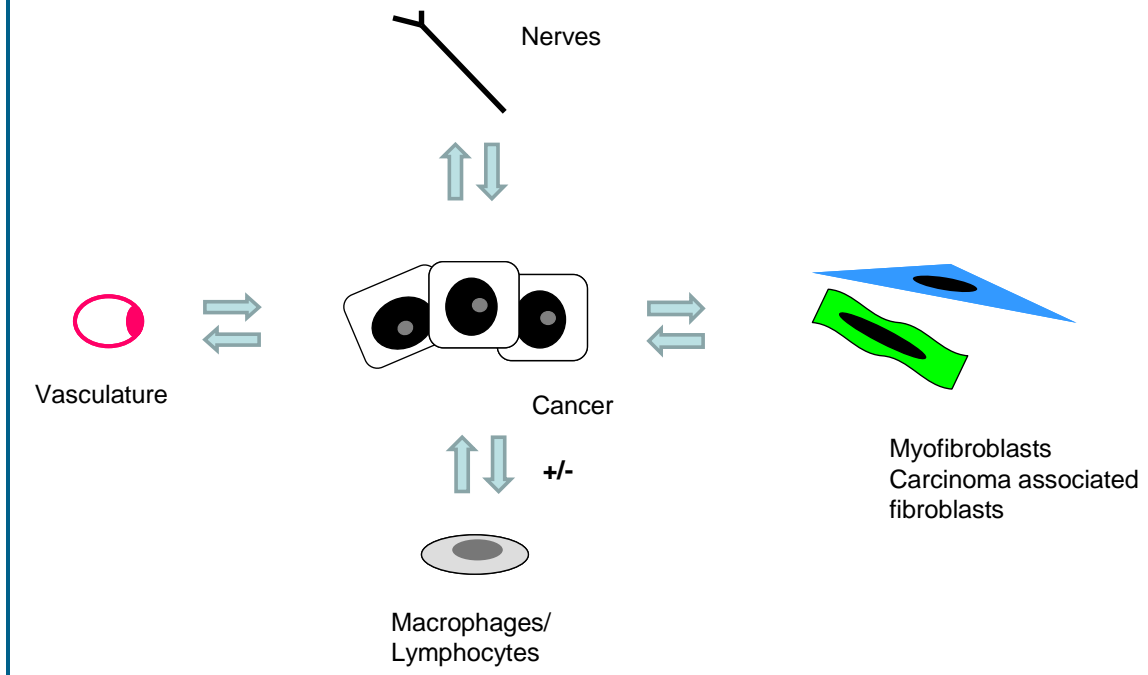
### Major Findings:

- The proportion of grade 3 prostatic reactive stroma predicts risk of PSA recurrence.
  - This observation was extended to prediction of prostate cancer specific death.
- Performed genomic profiling of grade 3 reactive stroma isolated using laser capture microdissection from prostate cancer tumor specimens.
  - Discovered a protein network that caused profound changes in signaling pathways from normal stromal cells.
  - Gene ontology (GO) analysis revealed classic oncogenic molecules and pathways including transcription factors, kinases, metabolism factors, and DNA damage repair pathways.
  - Identified an unexpected group of genes responsible for neurogenesis/axonogenesis in reactive stroma.
- Showed significant numbers of nerves in human prostate tumor specimens, even in specimens with hPIN.
  - Showed induction of neurite growth by a prostate cancer cell line, DU145 conditioned medium *in vitro*.
- Showed that nerve density is an early predictor of PSA recurrence following radical prostatectomy.
- Discovered that tumor cells close to nerves exhibit a significant reduction in apoptosis and an increase in proliferation.
- Reported that peri-neural invasion (PNI) diameter is a predictor of prostate cancer specific death.

