



SUMMARY

Randolph Fillmore, Florida Science Communications

The H. Lee Moffitt Cancer Center held its first *Advanced Prostate Cancer Collaboration* roundtable discussion November 24, 2008. The roundtable included faculty and staff from Moffitt, guests and visiting faculty from several medical and research institutions who presented updates on their research on advanced prostate cancer. Participants were greeted by William S. Dalton, Ph.D., M.D., President, CEO and Moffitt Cancer Center Director, James Mule, Ph.D., Executive Vice President, Julio Pow-Sang, M.D., chair of the Department of Genitourinary Oncology, and Lee Moffitt, founder of the Moffitt Cancer Center.

“We are honored to have the first of many Advanced Prostate Cancer Collaborations with invited experts in prostate cancer research from major medical and research institutions,” said Dalton.

Broad topics in advanced prostate cancer reported by researchers included information on: the prostate cancer (PCa) causative potential of gene fusion; comparing radiation therapy to a combination of radiation therapy and hormone therapy in healthy men with PCa and less healthy men with PCa; the ‘microenvironment of PCa; intermittent versus continuous hormone therapy; targeting cancer’s supporting cells in cancer’s ‘ecosystem’; vaccines that may boost the immune system; looking beyond the PSA to single nucleotide polymorphisms (SNPs); and the implications of the numbers of circulating tumor cells.

Following the research presentations, a case study was discussed followed by a question and answer period and wide-ranging open discussion.

Presentations began with **Arul M. Chinnaiyan, M.D.**, a Howard Hughes Medical Institute investigator and professor of pathology and urology at the University of Michigan medical School. Dr. Chinnaiyan discussed his current work investigating biomarkers for prostate cancer. He focused specifically on ‘gene fusion,’ a phenomenon identified in 2005 and recognized as a genetic causative factor in the development of PCa that opens a door for developing rational targets for therapy.

Gene fusion, explained Dr. Chinnaiyan, can be conceptualized as a chromosomal aberration where a ‘shuffling’ of genes causes two genes that are not supposed to be together to come together. The shuffling plays a role in signaling a cancer cell to grow uncontrollably when the scrambled genes ‘switch on’ a cascade of events.

Gene fusion has been identified in causing blood cancers, he said, but is now associated with prostate cancer as well.

“The drug Gleevec® can target gene fusion and block activity resulting from the fusion,” said Dr. Chinnaiyan.

Tests in animal models, he explained, revealed that removing the gene fusion caused tumors to slow their growth or shrink, suggesting that gene fusion can be taken advantage of as a specific biomarker and target for therapy, providing an opportunity to develop new drugs that could interfere with - or reverse - the fusion using inhibitors that block gene fusion expression.

He suggested that different ‘types’ of gene fusions may be treated differently depending on the aggressiveness of the tumor.

Anthony V. D’Amico, M.D., Ph.D., of Harvard University, professor and chief of the Department of Genitourinary Oncology at the Dana Farber Cancer Institute and Brigham and Women’s Hospital, compared treatment with radiation alone versus radiation in combination with hormone therapy in healthy and less healthy men with prostate cancer. Dr. D’Amico reported that while the study group of healthier men (nonsmokers, not over weight) with PCa but without concomitant disease, such as cardiovascular disease or diabetes did well on the combination therapy. Less healthy men with PCa who also had other serious health issues, such as cardiovascular disease (even those with resolved or successfully treated cases) or diabetes did less well and may have even been harmed by the combination therapy. They demonstrated lower survival curves with a two-fold decrease in survival rates.

“What does this say about the people who have other illnesses?” asked Dr. D’Amico. “These results reveal an opportunity to personalize medicine to overall health indices. We may be using too much hormonal therapy.”

He suggested that in future clinical trials patients could be stratified into groups based on co-morbidities.

Christopher J. Longothesis, M.D., director of the Genitourinary Cancer Center and Prostate Cancer Research program at the University of Texas M.D. Anderson Cancer Center, told participants that “something does not add up” with prostate cancer.

“It’s not like other solid tumors one finds in breast, lung or bladder cancer,” he said, explaining how PCa demonstrates an early, noncancerous epithelial stage before it eventually acts like other cancers.

Dr. Longothesis described a paradigm where PCa has a chemotherapy resistant phase in the epithelial stage where PCa looks like cancer, but it is not. He described a second stage in which PCa has a critical dependency on a ‘microenvironment’ where it can be locally targeted. Finally, he described a third stage in which systemic treatment is needed.

He also described a way of remodeling the microenvironment. He explained a study in which human prostate cancer cells were injected into a mouse model and the cancer cells attracted bone cells. If cells go from the bone to the cancer, he said, we might find a way to 'eavesdrop' on cancer is doing by looking at circulating bone cells to detect and quantify pathways of communication as cancer progresses.

"There is diversity in this disease and we have to be open to it," concluded Dr. Longothesis. "There is stromal (bone)-epithelial interaction as PCa progresses. Clinically, we have to understand this heterogeneity for the purposes of increasing the efficiency of our trial designs. If we continue to deal with these mixtures of different prostate cancers as one category, we will be frustrated in our clinical trials."

Dr. Longothesis recommended increasing the efficiency of clinical trials as well as reducing the toxicity threshold.

