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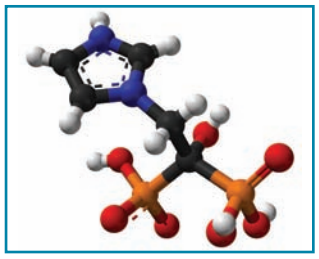
New MD Anderson President Ron DePinho on His Evolution as a Physician-Scientist

BY ERIC T. ROSENTHAL

He applied for the job only at the last minute, at the urgings of colleagues, but then soon realized after spending two days interviewing on the Houston campus he had visited many times before in other capacities how much he truly wanted to be president: "I was blown away by the magnitude of talent across all levels of the institution on a clinical level and the amount of resources and the capabilities. The esprit de corps and collaborative spirit offered a unique opportunity, and I knew then that I had to convince the Board of Regents."

Page 17



Myeloma: Early Start for Zoledronic Acid Further Reduces Risk of Skeletal Events p.13

Call for Increased Focus on Cancer Rehab p.22

JOE SIMONE Interviews 4 Oncologists about Their Recent Professional Moves p.5

CLL Debate: Older vs Newer Drug Combos for Frontline Therapy for Untreated, Symptomatic Patients p.44

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PERIODICALS

Prostate Cancer Biomarkers: Research Updates at AUA Annual Meeting

BY PEGGY EASTMAN

WASHINGTON, DC—Because better diagnostic tests for prostate cancer – especially ones that can distinguish indolent from aggressive disease—are needed, researchers are working to develop new biomarkers and genetic assays for clinical use. New data on some of these biomarkers were presented here at the American Urological Association Annual Meeting.

"They're sort of like the holy grail right now," said the moderator of a news briefing, Anthony Y. Smith, MD, Professor and Chief of Urology at the University of New Mexico School of Medicine. "I think we're moving toward molecular grading. Trying to sort out who needs to be treated and who doesn't is a critical issue," and biomarkers can provide tools to help in making those decisions.

PCA3 Predicts Small-Volume, Insignificant Prostate Cancer Preoperatively

The prostate cancer specific marker urinary prostate cancer antigen 3 (PCA3) can predict pathologically confirmed small-volume and insignificant prostate cancer preoperatively, according to a study presented by Alexander Haese, MD, PhD, Chief of Robotic Surgery at the Martini-Klinik of University Hospital, University of Hamburg in Germany, and his coauthors at Medical University of Graz, Austria.

In this study of 160 men in a US-European cohort, PCA3 scores were assessed using the Progensa assay, which is currently available in Europe and is being evaluated in the United States.

> There is now a rational basis for the combination of PCA3 and TMPRSS2:ERG gene fusion testing in prostate cancer diagnosis.

Using tumor volume data and PCA3 scores, the researchers used logistic regression models to identify endpoints for low-volume disease (less than 0.5 ml) and insignificant disease (using Epstein criteria). Low tumor volume and pathologically determined insignificant prostate cancer were present in 21.2% and 10% of study subjects, respectively. In these patients, PCA3 scores were significantly lower.

"Further exploration of its role as an additive marker [DRE] to select patients for active surveillance may be warranted," the researchers concluded of PCA3.

"The current dilemma is that serum PSA and digital rectal examination have low specificity; up to 75% of prostate biopsies are negative," said Dr. Haese. He noted that PCA3, which measures prostate cancer cells in post-DRE urine, is cancer specific and—unlike PSA—is not elevated by benign conditions.

PCA3 is currently approved in Europe for establishing the need for a biopsy, not

for determining candidates for active surveillance, he noted.

Combined PCA3 and TMPRSS2:ERG

There is now a rational basis for the combination of PCA3 and TMPRSS2:ERG gene fusion testing in prostate cancer diagnosis, according to a study from Radboud University Nijmegen Medical Center in the Netherlands. About half of prostate cancers have a genomic rearrangement that causes fusion of the genes TMPRSS2 and ERG; this gene fusion was discovered in 2005 by Arul Chinnaiyan, MD, PhD, a Howard Hughes Medical Institute researcher, Director of the Michigan Center for Translational Pathology and S.P. Hicks Professor of Pathology at the University of Michigan Medical School.

In the study reported at the AUA meeting, researchers tested 48 tissue samples from benign prostatic hyperplasia (BPH), 48 tissue samples from prostate cancer and 32 samples from normal prostate tissue. They measured PCA3 and TMPRSS2:ERG expression in these tissue samples.