### Discussion:

Dr. Ittmann and colleagues quantitatively described the neural component of the prostate cancer microenvironment. Human prostate cancer specimens revealed a higher density of nerves than normal prostate tissue and that the degree of neural invasion was associated with prostate cancer specific death. These data revealed that cancer cells in close proximity to nerves were actively growing and fewer were dying as compared to cells further away, suggesting that nerve cells in the tumor microenvironment are supporting prostate cancer cell growth and survival. Similarly, these data also showed that secreted factors from prostate cancer cells *in vitro* could induce the growth of neural cells. Together this highlights the cross-talk between the cancer cells and the surrounding microenvironment. Determination of peri-neural invasion (PNI) diameter may help to identify patients who require early aggressive treatment strategies and that nerve growth factor antagonists might be a novel treatment strategy.

## Working model of reactive stroma



**Dr. Ittmann's working model of the prostate cancer microenvironment illustrates neural invasion and the presence of highly reactive stromal cells play a role in the growth of the cancer.**

## 9. Drugging the Currently “Undruggable” Targets

**Presentation:** *Drugging the "Undruggable" Using Stapled Peptides*  
**Investigator:** Gregory Verdine, PhD  
**Institution:** Dana-Farber Cancer Institute

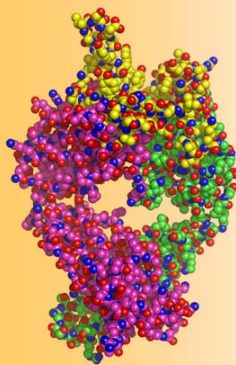
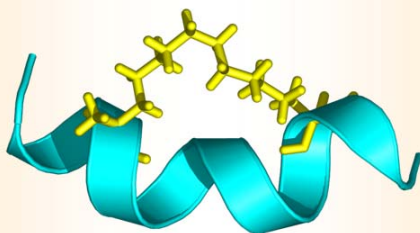
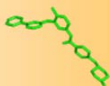
### Major findings:

- Created a new class of constrained molecules, synthetic stapled peptides, which are stable in blood permitting the use of small peptides as drugs.
  - These molecules can target protein-protein interactions and induce a dominant negative effect.
  - Stapled peptides maintain a 3-D protein-like structure unlike other peptides.
  - Stapled peptides can pass through cell membranes and are not limited to hydrophobic pockets.
- Previously published work using a stapled peptide antagonist to the pro-survival gene BCL-X<sub>L</sub> revealed significant reduction in disease in leukemia mouse models.