In discussing whether intermittent androgen blocking was better than continuous androgen blocking, **Daniel P. Petrylak, M.D.**, program director for Genitourinary Oncology Section at Columbia University Medical Center, said that patients on clinical trials could be stratified based on how they respond to androgen blockades. He suggested that looking at the number of circulating tumor cells may hold answers to which androgen receptor pathways need to be blocked. Greater than five circulating tumor cells has been associated with poorer outcomes while five and fewer than five circulating tumor cells have been associated with better outcomes, he said. He discussed two agents, CXP17 and MDV3100, that are under study as androgen blockers.

Dr. Petrylak suggested looking at whether intermittent hormone therapy could produce better results than continuous hormone therapy.

Kenneth J. Pienta, M.D., professor of internal medicine and urology and director of the Urologic Oncology program at the University of Michigan Comprehensive Cancer Center, discussed taking an 'ecosystems' approach to cancer. Dr. Pienta endorsed making the cancer microenvironment 'uninhabitable' for cancer by targeting specific aspects of the microenvironment. Less than 50 percent of tumor cells are cancer cells, he said, so we have been targeting only a small number of cells while there is 'a lot more to cancer than cancer cells.' For example, epithelial cells, osteoblasts, stem cells, progenitor cells are all interacting with cancer cells. To change the ecosystem of the microenvironment, he recommended targeting macrophage cells that comprise 50 percent of most tumor masses and are critical components of the ecosystem because they play a major supportive role for cancer. He suggested thinking of macrophage cells as 'invasive species' in the ecosystem, but cells that "don't need to be there."

"There are already drugs available that target cancer's supporting cells," he said, noting some of the clinical trials being conducted targeting drugs to cells other than cancer cells.

Immuno therapy is a nontoxic way to fight PCa, said **Johannes W. Vieweg, M.D.**, professor and founding chairman of the Department of Urology at the University of Florida School of Medicine. His approach is to boost

the patient's immune system using an immune vaccine. Among the vaccines available are those using whole cells; peptides; proteins; dendritic cells, viral vectors and nucleic acids.

However, Dr. Vieweg, who suggested that 'survival is a better end point than response,' noted that many patients come to his clinic seriously immune compromised and that dealing with immune suppression is an important first task since immunosuppression can mitigate the beneficial effects of a vaccine. Chemotherapy's profound effect on bone cells, where immune cells are generated, renders a vaccine less effective than it could be. Accordingly, after successfully 'rescuing' the patient from immune suppression, he advocated a 'multi-modal' approach for the highest likelihood of success. Unlike with chemotherapy, he added, there is a specific recognition of the cancer with vaccines. Dr. Vieweg closed his talk by suggesting that 10 years was too long to bring a drug to market. Safety is important, he said, but we must make therapies available sooner if therapies have been shown to be safe. Cancer vaccines, he concluded, are nontoxic and could be brought to the clinic sooner than drugs in which safety must first be shown.

The final presenter, **Daniel W. Lin, M.D.**, associate professor and director of the Division of Urologic Oncology at the University of Washington, looked 'beyond the PSA' and at several biomarkers, including circulating tumor cells - discussed earlier by Dr. Petrylak - germ lines, SNPs, and fusion proteins.

According to Dr. Lin, the number of circulating tumor cells, prognoses correlate with survival. Thus, isolating and looking at circulating PCa tumor cells can provide a window for making better prognoses and treatment decisions. For example, his research revealed that if the number of circulating tumor cells is less than five, patients survive longer than those who have more than five circulating tumor cells. However, there are challenges in detecting so few cells, he added.

In another approach he advocated looking at single nucleotide polymorphisms (SNPs), which represent a single change in genetic code, a change that can confer a difference in gene behavior. Any SNP that can be identified as causing a genetic susceptibility to PCa can be targeted for therapy, suggested Dr. Lin. Their recent study looked at 225 candidate genes and found several 'fascinating SNPs' with one relevant for PCa. Other SNPs are being investigated, he said. It may be that some SNPs can indicate mortality while others suggest treatments.

CASE STUDY

In part two of the roundtable, the panel heard a case study of a 49 year-old man diagnosed with PCa in 2006. The group evaluated his treatment and his survival status. It was noted that his father died from prostate cancer at the age of 49, so inheritability and his genetic 'instability' were discussed. In the case study, the patient originally presented with a moderately high PSA, moderate PSA velocity and with a pelvic mass. A biopsy was performed. He had early hormone treatment and radiation prior to surgery and six cycles of vaccine therapy.

At one point following therapy his PSA had not risen significantly, but he did have high numbers of tumor cells in his blood. Discussion centered around 'consolidating' his therapy.

ROUNDTABLE OPEN DISCUSSION

Open discussion following the case study centered on a number of relevant topics, observations and questions:

1. Should men start getting baseline PSAs at age 35? And, should those with a genetic susceptibility be tested even earlier?
 - a. Obtaining functional imaging of gene expression would be useful and could possibly eliminate the need for biopsies.
2. Where are we in terms of targeting PCa's initiating cells?
 - a. We are a long way from targeting the progenitor population. We don't know what the PCA stem cell is.
3. Are we accelerating mortality with treatment?
4. Is early treatment better than late treatment?
5. When is combination therapy better than mono therapy?
6. We need more informatics support.
7. Clinical trials design may need revision. Many trials may be too restrictive.
8. Is our investment in trial design proportional to benefit?
9. What are the impediments to participation in clinical trials?
10. The current economic downturn is hurting clinical trials participation.
11. Insurance coverage of clinical trials is an important issue.

12. What other health factors are involved in PCa survival?
13. If we give chemotherapy too early are we creating chemo resistance by selecting a more aggressive clone?
14. The localized disease is many beasts.
15. We need national registration and national relational databases.

##