The PCA3 test had a sensitivity of 84.4 for prostate cancer, but included one false-positive and seven false negative samples. The TMPRSS2:ERG gene fusion test was positive in 8.3% of the BPH samples, 15.6% of the normal tissue samples and half of the prostate cancer samples. But when these two tests were combined, sensitivity and diagnostic accuracy soared. Using TMPRSS2:ERG along with PCA3 added only one false positive, and eliminated four of the seven false negatives seen with PCA3 alone.

In another, related study, Dr. Haese, Jack Groskopf, PhD, Director of Oncology Research and Development at Gen-Probe, and coauthors presented data on a new quantitative TMPRSS2:ERG gene fusion urine assay to predict the outcomes in prostate cancer patients scheduled for radical prostatectomy. Of 74 men from whom urine samples had been obtained before surgery, 28 had non-organ confined disease, and 69 had a Gleason score of 7 or higher.

In this study, 21 patients with

continued on page 40

→BIOMARKERS

continued from page 39

biopsy-confirmed Gleason 6 disease were upgraded to a pathologic Gleason grade of 7 or higher based on the test. The median TMPRSS2:ERG score was significantly higher in men with non-organ confined disease compared with those with organ-confined disease (80 vs 9).

The median TMPRSS2:ERG scores for patients with pathological upgrading was 32, compared with 2 for those whose Gleason scores were not upgraded. Dr. Haese said that test results seem to show a trend toward men who are upgraded, indicating that it is catching the most dangerous prostate cancers that need the most aggressive treatment.

Genetic Risk Variants on Chromosome 8q24 Associated with Prostate Cancer Aggressiveness

In another new study on genetic susceptibility, Brian T. Helfand, MD, PhD, Research Assistant Professor in the Department of Urology at Northwestern University's Feinberg School of Medicine, and colleagues reported a study showing that genetic risk variants on chromosome 8q24 are associated with prostate cancer aggressiveness. To date more than eight different risk alleles have been mapped to this region, he noted.

In this study, 1376 Caucasian men underwent radical prostatectomy from March 2003 to September 2009 at Northwestern and were genotyped for five different risk alleles located on chromosome 8q24. Three of the five 8q24 risk alleles were found to be present at higher frequencies in men with aggressive prostate cancer.

There was a much higher proportion of carriers of the 8q24 risk allele SNP (single nucleotide polymorphism) rs16902094 with aggressive disease compared with non-aggressive disease (44% vs 28%). Additionally, there was a much lower proportion of carriers of this allele who had insignificant prostate cancer.

The researchers concluded that future confirmatory studies in other populations are warranted, since this study was done in Caucasians. Asked by *OT* if the 8q24 risk allele pattern might also hold true for African Americans, who tend to have more aggressive prostate cancer and higher prostate cancer mortality, Dr. Helfand said, "I think African

Americans have a slightly different SNP risk profile."

But, he said, there are certain to be susceptibility alleles that put African Americans at higher risk. "This is just the tip of the iceberg," he noted of his research results. And Dr. Smith pointed out that in the United States, many people have a mixture of racial and ethnic origins—so their risk allele patterns could reflect that mixture.

Other Studies

The AUA news briefing also featured:

- A study from Osaka University Hospital in Japan, showing that genetic polymorphisms of the CYP17A1 gene may predict early progression after primary androgen-deprivation therapy in Japanese men with prostate cancer. Statistical significance was observed in patients with the SNP rs6162 and three others in predicting early cancer progression after androgen-deprivation therapy. The researchers recommended a larger validation study of their findings, which were observed in 214 study subjects.
- A study from Northeastern University and Brigham and Women's Hospital demonstrating that autoantibody signatures can serve as biomarkers to distinguish prostate cancer from BPH. Using a customized array platform, the researchers identified five autoantibody signatures to specific cancer targets that, when combined, proved to be more effective than PSA in differentiating prostate cancer from BPH, and could thus potentially reduce unnecessary biopsies in men with elevated PSA. There were 41 prostate cancer serum samples and 39 BPH serum samples in this study.

"These are tools that may prove useful for both detection and prognosis," Dr. Smith said of the biomarker and genetic research studies presented. "Will we be able to use these tools to tailor therapy? The answer is yes."

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—Anthony Y. Smith, MD