### Discussion:

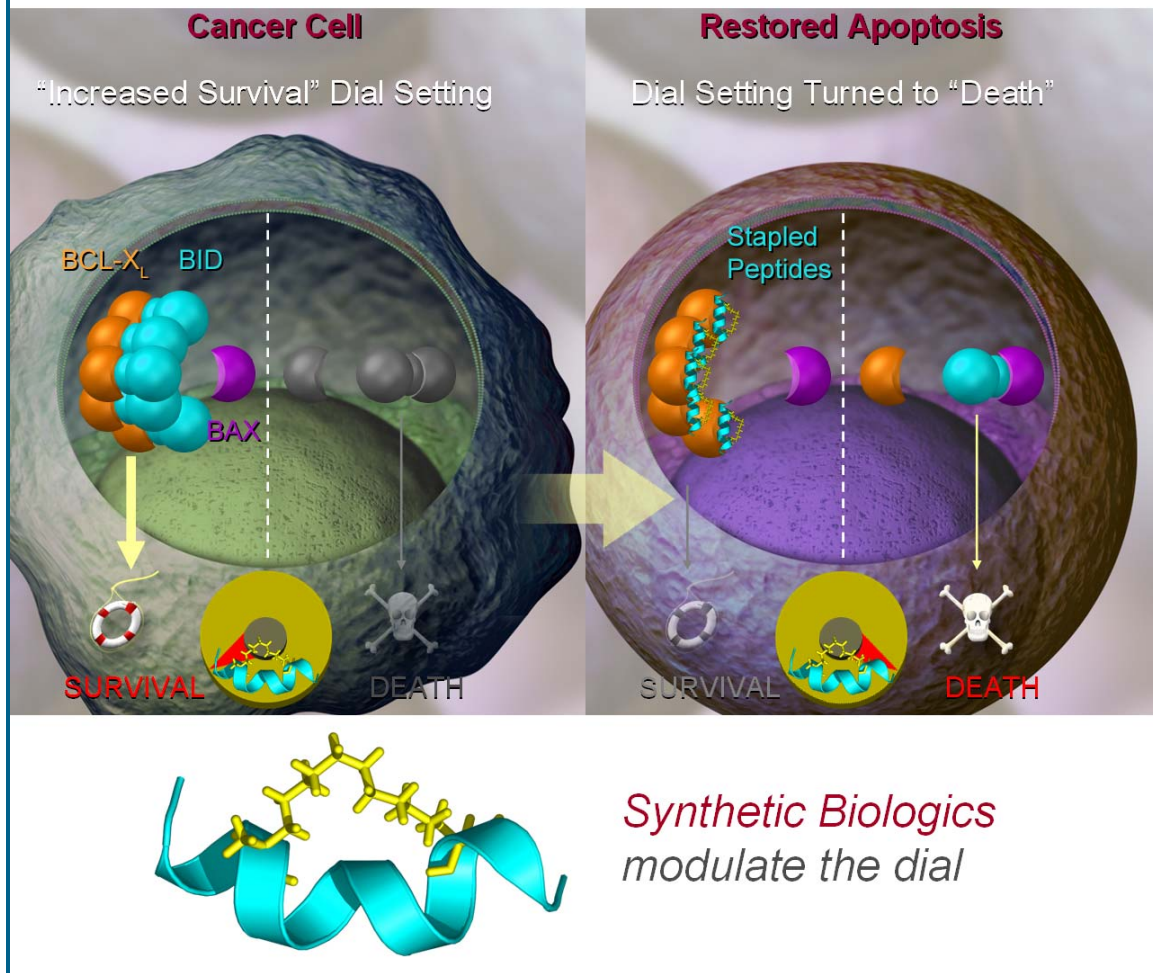
Stapled peptides are constrained synthetic peptides that are stable in blood and can enter cells. Unlike other available small molecules, stapled peptides are not limited to proteins with hydrophobic pockets (~10% of all proteins). Dr. Verdine presented data on two distinct stapled peptides, each of which demonstrated significant anti-tumor effects in leukemia mouse models. One stapled peptide was designed to block the pro-survival protein BCL-X<sub>L</sub> and another blocked a leukemia-specific oncogenic pathway (Notch1) critical for disease propagation. Oncogenic protein targets found inside the cell such as BCL-X<sub>L</sub> and Notch1, previously considered “undruggable,” might now be inhibited by stapled peptides.

## The Need for Entirely New Classes of Drugs

Biologics	Synthetic Biologics	Small Molecules
		
<p><b>~10% of All Prospective Targets</b></p> <p>Limited to targets outside the cell</p>	<p><b>~80% “Undruggable”</b></p> <p><i>Synthetic biologics combine the synthetic accessibility and cell permeability of small molecules with the versatile surface-recognition capabilities of biologics.</i></p>	<p><b>~10% of All Prospective Targets</b></p> <p>Limited to targets with greasy pockets</p>

As many as 80% of the proteins found in a cell are currently “undruggable” because they either reside inside the cell (not on the surface) or they lack a specific structural configuration.

## Stapled BID BH3 Peptides Reactivate the Death Pathway



Using stapled protein technology Dr. Verdine’s lab can switch a cancer cells’ “dial” from survival to death by interfering with proteins inside the cell.



**Presentation:** *DNA-programmed Chemistry - An Approach to Macrocyclic Lead Compounds for Protein-Protein Interactions*  
**Investigator:** Nick Terrett, PhD  
**Institution:** Ensemble Discovery Corp.

**Major Findings:**

- Macrocycles (MW 700-1000) have large surface areas and diverse building blocks to mimic protein epitopes. Important properties include:
  - Numerous distributed binding interactions- harbor extended binding motifs.
  - Cyclic structure enables enhanced affinity.
  - Can be engineered to have drug-like pharmaceutical properties, such as metabolic stability and cell membrane permeability.
- Two discovery platforms: a chemical library of ~500,000 compounds which uses a DNA scaffold to permit synthesis and screening of compounds
  - currently synthesized ~1400 macrocycles as discrete, individual compounds
- Have used affinity selection to identify compounds from the library that bind to specific proteins of interest.
  - Using this technology has successfully identified tumor necrosis factor receptor (TNFR) antagonists with unprecedented activity.

**Discussion:**

This technology represents a new discovery platform for anti-neoplastic medicines. The lead investigators are designing agents termed macrocycles that can target cancer proteins that were once considered “undruggable.” These macrocycles exploit a chemical space between currently available small molecules and larger compounds such as biologics and antibodies. Macrocycles are considered superior because of their ability to enter cells and target proteins with high specificity. Dr. Terrett showed promising data on a specific macrocycle that targets the tumor necrosis factor receptor (TNFR) with significant inhibitory activity. These macrocycles represent a new class of compounds that might be used to treat advanced prostate cancer in the future.

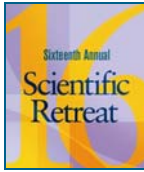
**Presentation:** *Post-Transcriptional Modulation of Gene Expression by Small Molecules for Therapy of Cancer*  
**Investigator:** Langdon Miller, MD  
**Institution:** PTC Therapeutics

**Major findings:**

- Discovery and development of compounds (~200,000 compound library) that modulate protein translation.
- Have identified an orally active inhibitor of VEGF production (PTC299) with anti-angiogenic activity.
- PTC299 also downregulates IL6, IL8, VEGF-C, -A, and osteopontin.
- PTC299 is active alone and in combination with docetaxel or bicaclutamide in prostate cancer xenograft models (e.g. LNCaP and PC3)
- In prostate cancer xenograft models, data suggest that PTC299 may ameliorate tumor- or chemotherapy-related cachexia.
- Phase I clinical trials have been completed in patients with solid tumors:
  - Generally safe
  - Circulating VEGF and IL6 levels were reduced - potential response biomarkers.
- Phase IIb clinical trial in castration-resistant prostate cancer (CRPC) is planned and will activate pending funding.

**Discussion:**

PTC299 is the lead oncology compound from PTC Therapeutics. PTC299 blocks cellular production of vascular growth factor (VEGF) which is critical to initiating the growth of tumor blood vessels (angiogenesis). Its low level of toxicity suggests that it may be superior to other anti-VEGF molecules. Phase I clinical trials in the treatment of multiple cancers reveal that PTC299 controls tumor growth in certain patients and is well tolerated. Phase II clinical testing in patients with CRPC is being considered through the PCF-DoD Therapy Consortium.



## 2009 Program Agenda

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**Thursday, September 24, 2009**

**Welcome and Introduction**

**1:30PM**

**1:40PM – 2:00PM**

**SPECIAL LECTURE**

**Acceleration of Therapy Development for Prostate Cancer  
with Information Rich Clinical Investigation**

Christopher Logothetis, MD  
University of Texas MD Anderson Cancer Center

**Prostate Cancer Somatic Genomics**

**2:00PM – 3:30PM**

**Moderator:**

Pete Nelson, MD  
Fred Hutchinson Cancer Research Center

**2:00PM – 2:15PM**

**Steroid Hormone Receptors in Prostate Cancer: A Hard Habit  
to Break?**

Gerhardt Attard, MD, PhD  
The Institute of Cancer Research and the Royal Marsden NHS  
Foundation Trust

**2:15PM – 2:30PM**

***In Vivo* Deconstruction of the microRNA Oncogenic Network  
in Prostate Cancer**

Pier Paolo Pandolfi, MD, PhD  
Beth Israel Deaconess Medical Center

**2:30PM – 2:45PM**

**The Next Generation of Gene Fusion in Prostate Cancer**

Arul M. Chinnaiyan, MD, PhD  
University of Michigan

**2:45PM – 3:00PM**

**Characterizing the Prostate Cancer Genome**

Levi Garraway, MD, PhD  
Dana-Farber Cancer Institute

**3:00PM – 3:30PM**

**Discussion**

**Challenge Award Discovery Reports – Session 1**

**3:30PM – 5:00PM**

**Moderator:**

Howard R. Soule, PhD  
Prostate Cancer Foundation

**3:30PM – 3:45PM**

**Prostate Cancer Targeted Therapies Directed to the Androgen-Receptor Signaling Axis as a Model for Drug Development**

Howard Scher, MD  
Memorial Sloan-Kettering Cancer Center

**3:45PM – 4:00PM**

**Consortium for the Development and Analysis of Relevant Prostate Cancer Model Systems**

Robert Vessella, PhD  
University of Washington Medical Center

**4:00 PM – 4:15PM**

**Epigenetic Strategies in Androgen Receptor-Dependent Interchromosomal Networking and Translocation Events in Prostate Cancer**

Michael G. Rosenfeld, MD  
University of California, San Diego

**4:15PM – 4:30PM**

**Clinical and Biological Insights into Prostate Cancer Derived from the Microfluidic Capture of Circulating Tumor Cells**

Daniel Haber, MD, PhD  
Massachusetts General Hospital Cancer Center

**4:30PM – 5:00PM**

**Discussion**

**Selected Young Investigator Presentation: Class of 2008**

**5:00PM – 6:00PM**

**Moderator:**

**5:00PM – 5:10PM**

Donald S. Coffey, PhD  
Johns Hopkins University School of Medicine

**5:10PM – 5:20PM**

**Andrew Armstrong, MD**  
Duke University

**5:20PM – 5:30PM**

**Scott Dehm, PhD**  
University of Minnesota

**5:30PM – 5:40PM**

**Mohamed Arredouani, PhD**  
Beth Israel Deaconess Medical Center

**Gerhardt Attard, MD, PhD**  
Speaking Thursday, September 24, 2:00 pm

**Lorelei Mucci, ScD, MPH**  
Speaking Friday, September 25, 10:00 am

**5:40PM – 6:00PM**

**Discussion**

**6:00PM – 6:15PM**

**SPECIAL PRESENTATION**

**Prostate Cancer Foundation: Present and Future**

Jonathan W. Simons, MD  
Prostate Cancer Foundation

**Dinner & Posters**

**7:00PM – 10:00PM**

**Dinner and Poster Session I**

**7:45PM – 8:00PM**

**PCF Special Awards Presentation**

Howard R. Soule, PhD  
Prostate Cancer Foundation  
Stuart Holden, MD  
Prostate Cancer Foundation

**8:00PM – 8:15PM**

**Special Presentation: CTC Scientific Working Group and  
Efficacy Response Biomarker Validation**

Howard Scher, MD  
Memorial Sloan-Kettering Cancer Center

**8:15PM – 10:00PM**

**Poster Session I**

**Friday, September 25, 2009**

**Androgen Receptor in Lethal Prostate Cancer (Just When You Thought You Knew  
Something About AR...)**

**7:30AM – 9:00AM**

**Moderator:**

Donald J. Tindall, PhD  
Mayo Clinic

**7:30AM – 7:45AM**

**Molecular Portrait of Ligand-Independent Androgen  
Receptors in Castration Resistant Prostate Cancer**

Jun Luo, PhD  
Johns Hopkins University

**7:45AM – 8:00AM**

**Novel Alternative Pathways of AR Activation by Integrin Cell  
Surface Receptors**

Lucia R. Languino, PhD  
University of Massachusetts Medical School

<b>8:00AM – 8:15AM</b>	<b>Interaction of Ligand Dependent and Independent Androgen Receptors on Progression to Castrate Resistant Prostate Cancer</b> Steve R. Plymate, MD University of Washington School of Medicine
<b>8:15AM – 8:30AM</b>	<b>A Critical Role of the Androgen Receptor in Castration Resistant Prostate Cancer</b> Donald J. Tindall, PhD Mayo Clinic
<b>8:30AM – 9:00AM</b>	<b>Discussion</b>

<b>9:00AM – 10:00AM</b>	<b><u>KEYNOTE LECTURE</u></b>  <b>ETS Transcription Factors: The Promise of Cancer Genetics for Prostate Cancer</b>  <b>Barbara Graves, PhD</b> University of Utah  <b>Introduced by Arul M. Chinnaiyan, MD, PhD</b> University of Michigan
<b>9:45AM – 10:00AM</b>	<b>Discussion</b>

**Nutrition, Exercise, Supplements in the Prevention and Treatment of Prostate Cancer**

<b>10:00AM – 11:30AM</b>	<b>Moderator:</b> David Heber, MD, PhD University of California, Los Angeles
<b>10:00AM – 10:15AM</b>	<b>Do Antioxidants Prevent Risk of TMPRSS2:ERG Fusion Prostate Cancer?</b> Lorelei Mucci, ScD, MPH Harvard School of Public Health
<b>10:15AM – 10:30AM</b>	<b>Translational Research in Nutrition and Prostate Cancer</b> William Aronson, MD University of California, Los Angeles
<b>10:30AM – 10:45AM</b>	<b>An Update on Pomegranate Juice/Extracts in Prostate Cancer</b> Michael Carducci, MD The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University
<b>10:45AM – 11:00AM</b>	<b>Can a Low-Carbohydrate Very High-Fat Diet Actually be Good for Prostate Cancer?</b> Stephen Freedland, MD Duke University
<b>11:00AM – 11:30PM</b>	<b>Discussion</b>

**12:00PM – 1:00PM**  
**Lakeside Ballroom**

**SPECIAL LECTURE**

**Mike Milken**

Prostate Cancer Foundation

**Introduced by Stuart Holden, MD**

Prostate Cancer Foundation

**2:45PM – 4:00PM**

***PANEL DISCUSSION***

**Immunotherapy: Improvement of Treatment for Prostate Cancer**

***Moderator:***

Jedd Wolchok, MD, PhD

Memorial Sloan-Kettering Cancer Center

***Panelists:***

James Allison, PhD

Memorial Sloan-Kettering Cancer Center

Charles Drake, MD, PhD

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University

Mark Frohlich, MD

Dendreon Corporation

James L. Gulley, MD, PhD

National Institutes of Health

**3:30PM – 4:00PM**

**Audience Participation and Discussion**

**Prostate Stem Cell Biology and Clinical Translation**

**4:00PM – 5:00PM**

***Moderator:***

Owen N. Witte, MD

University of California, Los Angeles

**4:00PM – 4:20PM**

**Prostate Stem Cells and Cancer Progression**

Owen N. Witte, MD

University of California, Los Angeles

**4:20PM – 4:35PM**

**A Luminal Epithelial Stem Cell that is a Cell of Origin for Prostate Cancer**

Michael M. Shen, PhD

Columbia University Medical Center

<b>4:35PM – 4:50PM</b>	<b>Identification and Molecular Characterization of Human Prostate Cancer Stem Cells</b> Daniel P. Petrylak, MD Columbia University Medical Center
<b>4:50PM – 5:00PM</b>	<b>Discussion</b>

**Prostate Cancer Cell Metabolism**

<b>5:00PM – 6:15PM</b>	<b>Moderator:</b> Massimo Loda, MD Dana-Farber Cancer Institute
<b>5:00PM – 5:15PM</b>	<b>Metabolic Alterations in Prostate Cancer: Therapeutic Opportunities</b> Massimo Loda, MD Dana-Farber Cancer Institute
<b>5:15PM – 5:30PM</b>	<b>Tumors with PI3K Activation are Resistant to Dietary Restriction</b> Nada Kalaany, PhD Whitehead Institute for Biomedical Research
<b>5:30PM – 5:45PM</b>	<b>Regulation of Cancer Cell Metabolism by Pyruvate Kinase M2</b> Matthew Vander Heiden, MD, PhD Dana-Farber Cancer Institute
<b>5:45PM – 6:15PM</b>	<b>Discussion</b>

**Dinner & Posters**

<b>6:45PM – 9:30PM</b>	<b>Dinner and Poster Session II</b>
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**Saturday, September 26, 2009**

**Insulin-Like Growth Factor Axis**

<b>7:30AM – 9:00AM</b>	<b>Moderator:</b> Michael Pollak, MD McGill University
<b>7:30AM – 8:00AM</b>	<b>Extending the Paradigm of Hormonal Dependence to Insulin and IGFs</b> Michael Pollak, MD McGill University



<b>8:00AM – 8:15AM</b>	<b>Inhibition of Prostate Cancer with BMS-754807: A Selective IGF1R/IR Small Molecule Inhibitor</b> Marco Gottardis, PhD Bristol-Myers Squibb
<b>8:15AM – 8:30AM</b>	<b>Clinical Development of the Anti-IGF-IR Monoclonal Antibody Figitumumab</b> Antonio Gualberto, MD, PhD Pfizer Oncology
<b>8:30AM – 9:00AM</b>	<b>Discussion</b>

**Prostate Cancer Tumor–Stromal Interaction and Communication**

<b>9:00AM – 10:15AM</b>	<b>Moderator:</b> Kenneth J. Pienta, MD University of Michigan
<b>9:00AM – 9:15AM</b>	<b>Targeting the Tumor Ecosystem for Prostate Cancer Therapy</b> Kenneth J. Pienta, MD University of Michigan
<b>9:15AM – 9:30AM Advanced</b>	<b>An Absence of Stromal Caveolin-1 is Associated with</b>  <b>Prostate Cancer, Metastatic Disease and Epithelial Akt Activation</b> Michael Lisanti, MD, PhD Thomas Jefferson University
<b>9:30AM – 9:45AM</b>	<b>Reactive Stroma in Prostate Cancer</b> Michael Ittmann, MD, PhD Baylor College of Medicine and Michael E. DeBakey VAMC
<b>9:45AM – 10:15AM</b>	<b>Discussion</b>

**Drugging the Currently Undruggable Targets**

<b>10:15AM – 11:40AM</b>	<b>Moderator:</b> Marco Gottardis, PhD Bristol-Meyers Squibb
<b>10:15AM -10:25AM</b>	<b>Introduction</b> Marco Gottardis, PhD Bristol-Meyers Squibb
<b>10:25AM – 10:40AM</b>	<b>Drugging the "Undruggable" Using Stapled Peptides</b> Gregory Verdine, PhD Dana-Farber Cancer Institute
<b>10:40AM – 10:55AM</b>	<b>DNA-programmed Chemistry - An Approach to Macrocyclic Lead Compounds for Protein-Protein Interactions</b> Nick Terrett, PhD Ensemble Discovery Corp.

<b>10:55AM – 11:10AM</b>	<b>Post-Transcriptional Modulation of Gene Expression by Small Molecules for Therapy of Cancer</b> Langdon Miller, MD PTC Therapeutics
<b>11:10AM – 11:40AM</b>	<b>Discussion</b>

**PCF Challenge Award Discovery Reports - Session 2**

<b>11:40AM – 1:10PM</b>	<b>Moderator:</b> Howard R. Soule, PhD Prostate Cancer Foundation
<b>11:40AM – 11:55AM</b>	<b>Discovery of Inhibitors of TMPRSS2/ERG Function in Prostate Cancer</b> William Hahn, MD, PhD Dana-Farber Cancer Institute
<b>11:55AM – 12:10PM</b>	<b>Synergistic Targeting of AR and Androgen Metabolism in Prostate Cancer</b> Steven Balk, MD, PhD <sup>1</sup> and Pete Nelson, MD <sup>2</sup> <sup>1</sup> Beth Israel Deaconess Medical Center; <sup>2</sup> Fred Hutchinson Cancer Research Center
<b>12:10PM – 12:25PM</b>	<b>Prevention of Treatment and Disease-Related Morbidity During Androgen Deprivation Therapy: A Multicenter Proposal</b> Matthew Smith, MD, PhD <sup>1</sup> and Nancy L. Keating, MD, MPH <sup>2</sup> <sup>1</sup> Massachusetts General Hospital, <sup>2</sup> Harvard Medical School
<b>12:25PM – 12:40PM</b>	<b>CTLA-4 Blockade in Therapy of Prostate Cancer: Therapeutic Mechanisms and New Directions</b> Pam Sharma, MD, PhD University of Texas MD Anderson Cancer Center
<b>12:40PM – 1:10PM</b>	<b>Discussion</b>

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